THÈSE

Pour obtenir le grade de

DOCTEUR DE L'UNIVERSITÉ GRENOBLE ALPES

École doctorale : ISCE - Ingénierie pour la Santé la Cognition et l'Environnement
Spécialité : MBS - Modèles, méthodes et algorithmes en biologie, santé et environnement
Unité de recherche : Hypoxie et Physiopathologie

Données observationnelles pour l'identification et l'évaluation de médicaments induisant des pathologies vasculaires et respiratoires

Observational data for the identification and evaluation of drugs that induce vascular and respiratory pathologies

Présentée par :

Clément JAMBON--BARBARA

Direction de thèse :

Jean-luc CRACOWSKI PROFESSEUR DES UNIVERSITES - PRATICIEN HOSPITALIER, UNIVERSITE GRENOBLE ALPES	Directeur de thèse
Charles KHOURI DOCTEUR EN SCIENCES, UNIVERSITE GRENOBLE ALPES	Co-encadrant de thèse

Rapporteurs :

ANTOINE PARIENTE
PROFESSEUR DES UNIVERSITES - PRATICIEN HOSPITALIER, UNIVERSITE DE BORDEAUX
CLEMENCE LEYRAT
ASSOCIATE PROFESSOR, LONDON SCHOOL HYGIENE TROPICAL MEDICINE

Thèse soutenue publiquement le **5 septembre 2025**, devant le jury composé de :

DAVID MONTANI, PROFESSEUR DES UNIVERSITES - PRATICIEN HOSPITALIER, UNIVERSITE PARIS-SACLAY	Président
JEAN-LUC CRACOWSKI, PROFESSEUR DES UNIVERSITES - PRATICIEN HOSPITALIER, UNIVERSITE GRENOBLE ALPES	Directeur de thèse
ANTOINE PARIENTE, PROFESSEUR DES UNIVERSITES - PRATICIEN HOSPITALIER, UNIVERSITE DE BORDEAUX	Rapporteur
CLEMENCE LEYRAT, ASSOCIATE PROFESSOR, LONDON SCHOOL HYGIENE TROPICAL MEDICINE	Rapporteure
ELISE DUMAS, DOCTEURE EN SCIENCES, ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE	Examinatrice

Invités :

CHARLES KHOURI
DOCTEUR EN SCIENCES, UNIVERSITE GRENOBLE ALPES

Résumé

Données observationnelles pour l'identification et l'évaluation de médicaments induisant des pathologies vasculaires et respiratoires

Au-delà de la démonstration d'efficacité, la caractérisation du profil d'effets indésirables est un enjeu majeur du développement d'un médicament et de son évaluation post-commercialisation. Les essais cliniques apportent une quantité importante d'informations concernant les effets indésirables fréquents, mais restent souvent insuffisants pour détecter des effets rares ou à survenue tardive. Après la mise sur le marché, de nombreuses sources de données peuvent être utilisées (bases de pharmacovigilance, bases médico-administratives, données issues de la recherche animale, etc.) pour approfondir les connaissances sur le profil de sécurité des médicaments.

Les objectifs de ce travail sont d'étudier, d'identifier, de quantifier et de mieux comprendre les potentielles étiologies iatrogènes de trois pathologies vasculaires et respiratoires, caractérisées par des mécanismes physiopathologiques et une incidence dans la population très différents. Nous avons d'abord évalué une pathologie fréquente avec un délai de survenue relativement court et un diagnostic clinique évident : les ulcères cutanés ; ensuite, nous avons étudié une pathologie fréquente également, mais avec un délai de survenue et un temps entre les premiers symptômes et le diagnostic plus long : l'apnée du sommeil ; enfin, nous avons travaillé sur une pathologie rare, avec un long délai de survenue et un diagnostic complexe : l'hypertension artérielle pulmonaire (HTAP).

Nous avons, à cette fin, réalisé plusieurs études à partir de sources de données complémentaires disponibles pour l'évaluation de la sécurité des médicaments. Ce travail de thèse nous a permis d'explorer les intérêts et limites de différentes méthodologies qui permettent la caractérisation de potentiels effets indésirables. Il nous a également permis d'apprendre à identifier ces pathologies dans les bases de données médico-administratives et à appliquer ces différentes méthodologies pour quantifier le risque de survenue de ces pathologies avec des classes pharmacologiques dont le rôle était encore non confirmé dans la littérature. Enfin, l'analyse à grande échelle de ces bases permet de formuler de nouvelles hypothèses sur les causes iatrogènes de ces pathologies.

L'étude des étiologies iatrogènes de ces pathologies, et particulièrement de l'HTAP en raison de sa rareté, est à l'heure actuelle encore parcellaire. Des travaux de recherche complémentaires en pharmacovigilance et pharmacoépidémiologie sont nécessaires afin d'approfondir la connaissance de leurs facteurs de risque et personnaliser la prise en charge des patients.

Mots clés : Pharmacovigilance, Pharmacoépidémiologie, Hypertension Artérielle Pulmonaire, Ulcère cutané, Apnée du sommeil

Abstract

Observational data for the identification and evaluation of drugs that induce vascular and respiratory pathologies

Beyond demonstrating efficacy, characterising the adverse event profile is a major challenge in drug development and post-marketing evaluation. Clinical trials provide a substantial amount of information on common adverse events, but they are often insufficient to detect rare or late-onset events. After a drug is marketed, various data sources can be leveraged (pharmacovigilance databases, administrative healthcare databases, data from animal studies, etc.) to deepen our understanding of the drug safety profile.

The objectives of this work are to study, identify, quantify, and better understand the potential iatrogenic aetiologies of three vascular and respiratory diseases, each characterised by distinct pathophysiological mechanisms and population incidence. First, we assessed a common condition with a relatively short time to onset and a clear clinical diagnosis: skin ulcers. Then, we studied another common condition, but with a longer time to onset and a delay between the first symptoms and diagnosis: sleep apnoea. Finally, we investigated a rare disease with a long latency period and a complex diagnostic process: pulmonary arterial hypertension (PAH).

To achieve these objectives, we conducted several studies based on complementary data sources available for drug safety evaluation. This thesis permitted to explore the strengths and limitations of various methodologies used to characterise potential adverse drug reactions. It also allowed us to learn how to identify these pathologies within administrative healthcare databases and to apply these diverse methodological approaches to quantify the risk of these conditions occurring with pharmacological classes whose involvement had not yet been confirmed in the literature. Lastly, large-scale analyses of these data empower the formulation of new hypotheses regarding iatrogenic causes of these diseases.

The investigation of iatrogenic aetiologies, particularly for PAH due to its scarcity, remains incomplete. Further research in pharmacovigilance and pharmacoepidemiology is needed to better understand their risk factors and to personalise patient care.

Keywords: Pharmacovigilance, Pharmacoepidemiology, Pulmonary Arterial Hypertension, Skin ulcer, Sleep apnoea

Remerciements

A M. le Professeur David Montani, merci d'avoir accepté de juger ce travail et présider ce jury. C'est un honneur et un plaisir et j'espère que nos collaborations sur l'HTAP ne font que commencer.

A M. le Professeur Antoine Pariente et Mme. la Docteure Clémence Leyrat, merci d'avoir accepté d'être les rapporteurs de ce travail.

A Mme. la Docteure Elise Dumas, merci d'avoir accepté de juger ce travail et de participer à ce jury.

A M. le Professeur Jean-Luc Cracowski, merci Jean-Luc pour tout ce que tu m'as apporté ces 4 dernières années ! Et promis je reviens courir la semaine prochaine…

A M. le Docteur Charles Khouri, merci Charles, tu sais déjà forcément tout le bien que je pense et le plaisir que j'ai à travailler avec toi, donc je vais juste remercier le jus de betterave.

A M. le Professeur Matthieu Roustit, merci de m'avoir fait découvrir cet univers et de m'avoir accepté en stage il y a 5 ans déjà, point de départ de toute cette aventure.

Merci à tous les collègues et amis du CRPV avec qui c'est si agréable de travailler et jouer : Marion, Bruno, Adeline, Nathalie, Bob.

Merci également à tous les étudiants (et plus) que j'ai côtoyés et qui ont participé à ce travail : Mathieu, Sarah Margot, Coline, Rémi, Joey, Marc, Marie et bien évidemment Alex.

A mes amis les vrais pharmaciens hospitaliers : Renan, Raphaël, Florian, Romane, Elodie, Thomas, Marvin.

Aux Grimpouzes, qui savent valoriser comme personne, Camille et Victor qui ont participé activement à ce travail avec leur force et leurs neurones.

A mes amis Oompa Loompas pour tous les bons moments passés ensemble.

A ma famille, pour tout ce qu'on partage ensemble.

A U2, Miaou.

A tous ceux qui auront le courage de lire cette thèse sans s'arrêter aux remerciements.

TABLE DES MATIERES

Table des matières ____ 4
Abréviations ____ 6
Partie 1 – Introduction à la thèse ____ 7
1. L'évaluation de la sécurité du médicament ____ 9
1.1. Les études pré-cliniques ____ 10
1.2. Les essais cliniques ____ 11
1.3. La pharmacovigilance ____ 14
1.4. La pharmacoépidémiologie ____ 17
2. Epidémiologie et physiopathologie de pathologies vasculaires et respiratoires ____ 24
2.1. Le syndrome d'apnées du sommeil ____ 24
2.2. Les troubles trophiques cutanés ____ 28
2.3. L'Hypertension Artérielle Pulmonaire ____ 31
3. Objectifs de la thèse ____ 36
Partie 2 – Détection de signaux ____ 37
1. Validity, relevance and interpretation of pharmacovigilance disproportionality analyses ____ 39
2. Signal detection of drugs associated with obstructive and central sleep apnoea ____ 42
3. Conclusion de la partie ____ 51
Partie 3 – Identifier les événements : Développement et Validation d'algorithmes ____ 53
1. Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France ____ 55
2. Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in the French Healthcare Database ____ 63
3. Conclusion de la partie ____ 71
Partie 4 – Evaluation des signaux ____ 73
1. Ticagrelor after acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors ____ 75
2. Use of Bisphosphonates and the Risk of Skin Ulcer: A National Cohort Study Using Data from the French Health Care Claims Database ____ 113
3. Second- and Third-generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study ____ 126
4. Conclusion de la partie ____ 160
Partie 5 – Discussion et perspectives ____ 163
1. Detection and evaluation of drug-associated pulmonary arterial hypertension ____ 165
Conclusion ____ 195
References ____ 196
Annexes 1 – Autres travaux en relation avec la thèse ____ 207

1. Understanding the variability of pharmaco-epidemiological studies assessing the risk of appendicitis with mRNA COVID-19 vaccines _____ 207

2. Regional Heterogeneity of the Results of Glucagon-Like Peptide 1 Receptor Agonist Trials in Type 2 Diabetes: A Reanalysis of Individual Participant Data _____ 212

3. Impact of islet transplantation on diabetic complications and mortality in patients living with type 1 diabetes _____ 223

Annexes 2 – Supplementary Materials des articles _____ 234

1. Signal detection of drugs associated with obstructive and central sleep apnoea _____ 234

2. Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France _____ 249

3. Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in the French Healthcare Database _____ 257

4. Ticagrelor after acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors _____ 266

5. Use of Bisphosphonates and the Risk of Skin Ulcer: A National Cohort Study Using Data from the French Health Care Claims Database _____ 302

6. Second- and Third-generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study _____ 317

ABREVIATIONS

ANSM : Agence National de Sécurité du Médicament et des produits de santé

ATP : adénosine triphosphate

CONSORT : Consolidated Standards of Reporting Trials

FAERS : FDA Adverse Event Reporting System

FDA : Food and Drug Administration

HTAP : Hypertension Artérielle Pulmonaire

IC : Information Component

KCNK3 : canal potassique sortant de la sous-famille K membre 3

mPAP : pression pulmonaire moyenne

OMS : Organisation Mondiale de la Santé

PAWP : pression artérielle pulmonaire d'occlusion

PVR : résistance vasculaire pulmonaire

SNDS : Système National des Données de Santé

SUR 1 : sous-unités des récepteurs aux sulfonylurées 1

SUR 2 : sous-unités des récepteurs aux sulfonylurées 2

TTE : Target Trial Emulation

VIH : Virus de l'Immunodéficience Humaine

WSPH : World Symposium on Pulmonary Hypertension

PARTIE 1 – INTRODUCTION A LA THESE

1. L'évaluation de la sécurité du médicament

Au-delà de la démonstration d'efficacité, la caractérisation du profil d'effets indésirables des médicaments, indispensable dans l'évaluation de la balance bénéfice/risque, est un enjeu majeur du développement du médicament et de sa surveillance post-commercialisation. Lors de la commercialisation d'un médicament les données à propos de ce profil d'effets indésirables proviennent des phases de développement précliniques, toxicologiques et des patients exposés dans les essais cliniques. Après leur commercialisation, les méthodes d'identification de nouveaux effets indésirables médicamenteux sont généralement classées entre deux groupes distincts. Les méthodes qui permettent de générer des hypothèses et de détecter de nouveaux effets indésirables potentiel, appelés signaux de pharmacovigilance. La validation ensuite, qui consiste à évaluer, confirmer ou infirmer ces signaux, et à quantifier le surrisque et l'impact sur la population de cet effet indésirable. Ces différentes méthodes et sources de données forment un continuum de génération de preuves pour la sécurité du médicament aboutissant finalement à une prise de décision régulatoire (Figure 1).

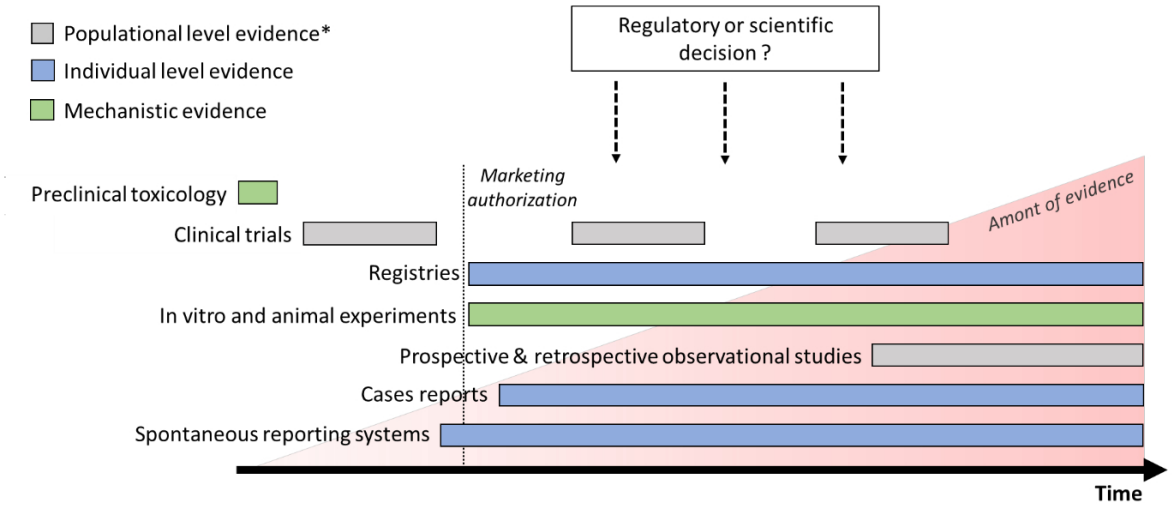


Figure 1. Types de sources de données disponibles pour la surveillance des effets indésirables. Extrait de (Hlavaty et al., Advances in Pulmonary Hypertension, in revision).

1.1. Les études pré-cliniques

Avant toute première utilisation chez l'humain, les données pharmacocinétiques, pharmacodynamiques pré-cliniques chez l'animal et la structure chimique de la molécule apportent déjà une information importante sur le profil de toxicité potentiel par comparaison avec les données accumulées avec d'autres médicaments apparentés. Les modèles murins sont ainsi particulièrement importants pour comprendre les mécanismes expliquant l'efficacité ou l'impact délétère des médicaments avant la commercialisation d'un médicament mais également pour trouver des explications physiopathologiques à un potentiel nouvel effet indésirable. Par exemple, chez les rats, l'administration intrapéritonéal de mitomycine C reproduit l'apparition de maladie veino-occlusive pulmonaire, ce qui supporte le rôle de ce médicament dans le développement de cette pathologie (1). Inversement, l'exposition à la dexfenfluramine, au dasatinib ou au rodastristat, trois médicaments connus ou suspectés pour induire des hypertensions artérielles pulmonaires, chez des rats a montré un effet paradoxalement protecteur de ces molécules (2,3). Ces observations illustrent que les études sur modèles murins sont imparfaites pour valider les signaux d'effets indésirables chez l'humain, et que ces données doivent être interprétées avec une grande précaution (2).

Les modèles cellulaires peuvent également apporter des informations complémentaires et aider à la réflexion sur la survenue d'effets indésirables. Par exemple, toujours concernant la survenue d'hypertension artérielle pulmonaire, il a été montré que l'exposition au dasatinib réduit l'expression et la fonction du canal potassique sortant de la sous-famille K membre 3 (KCNK3), ce qui contribue à la constriction artérielle pulmonaire, et la dysfonction des cellules musculaires lisses et des cellules endothéliales pulmonaires (4). En revanche, de nombreux résultats paradoxaux ont été observés avec les modèles in vitro. Par exemple, l'activation des sous-unités des récepteurs aux sulfonylurées 1 (SUR1) et 2 (SUR2) des canaux potassiques sensibles à l'ATP a montré une relaxation des artères pulmonaires dans les modèles expérimentaux alors que le diazoxide, un activateur de la sous-unité SUR1, a été associé avec

la survenue d'hypertensions pulmonaires chez les enfants traités pour hypoglycémie néonatal (5–7).

Ainsi, les modèles cellulaires et animaux offrent les premières informations sur la sécurité des médicaments avant toute administration chez l'humain ou sont utilisés pour comprendre des réactions inattendues, mais restent grandement limités dans leur extrapolabilité car ils ne reproduisent pas tout le spectre de la maladie. De plus, l'évaluation de l'impact des médicaments grâce à ces modèles est limité par l'absence (ou la différence) de métabolisation, par la différence des doses utilisées avec ce qui est retrouvé dans en concentration plasmatique chez l'humain, et par la difficulté de reproduire la durée d'exposition.

1.2. Les essais cliniques

Dans le parcours du développement des médicaments, suite aux études pré-cliniques sur des modèles cellulaires ou animaux, les premières études chez l'humain sont réalisées. Pour évaluer l'efficacité d'un nouveau médicament, les essais cliniques sont toujours considérés comme le *Gold Standard* de l'évaluation du médicament avant sa mise sur le marché. Ils sont le plus souvent réalisés en comparaison par rapport à un placebo ou à un traitement de référence dans la pathologie déjà mis sur le marché. Cependant, la détection et l'évaluation du profil d'effets indésirables, même si elle est obligatoire et indispensable à l'estimation de la balance bénéfice/risque d'un médicament, reste un objectif secondaire (8). Plusieurs recommandations pour rapporter les résultats des essais cliniques, et notamment les résultats concernant la sécurité du médicament ont émergé. Le groupe *Consolidated Standards of Reporting Trials* (CONSORT) recommande depuis 2004 le rapport complet des effets indésirables graves ou inattendus et souligne l'importance de la transparence dans le rapport des effets indésirables (9–11).

Néanmoins, les effets indésirables sont souvent simplement rapportés comme un événement binaire avec le nombre et le pourcentage correspondant de patients présentant l'effet indésirable pour chaque groupe de traitement (12). Bien que cette présentation de la survenue d'effets indésirables puisse faciliter l'interprétation de la sécurité du médicament, ne s'appuyer que sur cette mesure est limité et peut donner une interprétation biaisée de la réalité (13). En effet, les effets indésirables récurrents (effets qui surviennent plus d'une fois chez un même patient) sont fréquents dans les essais cliniques, et en comptant ces événements comme un seul, l'estimation du risque d'effets indésirables peut être sous-estimé. De plus, les différences de durée de suivi et de sortie d'étude entre les études induit des différences de durées d'exposition entre les groupes. Ces variations peuvent influencer la probabilité de survenue d'effets indésirables (un patient suivi 10 ans a une plus grande probabilité de présenter l'effet qu'un patient suivi 1 an) (14). Enfin, les résultats d'essais cliniques présents dans les sources publiques (articles de journaux scientifiques, résumés de congrès, communications orales, etc.) sont souvent incomplets (15–20). De plus, le biais de *reporting*, qui correspond à la sélection de la présentation des résultats qui semblent le plus intéressant, ceux qui ont atteint la significativité statistique par exemple, peut induire une surestimation de l'effet bénéfique du traitement et une sous-estimation du risque d'effets indésirables (20–22).

De par leurs critères d'inclusion, et plus encore d'exclusion, particulièrement strictes, les patients de populations particulières (personnes âgés, multi-comorbides, femmes enceintes, etc.) sont souvent absents des essais cliniques. Ainsi, l'échantillon de patients qui est finalement inclus n'est que rarement totalement représentatif de la population utilisatrice du médicament dans la population générale (23,24). De plus, les essais cliniques, comme toutes études avant la mise sur le marché, sont par définition limités dans le temps, pour que le médicament soit commercialisé. Cette durée, relativement courte, des essais cliniques par rapport à l'exposition réelle des patient après commercialisation est inadéquate à l'évaluation de la sécurité d'un médicament utilisé à long terme et à la détection des effets indésirables d'apparition tardive

comme les cancers par exemple (25). Enfin, afin de maximiser l'efficacité du nouveau traitement et pour des raisons de faisabilité, ils n'incluent au mieux que quelques milliers de patients très sélectionnés, et bien mieux suivis et surveillés concernant la posologie, le dosage, et l'observance que les patients dans la population générale. Même les plus grands essais cliniques ne permettent pas de garantir, avec une puissance suffisante, la détection d'un effet indésirable dont la probabilité de survenue est faible, la Table 1 présente la probabilité de détecter un effet en fonction de sa probabilité de survenue et de la taille de l'échantillon (26). En effet, il est admis qu'au cours des essais cliniques, un effet indésirable dont la fréquence est de 1/n, sera détecté avec 95% de chance si la population de l'essai est de 3N, il s'agit de la règle des 3N qui découle de la loi de Poisson. Par exemple, pour détecter un effet indésirable qui a une fréquence de survenue de 1%, il faudrait inclure 300 patients. Il est donc particulièrement difficile de détecter les effets indésirables rares qui peuvent survenir chez 1 patient sur 10 000 voire 1 patient sur 1 000 000 (27).

Table 1. Probabilité d'observer au moins un événement en fonction de la taille de l'échantillon et de la probabilité de survenue de l'événement. Adapté pour faire apparaître l'exemple de la règle des 3N de (Bouvenot et al. Lavoisier 2006) (26)

	Probabilité de survenue de l'événement				
Nombre de sujets inclus	1/100	1/500	1/1 000	1/50 000	1/100 000
100	63%	39%	9.5%	0.5%	0%
300	**95%**				
500	99%	63%	39%	1%	0.5%
1 000	100%	99%	63%	5%	1%
50 000	100%	100%	100%	63%	39%
100 000	100%	100%	100%	99%	63%

1.3. La pharmacovigilance

Malgré des règles d'accès au marché plus strictes dès le début du XXème siècle, les limites inhérentes aux essais cliniques décrites plus haut ont causé de nombreux scandales sanitaires qui ont appelé à des actions des autorités de régulation. La première encyclopédie dédiée aux effets indésirables est publiée en 1952 (28) suite à la découverte que le chloramphénicol pouvait induire des anémies aplasiques au début des années 1950 (29). Mais le drame sanitaire le plus connu et ayant joué un rôle majeur dans le développement de la pharmacovigilance et le suivi des effets indésirables des médicaments est le thalidomide et l'apparition de malformations dans les années 1960 (30).

Ainsi, les bases de pharmacovigilances ont été créés avec pour objectif la collecte et le suivi des effets indésirables rapportés à partir de la notification spontanée, c'est-à-dire la notification par un professionnel de santé ou un patient d'un effet indésirable survenue suite à la prise d'un médicament. A l'heure actuelle, trois bases de pharmacovigilances sont largement utilisées à travers le monde pour synthétiser les cas rapportés et mener des études de disproportionnalité, c'est-à-dire des études cherchant à observer une disproportion entre le nombre d'effets indésirables rapporté et le nombre attendu : la base de l'Agence Européenne du Médicament (EudraVigilance), la base de la Food and Drug Administration (FDA Adverse Event Reporting System, FAERS), et la base de l'Organisation Mondiale de la Santé (Vigibase®) gérée par l'Uppsala Monitoring Center (31–33). Différentes méthodes ont été développées afin d'évaluer, quantifier et prioriser ces signaux de disproportionnalité mais il n'existe pas de *gold standard* en terme de performance et de fiabilité du signal (34–37). Quatre types de méthodes pour le calcul de la disproportionnalité se distinguent : les méthodes fréquentistes ou classiques (le Reporting Odds Ratio et le Proportional Reporting Ratio) (38), les méthodes bayésiennes (le Multi-Item Gamma Poisson Shrinker et le Bayesian Confidence Propagation Neural Network) (39,40), les méthodes multivariées (41) et les méthodes d'intelligence artificielle. Une étude comparant la valeur prédictive positive et négative de ces différentes méthodes a retrouvé des

résultats relativement comparables, mais suggèrent une légère supériorité des méthodes bayésiennes (Figure 2) (42).



Figure 2. Courbes ROC des différentes méthodes de détection de signaux. Extrait de (Pham et al., Drug Safety 2019) (42). AR : Association Rules. Méthodes bayésiennes : BCPNN : Bayesian Confidence Propagation Neural Network, et GPS : Gamma Poisson Shrinker. Méthodes multivariées : LR : Logistic Regression, MCEM : Monte Carlo Expectation Maximization, et MCLR : Monte Carlo Logistic Regression. Méthodes fréquentistes : PRR : Proportional Reporting Ratio, et ROR : Reporting Odds Ratio. Méthodes d'intelligence artificielle : RF : Random Forest, et RGPS : Regression-adjusted GPS.

Ces méthodes bayésiennes qui sont maintenant utilisés en priorité par la FDA et par l'OMS sont particulièrement intéressantes lorsque le nombre de cas rapportés est faible (36). Le calcul de l'Information Component (IC), métrique de disproportionnalité utilisée par l'OMS, est présenté en Table 2 avec un exemple de calcul pour le signal entre l'effet indésirable apnée du sommeil et le médicament ticagrelor (39,43–45).

Table 2. Calcul et interprétation de l'Information Component. Exemple pour le couple ticagrelor-apnée du sommeil

$N_{observed}$	N_{drug}	$N_{reaction}$	N_{total}	$N_{expected}$	IC025	IC	Interprétation
119	26 824	14 067	28 063 942	13.45	2.83	3.10	Signal

$N_{observed}$: Nombre de cas observé dans la base pour ce couple médicament-effet indésirable.

N_{drug} : Nombre de cas total dans la base pour ce médicament.

$N_{reaction}$: Nombre de cas total dans la base pour cet effet indésirable.

N_{total} : Nombre de cas total dans la base pour tous les médicaments et tous les effets indésirables.

$N_{expected}$: Nombre de cas attendu si le couple médicament-effet indésirable se comportait comme tous les autres couples de la base. $N_{expected} = (N_{drug} \times N_{reaction}) / N_{total}$.

IC025 : Borne inférieur de l'intervalle de crédibilité à 95% de l'Information Component.

IC : Information Component. $IC = Log_2[(N_{observed} + 0.5) / (N_{expected} + 0.5)]$.

Interprétation : Le signal est considéré comme positif lorsque $IC025 > 0$.

L'une des principales limites de ces analyses est la difficulté de prise en compte des biais inhérents à la notification spontanée des effets indésirables et aux facteurs de confusions entre les groupes. En effet, la notification d'effets indésirables aux systèmes de pharmacovigilance est conditionnée par de nombreux facteurs comme la nature de l'effet indésirable, sa gravité, sa nouveauté ainsi que la nouveauté du médicament en cause (effet Weber (46)), sa médiatisation (exemple de l'affaire du Levothyrox® qui fait de la France le premier pays notificateur au monde pour ce médicament (47)), son temps de survenue après l'instauration du traitement mais également par le type de déclarant (patient ou professionnel de santé par exemple) (48–50). Ainsi, seule une faible proportion, très variable et inconnue, des effets indésirables présentés par les patients est notifiée, et la qualité et l'exhaustivité des informations recueillies sont très hétérogènes selon le rapporteur, mais aussi selon la base de données qui collige ces notifications. Les bases de notifications spontanées sont donc soumises à une sous-notification et à une notification sélective importantes (51–54). Enfin, il est possible que certaines notifications spontanées reçues à la fois par les autorités sanitaires (Agence National de Sécurité du Médicament et des produits de santé, ANSM en France) et par l'industriel qui commercialise

le médicament puissent être rentrées en double dans les bases de pharmacovigilance si elles ne sont pas détectées comme des doublons avant. De nombreuses méthodes ont été développées afin d'identifier et de prendre en compte ces biais (50,55). Récemment des recommandations pour rapporter les résultats des analyses de disproportionnalité ont également été publié pour améliorer la transparence, la précision et l'interprétation de ces études (56,57). Cependant, leur impact sur l'amélioration de la validité, et les performances des analyses de disproportionnalité en fonction du couple médicament-effet indésirable étudié, est encore mal défini. Malgré ces limites, la notification spontanée a démontré son rôle central dans l'identification de nouveaux signaux d'effets indésirables, particulièrement s'ils sont rares, mais permet difficilement l'identification d'effets indésirables retardés, et elle ne permet pas la validation de ces signaux ni la quantification du risque (51).

1.4. La pharmacoépidémiologie

La pharmacoépidémiologie est l'étude de l'utilisation et des effets des médicaments sur un grand groupe de personnes (58). Bien que la discipline soit relativement nouvelle, avec les premières publications d'études d'utilisation au milieu des années 1960s (59–61), ces contributions sont déjà importantes et bien reconnues pour avoir participer à obtenir de meilleures informations sur l'incidence des effets indésirables, l'efficacité de traitements dans des populations particulières ou encore caractériser les usages des médicaments dans la population générale. Ainsi, la proportion de médicaments pour laquelle la FDA a demandé une étude post autorisation de mise sur le marché est passé d'environ 30% dans les années 1970s à 70% dans les années 1990s (58). Il est important de noter que souvent, l'évaluation des effets indésirables ne retrouve pas de surrisque significatif, et même si ce résultat peut paraitre décevant d'un point de vue académique, il est en réalité rassurant quant à la sécurité des médicaments mis sur le marché (58). La Figure 3 reprend les recommandations de

l'International Council for Harmonisation pour générer des preuves adéquates lorsque nous voulons répondre à une question régulatoire sur la sécurité d'un médicament (62). Jusqu'à présent les études de pharmacoépidémiologie n'étaient utilisées que pour étudier les profils de sécurité des médicaments puisque jugées trop peu fiables pour être considérées comme étude pivot dans l'évaluation de l'efficacité clinique (63–65). Cependant, depuis peu, les agences de régulation d'accès au marché envisagent de prendre en considération ces études observationnelles dans l'évaluation du médicament (66,67). En effet, les progrès méthodologiques pour s'affranchir d'un maximum de biais, les plus grands recueils de données, et l'amélioration des pratiques de transparence (enregistrement au préalable du protocole d'étude par exemple) ouvrent la possibilité d'utiliser ces études en complément des essais cliniques randomisés pour la prise de décision, la modification des stratégies thérapeutiques ou l'élaboration de recommandations (68–70).

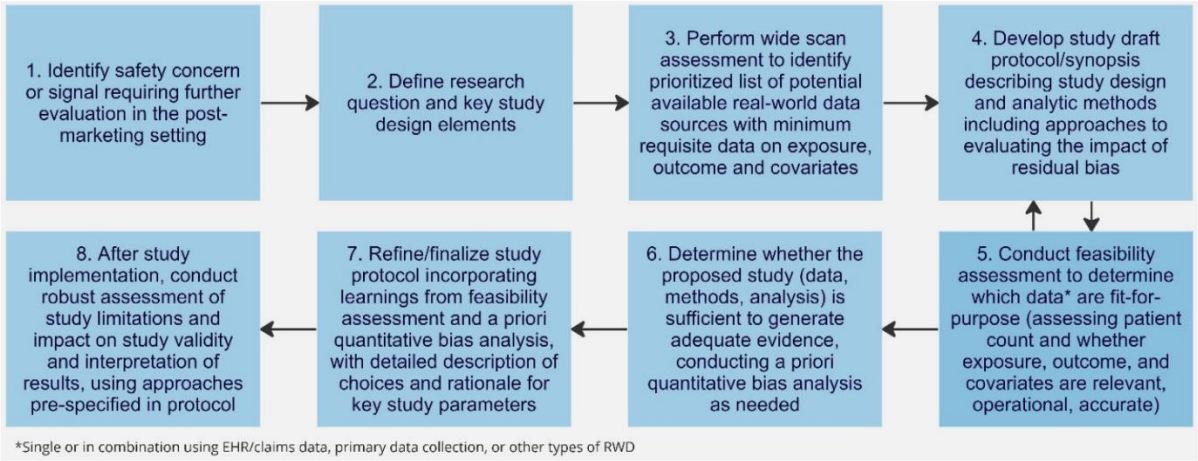


Figure 3. Cadre pour la génération d'un niveau de preuve satisfaisant dans l'étude du profil de sécurité d'un médicament. Extrait de (European Medicines Agency, 2024) (62).

Actuellement, la majorité des études de pharmacoépidémiologie sont réalisées sur bases de données, et plus précisément sur bases de données médico-administratives, c'est-à-dire des bases créées dans un objectif premier de comptabilité et pas recherche. Il existe de nombreuses bases de données médico-administratives dans chaque pays, toutes relativement différentes selon le régime de protection sociale, la méthode de codage ou encore le nombre de soins

soumis au remboursement. Nous allons faire un focus sur la base de données médico-administratives française : le Système National des Données de Santé (SNDS).

Le SNDS est une base de données médico-administratives, couvrant l'ensemble de la population française (environ 67 millions de patients). Chaque personne est anonymisé et identifié par un numéro unique à l'intérieur de la base. Depuis 2006, le SNDS collige tous les remboursements de soins ambulatoires, incluant les médicaments, les tests d'imagerie ou encore les prélèvements biologiques par exemple, et les soins hospitaliers, incluant les diagnostics médicaux codés selon la classification internationale des maladies 10ème révision et les procédures médicales réalisées. De plus, les dépenses de santé liées aux affections longues durées, comme le cancer ou le diabète par exemple, sont totalement remboursés et leur diagnostic est codé de la même manière que les diagnostics hospitaliers. Le SNDS a maintenant été largement utilisé et décrit et une majorité des codes d'identification des comorbidités ont déjà été validés et/ou utilisés (71–73). Les différentes données accessibles dans le SNDS sont représentées sur la Figure 4.

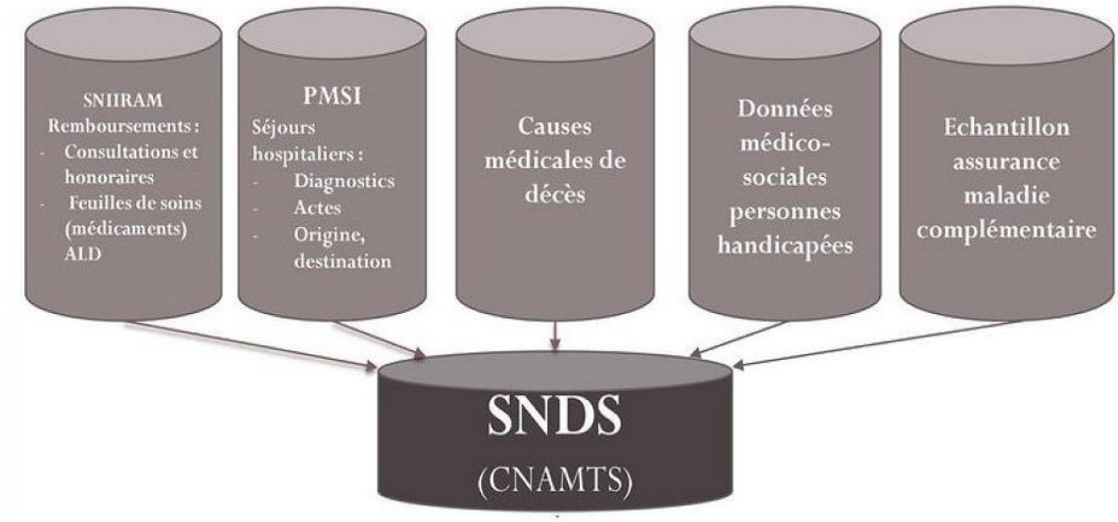


Figure 4. Chaînage des différentes sources de données dans le SNDS. SNIIRAM : Système National d'Information Inter-Régimes de l'Assurance Maladie (soins ambulatoires) ; PMSI : Programme de Médicalisation des Systèmes d'Information (soins hospitaliers) ; CNAMTS : Caisse Nationale d'Assurance Maladie des Travailleurs Salariés.

Dans l'objectif de réaliser des études de pharmacoépidémiologie de qualité, l'idée d'utiliser les données observationnelles pour réaliser une émulation d'un essai randomisé hypothétique (l'essai cible) est de plus en plus répandue (74,75). Le concept d'émulation d'un essai cible ou *« Target Trial Emulation (TTE) »* a été formalisée en 1986 par Robins (76). Le guide pour réaliser des études d'inférence causale en utilisant des données de santé issues de la pratique clinique courante pour évaluer les effets des médicaments (PRINCIPLED) recommande spécifiquement la rédaction de protocole de l'essai cible dès la première étape de la préparation de l'étude (Figure 5) (70). Un exemple de spécification du protocole de l'essai cible pour une étude observationnelle évaluant l'effectivité du liraglutide dans la survenue d'événements cardiovasculaires majeurs est présenté Table 3.

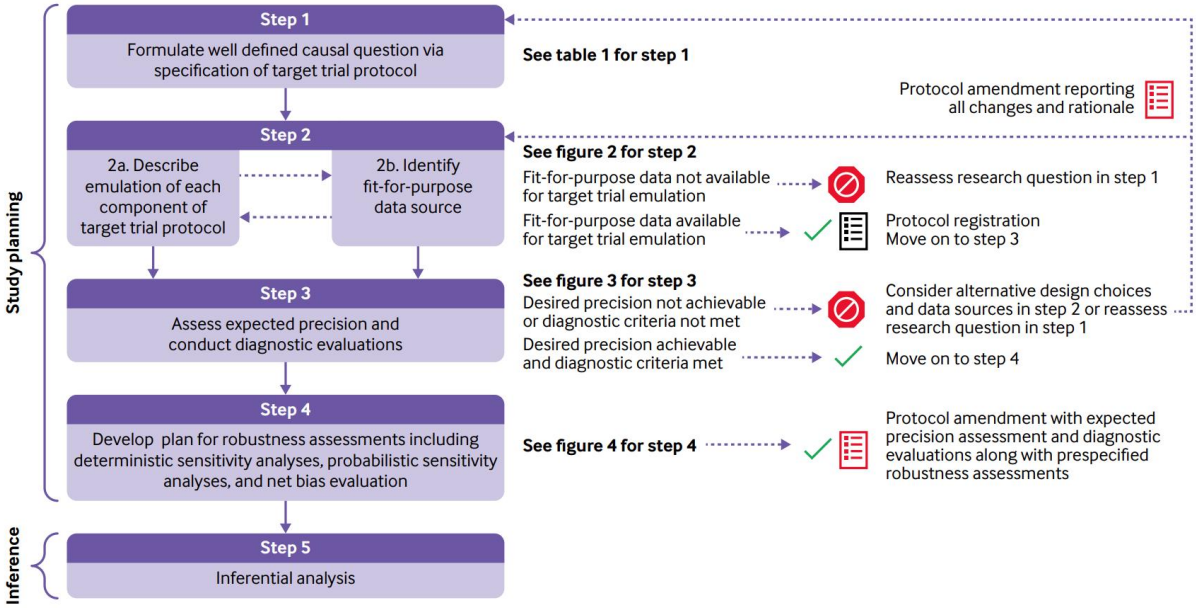


Figure 5. Guide pour la réalisation d'études inférentielles utilisant des données de santé issues de la pratique clinique courante. Extrait de (Desai et al., BMJ 2024) (70).

Table 3. Spécification de l'essai cible (essai clinique pivot du liraglutide (77)) et son émulation dans le SNDS

	Original RCT	**SNDS Emulation**
Treatment strategies	Initiation of liraglutide, or placebo	First prescription of liraglutide, or DPP4i
Treatment assignment	Individuals are randomly assigned to liraglutide, or placebo at baseline; blinded	Treatment is not assigned randomly Randomization was emulated using 1:1 PS matching
Outcomes	Composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	Composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke
Follow-up	Follow-up starts at treatment assignment and ends at the outcome occurrence, death, loss to follow-up, or up to 5 y of follow-up, whichever comes first	Same as target trial; loss to follow-up was defined as the end of registration within the database, or end of the SNDS data availability (31 December 2023)
Causal contrasts	Intention to treat effect	Observational analogue of the intention-to-treat effect, i.e. as-started

Ainsi, la réalisation explicite de l'émulation d'un essai cible aide à éliminer les biais liés au design de l'étude, et particulièrement les biais de sélection et de temps immortel (78,79). Pour rappel, le biais de temps immortel survient lorsqu'un patient est classé comme exposé à son entrée dans la cohorte mais avant sa première prise de traitement. Ce temps entre l'entrée dans la cohorte et le début de l'exposition est appelé « immortel » puisqu'aucun événement ne peut survenir durant cette période car le patient mal classé est obligatoirement en vie (ne présente pas l'événement) pour pouvoir recevoir le traitement. Ce biais de classification va systématiquement produire un résultat faux et protecteur pour le groupe exposé (80,81). Cependant, si l'émulation d'un essai cible permet de gérer les biais dues au design de l'étude en réalisant une étude qui se rapproche de ce que l'on ferait dans un essai clinique, elle ne permet pas de s'affranchir des biais liés aux données, ni de gérer les facteurs de confusion qui peuvent être présents.

Pour gérer la confusion et rendre les patients entre les groupes comparables, une multitude de méthodologies existe, nous nous concentrerons ici sur celles qui se basent sur le calcul d'un score de propension, qui sont les plus utilisées à l'heure actuelle (82). Les méthodes basées sur le calcul d'un score de propension permettent d'équilibrer les patients exposés et les patients contrôles sur les facteurs de confusion connus qui ont permis le calcul du score (83). En effet, là où les essais cliniques randomisés permettent l'échangeabilité totale entre les groupes, les études observationnelles, même avec une excellente gestion de la confusion, ne peuvent garantir cette échangeabilité entre les deux groupes que sur les facteurs de confusion connus. Le score de propension correspond à la probabilité conditionnelle pour un patient d'être assigné au groupe traitement en fonction de certaines covariables (les facteurs de confusion connus) définies (82). Après l'estimation du score de propension, l'équilibre entre les groupes peut être atteint de différentes manières, par appariement, par stratification, ou par pondération par exemple (84).

L'appariement sur le score de propension est réalisé en appariant chaque patient du groupe exposé à un, ou plus, patient du groupe non-exposé dont le score de propension est dans un intervalle pré-spécifié (le caliper) autour de la valeur du score de propension du patient exposé. Par exemple, un patient du groupe exposé a un score de propension de 0.67, il va être apparié à un (ou plus) autre patient avec un score de 0.67 ± le caliper pré-spécifié. Si c'est la méthode la plus utilisée (85), elle présente la limite majeure d'exclure tous les patients qui ont un score en dehors du caliper, et donc de potentiellement perdre en représentativité de la population. Inversement, la pondération par le score de propension présente l'avantage de garder la quasi-totalité de la population du groupe exposé et du groupe non-exposé (86). Le choix de la méthode de gestion de la confusion doit être fait selon les caractéristiques de la cohorte à l'étude : nombre de patients contrôles disponibles, distribution des scores de propension entre les deux groupes, etc., comment choisir la méthode de pondération à utiliser est représenté Figure 6.

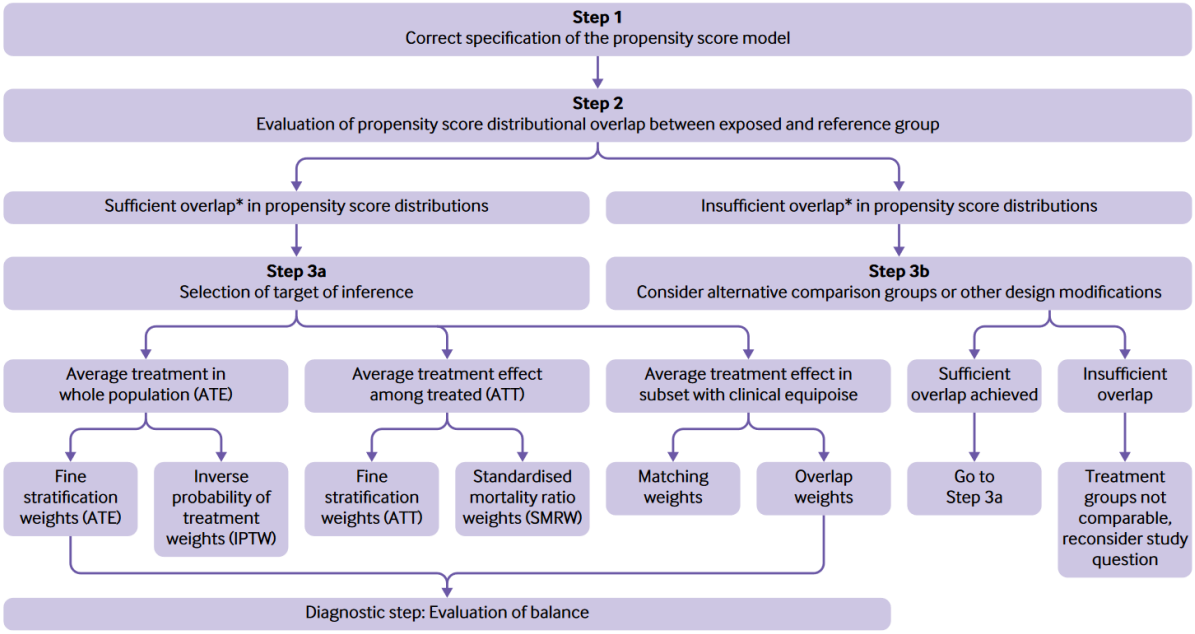


Figure 6. Facteurs à considérer pour choisir la bonne méthodologie de pondération sur le score de propension. Extrait de (Desai et al., BMJ 2019) (86).

Un des objectifs de cette thèse est l'utilisation de différents schémas d'étude et méthodologies pour étudier, identifier, quantifier et mieux comprendre les potentielles étiologies iatrogènes de trois pathologies vasculaires et respiratoires, caractérisées par des mécanismes physiopathologiques, une durée d'apparition, et une incidence dans la population très différents.

2. Epidémiologie et physiopathologie de pathologies vasculaires et respiratoires

Les travaux qui constituent ce travail de thèse s'attachent à appliquer ces différentes méthodes afin de détecter et/ou d'évaluer des signaux de sécurité de médicament pouvant induire ou aggraver trois pathologies vasculaires et respiratoire : le syndrome d'apnées du sommeil, les ulcères cutanés et l'hypertension artérielle pulmonaire.

2.1. Le syndrome d'apnées du sommeil

Le syndrome d'apnées du sommeil est caractérisé par des épisodes d'apnées (interruptions complètes de la respiration) et/ou d'hypopnées (interruptions partielles) durant le sommeil. L'origine de ces apnées peut être à prédominance obstructive, ce qui correspond au collapsus complet (apnées) ou partiel (hypopnées) des voies aériennes supérieures : ce sont les apnées du sommeil obstructives, ou être causées par des problèmes de contrôle de la respiration : ce sont les apnées centrales (87). L'apnée obstructive du sommeil est beaucoup plus fréquente que l'apnée centrale avec une prévalence mondiale estimée à près d'un milliard de patients (Figure 7) (88).

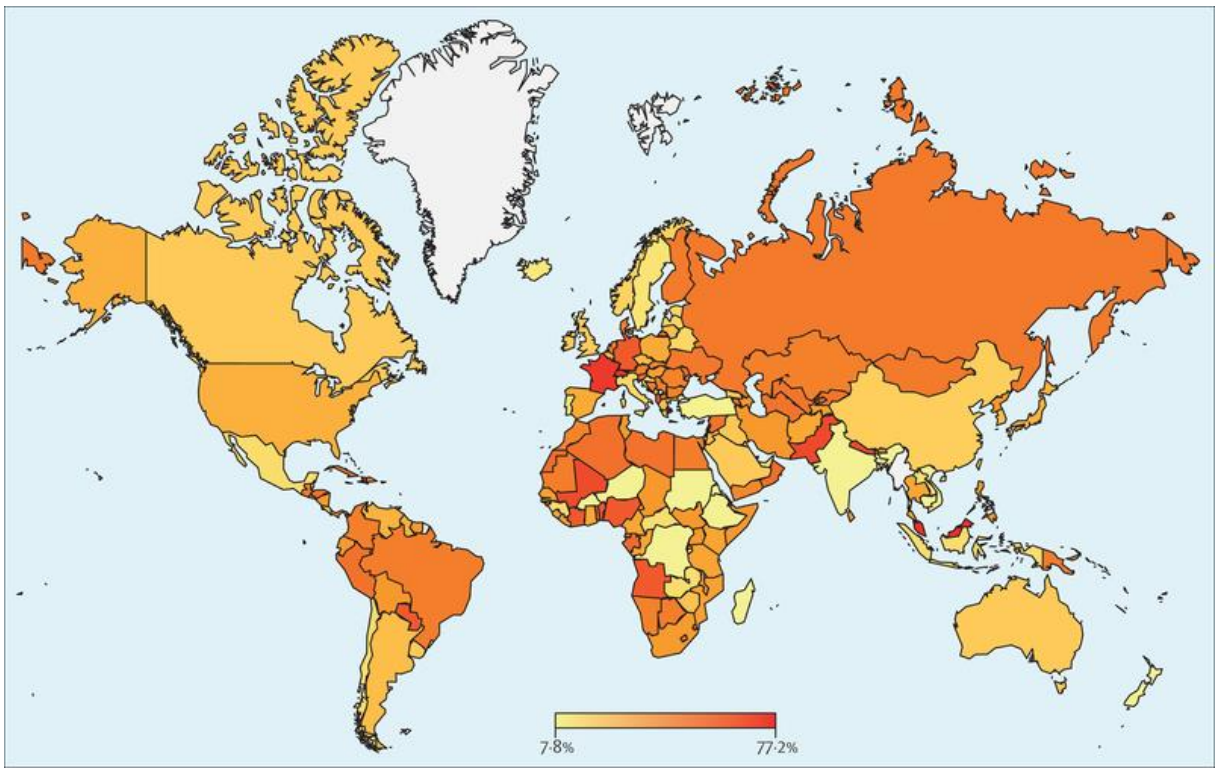


Figure 7. Heatmap mondiale de la prévalence estimée de l'apnée obstructive du sommeil pour chaque pays. Extrait de (Benjafield et al., Lancet Respir Med 2019) (88).

Les collapsus des voies aériennes supérieures se produisent en arrière de la base de la langue et/ou au niveau du voile du palais. Les muscles dilatateurs du pharynx assurent le maintien de la perméabilité des voies aériennes supérieures pendant l'éveil mais leur tonus diminue au cours du sommeil. L'apnée se produit lorsque l'équilibre entre la contraction de ces muscles, qui assurent l'ouverture des voies aériennes supérieures, et la pression négative inspiratoire, qui tend à les fermer, est perturbé (87). Suite à chaque épisode d'apnée et/ou hypopnée, des micro-éveils sont générés, ce qui permet l'activation des muscles dilatateurs du pharynx et le rétablissement de la perméabilité. Ces micro-éveils fréquents au cours de la nuit ont pour effet la déstructuration du sommeil, signalée par une réduction significative du sommeil profond. Ainsi, l'apnée du sommeil est une cause majeure de somnolence diurne excessive, d'altérations de la qualité de vie, et est associée à une augmentation de l'incidence de pathologies cardio-métaboliques comme l'hypertension artérielle, le diabète de type 2, la fibrillation atriale ou l'insuffisance cardiaque (89,90).

Le diagnostic et la sévérité du syndrome d'apnées du sommeil sont estimés par le nombre d'apnées et d'hypopnées par heure de sommeil, ce qui correspond à l'index d'apnées-hypopnées. Les apnées et hypopnées sont définies comme une cessation complète, ou une baisse d'au moins 50% du flux d'air pendant au moins 10 secondes. Le diagnostic est objectivé par l'examen de référence, la polysomnographie, et est confirmé lorsque l'index d'apnées-hypopnées est supérieur à 5 événements par heure au cours du sommeil.

Le syndrome d'apnées du sommeil est une pathologie multifactorielle avec une présentation clinique hétérogène (91,92). Parmi les principaux facteurs de risque, l'âge, l'obésité, et le fait d'être un homme sont les prédominants, mais l'exposition à certains médicaments peut également induire une apnée du sommeil (Figure 8) (93). En effet, plusieurs médicaments ont été suspectés d'induire ou d'aggraver la sévérité de l'apnée du sommeil à travers plusieurs mécanismes pharmacologiques, comme les opioïdes, les benzodiazépines, le baclofène, ou encore la testostérone (94). De plus, de nouveaux signaux de pharmacovigilance ont récemment été identifiés avec le ticagrelor ou les antipsychotiques par exemple (94,95).

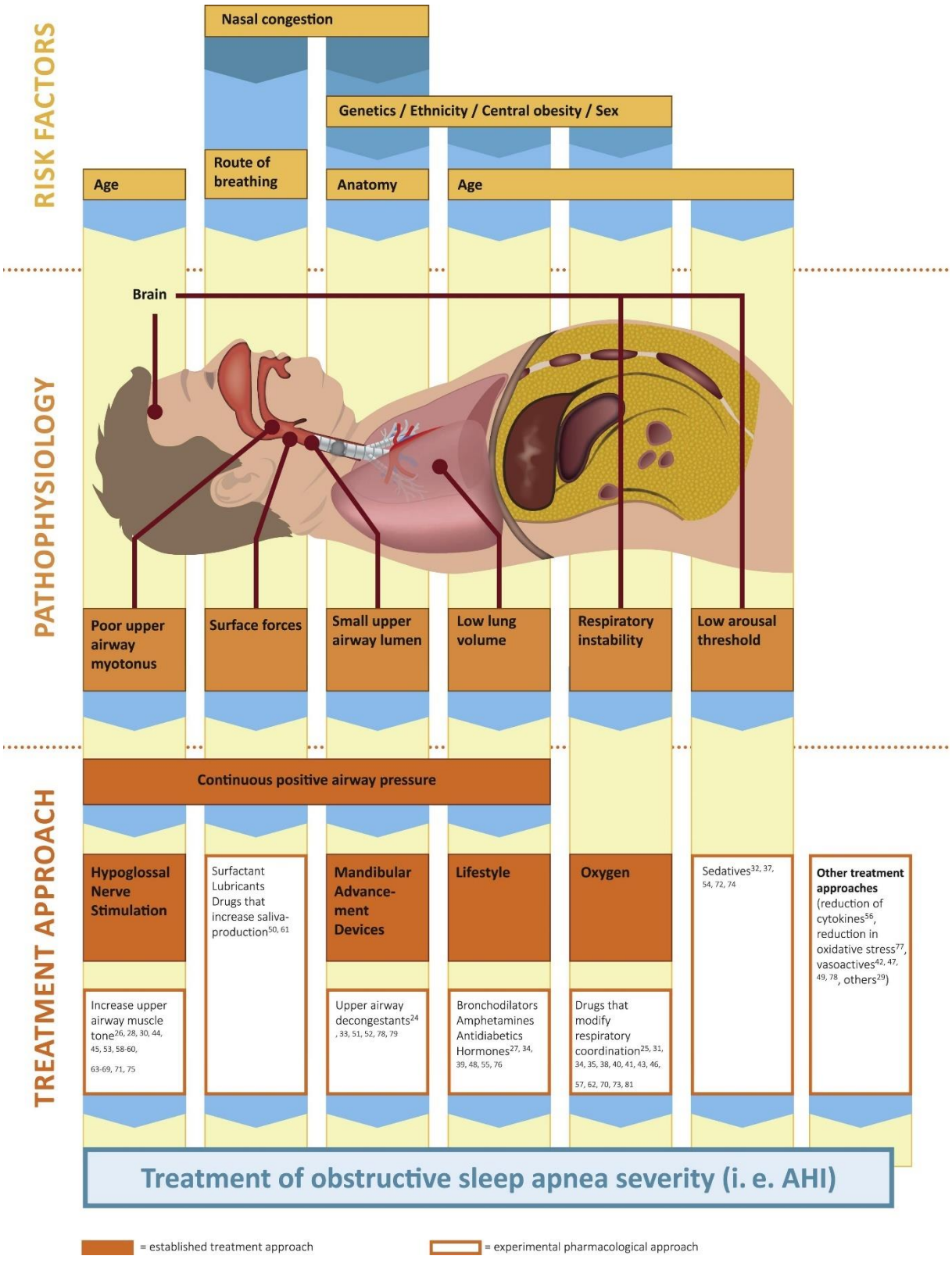


Figure 8. Facteurs de risque, physiopathologie et traitements du syndrome d'panées du sommeil. Extrait de (Gaisl et al., Sleep Medicine Reviews 2019) (93).

Etant donné la prévalence extrêmement importante de l'apnée du sommeil, son impact individuel (somnolence diurne par exemple) et sociétal, la détection et l'évaluation de signaux

n'entrainant ne serait-ce qu'un petit surrisque de développer ou aggraver la pathologie avec certains médicaments est d'un intérêt considérable.

2.2. Les troubles trophiques cutanés

Les plaies chroniques sont caractérisées par leur incapacité à guérir, à cicatriser convenablement, dans un intervalle de temps défini. Cependant, il n'y a pas, à l'heure actuelle, de définition précise de la durée de cicatrisation pour diagnostiquer une plaie chronique (96). En France, la définition de la Haute Autorité de Santé (HAS) fait foi et elle a admis qu'une plaie était définie comme chronique après 4 à 6 semaines d'évolution (97). Il est estimé que 25 à 50% des plaies chroniques ne sont pas entièrement guéries après 6 mois de traitement optimal, ce qui induit une morbidité et un coût significatif pour la société avec une estimation à près de 1 milliard d'euros en 2011 (965 millions d'euros exactement) (98,99). Au niveau mondial, il est estimé que 1 à 2% de la population seront touchés par une plaie chronique au cours de leur vie (100,101). Cette prévalence est retrouvée dans une étude menée par l'Assurance Maladie dans la base du Système National des Données de Santé (SNDS) en 2012 qui a identifié 667 194 patients avec une plaie chronique, soit environ 1% de la population française (99,102).

Les plaies chroniques sont relativement hétérogènes en termes d'étiologie, de localisation ou de de type. Elles affectent habituellement les adultes et ont pour étiologies principales : la complication d'insuffisances veineuse ou artérielle, qui induisent des ulcères vasculaires en majorité ; le diabète et les neuropathies qui induisent préférentiellement des ulcères de pied diabétique ; et l'incapacité de se déplacer ou des blessures à la moelle épinière qui induisent des ulcères de pression, également appelés escarres (96). Ainsi, la désignation de plaies chroniques comprend les trois différents types d'ulcères cutanés. Selon l'étude de Rames et al., les ulcères cutanés les plus communs sont les ulcères vasculaires qui représentent 66% des

ulcères cutanés en France, puis les escarres qui en représentent 23% et enfin les ulcères de pied diabétique sont les plus rares avec 11% des ulcères en France (99).

Rodrigues et al. ont particulièrement bien défini le processus pour la guérison normale des plaies (103). Le processus de guérison normale d'une plaie comprend une séquence linéaire d'événements avec une phase d'hémostase et de coagulation au début, suivi d'une phase d'inflammation, puis d'une phase de prolifération cellulaire et de migration et enfin d'une phase de remodelage (104). Cependant, cette succession linéaire d'événements dans le cas d'une guérison normale n'est pas retrouvée lors de la formation de plaies chroniques, chaque phase se déroule à des moments aléatoires et sans durée définie (96,103–105). La figure 9 représente graphiquement la différence entre une guérison normale induisant une plaie aiguë et une guérison anormale qui induit la formation d'une plaie chronique.

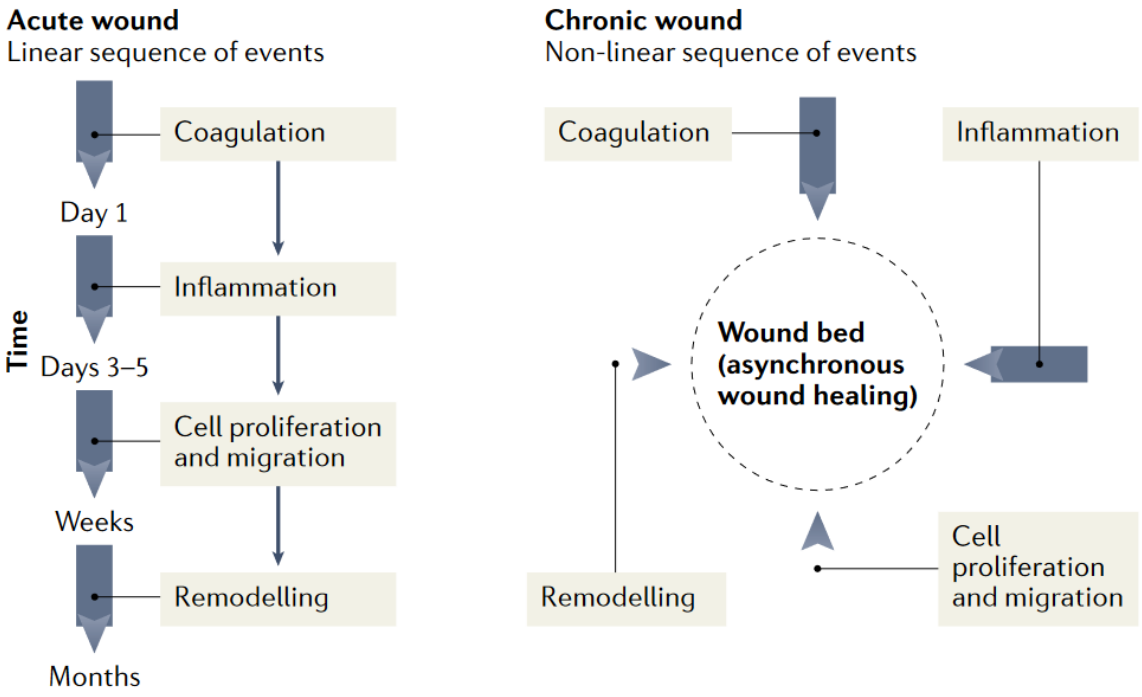


Figure 9. Phases de guérison d'une plaie aiguë et d'une plaie chronique. Extrait de (Falanga et al., Nature Reviews Disease Primers 2022) (96).

Plusieurs facteurs peuvent être impliqués dans la formation d'ulcères cutanés tels que les infections, les insuffisances veineuses ou artérielles, le diabète, les cancers ou encore la sous-nutrition par exemple. Les médicaments, encore trop peu étudiés, sont également un facteur

important de survenue d'ulcères cutanés. En effet, de nombreux médicaments récemment mis sur le marché, tels que les inhibiteurs de tyrosine-kinase ou les anti-angiogéniques, présentent des effets indésirables vasculaires. Différents mécanismes sont impliqués, parfois simultanément, en fonction des différentes classes médicamenteuses : induction d'un effet pro-thrombotique, vasoconstriction, raréfaction capillaire, dysfonction endothéliale. L'ensemble de ces mécanismes est impliqué directement ou indirectement dans la régulation de la microcirculation cutanée, et donc dans la physiopathologie des ulcères cutanés et de leur cicatrisation. Une précédente étude réalisée à partir des données agrégées de la base de pharmacovigilance de l'OMS, Vigibase ®, des données de la littérature et d'expertise a permis de générer plusieurs signaux potentiels (106). Les 13 classes médicamenteuses identifiées et leurs mécanismes physiopathologiques dans la formation d'ulcères cutanés sont résumés sur la Figure 10.

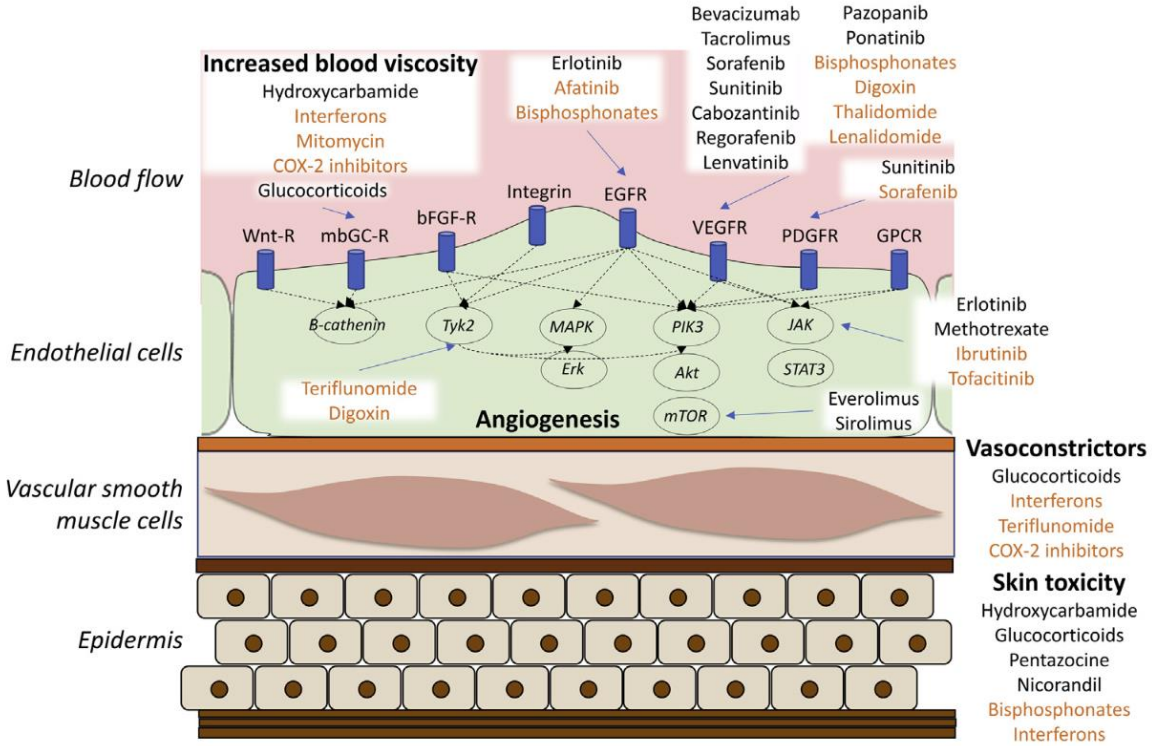


Figure 10. Représentation schématique des mécanismes iatrogènes d'ulcères cutanés. Extrait de (Duron et al., Journal of the American Academy of Dermatology 2021) (106).

2.3. L'Hypertension Artérielle Pulmonaire

L'hypertension pulmonaire est une pathologie hémodynamique caractérisée par une augmentation de la pression pulmonaire moyenne (mPAP), évaluée par cathétérisme cardiaque droit qui est le *gold standard* diagnostique au-dessus de la valeur normale, c'est-à-dire au-dessus de 20 mmHg (7,107–109). La différenciation en hypertension pulmonaire pré- ou post-capillaire se fait par la mesure de la pression artérielle pulmonaire d'occlusion (PAWP) et de la résistance vasculaire pulmonaire (PVR), également mesurées par cathétérisme cardiaque droit. La stratification des différents types hémodynamiques des hypertensions pulmonaires selon leurs mesures au cathétérisme cardiaque droit est représentée en Table 4.

Table 4. Critères hémodynamiques pour définir l'hypertension pulmonaire. Adapté de (Kovacs et al., European Resipratory Journal 2024) (7)

Type d'hypertension pulmonaire	Caractéristiques hémodynamiques
PH	mPAP > 20 mmHg
Pre-capillary PH	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR > 2 WU
Isolated post-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR ≤ 2 WU
Combined post- and pre-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR > 2 WU
Exercise PH	Pente mPAP/CO > 3 mmHg/L/min entre le repos et l'exercice
PH : Hypertension pulmonaire ; mPAP : Pression pulmonaire moyenne ; PAWP : Pression artérielle pulmonaire d'occlusion ; PVR : Résistance vasculaire pulmonaire ; WU : Wood units ; CO : Débit cardiaque.	

L'hypertension pulmonaire est un enjeu majeur de santé publique, affectant tous les groupes d'âges et avec une prévalence estimée à environ 1% de la population mondiale (108,109). Cependant, la prévalence de la pathologie est particulièrement hétérogène selon le sous-groupe

de la pathologie. En effet, les hypertensions pulmonaires sont classées en 5 sous-groupes différents, illustrés en Figure 11 :

- Groupe 1 : les hypertensions artérielles pulmonaires (HTAP)
- Groupe 2 : les hypertensions pulmonaires associées à une pathologie cardiaque gauche, comme l'insuffisance cardiaque par exemple
- Groupe 3 : les hypertensions pulmonaires associées à une pathologie pulmonaire ou à l'hypoxie, comme la bronchopneumopathie chronique obstructive.
- Groupe 4 : les hypertensions pulmonaires associées à une obstruction de l'artère pulmonaire, également appelée hypertensions pulmonaires thromboemboliques chroniques (CTEPH)
- Groupe 5 : les hypertensions pulmonaires d'origine inconnue ou multifactorielle, on retrouve par exemple les hypertensions pulmonaires liées aux insuffisances rénales

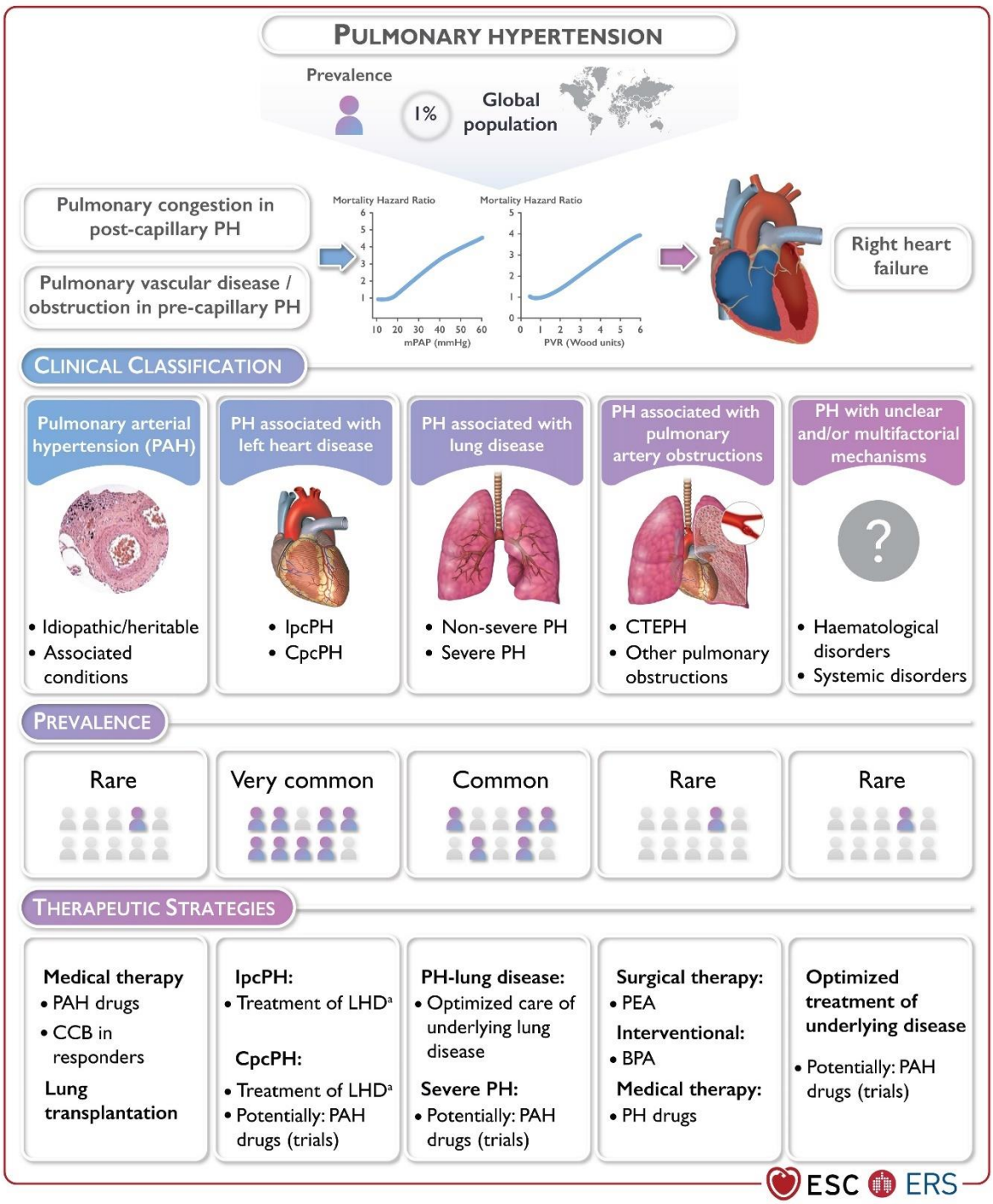


Figure 11. Illustration des différentes Hypertensions Pulmonaires. Extrait de (Humbert et al., European Heart Journal 2022) (108).

L'incidence et la prévalence de l'HTAP sont estimées à respectivement environ 6 et 19-28 cas par million d'habitants et par an dans le monde (110,111). Il s'agit d'une pathologie sévère avec une médiane de survie actuellement de 6 ans. D'après les données issues des registres d'HTAP, environ 50% des HTAP sont associées à une pathologie, dont les connectivites,

l'infection au VIH, l'hypertension portale et les pathologies congénitales cardiaques idiopathiques ou sont héréditaires (mutation du gène BMPR2 par exemple (112). L'autre moitié des HTAP sont idiopathiques, dont environ 10% sont iatrogènes, c'est-à-dire associées à des médicaments ou toxines (112).

De nombreux médicaments et toxines ont été identifiés comme pourvoyeurs potentiels d'HTAP et sont classés en 2 catégories distinctes par le *World Symposium on Pulmonary Hypertension (WSPH)* : association définitive ou possible (6,7,113–118). Le nombre et le type de médicaments potentiellement impliqués dans la survenue d'HTAP n'a fait que grandir depuis la première liste de 9 médicaments suspects écrite lors du premier WSPH à Evian en 1998 (119). La mise à jour de cette liste lors du *7th WSPH*, considère maintenant 25 médicaments ou toxines comme étant probablement ou définitivement associés à l'HTAP, et est présenté en Table 5 (7). Cependant, seulement 9 de ces substances sont considérés comme définitivement associés à l'HTAP, et certaines sont suspectés depuis des dizaines d'années comme le St John's wort ou le L-tryptophan, ce qui souligne la difficulté importante d'établir une relation causale entre HTAP et médicaments (120–123).

Table 5. Drugs and toxins associated with PAH

Definite association	Possible association
Aminorex	Alkylating agents [a]
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C [a]	Direct-acting antiviral agents against hepatitis C virus
Toxic rapeseed oil	(sofosbuvir)
	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Lefunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene) [a]
	St John's wort

[a] PAH with features of venous (pulmonary veno-occlusive disease)/capillary (pulmonary capillary haemangiomatosis) involvement.

3. Objectifs de la thèse

Les objectifs de ce travail sont — à travers différentes méthodologies adaptées aux mécanismes physiopathologiques, aux durées d'apparition et aux incidences particulières de trois pathologies vasculaires et respiratoires — de détecter de nouveaux signaux de pharmacovigilance ; de développer et valider des algorithmes efficaces pour l'identification de ces pathologies dans les bases de données médico-administratives ; d'évaluer des signaux de pharmacovigilance identifiés dans ces pathologies.

Cette thèse sera présentée en trois parties. Dans la première partie, nous nous intéresserons aux travaux portant sur l'interprétation des études de disproportionnalité et la détection de nouveaux signaux ; puis à l'identification de nos pathologies d'intérêt dans la seconde partie ; et enfin à l'évaluation des signaux de pharmacovigilance dans la dernière partie. Nous finirons ce travail sur une discussion générale traitant des perspectives quant à l'évaluation de la sécurité des médicaments, en prenant l'exemple d'une des trois pathologies dont nous traiterons tout au long de ce manuscrit : l'Hypertension Artérielle Pulmonaire.

PARTIE 2 – DETECTION DE SIGNAUX

1. Validity, relevance and interpretation of pharmacovigilance disproportionality analyses

Nous l'avons vu en introduction, les analyses de disproportionnalité sur les bases de notification spontanée de pharmacovigilance ont une importance cruciale dans la surveillance de la sécurité des médicaments. Cependant, certaines limites inhérentes à ce type de données, et à ce type d'analyses nous empêchent de quantifier le risque d'effets indésirables avec la prise d'un médicament, ni de conclure causalement à un lien. Ce travail s'est interrogé sur la validité de l'interprétation d'une analyse de disproportionnalité explorant les risques cardiovasculaires de certains médicaments anti-ostéoporotiques (124).

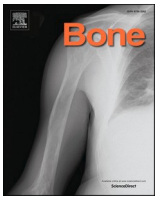
Bone 170 (2023) 116685



Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Correspondence



Validity, relevance and interpretation of pharmacovigilance disproportionality analyses

Dear Editor,

We read with interest the study from Rodriguez and colleagues aiming at exploring the cardiovascular safety profile of some anti-osteoporotic medication (alendronate, zoledronic acid and teriparatide) [1]. The topic is of importance given the discrepancies in results of pre-clinical, clinical and observational studies suggesting in one hand a higher risk of cardiac arrythmia and in the other hand cardioprotective effects with bisphosphonates [2–6]. The overall consequences of these paradoxical effects, notably on thromboembolic events, are still debated [3,5].

Whether we agree with the interest in studying this research question we think that the method used in this study cannot add further credible and relevant evidence in a decision-making process. Indeed, disproportionality analyses of spontaneously reported data compare the drug exposure of cases of an adverse reaction of interest with that of cases with other reported reactions, called "non-cases" [7,8]. As acknowledged by the authors, these methods are subject to several bias such as selective reporting, confounding indication bias and competition between drugs or events in the database [7,8]. The positive prognostic value of a disproportionality signal ranges from 0.2 to 0.6 according to the threshold of signal detection and the drug-adverse event pair studied [9–11]. This positive prognostic value is even probably lower given that these biases are accentuated in the present study. In fact, the background risk of cardiovascular events in the exposed population (i.e. cases) is very different from the comparator group (i.e. non-cases) constituted by all other drugs in the database. All positive signals will therefore be driven in total or in part, by these confounding factors that are non-addressable in pharmacovigilance databases given the lack of data on co-morbidities, antecedents and all other cardio-vascular risk factors. Moreover, the comparison between bisphosphonates and teriparatide is subject to several bias. Firstly, some bisphosphonates such as zoledronic acid (but not teriparatide) are indicated, beyond osteoporosis, in bone metastasis of cancer, these patients displaying a higher background risk of cardiovascular events, i.e. an indication bias [12]. Secondly, while bisphosphonate are the major first line therapy in osteoporosis, teriparatide is restricted to a sub population at extremely high risk, and both populations do not compare. Therefore, the quantitative head-to-head comparisons shown in Fig. 1 are misleading.

We also emphasize the need for an appropriate presentation and interpretation of the results of disproportionality analyses to limit unjustified safety warnings [13–15]. In any cases Odds Ratio can be estimated through analyzing spontaneously reported adverse events. Moreover, the authors adequately stated in the limit section that "the design of this study is observational and thus causality cannot be determined." However, the conclusion in the abstract seems to largely overinterpret the results (also called spin) when stating: "Osteoporosis medication use is associated with adverse cardiac events, except for MI, and these appear to be more common with oral and intravenous bisphosphonates than teriparatide." This conclusion should be rewritten to "Osteoporosis medication use is associated with an increased report of adverse cardiac events, except for MI, and these adverse cardiac events appear to be more frequently reported with oral and intravenous bisphosphonates than teriparatide."

Overall, we recognize the importance to study cardiovascular adverse effects of bisphosphonates but we think that the study conducted by Rodriguez and colleagues by its intrinsic limits cannot add robust evidence on this topic. Indeed, given the above described limitations, the interest in conducting pharmacovigilance analyses when observational pharmacoepidemiological studies are already available need to be well balanced and the added value clearly specified (e.g. by focusing on populations not previously addressed by observational studies) [16]. We therefore call for well-designed pharmacoepidemiological studies to add relevant further evidence on this signal.

Data availability

No data was used for the research described in the article.

References

[1] A.J. Rodriguez, N. Nerlekar, P.R. Ebeling, Cardiac adverse events in bisphosphonate and teriparatide users: an international pharmacovigilance study, Bone (2022), 116647, https://doi.org/10.1016/j.bone.2022.116647.
[2] L. Pijnenburg, J.-E. Salem, B. Lebrun-Vignes, J. Sibilia, R.-M. Javier, L. Arnaud, Atrial fibrillation in patients treated with intravenous zoledronic or pamidronic acid: a pharmacoepidemiological study, Eur. J. Endocrinol. 184 (2021) 437–444, https://doi.org/10.1530/EJE-20-0650.
[3] D.H. Kim, J.R. Rogers, L.A. Fulchino, C.A. Kim, D.H. Solomon, S.C. Kim, Bisphosphonates and risk of cardiovascular events: a meta-analysis, PLoS ONE 10 (2015), e0122646, https://doi.org/10.1371/journal.pone.0122646.
[4] R. Bhuriya, M. Singh, J. Molnar, R. Arora, S. Khosla, Bisphosphonate use in women and the risk of atrial fibrillation: a systematic review and meta-analysis, Int. J. Cardiol. 142 (2010) 213–217, https://doi.org/10.1016/j.ijcard.2009.11.041.
[5] B. Huang, F. Huang, Y. Gui, Y. Peng, W. Liu, K. Huang, C. Zhang, Z. Zuo, Y. Liao, T. Xia, S. Chen, X. Pu, M. Chen, Association between bisphosphonates therapy and incident myocardial infarction: meta-analysis and trial sequential analysis, J. Cardiovasc. Pharmacol. 66 (2015) 468–477, https://doi.org/10.1097/FJC.0000000000000298.
[6] L. Li, G.-P. Chen, Y. Yang, Y. Ye, L. Yao, S.-J. Hu, Chronic inhibition of farnesyl pyrophosphate synthase attenuates cardiac hypertrophy and fibrosis in spontaneously hypertensive rats, Biochem. Pharmacol. 79 (2010) 399–406, https://doi.org/10.1016/j.bcp.2009.08.033.
[7] E. Raschi, U. Moretti, F. Salvo, A. Pariente, I.C. Antonazzo, F.D. Ponti, E. Poluzzi, Evolving roles of spontaneous reporting systems to assess and monitor drug safety, 2018, https://doi.org/10.5772/intechopen.79986.
[8] J.-L. Faillie, Case-non-case studies: principle, methods, bias and interpretation, Therapie 74 (2019) 225–232, https://doi.org/10.1016/j.therap.2019.01.006.
[9] M. Pham, F. Cheng, K. Ramachandran, A comparison study of algorithms to detect drug-adverse event associations: frequentist, bayesian, and machine-learning approaches, Drug Saf. 42 (2019) 743–750, https://doi.org/10.1007/s40264-018-00792-0.

https://doi.org/10.1016/j.bone.2023.116685
Received 5 January 2023; Accepted 24 January 2023
Available online 8 February 2023
8756-3282/© 2023 Elsevier Inc. All rights reserved.

[10] R. Harpaz, W. DuMouchel, P. LePendu, A. Bauer-Mehren, P. Ryan, N.H. Shah, Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system, Clin. Pharmacol. Ther. 93 (2013) 539–546, https://doi.org/10.1038/clpt.2013.24.
[11] C. Khouri, T. Nguyen, B. Revol, M. Lepelley, A. Pariente, M. Roustit, J.-L. Cracowski, Leveraging the variability of pharmacovigilance disproportionality analyses to improve signal detection performances, Front. Pharmacol. 12 (2021). https://www.frontiersin.org/articles/10.3389/fphar.2021.668765. (Accessed 23 December 2022).
[12] A.A. Khorana, N. Mackman, A. Falanga, I. Pabinger, S. Noble, W. Ageno, F. Moik, A.Y.Y. Lee, Cancer-associated venous thromboembolism, Nat. Rev. Dis. Primers. 8 (2022) 1–18, https://doi.org/10.1038/s41572-022-00336-y.
[13] C. Khouri, B. Revol, M. Lepelley, A. Mouffak, C. Bernardeau, F. Salvo, A. Pariente, M. Roustit, J.-L. Cracowski, A meta-epidemiological study found lack of transparency and poor reporting of disproportionality analyses for signal detection in pharmacovigilance databases, J. Clin. Epidemiol. 139 (2021) 191–198, https://doi.org/10.1016/j.jclinepi.2021.07.014.
[14] A. Mouffak, M. Lepelley, B. Revol, C. Bernardeau, F. Salvo, A. Pariente, M. Roustit, J.-L. Cracowski, C. Khouri, High prevalence of spin was found in pharmacovigilance studies using disproportionality analyses to detect safety signals: a meta-epidemiological study, J. Clin. Epidemiol. 138 (2021) 73–79, https://doi.org/10.1016/j.jclinepi.2021.06.022.
[15] C. Khouri, M. Fusaroli, F. Salvo, E. Raschi, Transparency and robustness of safety signals, BMJ 379 (2022), o2588, https://doi.org/10.1136/bmj.o2588.
[16] E. Raschi, F. Salvo, C. Khouri, Conceiving, conducting, reporting, interpreting, and publishing disproportionality analyses: a call to action, Br. J. Clin. Pharmacol. 88 (2022) 3535–3536, https://doi.org/10.1111/bcp.15269.

Benjamin Cortes[a], Clément Jambon-Barbara[b,c], Jean-Luc Cracowski[b,c], Charles Khouri[b,c,*]

[a] *Pharmacy Department, Grenoble Alpes University Hospital, F-38000 Grenoble, France*

[b] *Pharmacovigilance Unit, Grenoble Alpes University Hospital, F-38000 Grenoble, France*

[c] *Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, Grenoble, France*

[*] Corresponding author at: Centre Régional de Pharmacovigilance, CHU Grenoble Alpes, 38043 Grenoble Cedex 09, France.
E-mail address: CKhouri@chu-grenoble.fr (C. Khouri).

2. Signal detection of drugs associated with obstructive and central sleep apnoea

Plusieurs médicaments sont suspectés de causer ou d'aggraver un syndrome d'apnées du sommeil, et de nouveaux signaux de pharmacovigilance sont identifiés fréquemment (94,95). Devant les limites énoncées des analyses de disproportionnalité seules, nous avons réalisé un travail de détection de signaux en mêlant deux bases de données et deux méthodologies différentes. En effet, nous avons réalisé une analyse de disproportionnalité dans la base de pharmacovigilance de l'OMS, mais également une série d'analyses en symétrie de séquence dans la base médico-administrative Française. L'analyse en symétrie de séquence étant considéré comme une des méthodes les plus prometteuses pour la détection de signaux depuis les bases médico-administratives (125–128). Enfin, nous avons priorisé les signaux en ne conservant que ceux qui étaient significatifs avec les deux méthodologies et en excluant les classes médicamenteuses trop sujettes à un biais de détection de type biais protopathique (médicaments des sphères cardiovasculaires et respiratoires).

Sleep Medicine 124 (2024) 315–322

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Signal detection of drugs associated with obstructive and central sleep apnoea

C. Jambon-Barbara [a,b], B. Revol [a,b], A. Hlavaty [a,b], M. Joyeux-Faure [b], J.C. Borel [b], J.L. Cracowski [a,b], J.L. Pepin [b,c,1], C. Khouri [a,b,d,1,*]

[a] Grenoble Alpes University Hospital, Pharmacovigilance Unit, F-38000, Grenoble, France
[b] Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, F-38000, Grenoble, France
[c] Grenoble Alpes University Hospital, EFCR Laboratory, Grenoble, France
[d] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000, Grenoble, France

ARTICLE INFO

Keywords:
Sleep apnoea
Sequence symmetry analysis
Disproportionality analysis

ABSTRACT

We aim to discover new safety signals of drug-induced sleep apnoea (SA), a global health problem affecting approximately 1 billion people worldwide.

We first conducted a series of sequence symmetry analyses (SSA) in a cohort composed from all patients who received a first SA diagnosis or treatment between 2006 and 2018 in the Echantillon Généraliste des Bénéficaires (EGB), a random sample of the French healthcare database. We used two primary outcomes to estimate the sequence ratio (SR) for all drug classes available in France: a sensitive one (diagnosis or treatment of SA) and a specific one (Positive Airway Pressure (PAP) therapy). We then performed disproportionality analyses using the "Bayesian neural network method" on all cases of sleep apnoea (MedDRA high level term) reported up to November 2023 in the World Health Organisation (WHO) pharmacovigilance database.

Among the 728,167 individuals, 46,193 had an incident diagnosis or treatment for SA and 17,080 had started an incident treatment by PAP therapy. Fifty-eight drug classes had a significant SR, with 7 considered highly plausible: opium alkaloids and derivatives, benzodiazepine derivatives, other centrally acting agents, other anxiolytics, carbamic acid esters, quinine and derivatives and antivertigo preparations; with consistent signals found for the first 3 drug classes in the disproportionality analysis.

In this signal detection study, we found that opioids, benzodiazepines (but not Z-drugs) and myorelaxing agents are associated with the onset or aggravation of SA. Moreover, a new safety signal for antivertigo preparations such as betahistine emerged and needs to be further explored.

1. Introduction

Sleep apnoea (SA) is characterized by repeated episodes of apnoea and hypopnoea during sleep, with either predominant obstructive features corresponding to pharyngeal collapses (i.e. obstructive sleep apnoea (OSA)) or abnormalities or instability of respiratory control (i.e. central sleep apnoea (CSA)) [1]. The most common sleep-disordered breathing is OSA affecting approximately 1 billion people worldwide [2]. Sleep apnoea is a major cause of excessive daytime sleepiness, alterations in quality of life and is associated with an increased incidence of cardio-metabolic diseases, such as hypertension, type 2 diabetes mellitus, atrial fibrillation or cardiac failure [3,4]. A complex interplay between several pathophysiological mechanisms have been described, including compromised pharyngeal anatomy, impaired pharyngeal dilator muscle function, low respiratory arousal threshold and unstable respiratory control [1,5].

Several drugs have been suspected of causing or aggravating severity of sleep apnoea through diverse pharmacological actions impacting some SA pathophysiological mechanisms, such as opioids, benzodiazepines, baclofen or testosterone [6]. In addition, new safety signals have recently emerged with drugs such as ticagrelor or antipsychotics [6,7]. Given the wide prevalence of sleep apnoea, its massive individual and societal impact, the demonstration of even a small increase in the risk of developing or worsening sleep apnoea with the use of certain

* Corresponding author. Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
E-mail address: ckhouri@chu-grenoble.fr (C. Khouri).
[1] co-last authors.

https://doi.org/10.1016/j.sleep.2024.09.045
Received 15 May 2024; Received in revised form 31 August 2024; Accepted 29 September 2024
Available online 2 October 2024
1389-9457/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

medications is of considerable interest.

We therefore conducted a series of sequence symmetry analyses using a random sample of French healthcare database (Echantillon Généraliste des Bénéficiaires, EGB) to generate new signals about iatrogenic impact of drugs on SA. Sequence Symmetry Analysis (SSA) is a hypothesis-generating method evaluating the asymmetry in the distribution of events before and after initiation of a specific drug. SSA is based on the assumption that if a medication causes an adverse event, this medication will be prescribed more often before than after occurrence of this event; thus the time sequence drug exposure - outcome should be more frequent that the time sequence outcome - drug exposure [8]. The SSA allows estimating the sequence ratio (SR) which is an estimate of the incidence rate ratio of newly diagnosed outcome in exposed versus non-drug exposed person-times. SSA is considered as one of the most promising methods to detect safety signals in claims databases and have been thoroughly validated [9–12]. Nevertheless, to complement the findings of the SSA and to increase their robustness we used a second signal detection method (i.e. disproportionality analysis) based on cases of drug induced SA reported in the WHO pharmacovigilance database. Disproportionality analyses are widely used stakeholders, agencies and researchers to generate signals of potential new adverse drug reactions, by quantifying the degree to which a drug-adverse event combination is disproportionality reported compared to what would be expected in the absence of any association between the drug and the event [13,14].

In this study, we sought to discover new safety signals of drug induced sleep apnoea by investigating all drugs available and eligible to reimbursement in France between 2006 and 2018 using series of SSA. To increase the robustness of our findings, the second step was to confirm and complement signals by performing disproportionality analyses in the World Health Organization (WHO) pharmacovigilance database.

2. Methods

Using the French healthcare database, we performed a Sequence Symmetry Analysis to estimate the incidence rate ratio of being diagnosed or treated for sleep apnoea after the initiation of any drug class in the preceding year [15]. For detected and refined signals of the SSA we performed a disproportionality analysis in the WHO pharmacovigilance database to further explore robustness of the signals. We reported the SSA and the disproportionality analysis according to STROBE and READUS-PV recommendations [16–18].

2.1. Data source

We conducted this study using data extracted from the “Echantillon Généraliste des Bénéficiaires” (EGB) which is a random representative sample (to the 1/97th) of the French population covered by the national health insurance scheme, and contains data from approximately 700,000 individuals [19]. The patients are representative in age, sex and health care expenditure of the French general population. The database contains anonymized individual patient data linked to the hospital discharge summary database (Programme de Médicalisation des Systèmes d’Information, PMSI) that contains the following hospital data: dates of entry and discharge, diagnosis coded using ICD-10 (International Classification of Diseases, 10th revision), codes of the main medical procedures. The EGB is also linked to reimbursement of outpatient medical examinations and care (delivery date, unique drug identification code, ATC codes) [19–21]. For each eligible patient, demographic data (age, sex, date of death, etc.) and registration as having a long-term condition are available (extracted from ICD-10 codes, date of beginning and end of disease). The French healthcare database have been previously described and widely used in pharmacoepidemiology and for sequence symmetry analysis [10,19].

2.2. Study population

The base cohort was formed by identifying all patients who received a first (i.e. without presence of the outcome in the year before the index date) sleep apnoea diagnosis or treatment, between 2006 and 2018 with at least 1 year of data available before the outcomes and 1 year after. One year exposure time window prior and after outcome was chosen because of the likely time long course of the development and diagnosis of sleep apnoea. Moreover, this time window have shown the best sensitivity and positive predictive value for detecting safety signals [22]. The codes used for comorbidities identification have been previously validated by French institutions and are presented in the Supplementary Material (Table S1) [23–25].

2.3. Outcome

Two main outcomes were used for generating signals.

- a sensitive composite outcome aggregating diagnosis and treatment of sleep apnoea comprising hospital diagnosis identified by ICD-10 codes, Continuous Positive Airway Pressure (CPAP) or Adaptive Servo-Ventilation (ASV) initiation, Mandibular Advancement Splints (MAS), respiratory polygraphy or polysomnography;
- A specific outcome only including PAP therapy (CPAP or ASV).

All codes used for outcome identification are available in Supplementary Material (Table S2). Every PAP therapy codes have been previously reviewed by sleep apnoea clinical experts in our team and previously used in observational studies on CPAP in the French healthcare database [26,27]. We did not include bilevel positive airway pressure (BiPAP) therapy codes as this is used for non-invasive ventilation in chronic respiratory failure rather than in sleep apnoea. PAP therapy codes description is presented in Supplementary Material (Table S3).

2.4. Exposure

Each drug class of the fourth level of the ATC classification was analysed independently. Incident exposure was defined as a new prescription of a given drug class (i.e. no exposure with the same drug or another drug pertaining to the same class 1-year prior) (Fig. 1).

2.5. Signal detection and refinement

We defined SSA signals as: 1/drug classes associated with a lower boundary of the confidence interval of the sequence ratio (SR 95 % CI_{LB}) > 1 using the “sensitive outcome” and 2/a mean SR > 1 using the specific outcome (i.e. only CPAP or ASV).

Secondly, we excluded all drug classes with less than 50 exposed in at least one sequence. SSA results are exposed to detection bias and confounding factors [12]. Indeed, incident diagnosis of a cardiovascular disease (e.g. hypertension or myocardial infarction) may have leaded to the prescription of a new medication and prompted the diagnosis of sleep apnoea falsely increasing the sequence exposure- > outcome [28]. We therefore excluded all signals associated with drug classes indicated in cardiovascular diseases and respiratory disorders. Lastly, given the supposed pathophysiology of drug-induced sleep apnoea we excluded all drugs with short and intermittent exposure (i.e. antibiotics, vaccines, imaging contrast agents …).

2.6. Disproportionality analysis in the WHO pharmacovigilance database

To assess the consistency of the signals and further characterize patients and sleep apnoea patterns, we used a different but complementary method for signal detection in analysing cases reported in the WHO pharmacovigilance database, VigiBase [22]. VigiBase is the world’s

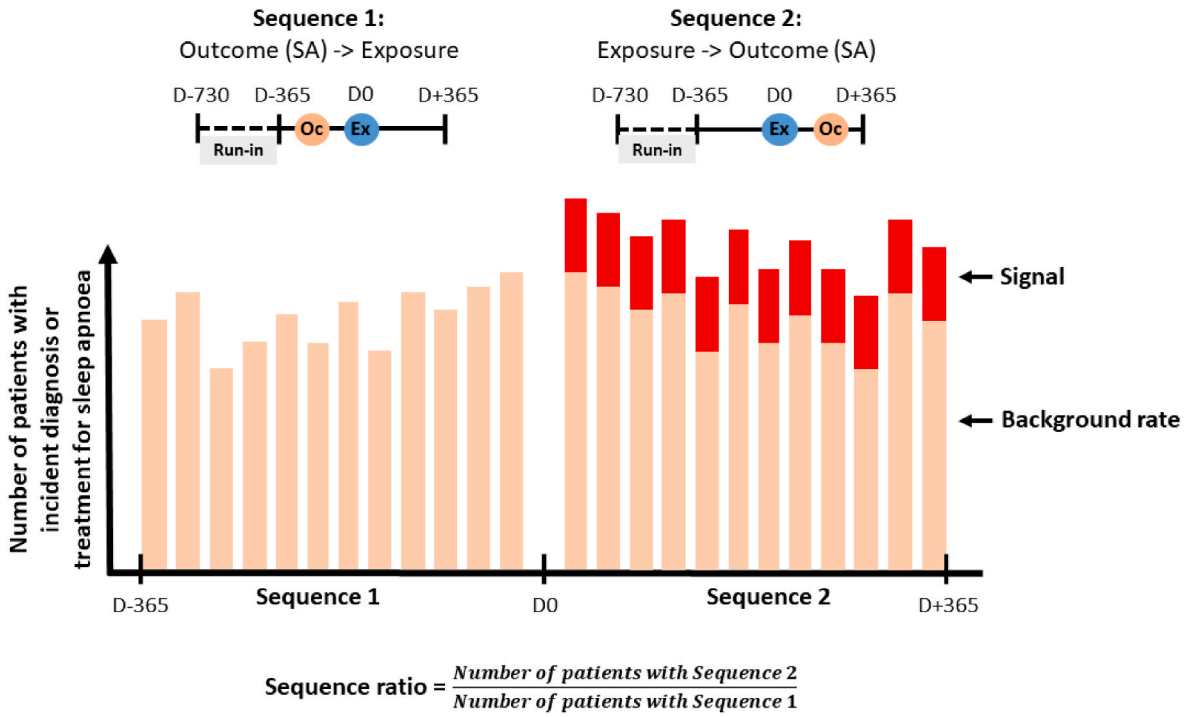


Fig. 1. Sequence symmetry analyses study design. *SA: Sleep Apnoea; Oc: Outcome; Ex: Exposure; D0: Day 0 (i.e. index date).*

largest pharmacovigilance database collecting reports from among the 150 countries participating in the WHO Programme for International Drug Monitoring since 1968. At the date of extraction (November 2023) more than 28 million of individual cases safety reports (ICSRs) were reported in this database. We performed series of disproportionality analyses that enable the exploration of pharmacovigilance databases to identify higher than expected statistical associations between drugs and adverse events, known as signal or statistic of disproportionate reporting (SDRs) [29]. We selected drug-events combination of interest using the drug classes with plausible signals found by the SSA method and the MedDRA high level term "sleep apnoea" (for drugs considered as suspect or interacting). The comparator group was constituted by all drugs and events of the database without restriction.

2.7. Statistical analyses

We calculated crude sequence ratios (SRs) as the number of patients who initiated a drug class in the year before outcome divided by the number of patients who initiated a drug class in the year after outcome. The 95 % confidence intervals were obtained by bootstrapping each SR a thousand times [12,30].

For refined signals (i.e. after exclusion of drug classes with less than 50 exposed subjects in at least one sequence, affected by detection and confounding bias and with intermittent exposure) we estimated mean age, proportion of male and mean time to outcome (i.e. time between first exposure and outcome) for patients exposed in the 1-year prior the outcome. Moreover, we performed the same SSA for each drug pertaining to these drug classes (ATC5 level). Finally, to account for trends in exposure and/or outcome during study period, we thus adjusted the crude SRs with null-effect sequence ratio (SRnull). SRnull is the expected sequence ratio in the absence of any causal association, taking into account the trend in the diagnosis of sleep apnoea relative to the trend in prescribing the drug of interest. We calculated the SRnull and 95%CI of the adjusted SR using the formula from Hallas in 1996 adjusted for time restriction by Tsiropoulos et al., in 2009 [31–33].

We tested gender difference for drug-based sleep apnoea on these refined signals using same SSA as in our primary analysis stratified on sex and looking at the overlap of their 95%CI.

We extracted and synthetized main characteristics of cases of sleep apnoea reported in the WHO pharmacovigilance database (sex, age, comorbidities, pattern of reported sleep apnoea MedDRA terms, time to onset, country of reporting). We performed the disproportionality analyses using the same drug classes as in the SSA (ATC4 level) and for individual drugs pertaining these classes (ATC5 level). We used the "Bayesian neural network method" which display the best specificity and sensitivity to detect adverse drug reactions [34,35]. A disproportionality signal was deemed significant if the lower boundary of the 95 % credibility interval of the Information Component (IC025) was superior to 0 [34,36].

All statistical analyses were performed with SAS EG® (SAS Institute, Cary, NC, USA), 7.13, R, version 4.2.1 (R Foundation) and Python 3.10.9.

Neither committee approval nor informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority (CNIL) agreement.

3. Results

3.1. Study population in the French EGB database

Among the 728,167 EGB individuals, 46,193 had an incident diagnosis or treatment for sleep apnoea (sensitive outcome) and 17,080 had started an incident treatment by PAP (specific outcome). Their main characteristics are presented in Table 1.

3.2. Signal detection and refinement: sequence symmetry analysis

Two hundred and eighty-four and 71 drug classes were associated with a SR $>$ 1 and a SR 95 % CI_{LB} $>$ 1 for the sensitive outcome, respectively. For the specific outcome, 203 and 22 drug classes were associated with a SR $>$ 1 and a SR 95 % CI_{LB} $>$ 1, respectively. According to our definition of SSA signals (i.e. SR 95 % CI_{LB} $>$ 1 for the sensitive outcome and SR $>$ 1 for specific outcome) we considered 58 drug classes for further exploration (Supplementary Table S4).

Table 1
Baseline Characteristics of population.

Variable	Patients with sleep apnoea diagnosis/treatment (n = 46,193)	Patients with PAP treatment (n = 17,080)
Age, years	55 (43–66)	59 (50–69)
Female sex	20,102 (43.5)	6032 (35.3)
Comorbidity		
Stroke	831 (1.80)	355 (2.08)
Heart failure	1297 (2.81)	493 (2.89)
Coronary heart disease	834 (1.81)	365 (2.14)
Chronic respiratory disease	8621 (18.7)	3191 (18.7)
Hypertension	15,180 (32.9)	10,176 (59.6)
Type 2 Diabetes	7769 (16.8)	4351 (25.5)
Obesity	8051 (17.4)	4142 (24.3)
Smoking status	5949 (12.9)	2853 (16.7)

All variables are presented as n (%) or median (interquartile range).

Among these 58 drug classes, 5 were excluded because low number of exposed patients (n < 50 1-year prior exposure or after outcome), 14 because of intermittent exposure or topical galenic form (mainly antibiotics and radiographic contrast agents) and 32 because of a high risk of detection and confounding bias, corresponding to drug used in the management of SA symptoms or comorbidities (mainly cardiovascular, anti-asthmatic and antimigraine drugs) (Supplementary Table S4).

Therefore, the signals generated by the SSA method were considered plausible for 7 drug classes described in Table 2. The adjusted SR using null-sequence ratio were consistent with the primary analysis and are presented in Supplementary Table S5.

After stratification on sex, all sequence ratios estimate for the 7 signals were consistent (i.e. confidence intervals overlapped) and are presented in Supplementary Material Table S6.

3.3. Disproportionality analysis in the WHO pharmacovigilance database

On November 2023, 28,556,022 ICSRs were reported in the WHO pharmacovigilance database, of which 14,276 ICRS in the HLT "sleep apnoea". The main reported symptoms (PT) were non-specific "sleep apnoea syndrome" (in 94.5 % of ICSRs) whether obstructive and central sleep apnoea syndromes represented only 4.4 % and 1.2 % of reported cases, respectively. Most cases originated from United States of America (81.1 %), Canada (3.6 %) and France (3.4 %) and there was approximately as many cases concerning women as men (sex ratio female to male of 1.06). Among the cases for which the age is known, the 45–64 age group was the most represented (47.9 %).

Overall, we found that 3 of the 7 selected drug classes were associated with a significant SDR in the disproportionality analysis. No case was reported with "Other anxiolytics", "Quinine and derivatives" and only 9 cases with "Antivertigo preparations" (Fig. 2 and Table 3). The proportion of reported central sleep apnoea among drug classes (among cases with OSA or CSA) ranged from 0 % for opioids to 81 % for the "other centrally agents drug class" (e.g. baclofen).

Among these drugs class, 7 drugs shown individually a significant signal of disproportionate reporting (baclofen, cyclobenzaprine, diazepam, hydrocodone bitartrate, meclozine, temazepam, tizanidine).

4. Discussion

In this study, we used robust and complementary methods to generate and confirm hypotheses about potential causal associations between drugs and onset of sleep apnoea [9–12]. We deliberately focused on the most plausible signals, with consistent results in the SSA, no plausible bias, and enough exposed patients. A sensitive approach (i.e. summing significant associations generated from each method) may have yielded hundreds of signals, biased for most of them. As a consequence, we assume that some known and unknown drugs have been missed by this approach (e.g. ticagrelor, testosterone, sufentanil …). Moreover, to compensate some weakness of the SSA, i.e. power, outcome misclassification and protopathic bias, we also performed a disproportionality analysis using the WHO pharmacovigilance database.

Table 2
Drug classes associated with a signal in the sequence symmetry analysis using the French healthcare database for the sensitive and specific outcome. Sequence Ratio (SR 95%CI) are presented along with number (N) and characteristics of patients exposed 1-year prior the outcomes.

ATC drug class name (code)	Individual drugs with a signal[a]	Sensitive outcome					Specific outcome				
		N	SR (95 % CI)	Age (mean ± sd)	Male sex (%)	Time to onset (days) (mean ± sd)	N	SR (95 % CI)	Age (mean ± sd)	Male sex (%)	Time to onset (days) (mean ± sd)
Opioids											
Opium alkaloids and derivatives (R05DA)	Codeine, Pholcodine, Dextromethorphan	2011	1.17 (1.09–1.26)	50.2 (19.8)	58.1	172.7 (108.2)	611	1.03 (0.90–1.17)	57.6 (13.6)	64.2	175.8 (106.2)
Benzodiazepines											
Benzodiazepine derivatives (N05CD)	Lormetazepam, Loprazolam	404	1.34 (1.13–1.58)	53.8 (16.9)	41.1	168.6 (102.8)	132	1.24 (0.91–1.62)	58.3 (12.5)	45.5	187.0 (109.4)
Other anxiolytics (N05BX)	Etifoxine	674	1.23 (1.08–1.39)	51.4 (15.4)	45.8	175.5 (105.7)	193	1.21 (0.95–1.52)	55.7 (13.1)	57.5	187.6 (110.4)
Myorelaxing drugs											
Carbamic acid esters (M03BA)	Methocarbamol	209	1.35 (1.06–1.70)	51.5 (14.1)	51.7	182.9 (102.8)	61	1.16 (0.78–1.81)	54.3 (13.2)	70.5	202.9 (94.2)
Other centrally acting agents (M03BX)	Thiocolchicoside, Tetrazepam	1315	1.18 (1.07–1.29)	52.0 (15.3)	56.5	176.5 (106.6)	423	1.10 (0.93–1.29)	55.2 (13.6)	64.3	178.7 (109.0)
Quinine and derivatives (M09AA)	Quinine benzoate	185	1.54 (1.17–2.03)	59.9 (13.5)	57.8	172.7 (103.0)	54	1.35 (0.85–2.13)	59.6 (12.2)	63.0	192.0 (101.2)
Antivertigo											
Antivertigo preparations (N07CA)	Betahistine, Acetylleucine, Flunarizine	981	1.33 (1.19–1.49)	56.4 (16.0)	46.6	166.1 (107.6)	317	1.10 (0.91–1.31)	60.7 (14.2)	55.8	172.6 (102.1)

[a] significant SSA 95 % CI_{LB} using the sensitive outcome.

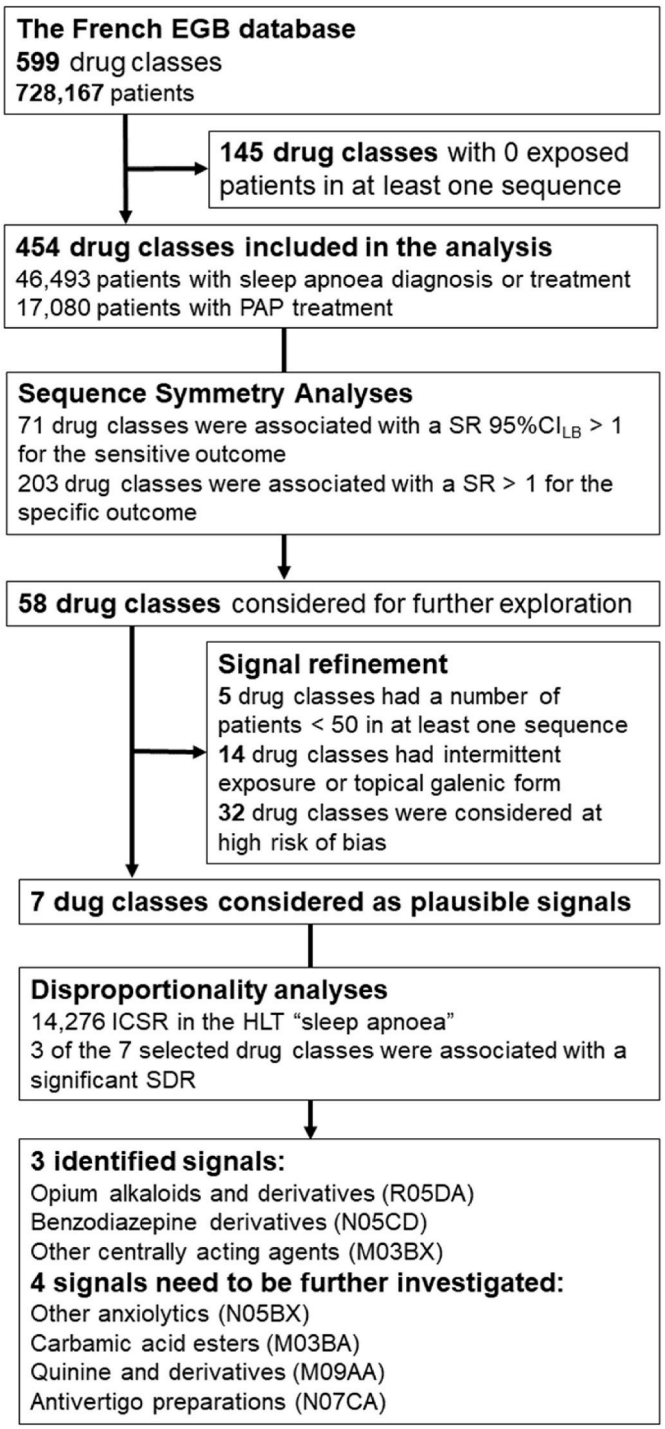


Fig. 2. Study analyses flowchart. *EGB: Echantillon Généraliste des Bénéficiaires; PAP: Positive Airway Pressure; SR: Sequence Ratio; 95%CI$_{LB}$: Lower bound of the 95 % confidence interval; ICSR: Individual Case Safety Reports; HLT: High Level Term; SDR: Signals of Disproportionate Reporting.*

Overall, three drug classes were associated with significant and robust signals using data from the French Healthcare database and data from the WHO pharmacovigilance database: opium alkaloids and derivatives (codeine, pholcodine, dextromethorphan), benzodiazepine derivatives (lormetazepam, loprazolam), and other centrally acting agents (thiocolchicoside, tetrazepam). While the methods used in this study are hypothesis-generating the probability of a causal association between these drug classes is high. Indeed, all these drugs are associated with plausible mechanisms of sleep apnoea triggering or aggravation in severity.

Opioids can induce both central and obstructive sleep apnoea dose dependent reduction in respiratory drive and upper airway muscles tone [37–39]. By design, we were unable to identify specific opioids drugs previously identified as triggers of SA (e.g. morphine, remifentanil, and fentanyl) because they are restricted to prescription in hospitalized patients in acute conditions. The novelty of our results suggests that less potent opioids such as codeine may also trigger or aggravate SA. These results may have significant health impact given the wide exposure to these drugs in the general population.

Benzodiazepine receptor agonists through GABA receptor agonism are associated with pharyngeal muscle relaxation, increased apnoea duration, and in turn with a higher burden of intermittent hypoxia [40, 41]. There is still a debate regarding the clinically relevant impact of exposure to these drugs on sleep apnoea. The findings are not consistent across clinical trials, with a Cochrane review finding no significant impact of benzodiazepines on OSA severity [42]. In our study, we found a robust signal for benzodiazepines but not for Z-drugs (i.e. zopiclone, zolpidem) which is consistent with several studies suggesting a distinctive impact of these drugs on sleep apnoea [43–45]. It is indeed hypothesized that benzodiazepines may have a greater effect on respiratory depression and that Z-drugs may have less significant muscle-relaxant effects, related to different GABA receptor affinities [40, 46]. Our results need to be replicated in real life cohort studies, given the risk of bias in our SSA due to the high prevalence of insomnia in the sleep apnoea population [47].

We also found a strong signal with centrally acting myorelaxing agents which can provoke upper airway collapses during sleep and depress respiratory drive [48]. Consistently, the analysis of the WHO pharmacovigilance database point toward a specific pattern of central sleep apnoea associated with exposure to these drugs. Our results provide further support for the link between sleep apnoea and exposure not only to baclofen but also to related drugs pertaining to the same drug class.

Four other drug classes displayed robust signals using the SSA but not using pharmacovigilance WHO database: two other myorelaxing drug classes (carbamic acid esters and quinine and derivatives), other anxiolytics and antivertigo preparations. Whether these other myorelaxing agents and anxiolytics are causally related to SA or innocent bystanders given their frequent co-prescription with drugs known to induce SA remains to be further studied. Association between antivertigo preparations and SA was unexpected and may be considered as a new safety signal. Indeed, histaminergic drugs such as betahistine have recently been tested in OSA in RCT but leaded to aggravation of OSA severity through increased respiratory control instability (i.e. loop gain) [49].

In this signal detection study, we have decided to primarily generate signals with a SSA applied to a healthcare database and not by using spontaneous reporting systems. Two reasons underpin this research strategy: 1/SSA has been shown to have high specificity whether spontaneous disproportionality analyses perform poorly in identifying signal for multifactorial diseases with high background rate; 2/the potential long latency period between drug initiation and diagnosis of sleep apnoea make it difficult to link drugs with no previous awareness on potential associations in spontaneous reporting systems (under-reporting) [50]. For example, in a previous study using disproportionality analysis alone in the WHO pharmacovigilance database, most of the identified signals of disproportionate reporting could be explained by an indication bias related to comorbidities or consequences of sleep apnoea (i.e. osteoporosis, heart failure, diabetes …) [51].

We also reviewed other compounds known or suspected to be associated with sleep apnoea to better understand the reasons for having missed them in our study [6]. As evoked previously we a priori excluded all cardiovascular and respiratory drugs because of a risk of bias using our method (see. Signal detection and refinement section). For example, ticagrelor, a P2Y12 inhibitor used to prevent the recurrence of thromboembolic events, displayed a strong signal among the "Platelet

Table 3
Results of the disproportionality analysis in the WHO pharmacovigilance database presenting Information Component estimates with 95 % Credibility Intervals (IC (95 % CrI)), with main characteristics of cases. CSA: central sleep apnoea.

ATC drug class name (code)	Individual drugs with a signal	Nobs	IC (95 % CrI)	Age (mean + sd)	Male sex (%)	Median time to onset (Q1-Q3)	Proportion of CSA
Opioids							
Opium alkaloids and derivatives (R05DA)	Hydrocodone	62	**0.49 (0.12, 0.82)**	49.9 (14.3)	45.3	NA	0 %
Benzodiazepines							
Benzodiazepine derivatives (N05CD)	Temazepam	46	**0.73 (0.29, 1.12)**	50.3 (17.7)	43.5	595 days (298.5–891.5)	40 %
Other anxiolytics (N05BX)		0	NA	NA	NA	NA	
Myorelaxing drugs							
Carbamic acid esters (M03BA)		11	0.89 (−0.09, 1.60)	50.1 (7.5)	45.5	NA	0 %
Other centrally acting agents (M03BX)	Baclofen Tizanidine Diazepam Cyclobenzaprine	211	**1.76 (1.56, 1.95)**	47.0 (17.0)	48.8	18 days (5.0–60.0)	81 %
Quinine and derivatives (M09AA)		0	NA	NA	NA	NA	NA
Antivertigo							
Antivertigo preparations (N07CA)	Meclozine	9	−1.01 (−2.11, −0.22)	59.6 (5.7)	11.1	1232 days	NA

aggregation inhibitors (B01AC)" drug class, which is consistent with previous studies [7,52–54]. This signal has been previously evaluated in a dedicated cohort study using the French Healthcare database [55]. Male hormones, such as testosterone are also suspected to worsen sleep apnoea but were not associated with a significant signal in our study (SR (95%CI) of 0.96 (0.33–2.00), n = 32). Whether this is due to a lack of power, an inadequate follow up duration in our study or a non-clinically relevant increase in AHI remains to be further explored. We also probably underestimated some drugs causing weight gain, such as paroxetine, mirtazapine, anticonvulsants or antipsychotics. We hypothesise that our 1-year time frame period is too short to assess weight gain triggering sleep apnoea symptom and patients' inclusion in the care pathway.

The results of our study need to be interpreted in view of the following limitations. The SSA is a case-only design and thus immune to time-independent confounders. However it is particularly susceptible to protopathic bias and innocent bystander effect [12,15]. These biases are well illustrated by the signals generated for all cardiovascular drugs thus underlying the importance of clinical and pharmacological expertise in interpreting the results. As stated early in the discussion we voluntary applied stringent criteria to select signals in order to increase the positive predictive value of the signals generated. Given we were unable to clearly discriminate between CPAP, and ASV in the EGB database due to the use of same reimbursement codes in France, we applied the same selection criteria for both central and obstructive SA. The signal generated by the disproportionality analysis may also be distorted by several factors such as selective reporting, previous awareness and confounding factors [50]. However, mixing these two signal detection methods based on data generated by very different process may compensate the weakness of each study design.

5. Conclusion

In this signal detection study, we found that opioids (event with lower potency), benzodiazepines (but not Z-drugs) and myorelaxing agents are associated with the onset or aggravation of sleep apnoea. Moreover, we found an unexpected safety signal for antivertigo preparations such as betahistine which need to be further explored. Given the wide prevalence of sleep apnoea in the general population, the demonstration of even a small increase in the risk of developing or worsening the disease with the use of certain medications is of considerable interest as an actionable factor to prevent or treat sleep apnoea.

Financial Disclosure

None.

Data sharing statement

VigiBase is publicly accessible at https://www.vigiaccess.org/. According to data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or organisation (public or private; for-profit or non-profit), can access anonymized SNDS data to do a study, research, or an evaluation of public interest, upon authorisation from the French Data Protection Office (See https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html). Codes used to perform the analyses are available on demand of the corresponding author.

CRediT authorship contribution statement

C. Jambon-Barbara: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **B. Revol:** Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **A. Hlavaty:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **M. Joyeux-Faure:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **J.C. Borel:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation. **J.L. Cracowski:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization. **J.L. Pepin:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Conceptualization. **C. Khouri:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Jean-Christian Borel reports a relationship with Agiradom that includes: employment. Jean-Louis Pepin reports a relationship with Air

Liquide Foundation that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Agiradom that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Fisher & Paykel Healthcare Inc that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Mutualia that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Philips that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with ResMed that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with VitalAire France that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Boehringer Ingelheim Ltd that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Jazz Pharmaceuticals that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Night Balance that includes: consulting or advisory and funding grants. Jean-Louis Pepin reports a relationship with Sefam that includes: consulting or advisory and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank VigiBase for giving us access to the data. The data supplied to VigiBase come from a variety of sources and the likelihood of a causal relationship is not the same in all reports. The information does not represent the opinions of the UMC or the World Health Organization.

We thank AGIR à Dom for support in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.09.045.

References

[1] Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primer 2015 Jun 25;1:15015.
[2] Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019 Aug;7(8):687–98.
[3] Cowie MR, Linz D, Redline S, Somers VK, Simonds AK. Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2021 Aug 10;78(6):608–24.
[4] Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American heart association. Circulation 2021 Jul 20;144(3):e56–67.
[5] Pépin JL, Eastwood P, Eckert DJ. Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. Eur Respir J 2022 Jun;59(6):2101788.
[6] Jullian-Desayes I, Revol B, Chareyre E, Camus P, Villier C, Borel JC, et al. Impact of concomitant medications on obstructive sleep apnoea. Br J Clin Pharmacol 2017 Apr;83(4):688–708.
[7] Revol B, Jullian-Desayes I, Tamisier R, Puel V, Mallaret M, Joyeux-Faure M, et al. Ticagrelor and central sleep apnea. J Am Coll Cardiol 2018 May 22;71(20):2378–9.
[8] Petri H, de Vet HC, Naus J, Urquhart J. Prescription sequence analysis: a new and fast method for assessing certain adverse reactions of prescription drugs in large populations. Stat Med 1988 Nov;7(11):1171–5.
[9] King CE, Pratt NL, Craig N, Thai L, Wilson M, Nandapalan N, et al. Detecting medicine safety signals using prescription sequence symmetry analysis of a national prescribing data set. Drug Saf 2020 Aug 1;43(8):787–95.
[10] Maura G, Billionnet C, Coste J, Weill A, Neumann A, Pariente A. Non-bleeding adverse events with the use of direct oral anticoagulants: a sequence symmetry analysis. Drug Saf 2018 Sep 1;41(9):881–97.
[11] Arnaud M, Bégaud B, Thurin N, Moore N, Pariente A, Salvo F. Methods for safety signal detection in healthcare databases: a literature review. Expert Opin Drug Saf 2017 Jun 3;16(6):721–32.
[12] Lai ECC, Pratt N, Hsieh CY, Lin SJ, Pottegård A, Roughead EE, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. Eur J Epidemiol 2017 Jul;32(7):567–82.
[13] Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, Friedman C. Novel data mining methodologies for adverse drug event discovery and analysis. Clin Pharmacol Ther 2012 Jun;91(6):1010–21.
[14] Dhodapkar MM, Shi X, Ramachandran R, Chen EM, Wallach JD, Ross JS. Characterization and corroboration of safety signals identified from the US food and drug administration adverse event reporting system, 2008-19: cross sectional study. BMJ 2022 Oct 5;379:e071752.
[15] Lund LC, Jensen PH, Pottegård A, Andersen M, Pratt N, Hallas J. Identifying diabetogenic drugs using real world health care databases: a Danish and Australian symmetry analysis. Diabetes Obes Metab 2023 May;25(5):1311–20.
[16] Vandenbroucke JP, Elm E von, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007 Oct 16;147(8):W–163.
[17] Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The reporting of a disproportionality analysis for drug safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): development and statement. Drug Saf 2024 Jun;47(6):575–84.
[18] Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The REporting of A disproportionality analysis for DrUg safety signal detection using individual case safety reports in PharmacoVigilance (READUS-PV): explanation and elaboration. Drug Saf 2024 Jun;47(6):585–99.
[19] Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017 Aug;26(8):954–62.
[20] Quantin C, Bouzelat H, Allaert FA, Benhamiche AM, Faivre J, Dusserre L. Automatic record hash coding and linkage for epidemiological follow-up data confidentiality. Methods Inf Med 1998 Sep;37(3):271–7.
[21] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique 2010 Aug;58(4):286–90.
[22] Wahab I A, Pratt NL, Kalisch LM, Roughead EE. Comparing time to adverse drug reaction signals in a spontaneous reporting database and a claims database: a case study of rofecoxib-induced myocardial infarction and rosiglitazone-induced heart failure signals in Australia. Drug Saf 2014 Jan;37(1):53–64.
[23] Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur 2021 Sep;8:100158.
[24] Quantin C. Etude des algorithmes de définition de pathologies dans le Système Nationale d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM). Caisse National d'Assurance Maladie 2015 Aug:272. Available from: https://assurance-maladie.ameli.fr/sites/default/files/2014_etude-algorithmes-definition-pathologies-partie-1_cartographie.pdf.
[25] Géodes - Santé publique France - Indicateurs : cartes, données et graphiques [Internet]. [cited 2022 Oct 25]. Available from: https://geodes.santepubliquefrance.fr/#view=map2&c=indicator.
[26] Pépin JL, Bailly S, Rinder P, Adler D, Benjafield AV, Lavergne F, et al. Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis. Chest 2022 Jun;161(6):1657–65.
[27] Pépin JL, Tamisier R, Benjafield AV, Rinder P, Lavergne F, Josseran A, et al. CPAP resumption after a first termination and impact on all-cause mortality in France. Eur Respir J 2023 Dec 22:2301171.
[28] Chen A, Ju C, Mackenzie IS, MacDonald TM, Struthers AD, Wei L, et al. Impact of beta-blockers on mortality and cardiovascular disease outcomes in patients with obstructive sleep apnoea: a population-based cohort study in target trial emulation framework. Lancet Reg Health Eur 2023 Oct;33:100715.
[29] Council for International Organizations of Medical Sciences. In: Practical aspects of signal detection in pharmacovigilance: report of CIOMS Working Group VIII. Geneva: CIOMS; 2010. p. 143.
[30] Pratt NL, Ilomäki J, Raymond C, Roughead EE. The performance of sequence symmetry analysis as a tool for post-market surveillance of newly marketed medicines: a simulation study. BMC Med Res Methodol 2014 May 15;14:66.
[31] Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. Epidemiol Camb Mass 1996 Sep;7(5):478–84.
[32] Tsiropoulos I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. Pharmacoepidemiol Drug Saf 2009 Jun;18(6):483–91.
[33] Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. Br Med J Clin Res 1988 May 7;296(6632):1313–6.
[34] Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998 Jun;54(4):315–21.
[35] Pham M, Cheng F, Ramachandran K. A comparison study of algorithms to detect drug–adverse event associations: frequentist, bayesian, and machine-learning approaches. Drug Saf 2019 Jun;42(6):743–50.
[36] Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res 2013 Feb;22(1):57–69.
[37] Mogri M, Desai H, Webster L, Grant BJB, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. Sleep Breath Schlaf Atm 2009 Mar;13(1):49–57.
[38] Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. Anaesth Intensive Care 2011 Jul;39(4):545–58.

[39] Lee-Iannotti J, Parish JM. The epidemic of opioid use: implications for the sleep physician. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 2014 Jun 15;10 (6):645–6.
[40] Berry RB, Kouchi K, Bower J, Prosise G, Light RW. Triazolam in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1995 Feb;151(2):450–4.
[41] Dergacheva O, Fleury-Curado T, Polotsky VY, Kay M, Jain V, Mendelowitz D. GABA and glycine neurons from the ventral medullary region inhibit hypoglossal motoneurons. Sleep 2020 Jun 15;43(6):zsz301.
[42] Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2015;7. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011090.pub2/full. [Accessed 25 October 2023].
[43] Carberry JC, Fisher LP, Grunstein RR, Gandevia SC, McKenzie DK, Butler JE, et al. Role of common hypnotics on the phenotypic causes of obstructive sleep apnoea: paradoxical effects of zolpidem. Eur Respir J 2017 Dec;50(6):1701344.
[44] Hsu TW, Chen HM, Chen TY, Chu CS, Pan CC. The association between use of benzodiazepine receptor agonists and the risk of obstructive sleep apnea: a nationwide population-based nested case-control study. Int J Environ Res Public Health 2021 Sep 15;18(18):9720.
[45] Nigam G, Camacho M, Riaz M. The effect of nonbenzodiazepines sedative hypnotics on apnea-hypopnea index: a meta-analysis. Ann Thorac Med 2019;14(1): 49–55.
[46] Carter SG, Berger MS, Carberry JC, Bilston LE, Butler JE, Tong BKY, et al. Zopiclone increases the arousal threshold without impairing genioglossus activity in obstructive sleep apnea. Sleep 2016 Apr 1;39(4):757–66.
[47] Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M. Insomnia. Lancet 2022 Sep 24;400(10357):1047–60.
[48] Finnimore AJ, Roebuck M, Sajkov D, McEvoy RD. The effects of the GABA agonist, baclofen, on sleep and breathing. Eur Respir J 1995 Feb;8(2):230–4.
[49] Messineo L, Loffler K, Chiang A, Osman A, Taranto-Montemurro L, Eckert DJ. The combination of betahistine and oxybutynin increases respiratory control sensitivity (loop gain) in people with obstructive sleep apnea: a randomized, placebo-controlled trial. Nat Sci Sleep 2022 Jun 7;14:1063–74.
[50] Raschi E, Moretti U, Salvo F, Pariente A, Antonazzo IC, Ponti FD, et al. Evolving roles of spontaneous reporting systems to assess and monitor drug safety. Pharmacovigilance. IntechOpen 2019. Available from: https://doi.org/10.5772/intechopen.799862.
[51] Linselle M, Sommet A, Bondon-Guitton E, Moulis F, Durrieu G, Benevent J, et al. Can drugs induce or aggravate sleep apneas? A case–noncase study in VigiBase ® , the WHO pharmacovigilance database. Fundam Clin Pharmacol 2017 Jun;31(3): 359–66.
[52] Giannoni A, Emdin M, Passino C. Cheyne-Stokes respiration, chemoreflex, and ticagrelor-related dyspnea. N Engl J Med 2016 Sep 8;375(10):1004–6.
[53] Puel V, Théophile H, Godard I, Raymond N, Miremont-Salamé G, Gosse P, et al. Ticagrelor and central sleep apnoea: impact of withdrawal and reintroduction. Br J Clin Pharmacol 2019 Aug;85(8):1855–8.
[54] Paboeuf C, Priou P, Meslier N, Roulaud F, Trzepizur W, Gagnadoux F. Ticagrelor-associated shift from obstructive to central sleep apnea: a case report. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 2019 Aug 15;15(8):1179–82.
[55] Barras SM, Revol B, Jambon-Barbara C, Khouri C. TICAPNEA project. OSF; 2024. Available from: https://osf.io/5wav4/. [Accessed 29 August 2024].

3. Conclusion de la partie

Les travaux que nous avons menés sur la détection de signaux de sécurité nous ont permis de repréciser l'interprétation des analyses de disproportionnalité, et leur utilité en regard de la littérature déjà existante. Devant l'importance de la question de recherche évaluant le risque cardiovasculaire suite à l'exposition aux biphosphonates, nous appelons à conduire des études de pharmacoépidémiologie de qualité pour augmenter le niveau de preuve concernant ces signaux.

Ces travaux nous ont également permis d'identifier un nouveau signal de sécurité inattendu concernant le risque de syndrome d'apnées du sommeil avec les préparations anti-vertigineuses, et plus spécifiquement la betahistine qui mérite d'être plus largement étudié.

PARTIE 3 – IDENTIFIER LES EVENEMENTS : DEVELOPPEMENT ET VALIDATION D'ALGORITHMES

1. Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France

Avant la réalisation d'études de pharmacoépidémiologie, il est indispensable de savoir correctement identifier nos événements d'intérêt dans les bases de données médico-administratives. Identifier les patients avec un ulcère cutané dans ces bases nécessitent l'utilisation d'un algorithme qui se base sur les données de remboursements ambulatoires ainsi que sur les codes de diagnostics hospitaliers (129). Cependant, à notre connaissance cet algorithme n'a pas été validé et ses performances sont inconnues. L'objectif de ce travail est donc double : 1/ Valider les codes de diagnostics hospitaliers en les confrontant aux dossiers médicaux de centre hospitalier de Grenoble et si les codes diagnostics ont des performances suffisantes ; 2/ Valider l'algorithme déjà développé en confrontant les patients identifiés aux codes diagnostics retrouvés lors de séjours hospitaliers.

Therapie xxx (xxxx) xxx—xxx

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com



PHARMACOEPIDEMIOLOGY

Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France

Clément Jambon-Barbara[a,b], N'dah Mathieu Ouattara[a], Claire Bernardeau[a], Frédéric Olive[c], Sophie Blaise[b,d], Jean-Luc Cracowski[a,b], Charles Khouri[a,b,e,*]

[a] *Pharmacovigilance Department, Grenoble-Alpes University Hospital, University Grenoble-Alpes, 38000 Grenoble, France*
[b] *HP2 Laboratory, Inserm U1300, HP2, 3University Grenoble-Alpes, 8000 Grenoble, France*
[c] *Public Health Department, Grenoble-Alpes University Hospital, University Grenoble-Alpes, 38000 Grenoble, France*
[d] *Vascular Medicine Department, Grenoble-Alpes University Hospital, University Grenoble-Alpes, 38000 Grenoble, France*
[e] *Inserm CIC1406, Grenoble-Alpes University Hospital, University Grenoble-Alpes, 38000 Grenoble, France*

Reçu le 15 avril 2024 ; accepté le 6 février 2025

KEYWORDS
Validation ;
Algorithm ;
ICD-10 codes ;
Skin ulcer ;
Healthcare database

Summary
Purpose. — This study has two main objectives: 1/ to validate the International Classification of Diseases, 10th revision (ICD-10) diagnostic codes of skin ulcer in one French hospital using medical charts; 2/ to validate an out-hospital algorithm against ICD-10 codes using a healthcare database.
Methods. — We first validated in-hospital ICD-10 codes for pressure, diabetic and vascular skin ulcers using the Grenoble University Hospital medical charts. Secondly, we assessed the validity of an out-hospital algorithm using dressing reimbursements, medical exams and comorbidities to identify skin ulcers using the French ''*échantillon généraliste des bénéficiaires*'' database. We then compared the type of skin ulcers in patients hospitalized 1 year around the out-hospital skin ulcer identification date. We calculated specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV).

* Corresponding author. Centre regional de pharmacovigilance, CHU de Grenoble-Alpes, CS 10217, 38043 Grenoble cedex, France.
Adresse e-mail : ckhouri@chu-grenoble.fr (C. Khouri).

https://doi.org/10.1016/j.therap.2025.02.003
0040-5957/© 2025 The Author(s). Published by Elsevier Masson SAS on behalf of Société française de pharmacologie et de thérapeutique. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Pour citer cet article : C. Jambon-Barbara, N.M. Ouattara, C. Bernardeau et al., Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France, Therapies, https://doi.org/10.1016/j.therap.2025.02.003

Results. — The performances of ICD-10 codes for identifying patients with vascular, diabetic and pressure ulcers were all superior to 70%. The out-hospital identification of skin ulcers selected very different patients, younger and with less comorbidities than those hospitalized for skin ulcers. In patients hospitalized 1 year before or after the first dispensation of wound dressings, the concordance with ICD-10 codes was modest. Indeed, patients are wrongly classified as pressure ulcers, vascular ulcers and diabetic foot ulcers in respectively 27.7%, 52.0% and 48.8% of skin ulcers.

Conclusion. — We found that performances of the in-hospital identification of pressure, vascular and diabetic foot ulcers were high allowing to use them to conduct observational studies in healthcare databases. However, outpatient identification retrieved heterogeneous performance, we therefore advise researchers using the latter to perform a sensitivity analysis restricted to hospitalized patients.

© 2025 Les Auteurs. Publié par Elsevier Masson SAS au nom de Société française de pharmacologie et de thérapeutique. Cet article est publié en Open Access sous licence CC BY (http://creativecommons.org/licenses/by/4.0/).

Abbreviations

ICD-10	International Classification of Diseases; 10th revision
EGB	*échantillon généraliste des bénéficiaires*
PPV	positive predictive value
NPV	negative predictive value
PMSI	*programme de médicalisation des systèmes d'information*
LPP	*liste des produits et prestations*
CCAM	*classification commune des actes médicaux*
PVD	peripheral vascular disease
TP	true positive
FP	false positive
FN	false negative
TN	true negative

Introduction

It is estimated that in developed countries, the lifetime incidence of chronic wounds is about 1—2% of the population, negatively affecting patient individual's quality of life (pain and social discomfort) and representing a substantial economic burden to healthcare systems [1—3]. Vascular disease, diabetes and aging are the main factors contributing to chronic skin ulceration, causing the three main types of skin ulcer: vascular (venous or arterial) ulcers, diabetic foot ulcers and pressure ulcers, respectively [4]. Venous leg ulcers are the most common chronic wound, with a prevalence ranging from 1.5 to 3 per 1000 persons [5]. Moreover, among the 550 million people worldwide having diabetes, approximately 18.6 million people develop a foot ulcer each year [6,7] and prevalence rates of pressure ulcers ranges from 3 to 31% in long-term care facilities [8].

Using claims and electronic health record databases could be an important way of exploring and better understanding risk factors, prognostic and evolution of skin ulcers. However, identifying patients with skin ulcers in these databases requires the use of algorithms combining in-hospital and potentially out-hospital data depending on the scope of the research question and the type and severity of studied skin ulcers. The French Health Insurance previously applied an algorithm on the French healthcare database using out-hospital reimbursement of dressing and comorbidities to identify types of skin ulceration [9—12]. However, this algorithm has not been validated yet and to our knowledge, no previous study has validated the in-hospital International Classification of Diseases, 10th revision (ICD-10) diagnoses codes for skin ulcers. Therefore, this study has two main objectives: 1/ to validate the ICD-10 diagnostic codes of skin ulcer using in-hospital medical charts; 2/ to validate the out-hospital algorithm developed by the French Health Insurance against ICD-10 codes using the *échantillon généraliste des bénéficiaires* (EGB) database, a random representative sample of the French population covered by the national health insurance scheme [13].

Methods

Validation of in-hospital ICD-10 diagnosis code

Data source

We only used data available from The Grenoble-Alpes University Hospital medical charts, which means no outpatient data (e.g., on the use of drugs or bandages outside hospital) were available.

We considered every medical record of patients hospitalized for skin ulcers between 01/01/2013 and 31/12/2022 with at least one diagnostic code of skin ulcers (Table 1). We then randomly selected 50 patients for each type of ulcer (i.e., diabetic, pressure and venous), corresponding to our ''cases''. We also randomly selected 50 ''non-cases'' patients for each type of ulcer from: (1) patients hospitalised in a diabetic ward for diabetic ulcers; (2) patients

Table 1 Skin ulcer ICD-10 codes.

ICD-10 code: pressure ulcer	L89
ICD-10 codes: vascular ulcer	L97, I778, I830, I832
ICD-10 codes: diabetic foot ulcer	E105, E115, E125, E135, E145

ICD-10: International Classification of Diseases, 10th revision.

hospitalised in a geriatric ward for pressure ulcers; and (3) patients who had had an echo-Doppler scan of the lower limbs for vascular ulcers. The 300 medical records were examined manually by two investigators (C.J.B., N.M.O.) for any mention of skin ulcers, whether as a principal or associated diagnosis. These two investigators worked independently of each other in a blinded fashion. Any disagreements were resolved by a third investigator (J.L.C.).

Statistical analysis

We estimated the performances of ICD-10 codes by using 2×2 contingency tables and by calculating the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV). In line with previous studies, we have defined the performance results as follows: high when values where $\geq 70\%$, modest between 50 and 70% and poor when values were < 50 percentage [14,15].

We compared them to the manual review of medical records, considered ad the gold standard.

All statistical analyses were performed with SAS EG® (SAS Institute, Cary, NC, USA) 7.13 and R, version 4.2.1 (R Foundation).

Validation of out-hospital algorithm

Data source

The *échantillon généraliste des bénéficiaires* (EGB) healthcare database. The patients included in this random sample of the French population are representative in age, sex and healthcare expenditure of the general population. The database contains anonymised individual patient data and is linked to the hospital discharge summary database (*programme de médicalisation des systèmes d'information* [PMSI]) that contains dates of entry and discharge, diagnosis coded using ICD-10 and codes of the main medical procedures. The EGB also contains reimbursement of outpatient care and drugs data from community pharmacy [16—18]. The EGB has been extensively used and validated for pharmacoepidemiology research [16,19,20].

The cohort was composed of all beneficiaries present in the EGB in 2006, affiliated throughout the study period to the general public health insurance scheme (88% of the patients included in the database). We identified skin ulcer using a list of wound dressings supplied using the List of products and services (*liste des produits et prestations* [LPP]) codes, i.e., at least 2 deliveries of wound dressing during 1 month. The list of dressings included hydrocolloid, foam, alginate, hydrogel, fiber, and active carbon dressings, as well as dressings containing hyaluronic acid, or petroleum jelly, those with interfaces and adhesive dressings. The LPP codes are presented in the Supplementary Material (Table S1). We identified vascular, diabetic and pressure ulcers through the algorithm. Firstly, we identified any use of an anti-bedsore mattress, cushion, or compression bandage supply by LPP codes; and hospitalization for orthopaedic surgery or realization of an echo-Doppler by the medical procedure codes (''*classification commune des actes médicaux*'') presented in the Supplementary Material (Table S2—S5). Then, we defined the index date as the first reimbursement related to an episode of cutaneous ulcer, i.e., at least two deliveries of dressings during one month not associated with an orthopaedic surgery procedure in the 30 days preceding the delivery of dressings.

Statistical analysis

We estimated and have defined the same performance characteristics as in the in-hospital validation. We compared patients with a skin ulcer identified by the out-hospital algorithm with patients hospitalized for skin ulcer 1 year before or after the index date (i.e., initiation of wound dressings). The latter ones were considered the gold standard for the performance calculations.

All statistical analyses were performed with SAS EG® (SAS Institute, Cary, NC, USA) 7.13 and R, version 4.2.1 (R Foundation).

Results

Study cohorts

In the Grenoble University Hospital between 01/01/2013 and 31/12/2022, 14,128 patients were hospitalized for a skin ulcer (ICD-10 diagnosis): 12,278 for a pressure ulcer, 1429 for a vascular ulcer and 421 for a diabetic foot ulcer (Fig. 1).

In the EGB, between 01/01/2006 and 31/12/2019, 20,218 patients were hospitalized for skin ulcer with one of the ICD-10 code of interest and 70,282 patients were identified with a skin ulcer by the out-hospital algorithm. Among the latter, 2705 were hospitalized for skin ulcer in the year preceding or following the initiation of wound dressing dispensation (Fig. 2).

Characteristics of the 70,282 patients identified with the algorithm and the 20,218 patients identified by the ICD-10 hospitalization codes in the EGB are presented in Table 2. All of the measured characteristics were significantly different between the two identification methods.

ICD-10 hospitalization codes validation in the Grenoble University Hospital medical records

We randomly selected 300 patients (50 cases and 50 non-cases of each skin ulcer type) from the 14,128 hospitalized

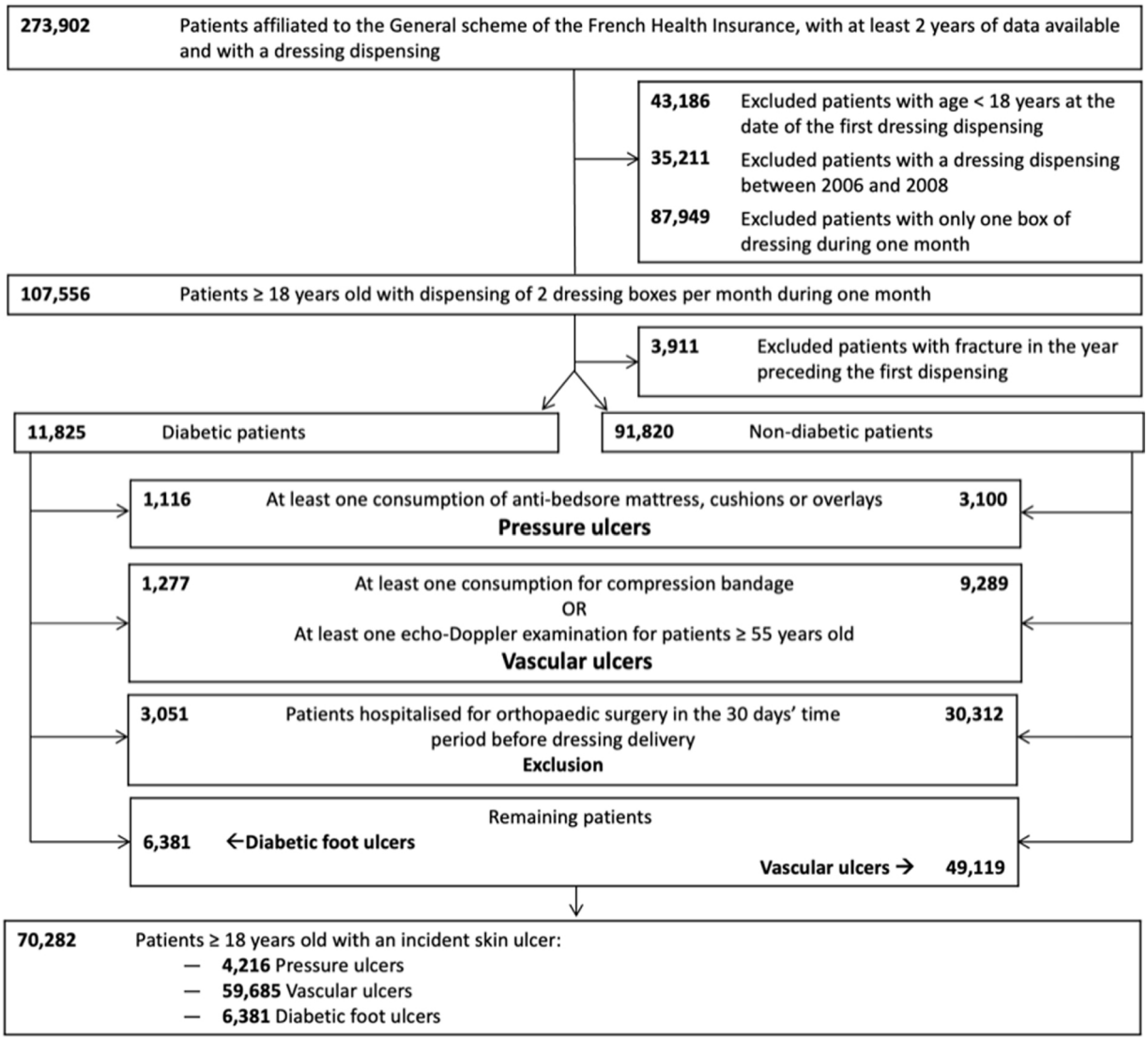


Figure 1. Flowchart of the selection of medical charts in the Grenoble University Hospital.

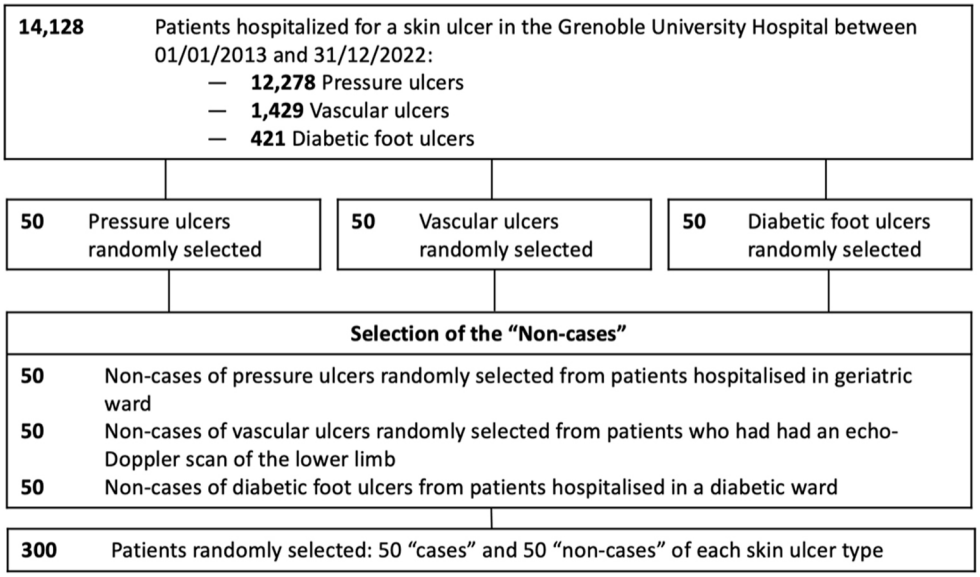


Figure 2. Flowchart of the selection of skin ulcers using out-hospital data in the French healthcare database.

Table 2 Patient characteristics of the EGB cohort.

Characteristic	Out-hospital algorithm ($n = 70,282$)	In-hospital ICD-10 codes ($n = 20,218$)	*P*-value
Male	32,529 (46.3)	10,021 (49.6)	< 0.0001
Age, years (mean ± SD)	54.9 ± 20.4	76.0 ± 14.7	< 0.0001
Hypertension	21,322 (30.3)	15,378 (76.1)	< 0.0001
Hyperlipidaemia	15,082 (21.5)	10,134 (50.1)	< 0.0001
Obesity	5718 (8.14)	4282 (21.2)	< 0.0001
Tobacco use	7439 (10.6)	4560 (22.6)	< 0.0001
Diabetes	9179 (13.1)	10,213 (50.5)	< 0.0001
Urinary incontinence	689 (0.98)	716 (3.54)	< 0.0001
Faecal incontinence	86 (0.12)	216 (1.07)	< 0.0001
Thrombosis	1152 (1.64)	1688 (8.35)	< 0.0001
PVD	941 (1.34)	1184 (5.86)	< 0.0001
Hospitalization[a]	2705 (3.85)		
Before index date	961 (1.37)		
After index date	1744 (2.48)		

Data are given as *n* (%) unless otherwise specified. EGB: *échantillon généraliste de bénéficiares*; ICD-10: International Classification of Diseases 10th revision; PVD: peripheral vascular disease.
[a] Hospitalization 1 year before or after index date (wound dressing reimbursement).

Table 3 Example of a 2 × 2 contingency table: pressure ulcer.

Variable	Pressure ulcer[a]	Not-pressure ulcer[a]	Total
Positive test[b]	TP: 35	FP: 15	50
Negative test[c]	FN: 6	TN: 44	50
Total	41	59	100

FP: false positive; FN: false negative; ICD-10: International Classification of Diseases, 10th revision; TN: true negative; TP: true positive.
[a] As determined by the gold standard chart review of primary clinical data.
[b] Patients selected by their ICD-10 hospitalization code. For pressure ulcers: L89.
[c] Patients selected from the different non-case pools. For pressure ulcers non-cases: patients hospitalised in a geriatric ward.

Table 4 Performance characteristics for each skin ulcer type in hospitalized patients.

Ulcer type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pressure	85.3	74.6	70.0	88.0
Vascular	91.8	90.2	90.0	92.0
Diabetic foot	90.7	97.8	98.0	90.0

NPV: negative predictive value; PPV: positive predictive value.

patients in the Grenoble University Hospital and constructed one contingency table for each type of ulcer. An example of a 2 × 2 contingency table with pressure ulcers is presented in Table 3 and performance characteristics of each skin ulcer types are presented Table 4. Overall, the performances were considered as high for all estimates specificity, sensitivity, PPV and NPV.

Out-hospital algorithm validation in the French healthcare database

Among the 2705 patients identified with a skin ulcer by the algorithm and hospitalized in the EGB for skin ulcer in the year around the index date, we retrieved 730 (27.0%) pressure ulcers, 1159 (42.8%) vascular ulcers, 816 (30.2%) diabetic foot ulcers. Seventy-two percent of pressure ulcers retrieved by the algorithm were hospitalized for a pressure ulcer, 48% of vascular ulcers retrieved by the algorithm were hospitalized for a vascular ulcer and 51% of diabetic foot ulcers retrieved by the algorithm were hospitalized for a diabetic foot ulcer. Skin ulcer types identified by the algorithm and the hospitalization codes are presented in Table 5.

Overall, specificity of skin ulcer identification ranged from 66.6% for vascular ulcers to 86.5 for pressure ulcers. However, sensitivity ranged from 43.8 to 68.9% for pressure and diabetic foot ulcer, respectively (Table 6).

Table 5 Skin ulcer types by identification method in the EGB.

Ulcer type	Pressure[a]	Vascular[a]	Diabetic foot[a]	Total
Pressure[b]	528 (72.3)	113 (15.5)	89 (12.2)	730 (27.0)
Vascular[b]	511 (44.1)	556 (48.0)	92 (7.94)	1159 (42.8)
Diabetic foot[b]	166 (20.3)	232 (28.4)	418 (51.2)	816 (30.2)
Total	1205 (44.6)	901 (33.3)	599 (22.1)	2705

Data are presented as *n* (%). Percentages are given in line. ICD-10: International Classification of Diseases, 10th revision.
[a] As determined by in-hospital diagnosis ICD-10 code.
[b] As determined by the out-hospital algorithm.

Table 6 Performance characteristics for each skin ulcer type in the EGB for hospitalized patients 1 year prior/after outpatient identification.

Ulcer type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pressure	43.8	86.5	72.3	65.7
Vascular	61.7	66.6	48.0	77.7
Diabetic foot	69.8	81.1	51.2	90.4

EGB: *échantillon généraliste des bénéficiaires*; NPV: negative predictive value; PPV: predictive positive value.

Discussion

In this study we assessed the performance of in-hospital ICD-10 diagnostic codes or out-hospital algorithm for identifying skin ulcers in the French healthcare database. We found that the performances of ICD-10 codes for identifying patients with vascular, diabetic and pressure ulcers could be considered good enough to be used in observational studies, with sensitivity, specificity, PPV and NPV superior to 70%.

The out-hospital identification of skin ulcers selected very different patients, younger and with less comorbidities than those hospitalized for skin ulcers which is consistent with what we would have expected, i.e., more severe conditions and ulcers in hospitalized patients. In patients hospitalized 1 year before or after the first dispensation of wound dressings, the concordance with ICD-10 codes was modest. Indeed, patients are wrongly classified as pressure ulcers, vascular ulcers and diabetic foot ulcers in respectively 27.7%, 52.0% and 48.8% of cases. Therefore, a non-negligible proportion of patients are probably wrongly classified by this method. Whether these patients do not present a skin ulcer or whether they present a misclassified skin ulcer remains to be further studied. Nevertheless, this out-hospital algorithm can be used as a compromise for identifying a large number of skin ulcers and not only the most serious cases requiring hospitalisation, which in the end represent only 3.8% of the identified ulcers. We can therefore advise researchers using out-hospital data for identifying patients with skin ulcers to perform sensitivity analysis restricted to hospitalised patients to assess the robustness of the results.

To our knowledge, our study is the first attempts to assess the validity of skin ulcer identification in the French healthcare database. A study on ICD-10 diagnosis codes realised in a Canadian hospital database yielded similar results with 90% PPV (high performances) for the identification of diabetic foot ulcers [21]. The outpatient classification algorithm needs to be optimized. As an example future researches may use machine learning and natural language processing to extract data from clinical notes or matching with external cohorts to improve and validate out-hospital algorithm.

This algorithm validation presents several limitations. First, the dates of medical records extraction and the EGB cohort constitution are not contemporaneous, we selected a larger time frame in the EGB cohort to ensure sufficient power. Second, even if each ulcer retrieved performances considered as high, pressure ulcers displayed the worst results. Potential explanations might be that the codes used to identify those ulcers are broader than the vascular and diabetic foot ones, or because decubitus ulcers are less mentioned in medical charts and often multifactorial. Third, there is no specific treatment of skin ulcers, the outpatient algorithm therefore uses dressing dispensing. This limit was partially addressed with the selection of only certain specific types of dressing to increase the likelihood of identifying a skin ulcer and with the exclusion of recent surgical procedures that is one of the main confounding factors. Fourth, the out-hospital algorithm was validated indirectly by reference to the ICD-10 diagnosis code in the EGB and not directly in the patients' electronic records. Fifth, this is a monocentric study using the in-hospital medical charts and we could not be sure that our results are generalizable to every region in France. However, we do not expect major differences of ICD-10 coding between the different French hospitals. It is nevertheless interesting to note, as one reviewer pointed out, that coding practices may differ between centres. Indeed, certain international recommendations such as those of the American Academy of Professional Coders for example, advocate the use of code L97 associated with an extended diabetes code. The L97 code, which is also used for arterial ulcers, wrongly leads to so-called vascular ulcer diagnoses when the patient is iden-

tified as having a diabetic foot. We therefore urge other researchers to replicate our study in order to assess the heterogeneity in the performance of these codes, and to develop new algorithms for identifying skin ulcers in medico-administrative databases.

Conclusion

In conclusion, this study evaluated the validity of in-hospital diagnosis codes in a single French hospital and out-hospital algorithms to identify patients suffering from skin ulcers. We found that performances of the in-hospital identification were high for the 3 types of skin ulcer with 70%, 90% and 98% PPV for pressure, vascular and diabetic foot ulcers respectively. However, outpatient identification retrieved lower performance in skin ulcer identification. We therefore strongly advise researchers using this outpatient identification method to perform sensitivity analyses restricted to hospitalised patients. Finally, it would be useful to test the validity these in-hospital and out-hospital algorithms on other populations and databases.

Funding

This work was supported by centre hospitalier universitaire Grenoble-Alpes (CHUGA). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.therap.2025.02.003.

Disclosure of interest

The authors declare that they have no competing interest.

Références

[1] Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care 2014;37:651—8.
[2] Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ 2014;17:347—56.
[3] Falanga V, Isseroff RR, Soulika AM, Romanelli M, Margolis D, Kapp S, et al. Chronic wounds. Nat Rev Dis Primer 2022;8:50.
[4] Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care 2015;4:560—82.
[5] Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002;46:381—6.
[6] Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017;376:2367—75.
[7] Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. JAMA 2023;330:62—75.
[8] Anthony D, Alosoumi D, Safari R. Prevalence of pressure ulcers in long-term care: a global review. J Wound Care 2019;28:702—9.
[9] Rames O, Sebo S, Pécault R, Agamaliyev E, Tuppin P, Rodde Dunet MH, et al. Plaies chroniques en France : prévalence, caractéristiques et évolution. Améliorer l'organisatoin de la prise en charge en sortie d'hospitalisation. France: Caisse Nationale d'Assurance Maladie; 2015, https://assurance-maladie.ameli.fr/etudes-et-donnees/2015-prise-en-charge-plaies-chroniques-parcours-soins. [Accessed 6 February 2025].
[10] Jambon-Barbara C, Bernardeau C, Bezin J, Roustit M, Blaise S, Cracowski JL, et al. Use of bisphosphonates and the risk of skin ulcer: a national cohort study using data from the French health care claims database. Drug Saf 2023;46:905—16.
[11] Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur 2021;8:100158.
[12] Fuentes S, Cosson E, Mandereau-Bruno L, Fagot-Campagna A, Bernillon P, Goldberg M, et al. Identifying diabetes cases in health administrative databases: a validation study based on a large French cohort. Int J Public Health 2019;64:441—50.
[13] Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: what interest for medical research? Rev Med Interne 2015;36:411—7.
[14] Gillmeyer KR, Nunez ER, Rinne ST, Qian SX, Klings ES, Wiener RS. Development and validation of algorithms to identify pulmonary arterial hypertension in administrative data. Chest 2021;159:1986—94.
[15] Carnahan RM, Moores KG. Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative and claims data: methods and lessons learned. Pharmacoepidemiol Drug Saf 2012;21(Suppl. 1):82—9.
[16] Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017;26:954—62.
[17] Quantin C, Bouzelat H, Allaert FA, Benhamiche AM, Faivre J, Dusserre L. Automatic record hash coding and linkage for epidemiological follow-up data confidentiality. Methods Inf Med 1998;37:271—7.
[18] Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique 2010;58:286—90.
[19] Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique 2017;65(Suppl. 4):S149—67.
[20] De Roquefeuil L, Studer A, Neumann A, Merlière Y. L'échantillon généraliste de bénéficiaires : représentativité, portée et limites. Prat Organ Soins 2009;40:213—23.
[21] Syed MH, Al-Omran M, Jacob-Brassard J, Ray JG, Hussain MA, Mamdani M, et al. ICD-10 diagnostic coding for identifying hospitalizations related to a diabetic foot ulcer. Clin Invest Med 2021;44:E11—6.

2. Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in the French Healthcare Database

De la même façon que le travail précédent, nous avons pour objectif d'obtenir un algorithme permettant l'identification précise des patients présentant une HTAP. Une revue systématique des algorithmes utilisés pour identifier les HTAP dans les bases de données médico-administratives a rapporté une faible performance de ceux ne se basant que sur les codes diagnostics hospitaliers avec une valeur prédictive positive d'environ 3% (130). Nous avons donc pris comme base de départ l'algorithme qui semblait le plus performant dans les bases de données médico-administratives américaines et développé par Gillmeyer et ses collègues (131). Cet algorithme n'ayant jamais été validé dans la base de données médico-administratives Française (le Système National des Données de Santé), nous avons pour objectif d'adapter cet algorithme aux spécificités françaises et de le valider.

Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in a French healthcare database

Clément Jambon-Barbara [1,2], Alex Hlavaty[1,2], Claire Bernardeau[1], Hélène Bouvaist[3], Marie-Camille Chaumais [4,5,6], Marc Humbert [4,7,8], David Montani [4,7,8], Jean-Luc Cracowski[1,2] and Charles Khouri [1,2,9]

[1]Pharmacovigilance Unit, Grenoble Alpes University Hospital, Grenoble, France. [2]Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, Grenoble, France. [3]Cardiology Unit, Grenoble Alpes University Hospital, Grenoble, France. [4]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France. [5]Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Pharmacy, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [6]Faculty of Pharmacy, Université Paris-Saclay, Saclay, France. [7]Faculty of Medicine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [8]AP-HP, Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Centre, Hôpital Bicêtre, DMU 5 Thorinno, Le Kremlin-Bicêtre, France. [9]Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, Grenoble, France.

Corresponding author: Charles Khouri (ckhouri@chu-grenoble.fr)

Shareable abstract (@ERSpublications)
Development and validation of an algorithm allowing identification of PAH patients in a French healthcare database https://bit.ly/3VXGt74

Cite this article as: Jambon-Barbara C, Hlavaty A, Bernardeau C, *et al*. Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in a French healthcare database. *ERJ Open Res* 2024; 10: 00109-2024 [DOI: 10.1183/23120541.00109-2024].

Copyright ©The authors 2024

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 2 Feb 2024
Accepted: 11 April 2024

Abstract

Introduction Pulmonary arterial hypertension (PAH) is a rare and severe disease for which most of the evidence about prognostic factors, evolution and treatment efficacy comes from cohorts, registries and clinical trials. We therefore aimed to develop and validate a new PAH identification algorithm that can be used in the French healthcare database "Système National des Données de Santé (SNDS)".

Methods We developed and validated the algorithm using the Grenoble Alpes University Hospital medical charts. We first identified PAH patients following a previously validated algorithm, using in-hospital ICD-10 (10th revision of the International Statistical Classification of Diseases) codes, right heart catheterisation procedure and PAH-specific treatment dispensing. Then, we refined the latter with the exclusion of chronic thromboembolic pulmonary hypertension procedures and treatment, the main misclassification factor. Second, we validated this algorithm using a gold standard review of in-hospital medical charts and calculated sensitivity, specificity, positive and negative predictive value (PPV and NPV) and accuracy. Finally, we applied this algorithm in the French healthcare database and described the characteristics of the identified patients.

Results In the Grenoble University Hospital, we identified 252 unique patients meeting all the algorithm's criteria between 1 January 2010 and 30 June 2022, and reviewed all medical records. The sensitivity, specificity, PPV, NPV and accuracy were 91.0%, 74.3%, 67.9%, 93.3% and 80.6%, respectively. Application of this algorithm to the SNDS yielded the identification of 9931 patients with consistent characteristics compared to PAH registries.

Conclusion Overall, we propose a new PAH identification algorithm developed and adapted to the French specificities that can be used in future studies using the French healthcare database.

Introduction

Pulmonary arterial hypertension (PAH) corresponding to group 1 of the pulmonary hypertension (PH) classification is a rare and severe disease with an estimated prevalence of 48 to 55 cases per million [1–3]. Given its scarcity, most of the evidence about risk and prognostic factors, evolution of the disease and treatment efficacy comes from cohorts and registries, on the one hand, and clinical trials on the other.

There is therefore a need to conduct large-scale epidemiological studies at the populational level to complement evidence from selected patients in expert centres included in registries and clinical trials [4]. However, routinely collected data (*i.e.* electronic health records and claims databases) are still underused in PAH, although they have great potential to assess risk factors of PAH or to conduct comparative effectiveness research. However, identifying patients with PAH in these databases is challenging due to the complexity and heterogeneity of the diagnostic criteria, as well as the lack of specific diagnostic codes dedicated to PAH. In the International Classification of Diseases Tenth Revision (ICD-10) coding system, PH diagnosis codes do not mirror the current World Health Organization (WHO) clinical classification [3, 5]. A systematic review of algorithms used to identify PAH in administrative databases showed that algorithms solely using ICD-10 PH diagnosis codes perform poorly with a positive predictive value (PPV) as low as 3% [6]. To overcome the limitation of the ICD-10 coding system, an increasing number of algorithms have been developed, but most of them have not been validated against patient medical charts [6, 7]. In response, a panel of PH experts convened to create best practices for the development of PAH identification algorithms in administrative databases [7]. Following these recommendations, Gillmeyer *et al*. [8] created and validated a collection of algorithms that can be used to identify PAH in administrative databases. However, these algorithms have never been validated in France using French healthcare administrative database "Système National des Données de Santé (SNDS)". The French healthcare database covers almost the entire French population and includes demographic data, healthcare encounters visits, drug and medical devices dispensing, chronic medical conditions, hospitalisations diagnoses, date and duration, procedures, diagnostic-related groups, and cause of death, making it powerful to study rare diseases and perform observational studies [9–11]. We therefore selected the algorithm displaying the best performance developed by Gillmeyer *et al.* [8] as a starting point to develop and validate an algorithm from the medical records of a PAH reference centre, *i.e.* Grenoble Alpes University Hospital, that can be used in the French SNDS to identify patients with PAH.

Methods

Data source

This study used two distinct data sources. Firstly, the algorithm development and validation study was conducted using data extracted from the Grenoble Alpes University Hospital medical charts. The Grenoble Alpes University Hospital is one of the PAH reference centres in France involved in the French PH Network PulmoTension [12, 13]. Secondly, we applied the final algorithm in the French healthcare database SNDS and compared the characteristics of the identified patients with those of the registries.

Algorithm development

Firstly, we applied the best performing Gillmeyer *et al.* [8] algorithm in identifying all adult patients hospitalised in Grenoble Alpes University Hospital with a PH diagnostic code (I27.0) between 1 January 2010 and 31 December 2022 [8]. We then excluded patients without specific PAH treatment 6 months prior or any time after PH diagnosis. The Anatomical Therapeutic Chemical (ATC) codes and "Unités Communes de Dispensation (UCD)" codes used to identify PAH treatments are detailed in supplementary table S1. Finally, we excluded patients without right heart catheterisation (RHC) performed 1 year prior or after PAH diagnosis to compose our first group of PAH cases.

Secondly, given patients with a chronic thromboembolic pulmonary hypertension (CTEPH or group 4 PH) often undergo RHC and receive treatments with pulmonary vasodilators, they could easily be misclassified as PAH. This was in fact identified by Gillmeyer *et al*. [8] as one of the limitations of their algorithm [8]. Therefore, we further excluded patients with CTEPH-specific procedures (*i.e.* pulmonary endarterectomy and balloon pulmonary angioplasty) and patients with a riociguat prescription to compose our second group of PAH cases. Codes used to identify RHC and CTEPH-specific procedures are detailed in supplementary table S2.

Algorithm validation

We used all medical charts of patients identified as PAH cases by the algorithms. We randomly selected the same number of medical records to compose our non-cases from the excluded patients (*i.e.* adult patients hospitalised in Grenoble Alpes University Hospital with a diagnostic code I27.0 and no RHC nor PAH treatment or no RHC and treated with PAH treatment or RHC and no-PAH treatment or with a CTEPH-specific condition).

Three authors (A. Hlavaty, C. Bernardeau and C. Jambon-Barbara) read two-thirds of all medical charts in parallel. Therefore, at least two persons read all the medical records blindly; divergences were resolved by discussion and case review among the team. Agreement between reviewers regarding presence of PAH was high, with a Cohen's κ value of 0.83 [14].

https://doi.org/10.1183/23120541.00109-2024

Statistical analysis

We created a 2×2 contingency table using reviewer-determined PAH as the gold standard, and we calculated performance characteristics for the final algorithm, *i.e.* specificity, sensitivity, PPV, negative predictive value (NPV) and accuracy. In line with previous studies, we have defined the performance results as follows: high when values were ⩾70%, modest between 50 and 70% and poor when values were <50% [8, 15].

Identification of PAH patients in the French healthcare database

We applied our final algorithm to identify all patients with PAH from 2008 to 2022 in the French healthcare database SNDS, which covers almost the entire French population. We compared patients' characteristics between ones identified in the SNDS by the algorithm and recent registry data in the literature [5, 12, 16]. The codes used for characteristics identification have previously been validated by French institutions [17–21] and are presented in supplementary table S3.

Ethics approval

For the Grenoble University Hospital medical records analysis, we received the authorisation from the Grenoble Institutional Medical Committee. For the algorithm use on the SNDS, neither committee approval nor informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority (CNIL) agreement.

Results

Study cohort

In the Grenoble Alpes University Hospital between 1 January 2010 and 30 June 2022, 2899 unique patients were hospitalised at least once for a PH (ICD-10 diagnosis code I27.0). We subsequently excluded 183 patients aged <18 years. Finally, we excluded 2219 patients with no PAH-specific treatment 6 months pre-diagnosis or at any time post-diagnosis and 120 patients with no RHC performed 1 year pre- or post-PH diagnosis. Overall, 377 adult patients were identified with PAH by the first algorithm and composed our first PAH group and 2339 patients composed our non-PAH group (figure 1). Then, we excluded 116 patients with a CTEPH-specific procedure and nine patients with a prescription of riociguat, thus our second PAH group was composed of 252 patients and 2464 patients were identified as non-PAH from which we randomly selected 252 patients to make up our non-case PAH group (figure 1).

Performance of algorithms

Among the 377 adult patients identified with PAH by the first algorithm, which composed our first PAH group, we retrieved only 177 genuine cases of PAH on reviewing medical charts (46.9%). Characterisation of the other 200 patients identified by the algorithm revealed considerable confusion with group 4 PH, *i.e.* CTEPH diagnosed in 122 patients (supplementary table S4).

Among the 252 adult PAH patients identified by the final algorithm (*i.e.* in further excluding 125 patients with a CTEPH-specific procedure or riociguat dispensing), we retrieved 171 PAH cases on reviewing medical charts (67.9%). Characterisation of the 81 patients wrongly classified as PAH retrieved only seven CTEPH cases, the majority being group 3 PH, which are associated with chronic respiratory diseases (table 1). Characterisation of the 252 randomly selected patients without PAH (*i.e.* non-cases) is detailed in table 1, and the 2×2 contingency table for the calculation of the different performance parameters is presented in supplementary table S5. Overall, the algorithm performed better than the first one with 67.9% PPV, a sensitivity of 91.0%, a specificity of 74.3%, an NPV of 93.3% and 80.6% accuracy.

Identification of PAH patients in the French healthcare database

Application of the final algorithm in the French administrative claims database SNDS retrieved 9931 patients with a PAH diagnosis between 1 January 2008 and 31 December 2022; that is, patients hospitalised with a diagnostic code I27.0 and with a PAH-specific treatment between 6 months pre-diagnosis or any time after and with an RHC procedure 1 year before or after diagnosis and no CTEPH-specific procedures nor riociguat dispensing.

Characteristics of patients identified from the SNDS are presented in table 2. As sickle cell disease is associated with group 5 PH, this characterisation informs us that 43 (0.43%) patients were misclassified as PAH.

Discussion

In this study we validated an algorithm to identify patients with PAH in the French healthcare database from medical charts of a French university hospital. We developed this algorithm based on previous validation studies conducted in the US administrative database Veterans Health Administration [8]. When

https://doi.org/10.1183/23120541.00109-2024

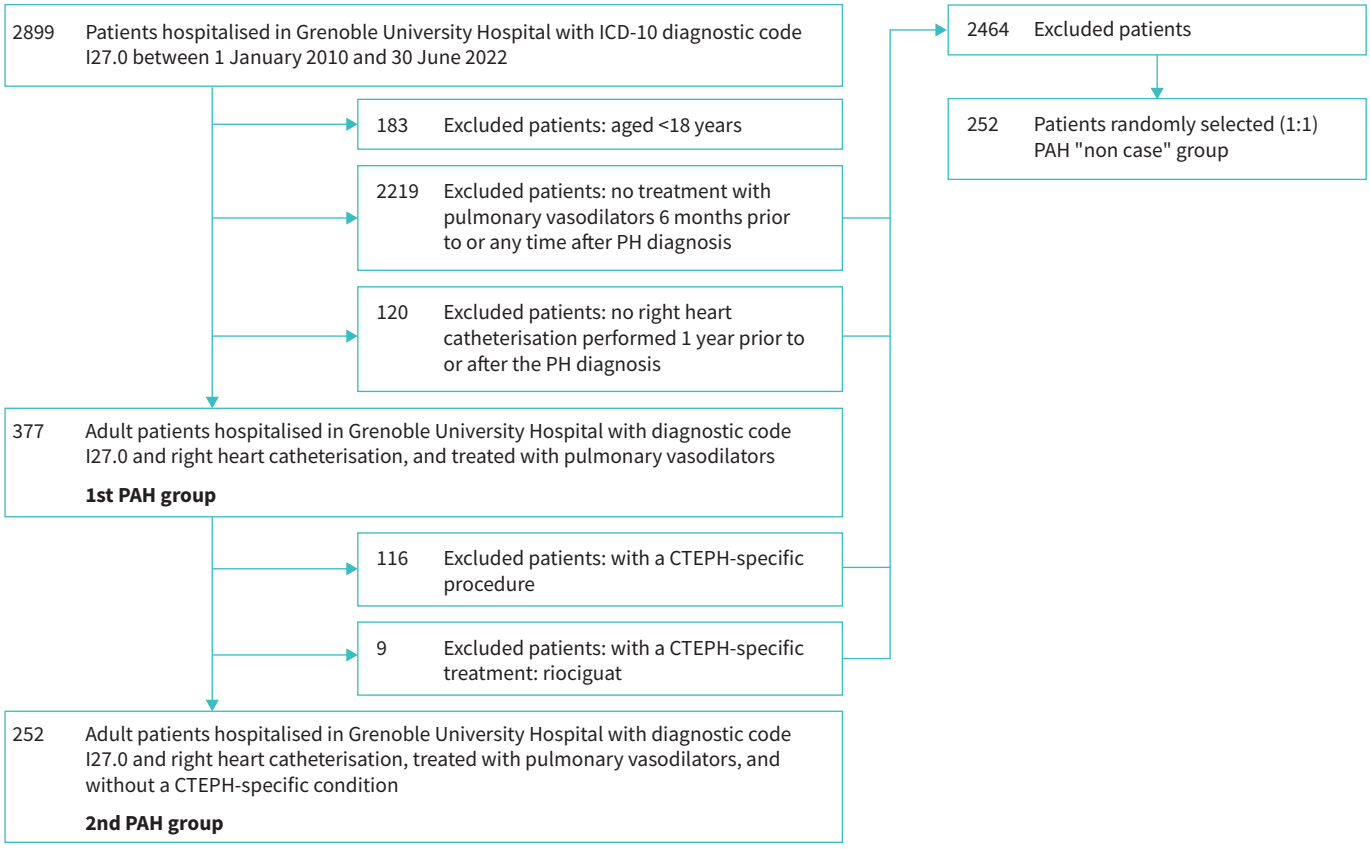


FIGURE 1 Flowchart of the algorithm identification of pulmonary arterial hypertension (PAH) cases and non-cases. ICD-10: International Classification of Diseases 10th revision; PH: pulmonary hypertension; CTEPH: chronic thromboembolic PH.

replicating the same algorithm in the Grenoble Alpes University Hospital, we found less convincing results with a PPV of about 50%. The addition of other decision rules, *i.e.* exclusion of patients with a CTEPH-specific procedure and treated by riociguat, has significantly improved the performance. Overall, the final algorithm achieved a rather good performance with a sensitivity higher than 90%, which means that the algorithm misses only a few PAH cases. Specificity was about 75%, and we can suppose that the patients who had undergone RHC and are under PAH-specific treatment have probably a mixed PH classified as disproportionate pulmonary hypertension in medical records but identified as group 3 PH in this study [22, 23].

In recent years, numerous code-based algorithms have been developed to identify PAH patients in administrative databases with highly variable performance [6, 24]. Overall, our study is in line with others showing that sensitivity decreases and specificity increases when further components are added to algorithms [6, 24, 25]. While very simple algorithms based solely on ICD-10 codes have shown insufficient performance to conduct studies in administrative databases, the choice of adding complexity to PAH identification must be tailored to the specific research question and the acceptable balance between sensitivity and specificity. Yet, in any case, sensitivity analyses by modifying algorithm definition and assessing the impact of misclassification error seem important to appraise the robustness of studies using PAH code-based algorithms.

After an in-depth review of all medical records of patients with genuine PAH but wrongly classified by the final algorithm, it appeared that for the vast majority they had undergone RHC earlier than 1 year pre-diagnosis. Further study may therefore explore the impact of the lag time between RHC and PH diagnosis on the performance of the algorithm. Moreover, recent studies using machine-learning approaches to identify and classify PH patients on electronic health records have proven their ability to identify patients who are likely to have pulmonary hypertension [26]. These methods could be used in combination with decision rules or may have the ability to identify new features to be included in algorithms to improve their performance. Lastly, linkage of in-hospital data repository or PAH registries

https://doi.org/10.1183/23120541.00109-2024

TABLE 1 Pulmonary hypertension (PH) characterisation of patients identified by the second algorithm

	Group 1 PH PAH	Group 2 PH	Group 3 PH	Group 4 PH CTEPH	Group 5 PH	No PH
PAH group	171 (67.9)	10 (3.97)	53 (21.0)	7 (2.78)	9 (3.57)	2 (0.79)
No-PAH group	17 (6.75)	105 (41.7)	41 (16.3)	38 (15.1)	3 (1.19)	48 (19.0)

Data are presented as n (%). PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic PH.

with electronic health records may allow the development of new algorithms or machine-learning approaches against a high-quality gold standard group of patients with a harmonised procedure for diagnosis [27, 28].

The application of this algorithm in the French healthcare database retrieved 9931 patients with PAH between 1 January 2008 and 31 December 2022. These numbers are in line with the incidence of PAH in developed countries, which is estimated to be ~6 cases/million adults, corresponding to about 6300 newly diagnosed patients with PAH during the study period [2, 5]. The characteristics of the patients identified by our algorithm in the French SNDS were consistent with recent registry data highlighting the changing epidemiology of PAH, with older patients, a lower predominance of women and a higher burden of comorbidities at diagnosis [5, 16].

Several limitations of these algorithms should be noted. First, although the claims database can confirm that a patient underwent RHC, the result of this exam is not available. Thus, the possibility of patient

TABLE 2 Patients' characteristics in the Système National des Données de santé (SNDS) (n=9931)

Female	5222 (52.6)
Age years, mean±SD	61.4±16.9
PAH treatment	9931 (100)
Phosphodiesterase 5 inhibitors	4007 (40.4)
Sildenafil	2279 (23.0)
Tadalafil	1728 (17.4)
Endothelin receptor antagonists	5505 (55.4)
Ambrisentan	1483 (14.9)
Bosentan	3994 (40.2)
Sitaxentan	28 (0.28)
Guanylate cyclase stimulators	0 (0.00)
Riociguat	0 (0.00)
Prostacyclin analogues	392 (3.93)
Epoprostenol	279 (2.80)
Iloprost	46 (0.46)
Treprostinil	67 (0.67)
Prostacyclin receptor agonist	27 (0.27)
Selexipag	27 (0.27)
PAH-associated conditions	
Systemic scleroderma	1200 (12.1)
Portal hypertension	542 (5.46)
HIV positive	276 (2.78)
Congenital heart disease	673 (6.78)
Comorbidities	
COPD	995 (10.0)
Heart failure	4537 (45.7)
Diabetes	3122 (31.4)
Hypertension	8473 (85.3)
VTE	1449 (14.6)
Chronic dialysis	163 (1.64)
Sickle cell disease	43 (0.43)

Data are presented as n (%) unless otherwise specified. PAH: pulmonary arterial hypertension; VTE: venous thromboembolic events (*i.e.* pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

https://doi.org/10.1183/23120541.00109-2024

misclassification remains. In addition, the unavailability of exam results in the French healthcare database prevented us from using ventilation/perfusion scan and computed tomography pulmonary angiography to further exclude CTEPH patients given that these procedures are also routinely performed in PAH patients to exclude a possible case of CTEPH. Second, with the multiplication of steps in an attempt to maximise specificity and minimise the risk of identifying CTEPH, the algorithm necessarily excludes some patients with genuine PAH, which likely reduces the sensitivity. Third, despite the fact that the non-PAH group was selected randomly, the possibility of sampling error remains, which can affect the precision of the estimates. Fourth, given that the algorithm validation was monocentric in the Grenoble University Hospital, one of the PAH reference centres in France, the generalisability elsewhere remains uncertain. In fact, as a reference centre the population is necessarily enriched for PAH as compared with the general population, and this could lead to an overestimation of the PPV. As prevalence of the disease is therefore lower in the SNDS, we could expect a lower PPV but a higher NPV than what we found in the algorithm validation. It would be interesting to replicate this study in other French hospitals. Moreover, the fact that the study was monocentric implied that we only had access to RHC and PAH-specific treatment performed and dispensed in the Grenoble Alpes University Hospital, meaning that we may have missed some patients who were diagnosed in Grenoble but performed RHC or took their treatment at another hospital. However, the number of patients who moved to another city or changed hospital during their medical care is supposed to be quite low, and this limitation should have only decreased PAH prevalence and therefore underestimated PPV.

Conclusion

Correctly identifying PAH is mandatory in order to conduct robust pharmaco-epidemiological studies. Starting from a US validated algorithm developed by Gillmeyer *et al*. [8] and adapted to the French specificities, we have developed and validated an algorithm with adequate performance for use in future studies using the French healthcare database.

Provenance: Submitted article, peer reviewed.

The medical records used during and/or analysed during the current study are not publicly available, a request must be made and accepted by the establishment's medical committee.

The datasets generated and/or analysed during the current study are not publicly available; publicly sharing SNDS data is forbidden by law according to The French national data protection agency (Commission Nationale de l'Informatique et des Libertés, CNIL); regulatory decisions AT/CPZ/SVT/JB/DP/CR05222O of June 14, 2005 and DP/CR071761 of August 28, 2007. To request data access please contact The National Institute for Health Data (Institut National des Données de Santé, INDS). C. Jambon-Barbara and C. Khouri had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: H. Bouvaist reports payment for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Merck, outside the submitted work. M. Humbert reports grants or contracts from Acceleron, AOP Orphan, Janssen, Merck and Shou Ti, outside the submitted work; consulting fees from 35 Pharma, Aerovate, AOP Orphan, Bayer, Chiesi, Ferrer, Janssen, Keros, Merck, MorphogenIX, Shou Ti and United Therapeutics, outside the submitted work; payment for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Janssen and Merck, outside the submitted work; and participation on a data safety monitoring or advisory board for Acceleron, Altavant, Janssen, Merck and United Therapeutics, outside the submitted work. D. Montani reports grants or contracts from Acceleron, Janssen and Merck MSD, outside the submitted work; consulting fees from Acceleron, Merck MSD, Janssen and Ferrer, outside the submitted work; payment or honoraria for speakers' bureaus from Bayer, Janssen, Boerhinger, Chiesi, GSK, Ferrer and Merck MSD, outside the submitted work. The remaining authors have nothing to disclose.

References

1 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.
2 Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. *Pulm Circ* 2021; 11: 2045894020977300.
3 Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.

https://doi.org/10.1183/23120541.00109-2024

4 Talwar A, Garcia JGN, Tsai H, *et al.* Health disparities in patients with pulmonary arterial hypertension: a blueprint for action. An Official American Thoracic Society Statement. *Am J Respir Crit Care Med* 2017; 196: e32–e47.
5 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022; 43: 3618–3731.
6 Gillmeyer KR, Lee MM, Link AP, *et al.* Accuracy of algorithms to identify pulmonary arterial hypertension in administrative data: a systematic review. *Chest* 2019; 155: 680–688.
7 Mathai SC, Hemnes AR, Manaker S, *et al.* Identifying patients with pulmonary arterial hypertension using administrative claims algorithms. *Ann Am Thorac Soc* 2019; 16: 797–806.
8 Gillmeyer KR, Nunez ER, Rinne ST, *et al.* Development and validation of algorithms to identify pulmonary arterial hypertension in administrative data. *Chest* 2021; 159: 1986–1994.
9 Bezin J, Duong M, Lassalle R, *et al.* The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017; 26: 954–962.
10 Tuppin P, Rudant J, Constantinou P, *et al.* Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Dépidémiologie Santé Publique* 2017; 65: S149–S167.
11 de Germay S, Conte C, Micallef J, *et al.* Performing pharmacoepidemiological studies using the French health insurance data warehouse (SNDS): how to translate guidelines into practice. *Therapie* 2023; 78: S0040-5957 (23)00026-4.
12 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
13 Montani D, Certain MC, Weatherald J, *et al.* COVID-19 in patients with pulmonary hypertension: a national prospective cohort study. *Am J Respir Crit Care Med* 2022; 206: 573–583.
14 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–174.
15 Carnahan RM, Moores KG. Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative and claims data: methods and lessons learned. *Pharmacoepidemiol Drug Saf* 2012; 21: Suppl. 1, 82–89.
16 Lau EMT, Giannoulatou E, Celermajer DS, *et al.* Epidemiology and treatment of pulmonary arterial hypertension. *Nat Rev Cardiol* 2017; 14: 603–614.
17 Quantin C. Etude des algorithmes de définition de pathologies dans le Système Nationale d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM). Caisse National d'Assurance Maladie, 2015; p. 272.
18 Semenzato L, Botton J, Drouin J, *et al.* Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *Lancet Reg Health Eur* 2021; 8: 100158.
19 Géodes – Santé publique France. Indicateurs: cartes, données et graphiques. Date last accessed: 25 October 2022. https://geodes.santepubliquefrance.fr/#view=map2&c=indicator
20 Hoisnard L, Pina Vegas L, Dray-Spira R, *et al.* Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors *versus* adalimumab: a nationwide cohort study. *Ann Rheum Dis* 2023; 82: 182–188.
21 Marcombes C, Penso L, Weill A, *et al.* Persistence of second-line biologics in psoriasis after first-line biologic failure: a nationwide cohort study from the French health insurance database (SNDS). *Br J Dermatol* 2023; 189: 561–568.
22 Hoeper MM, Andreas S, Bastian A, *et al.* Pulmonary hypertension due to chronic lung disease: updated Recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011; 154: Suppl. 1, S45–S53.
23 Seeger W, Adir Y, Barberà JA, *et al.* Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D109–D116.
24 Didden EM, Lu D, Hsi A, *et al.* Clinical evaluation of code-based algorithms to identify patients with pulmonary arterial hypertension in healthcare databases. *Pulm Circ* 2024; 14: e12333.
25 Sprecher VP, Didden E, Swerdel JN, *et al.* Evaluation of code-based algorithms to identify pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension patients in large administrative databases. *Pulm Circ* 2020; 10: 1–10.
26 Kogan E, Didden EM, Lee E, *et al.* A machine learning approach to identifying patients with pulmonary hypertension using real-world electronic health records. *Int J Cardiol* 2023; 374: 95–99.
27 Swinnen K, Quarck R, Godinas L, *et al.* Learning from registries in pulmonary arterial hypertension: pitfalls and recommendations. *Eur Respir Rev* 2019; 28: 190050.
28 Ong M, Klann JG, Lin KJ, *et al.* Claims-based algorithms for identifying patients with pulmonary hypertension: a comparison of decision rules and machine-learning approaches. *J Am Heart Assoc* 2020; 9: e016648.

https://doi.org/10.1183/23120541.00109-2024

3. Conclusion de la partie

Ces travaux nous ont permis de valider les méthodes d'identification des ulcères cutanés et des HTAP pour la conduite de futures études de pharmacoépidémiologie sur ces pathologies.

Malgré des codes diagnostics hospitaliers avec de bonnes performances, il semble que l'algorithme d'identification des ulcères cutanés, qui utilise également les remboursements ambulatoires de certains pansements ne retrouvent pas des performances suffisantes pour pouvoir être utilisé. Nous recommandons donc d'au moins toujours réaliser une analyse de sensibilité uniquement sur les patients hospitalisés lorsque l'ulcère cutané est la pathologie d'intérêt.

Nous avons adapté l'algorithme d'identification des HTAP précédemment développé par Gillmeyer et ses collègues (131) aux Etats-Unis en excluant les patients avec des procédures médicales spécifiques aux CTEPH. Les performances retrouvées étaient bonnes et permettent la réutilisation de cet algorithme dans de futurs études de pharmacoépidémiologie. Cependant, il est probablement nécessaire de développer d'autres algorithmes selon l'étiologie de l'HTAP. En effet, concernant les étiologies médicamenteuses, nous savons que certains patients vont spontanément régresser à l'arrêt du médicament en cause sans nécessité de traitement spécifique de l'HTAP (114). Nous prévoyons donc de développer et valider d'autres algorithmes en fonction des étiologies.

Nous n'avons à l'heure actuelle pas développé, ni validé d'algorithme d'identification de l'apnée du sommeil puisque cette pathologie est déjà largement identifiée et étudiée dans le SNDS (132,133). Cependant, nous comptons dans le futur valider les méthodes d'identification de cette pathologie ainsi que la fiabilité des codes de remboursement du traitement de première intention de l'apnée du sommeil : l'appareil à pression positive continue pour étudier l'efficacité de ce traitement.

PARTIE 4 – EVALUATION DES SIGNAUX

1. Ticagrelor after acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors

Le clopidogrel, le ticagrelor et le prasugrel sont trois traitements utilisés en prévention secondaire cardiovasculaire après un syndrome coronarien aiguë (134). Plusieurs séries de cas et analyses de disproportionnalité ont rapporté la survenue d'apnées centrales du sommeil chez des patients exposés au ticagrelor (94,95,135–137). L'agence Européenne du Médicament et la FDA ont inclus l'apnée du sommeil dans le résumé des caractéristiques du produit du ticagrelor mais pas du clopidogrel ni du prasugrel. Pour tester de la robustesse de nos résultats, nous avons conduit un grand nombre d'analyses de sensibilité, dont une analyse en sous-groupe entre le patients inclus avant ou après 2018, année à laquelle les premiers signaux d'apnées du sommeil sous ticagrelor sont apparus (95).

Nous avons réalisé de la fine stratification pour rendre les patients comparables en *Average Treatment among the Treated*, c'est-à-dire que nous avons fait ressembler les patients clopidogrel d'abord, et prasugrel ensuite, aux patients ticagrelor pour répondre à la question de recherche suivante : Quel est l'effet du ticagrelor sur la survenue d'apnées du sommeil chez les patients exposés au ticagrelor. Nous avons préféré cet estimand plutôt que l'*Average Treatment Effects* puisque notre rationnel était uniquement un surrisque du ticagrelor et non de tous les inhibiteurs des récepteurs aux P2Y12.

Ticagrelor after acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors: a population-based cohort study

Clément Jambon-Barbara, doctoral student (0000-0002-6619-4130)[1,2,*], Sarah Margot Barras, student[1,*], Jean-Louis Pépin, professor (0000-0003-3832-2358)[2,3], Jean-Luc Cracowski, professor (0000-0003-0787-1469)[1,2], Marie Joyeux-Faure, professor (0000-0001-8298-0038)[2,3], Charles Khouri, pharmacologist (0000-0002-8427-8573)[1,2,4,†], Bruno Revol, associated professor (0000-0003-2931-2940)[1,2,†]

[1] Grenoble Alpes University Hospital, Pharmacovigilance Department, F-38000 Grenoble, France.

[2] Univ. Grenoble Alpes, HP2 Laboratory, INSERM U1300, F-38000, Grenoble, France.

[3] Grenoble Alpes University Hospital, EFCR Laboratory, F-38000, Grenoble, France.

[4] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000, Grenoble, France.

*co-first authors

†co-last authors

Correspondence to: Clément Jambon-Barbara, Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France. Tel: +33 4 76 76 51 45. Fax: +33 4 76 76 56 55. E-mail: CJambonbarbara@chu-grenoble.fr

ABSTRACT

OBJECTIVE

To determine whether the use of ticagrelor after acute coronary syndrome (ACS) is associated with an incident risk of sleep apnoea or major adverse cardiovascular events (MACE) compared with other P2Y12 receptor inhibitors (clopidogrel and prasugrel).

DESIGN

Population-based cohort study using an active comparator, new-user design.

SETTING

French healthcare database, "Système National des Données de Santé (SNDS)", 2010–2023.

PARTICIPANTS

525,029 adults (≥18 years) who used a P2Y12 receptor inhibitor within 30 days after ACS.

MAIN OUTCOME MEASURES

The primary outcome was incident diagnosis of sleep apnoea, defined using diagnostic codes, medical examination codes and dispensing of approved treatments. The secondary outcome was MACE (as a composite of coronary heart disease, stroke, myocardial infarction, heart failure and all-cause death). Hazard ratio (HR) and 95% confidence interval (CI) values were estimated after fine stratification weighting based on propensity score.

RESULTS

In the first comparison cohort, 301,749 adults used ticagrelor (mean age 63.1 years; 25.5% female) and 160,886 used clopidogrel (63.2 years; 25.8% female). In the second comparison cohort, 301,505 individuals used ticagrelor (63.1 years; 25.4% female) and 62,346 used prasugrel (61.9 years; 28.1% female). Use of ticagrelor was associated with a 27% higher risk of new sleep apnoea diagnosis compared with clopidogrel (30.1 vs. 21.9 events per 1000 person-years; HR 1.27, 95% CI 1.21–1.32), and a 13% higher risk versus prasugrel (30.1 vs. 25.5 events per 1000 person-years; HR 1.13, 95% CI 1.08–1.20). Risk of MACE was lower

with ticagrelor versus clopidogrel (305.7 vs. 381.5 events per 1000 person-years; HR 0.84, 95% CI 0.83–0.85), and did not differ versus prasugrel (305.6 vs. 290.3 events per 1000 person-years; HR 0.99, 95% CI 0.97–1.00).

CONCLUSIONS

We identified an increased risk of sleep apnoea in adults using ticagrelor compared with clopidogrel or prasugrel after ACS. Ticagrelor was associated with a lower risk of MACE compared with clopidogrel only. These findings could inform future practice recommendations on post-ACS treatments.

Key words: ticagrelor; prasugrel; clopidogrel; acute coronary syndrome; sleep apnoea; adverse drug reactions

Summary boxes

What is already known on this topic?

- The antiplatelet P2Y12 receptor inhibitors clopidogrel, prasugrel and ticagrelor are used in combination with aspirin for the secondary prevention of acute coronary syndrome (ACS) events.
- Concerns have been raised about the development of central sleep apnoea as a potential adverse effect of ticagrelor, and this is included in the product's labelling.
- The consistency and clinical significance of developing sleep apnoea during treatment with ticagrelor have yet to be determined.

What this study adds

- The risk of a new sleep apnoea diagnosis in users of ticagrelor was 27% higher compared with clopidogrel users (hazard ratio [HR] 1.27, 95% confidence interval [CI] 1.21–1.32) and 13% higher compared with prasugrel users (HR 1.13, 95% CI 1.08–

1.20); the number needed to harm after one year of treatment was 122 for ticagrelor versus clopidogrel and 217 for ticagrelor versus prasugrel.

- Risk of major adverse cardiovascular events (MACE) was lower with ticagrelor versus clopidogrel (HR 0.84, 95% CI 0.83–0.85), but the same versus prasugrel (HR 0.99, 95% CI 0.97–1.00).
- A higher rate of sleep apnoea without any improvement in protection from recurrent MACE with ticagrelor versus prasugrel could inform changes to policy documents and guidelines that currently give equal recommendation to both agents.

INTRODUCTION

Clopidogrel, ticagrelor and prasugrel are antiplatelet P2Y12 receptor inhibitors that are used in combination with aspirin for the secondary prevention of acute coronary syndrome (ACS) events.[1] Ticagrelor has been widely reported to trigger dyspnoea unrelated to underlying cardiac or pulmonary dysfunction in exposed individuals, and this effect has been extensively studied.[2-6] Moreover, case series and pharmacovigilance disproportionality analyses reporting the onset of central sleep apnoea (CSA) in patients exposed to ticagrelor have raised awareness about this potential adverse effect.[7-12] European Medicines Agency and US Food and Drug Administration summaries of product characteristics for ticagrelor already include sleep apnoea in the special warnings and precautions for use section, but this information is not included in the documents for clopidogrel or prasugrel. Re-analysis of data from some of the randomised controlled trials with ticagrelor did not find excess cases of sleep apnoea in exposed patients.[13] However, clinical trials were not designed to identify such a specific adverse event because they had limited follow-up time and did not include objective evaluation of sleep and sleep apnoea, which is why large pharmaco-epidemiological studies are needed.

Whether the sleep apnoea signal in patients being treated with ticagrelor is clinically significant remains an open question. We suggest that a potential association between use of ticagrelor and the development of sleep apnoea may be of particular concern in patients with pre-existing cardiovascular and metabolic diseases given the negative impact that sleep apnoea is known to have on hypertension, type 2 diabetes, atrial fibrillation or cardiac failure.[14-17]

In this study, we used data from the French Healthcare database to assess the risk of sleep apnoea and major adverse cardiovascular events (MACE) associated with the use of ticagrelor compared with two other P2Y12 receptor inhibitors (clopidogrel or prasugrel).

METHODS

Study design and data source

This observational population-based study was exclusively conducted in the Système National des Données de Santé (SNDS) database, which contains anonymised individual data on demographics, outpatient healthcare consumption, inpatient care (including hospitalisations diagnoses, dates and duration, diagnoses for specific chronic conditions) and cause of death.[20] The SNDS overs 99% of the French population and operates as a medico-administrative database, with data collection conducted routinely and independently from any specific research objectives. It is currently one of the largest healthcare databases in the world, making it powerful enough to study rare diseases and perform pharmacoepidemiologic studies.[21-25] According to the agreement of the French Data Protection Supervisory Authority (CNIL) no informed consent was required to conduct this study because only anonymous data from the SNDS were used.

The reporting of this cohort study complies with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) and RECORD-PE (Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepdemiology) statements.[18,19] The protocol was published online before the study started (Open Science Framework registry, https://osf.io/5wav4/) and deviations from the initial protocol are shown in supplementary table A.

Study population

We designed two cohorts of incident new-users of ticagrelor, prasugrel, and clopidogrel after ACS who had no history of sleep apnoea, and compared the risk of sleep apnoea and MACE after cohort entry. We first identified a base cohort of all adult patients who had an incident

ACS event (i.e. no antecedent event in the previous two years) between June 2012 (the first month that ticagrelor was available in France) and December 2023. At least two years of medical history were required prior to the first ACS. Then we selected all patients who received a P2Y12 receptor inhibitor (clopidogrel, ticagrelor and prasugrel) for the first time in the following month. This condition was necessary to ensure the inclusion of new post-ACS patients and the inclusion of new-users of P2Y12 receptor inhibitors, thus minimising the possibility of prevalent user bias.[26]

The date of entry into the cohort was the date of the first prescription of a P2Y12 receptor inhibitor, avoiding a potential immortal time bias between ACS diagnosis and drug dispensing.[27] We excluded patients with a previous diagnosis of sleep apnoea, previous polysomnography or respiratory polygraphy, and those who had received treatments approved for sleep apnoea (continuous positive airway pressure [CPAP], adaptive servo-ventilation [ASV], or mandibular advancement splints [MAS]) at any time before entry into the cohort. This was to ensure the identification of incident cases of sleep apnoea, and to avoid the inclusion of patients with refractory sleep apnoea who may have discontinued their treatment, which has been shown to increase morbidity and mortality.[28,29] Finally, we excluded patients with a missing value or an error in one of their sociodemographic variables (birthdate, sex), and those who died before cohort entry.

Two different cohorts were created, one for each comparison: ticagrelor versus clopidogrel, and ticagrelor versus prasugrel. We used a propensity score fine stratification weighting to balance the drug groups for known confounding factors.[30,31] Within each cohort, we first estimated the propensity score of using ticagrelor versus its comparator using a multivariable logistic regression that included cohort entry year and all covariates measured at cohort entry (detailed in a separate paragraph). Thereafter, we trimmed the study population that did not fall within overlapping regions of the propensity score distribution and then created 100

propensity score strata based on the distribution of the ticagrelor-exposed patients. Ticagrelor users were assigned a weight of one, and clopidogrel and prasugrel users were weighted in proportion to the number of ticagrelor users in their corresponding stratum. This strategy estimated the average treatment effect of ticagrelor.

Patients who met the study inclusion criteria within each cohort were followed until the first diagnosis of sleep apnoea, switch to another P2Y12 receptor inhibitor, death from any cause, end of registration within the French Health Insurance database, end of prescription drug coverage duration (according to an as-treated approach) or end of the study period (December 31, 2023), whichever occurred first.

Outcomes

The primary outcome was sleep apnoea, defined as a first polysomnography or polygraphy, followed by either a hospital sleep apnoea diagnosis or the initiation of a specific approved treatment (CPAP, ASV or MAS). Available data do not allow us to differentiate between obstructive and central apnoeas. However, this methodology for identifying sleep apnoea has already been used in pharmacoepidemiologic studies[28,29,32] and allowed robust identification of moderate to severe sleep apnoea requiring treatment. All clinical codes used and a schematic representation of the outcome definition are shown in supplementary table B and supplementary figure A.

The secondary outcome was the first occurrence of a MACE, defined as a composite of coronary heart disease, stroke, myocardial infarction, heart failure, and all-cause death (clinical codes are shown in supplementary table C).

Covariates

We considered a wide range of potential confounders measured at the cohort entry date to estimate propensity scores, based on the relevant literature, and represented on a directed acyclic graph (DAG, supplementary figure B). Sociodemographic variables, age and sex were collected at the cohort entry date. Also considered, at any time prior to cohort entry, were hypertension, chronic obstructive pulmonary disease (COPD), active dialysis, diabetes, heart failure, venous thromboembolic events (pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism, and thrombosis), dyslipidaemia, non-alcoholic fatty liver diseases (NAFLD), pulmonary hypertension, cancers, arrythmia, transient ischaemic attack, stroke, smoking status, alcohol consumption, severe obesity, and coronary artery diseases. The number of hospitalisations and pulmonologist visits in the year before cohort entry was used as a proxy of health service availability and consumption. Finally, exposure to drugs previously reported as possibly associated with sleep apnoea (anticonvulsants, gabapentinoids, antidepressants, antipsychotics, baclofen, benzodiazepines and derivatives, corticosteroids, diuretics, hormonal contraceptives for systemic use, testosterone, montelukast, opioids, opium alkaloids and derivatives)[7] in the year before cohort entry was also considered. All clinical and treatment identification codes used are shown in supplementary table D.

Statistical analysis

All analyses were performed for each cohort separately. Descriptive statistics for quantitative parameters (mean ± standard deviation or median with interquartile range) and qualitative parameters (number of patients and percentage) were used to summarise the characteristics of the study population according to exposure status. The characteristics of patients starting ticagrelor were compared with those weighted by fine stratification using the standardised mean difference (SMD). An absolute SMD ≤10% indicates a negligible difference regarding

known potential confounders, and therefore balanced weighted cohorts.[33,34] Incidence rate (IR) and corresponding 95% confidence interval (CI) values were calculated using the Poisson distribution. Hazard ratio (HR) and 95% CI values were estimated using a Cox proportional hazards regression model, weighted by fine stratification. Finally, the number needed to harm (NNH) for each comparison was estimated as a clinically meaningful result. Several sensitivity analyses were performed for sleep apnoea and MACE outcomes. First, the exposure window was changed to a modified intention-to-treat approach, whereby patients were considered exposed from the time of first dispensing to the date of switch to another P2Y12 receptor inhibitor, death from any cause, end of registration within the SNDS database, end of the study period (December 31, 2023), or end of the one-year and two-year follow-up period in a first and second sensitivity analysis, respectively, whichever came first. Second, we fully replicated our study on population-matched cohorts instead of fine stratification weighted ones. Each exposed patient was matched with a control patient who had exactly the same cohort entry calendar year, and the closest propensity score value (±0.2*standard deviation). Third, the sleep apnoea outcome definition was modified to improve its sensitivity by no longer requiring a polysomnography or polygraphy plus diagnosis or treatment, but instead based on the occurrence of any of these criteria. To assess potential differences between the two active-comparator arms, we replicated all analyses in an independent new cohort comparing prasugrel and clopidogrel. In this cohort, we estimated the average treatment effect of prasugrel. Finally, we conducted four subgroup analyses: by age at cohort entry (age <65 vs. ≥65 years; by sex (male vs. female); with versus without severe obesity (given the higher prevalence of sleep apnoea in patients with obesity[14,35,36]); and by year of P2Y12 prescription (2012–2017 vs. 2018–2023) to assess a potential detection bias because the first reports suggesting an association between ticagrelor and sleep apnoea were published in 2018.[8,9,11]

All statistical analyses were conducted with SAS EG® (SAS Institute, Cary, NC, USA), 7.13, and R, version 4.4.0 (R Foundation) for graphical representations. We also used the fine stratification SAS macro developed by R. Desai.[30,31,37]

Patient and public involvement

This study was a secondary analysis of routinely collected claims data. No patients or members of the public were involved in setting the research question, defining the outcome measures, or in the design and implementation of the study.

RESULTS

Study population

A total of 1,819,451 individuals presented with a first-ever ACS (i.e. no ACS in the previous two years) during the study period, of whom 160,886 (30.6%) were exposed to clopidogrel, 301,756 (57.5%) to ticagrelor and 62,387 (11.9%) to prasugrel within 30 days and met the eligibility criteria (figure 1). Before weighting, the three treatment groups were quite different on several covariates; prasugrel users were younger with fewer comorbidities, fewer hospitalisations and healthier overall than clopidogrel-exposed patients (supplementary table E & F). After weighting, the groups were well balanced for all included covariates, with SMD values of <10%, except for age in the ticagrelor versus prasugrel cohort (SMD 10.6%) (table 1 and supplementary figures C & D for propensity scores distribution pre- and post-weighting). Results of the hypothesis-generating cohort comparing prasugrel users to clopidogrel users, are presented in supplementary tables G–K and supplementary figures E–H.

Sleep apnoea

For patients exposed to a P2Y12 receptor inhibitor after ACS, use of ticagrelor was associated with an increased risk of incident sleep apnoea compared with both clopidogrel (weighted incidence rate 30.13 vs. 21.95 per 1000 person-years, respectively; HR 1.27, 95% CI 1.21–1.32) and prasugrel (weighted incidence rate 30.14 vs. 25.52 per 1000 person-years, respectively; HR 1.13, 95% CI 1.08–1.20). The NNH for 1 year of treatment with ticagrelor versus clopidogrel and prasugrel was 122 and 217 patients, respectively (table 2, fig 2). Pre-specified subgroup analyses confirmed a consistent increased risk of sleep apnoea for ticagrelor compared with clopidogrel in each subgroup but not compared with prasugrel in women and the subgroup with obesity (figure 3).

Results were consistent in the sensitivity analysis that redefined sleep apnoea as the presence of diagnosis, clinical exams or treatments, and in both modified intention-to-treat sensitivity analyses (table 3). However, in the study replication with matching instead of fine-stratification weighting as confounding adjustment, there was a non-statistically significant increase in the risk of sleep apnoea with use of ticagrelor versus prasugrel (HR 1.06, 95% CI 0.99–1.13) (supplementary tables L & M).

Major adverse cardiovascular events

The risk of MACE was lower in ticagrelor users compared with clopidogrel users (weighted incidence rate 305.7 vs. 381.5 per 1000 person-years, respectively; HR 0.84, 95% CI 0.83–0.85). However, there was no significant difference in MACE risk between users of ticagrelor versus prasugrel users (weighted incidence rate 305.6 vs. 290.3 per 1000 person-years, respectively; HR 0.99, 95% CI 0.97–1.00) (table 2, figure 4). Results were consistent across all sensitivity analyses (table 3, supplementary table N).

DISCUSSION

In this cohort study of individuals with a first ACS event, we found that initiation of ticagrelor was associated with an increased risk of developing sleep apnoea compared with both clopidogrel and prasugrel. Ticagrelor was associated with a lower risk of MACE compared with clopidogrel (but not prasugrel).

The mechanisms underlying ticagrelor-related apnoea and dyspnoea are debated. The main ones suggested in the literature are a specific effect of ticagrelor on pulmonary C-fibres, contributing to the development of unstable respiratory control during sleep, or an increase in peripheral and central chemoreceptor sensitivity, due to blockade of microglial P2Y12 receptors.[6,38] Data from a recent study are consisting with this, suggesting that one month of exposure to ticagrelor increases peripheral and central chemoreceptor sensitivity, whereas clopidogrel exerts no such effects.[39] A major concern is that sleep-disordered breathing triggers a cascade of acute physiological consequences (including arterial oxygen desaturation, hypercapnia, sleep fragmentation and hypertension) that produce sympathetic activation, potentially worsening the underlying disease and leading to an increased risk of cardiovascular events and mortality.[16]

Our results regarding the increased risk of sleep apnoea during treatment with ticagrelor compared with other P2Y12 inhibitors is consistent with previous studies. A cross-sectional study enrolling patients with ACS and preserved ejection fraction, treated either with ticagrelor (n=30) or prasugrel (n=30), suggested an association between ticagrelor-related dyspnoea and central apnoea over the whole 24-hour evaluation period.[38] In addition, a prospective single-centre study including 121 patients after ACS, with no heart failure or sleep apnoea, also showed that 24/80 patients (30%) receiving ticagrelor had CSA with an apnoea-hypopnoea index of ≥15 events/h, compared with 7.3% of patients not taking ticagrelor.[11] Finally, a study including 141 patients (30 receiving ticagrelor) also concluded

that ticagrelor appeared to be associated with a higher CSA burden after adjusting for left ventricular ejection fraction and age (odds ratio 3.27, 95% CI 0.99–10.7).[12]

Our study also showed a significant lower risk of MACE (including all-cause mortality) in ticagrelor users compared with clopidogrel users, but an identical risk of MACE in those who used ticagrelor or prasugrel. These results are consistent with evidence that ticagrelor reduces the risk of mortality compared with clopidogrel, despite doubts about data integrity in the PLATO trial.[40] In that randomised trial,[41] which included 18,624 patients with ACS, 12-month rates of mortality (4.0 vs. 5.1%; HR 0.79, 95% CI 0.75–0.91) and recurrent myocardial infarction (5.8 vs. 6.9%; HR 0.84, 95% CI 0.75–0.95) were significantly lower in the ticagrelor group compared with clopidogrel. In addition, at least two randomised trials have directly compared prasugrel with ticagrelor. In the PRAGUE-18 study, 1,230 individuals with ACS were randomly assigned to treatment with prasugrel or ticagrelor.[42] There was no significant difference in the rate of the primary endpoint (death, reinfarction, urgent target vessel revascularisation, stroke, or serious bleeding at 30 days) between the prasugrel and ticagrelor groups (4.0% vs. 4.1%, respectively). Conversely, the ISAR-REACT 5 randomised, open-label trial (n=4,018) found that the primary endpoint (a composite of death, myocardial infarction, or stroke at one year) occurred more often in patients who received ticagrelor versus prasugrel (9.3% vs. 6.9%; HR 1.36, 95% CI 1.09–1.70).[43] Although concerns were raised about the generalisability of some underpowered subgroup analyses in ISAR-REACT 5, the main study finding was replicated in a cohort study of 17,642 propensity score-matched individuals published in 2024, which showed a significantly higher incidence of the composite primary endpoint (all-cause mortality, myocardial infarction or stroke) in the ticagrelor versus prasugrel group.[44] In our study, there was no significant difference in the rate of MACE in users of ticagrelor and prasugrel, but our study was primarily designed to explore the risk of sleep apnoea rather than MACE.

Over the past decade, ticagrelor, like prasugrel, has been recommended over clopidogrel as the first choice antiplatelet therapy in most cardiology guidelines.[45,46] Although our results do not challenge the benefit-risk ratio of ticagrelor, awareness of the potential risk for developing sleep apnoea during treatment with ticagrelor could have important implications for clinical practice, and redefine the place of ticagrelor in therapeutic strategy, especially compared with prasugrel.

At an individual level, understanding the role of ticagrelor in sleep apnoea and identifying this effect could help to improve the excessive daytime sleepiness and impaired quality of life observed after ACS. If sleep apnoea occurs during treatment with ticagrelor, a decision about whether to continue ticagrelor should be discussed because sleep apnoea resolves after medication withdrawal.[9,10] Angiolillo et al. evaluated discontinuation of ticagrelor due to the occurrence of dyspnoea in participants in the TWILIGHT trial[47] and found that patients who discontinued ticagrelor (and switched to another P2Y12 receptor inhibitor in most cases) did not show a higher risk of subsequent ischemic events compared with those still being treated with ticagrelor plus aspirin. A post hoc analysis of the TALOS-AMI randomised clinical trial also provides interesting insights into the potential consequences of discontinuing ticagrelor.[48] The results suggested that de-escalation to clopidogrel, compared with ongoing ticagrelor-based dual antiplatelet therapy, was a safe and reasonable option after myocardial infarction in patients with high ischaemic risk. Therefore, prasugrel or clopidogrel appear to be acceptable alternatives in cases of ticagrelor-related sleep apnoea. If ticagrelor is continued, appropriate treatment with positive airway pressure devices including CPAP or ASV should be considered and re-evaluated after ticagrelor discontinuation. We recommend that a new polysomnography be performed at the end of ticagrelor use to assess the relevance of continuing sleep apnoea treatment. In addition, routinely and continuously collected

telemetric data will facilitate assessment of the real long-term impact of ticagrelor use with respect to sleep apnoea development and its persistence after stopping ticagrelor therapy.

This study has several strengths. First, this is, to our knowledge, the first pharmaco-epidemiological study specifically designed to assess and quantify the risk of sleep apnoea associated with the use of ticagrelor compared with other P2Y12 receptor inhibitors (prasugrel or clopidogrel) in a post-ACS population. Second, using the SNDS allowed us to consider important potential confounders, including cardiovascular risk factors, availability of healthcare services, and prior exposure to drugs considered as possibly associated with sleep apnoea. Third, we used an active comparator, new-user design, thus minimising confounding by indication and biases related to the inclusion of prevalent users.[26] Fourth, our study investigated not only sleep apnoea but also the rate of MACE, which is clinically relevant in the post-ACS population. Finally, the results remained consistent in several sensitivity analyses, and in the study replication with matching as confounding adjustment, confirming the robustness of our findings.

Nevertheless, several limitations should be acknowledged. First, the major limitation, which is inherent to studies based on healthcare claims database, is the lack of sociodemographic information, particularly body mass index, which is a known risk factor of sleep apnoea. However, we did use ICD-10 codes and specific procedures related to severe obesity and performed a subgroup analysis, which yielded consistent results to the main analysis. Second, it is impossible to differentiate between obstructive sleep apnoea and CSA in the SNDS database because they are identified using the same codes, and no study to date has evaluated the feasibility and performance of codes to distinguish one type of sleep apnoea from the other. This lack of distinction would have been expected to only reduce the number of cases with CSA versus obstructive sleep apnoea, resulting in a reduced effect size. Moreover, we avoided misclassification of CSA as obstructive and vice versa, and performed a sensitivity

analysis using a second outcome definition that did not require a hospitalisation code (which had consistent results). Third, in-hospital dispensing of P2Y12 receptor inhibitors is not referenced in the SNDS, thus affecting the accuracy of our index date. However, we used an active comparator and any imprecision would equally affect the comparisons with clopidogrel or prasugrel. Moreover, we defined the index date as first P2Y12 inhibitor dispensing and not ACS hospitalisation, thus eliminating immortal time bias. Fourth, fewer clopidogrel users were eligible for the cohort than ticagrelor users, whereas reimbursement data and literature suggest greater use of clopidogrel overall. However, we restricted our population to prescriptions occurring in the month after an ACS to ensure that this was the indication for clopidogrel, which has a broader indication than ticagrelor or prasugrel. Finally, given that sleep apnoea is referenced in the European Medicines Agency and US Food and Drug Administration summaries of product characteristics for ticagrelor, we might expect a detection bias in favour of ticagrelor. However, our subgroup analysis on calendar index year did not find difference when stratified before or after the emergence of this safety signal in 2018; in fact, we instead found a counter-intuitive decrease in the point estimate.

Conclusions

Sleep apnoea was common among adults treated with ticagrelor for secondary prevention after ACS (IR of 30.1 per 1000 patients), and the risk of sleep apnoea in those taking ticagrelor was higher than in those taking another P2Y12 receptor inhibitor. Major adverse cardiovascular events occurred in more than 30% of patients, but ticagrelor use was associated with a lower risk compared with clopidogrel, and no difference in risk compared with prasugrel. These findings, and those of future pharmacoepidemiologic analyses, or clinical trials, may inform future practice recommendations on secondary prevention after

ACS, and redefine the place of ticagrelor in the therapeutic strategy, particularly in relation to the choice between ticagrelor and prasugrel.

DISCLOSURE STATEMENTS

Contributors: All authors conceived and designed the study, and acquired, analysed, or interpreted the data. SMB, CJB, JLP, JLC, MJF and CK reviewed the clinical codes. SMB and CJB conducted the statistical analyses and wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. BR obtained the funding. CK and BR are the guarantors, and accept full responsibility for the work and/or the conduct of the study. CK and BR attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by the AGIRADOM (grant Innovadom 2023), Grenoble Alpes University Hospital (grant AOI 2023) and by the Grenoble Alpes University (PhD funding). The funders had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication. SMB, CJB and CK have full access to all data and all authors have full access to the statistical reports and tables in the study. SMB, CJB, CK and BR take responsibility for the integrity of the data and the accuracy of the data analysis. JLP is supported by the French National Research Agency in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated care" from the Grenoble Alpes University Foundation and Sleep Health-AI MIAI artificial intelligence chair (ANR-19-P3IA-0003).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: JLP has received personal consulting fees, board engagements, and travel to conferences from Bioprojet, Jazz Pharmaceutical, ResMed, Philips, SEFAM and Idorsia. All other authors have no conflicts of interest to disclose.

Data sharing: According to data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or organisation (public or private; for-profit or non-profit), can access anonymised SNDS data to do a study, research, or an evaluation of public interest, upon authorisation from the French Data Protection Office (see https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html). Codes used to perform the analyses are available on demand from the corresponding authors.

Transparency: CK and BR (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

FIGURES

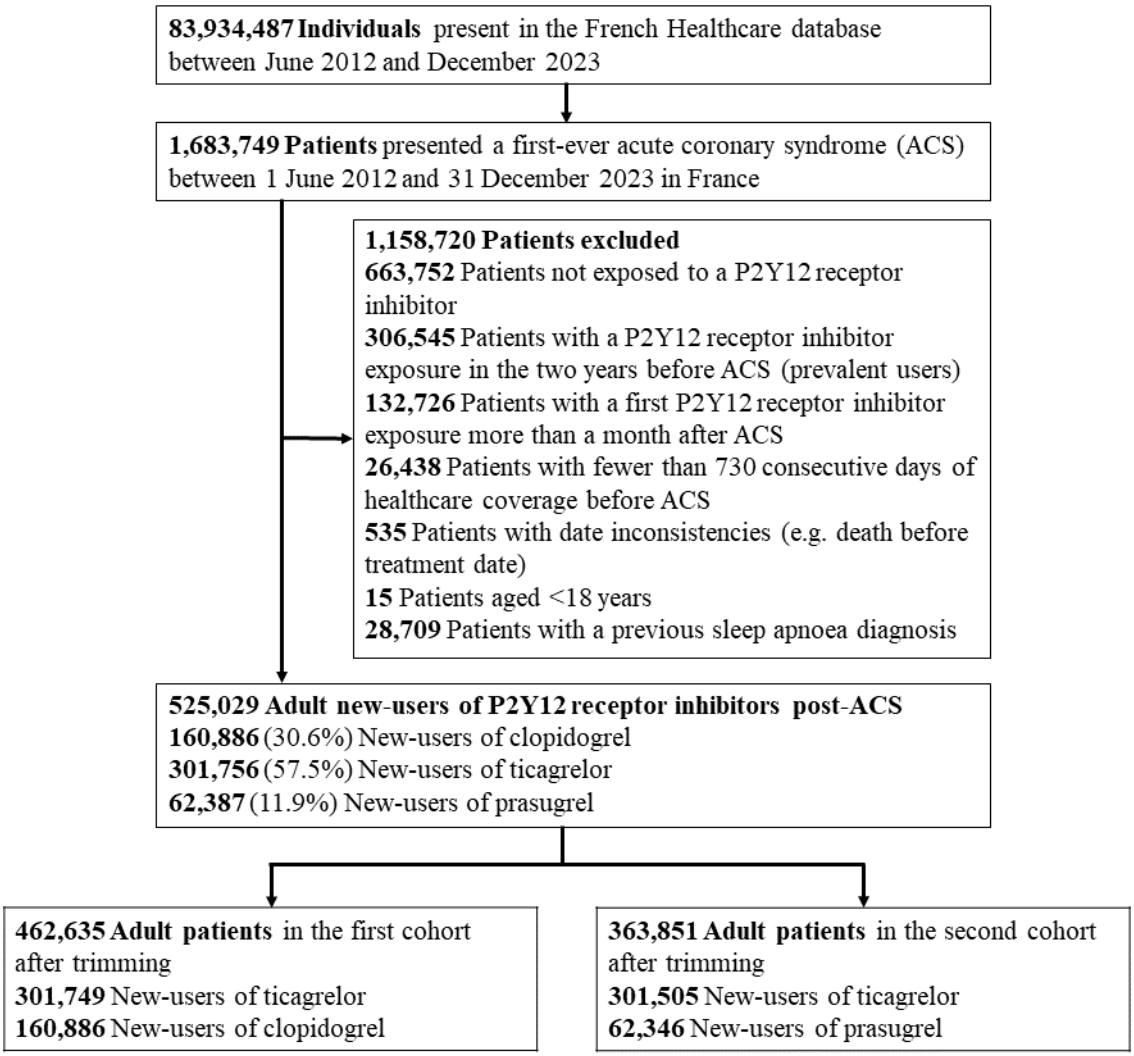


Fig 1 Study flowchart for study cohorts of ticagrelor users versus clopidogrel users, and ticagrelor users versus prasugrel users in the French healthcare database.

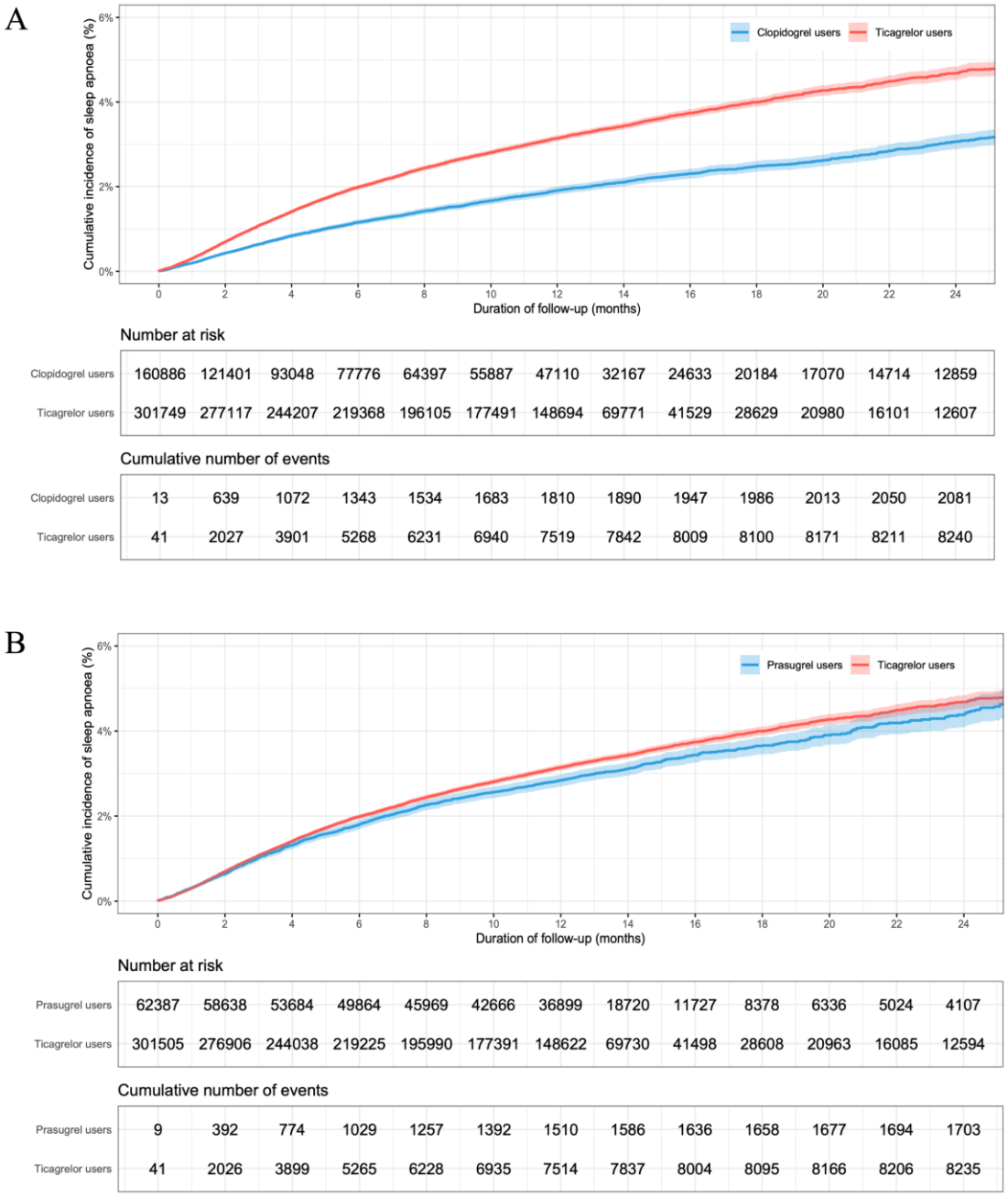


Fig 2 Cumulative incidence curves of sleep apnoea for ticagrelor use versus clopidogrel use (A), and ticagrelor use versus prasugrel use (B).

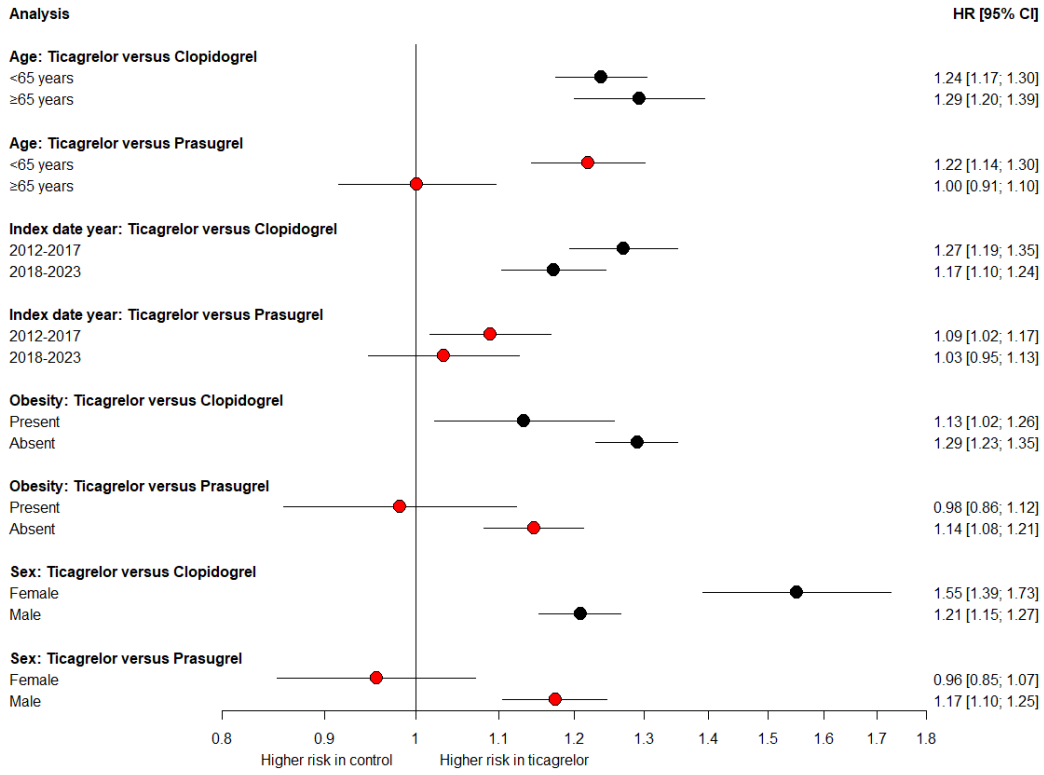


Fig 3 Forest-plot for subgroup analyses displaying hazard ratios for ticagrelor versus clopidogrel, or ticagrelor versus prasugrel and risk of sleep apnoea.

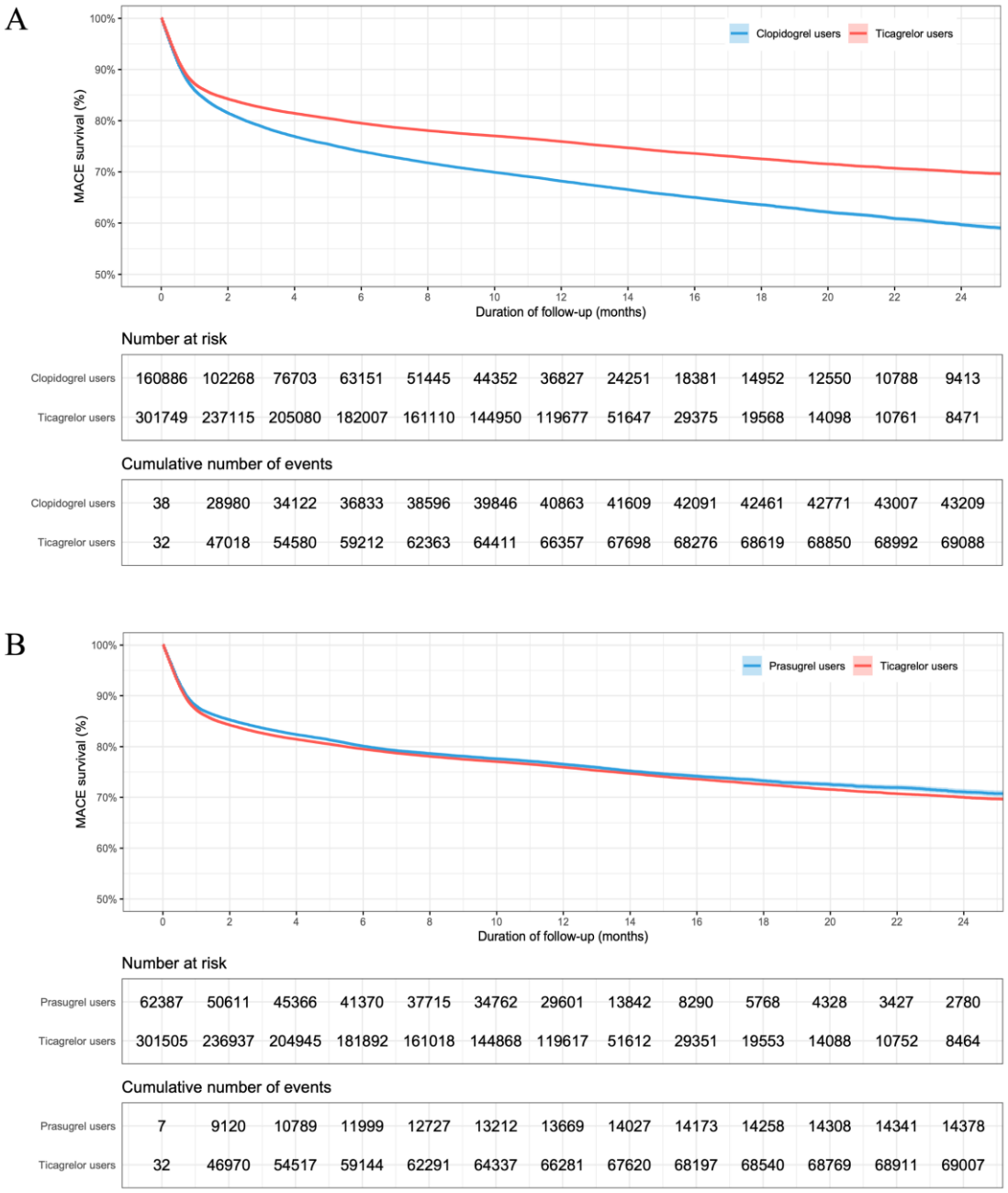


Fig 4 Kaplan-Meier survival curves of major adverse cardiovascular events (MACE) for ticagrelor use versus clopidogrel use (A), and ticagrelor use versus prasugrel use (B).

TABLES

Table 1. Characteristics of patients, by exposure status, after weighting

Characteristic[a]	Ticagrelor vs. clopidogrel			Ticagrelor vs. prasugrel		
	Ticagrelor users (n = 301,749)	**Clopidogrel users (n = 160,886)**	**SMD (%)**	**Ticagrelor users (n = 301,505)**	**Prasugrel users (n = 62,346)**	**SMD (%)**
Calendar year						
2012	3,057 (1.0)	14,170 (8.8)		3,057 (1.0)	7,681 (12.3)	
2013	15,373 (5.1)	19,231 (12.0)		15,373 (5.1)	9,637 (15.5)	
2014	19,024 (6.3)	16,797 (10.4)		19,024 (6.3)	8,441 (13.5)	
2015	22,206 (7.4)	15,192 (9.4)		22,207 (7.4)	7,052 (11.3)	
2016	25,941 (8.6)	13,481 (8.4)		25,942 (8.6)	6,050 (9.7)	
2017	29,106 (9.6)	13,160 (8.2)		29,097 (9.7)	4,143 (6.6)	
2018	31,763 (10.5)	12,377 (7.7)		31,673 (10.5)	2,734 (4.4)	
2019	32,803 (10.9)	12,018 (7.5)		32,700 (10.8)	2,232 (3.6)	
2020	30,592 (10.1)	10,714 (6.7)		30,582 (10.1)	3,005 (4.8)	
2021	30,822 (10.2)	11,257 (7.0)		30,823 (10.2)	4,043 (6.5)	
2022	30,531 (10.1)	11,232 (7.0)		30,513 (10.1)	3,621 (5.8)	

2023	30,531 (10.1)	11,257 (7.0)		30,514 (10.1)	3,707 (5.9)	
Female	76,867 (25.5)	41,526 (25.8)	–0.8	76,675 (25.4)	17548 (28.1)	–6.1
Age, years	63.1 ± 12.4	63.2 ± 13.4	–0.3	63.1 ± 12.4	61.9 ± 10.9	10.6
Severe obesity	30,407 (10.1)	14,998 (9.3)	2.6	30,346 (10.1)	5,193 (8.3)	6.0
Smoking status	51,578 (17.1)	25,249 (15.7)	3.8	51,519 (17.1)	9,286 (14.9)	6.0
Alcohol consumption	12,203 (4.0)	6,393 (4.0)	0.4	12,188 (4.0)	2,299 (3.7)	1.8
Cardiovascular history						
Hypertension	157,567 (52.2)	86,889 (54.0)	–3.6	157,322 (52.2)	32,017 (51.4)	1.7
Heart failure	4,475 (1.5)	2,052 (1.3)	1.8	4,374 (1.5)	1,343 (2.2)	–5.3
Arrythmia	12,975 (4.3)	6,029 (3.7)	2.8	12,851 (4.3)	3,221 (5.2)	–4.3
Transient ischaemic attack	1,873 (0.6)	879 (0.5)	1.0	1,835 (0.6)	397 (0.6)	–0.4
Stroke	6,031 (2.0)	2,858 (1.8)	1.6	5,864 (1.9)	1,673 (2.7)	–4.9
Comorbidities						
COPD	8,558 (2.8)	4,989 (3.1)	–1.6	8,551 (2.8)	1,964 (3.2)	–1.8
Dialysis	821 (0.3)	425 (0.3)	0.2	800 (0.3)	209 (0.3)	–1.3
Diabetes	51,534 (17.1)	28,571 (17.8)	–1.8	51,444 (17.1)	10,472 (16.8)	0.7
VTE	3,758 (1.2)	1,772 (1.1)	1.3	3,717 (1.2)	762 (1.2)	0.1

Dyslipidaemia	117,123 (38.8)	64,971 (40.4)	–3.2	116,933 (38.8)	24,173 (38.8)	0.0
NAFLD	1,919 (0.6)	984 (0.6)	0.3	1,913 (0.6)	335 (0.5)	1.3
Pulmonary hypertension	416 (0.1)	190 (0.1)	0.6	381 (0.1)	86 (0.1)	–0.3
Cancers	34,037 (11.3)	17,944 (11.2)	0.4	33,956 (11.3)	6,799 (10.9)	1.1
Drugs associated with sleep apnoea[b]						
Anticonvulsants	1,253 (0.4)	824 (0.5)	–1.4	1,251 (0.4)	364 (0.6)	–2.4
Gabapentinoids	5,928 (2.0)	3,364 (2.1)	–0.9	5,907 (2.0)	1,354 (2.2)	–1.5
Antidepressants	8,998 (3.0)	4,961 (3.1)	–0.6	8,985 (3.0)	2,080 (3.3)	–2.0
Antipsychotics	1,784 (0.6)	943 (0.6)	0.1	1,783 (0.6)	454 (0.7)	–1.7
Baclofen	691 (0.2)	420 (0.3)	–0.6	689 (0.2)	158 (0.3)	–0.5
Benzodiazepines	15,170 (5.0)	8,592 (5.3)	–1.4	15,150 (5.0)	3,567 (5.7)	–3.1
Corticosteroids	28,270 (9.4)	15,218 (9.5)	–0.3	28,241 (9.4)	6,054 (9.7)	–1.2
Diuretics	8,532 (2.8)	4,402 (2.7)	0.6	8,512 (2.8)	1,982 (3.2)	–2.1
Contraceptives	1,015 (0.3)	647 (0.4)	–1.1	1,012 (0.3)	240 (0.4)	–0.8
Testosterone	130 (0.0)	94 (0.1)	–0.7	125 (0.0)	39 (0.1)	–0.9
Montelukast	1,799 (0.6)	1,100 (0.7)	–1.1	1,798 (0.6)	504 (0.8)	–2.5
Opioids	25,847 (8.6)	13,789 (8.6)	0.0	25,822 (8.6)	5,463 (8.8)	–0.7

Opium derivatives	17,954 (5.9)	10,610 (6.6)	–2.7	17,929 (5.9)	4,228 (6.8)	–3.4
Number of hospitalisations[c]						
0	1,203 (0.4)	686 (0.4)	–0.4	1,203 (0.4)	248 (0.4)	0.0
1	240,127 (79.6)	126,974 (78.9)	1.6	240,050 (79.6)	48,825 (78.3)	3.2
2	44,176 (14.6)	24,497 (15.2)	–1.6	44,103 (14.6)	9,386 (15.1)	–1.2
3	10,363 (3.4)	5,632 (3.5)	–0.4	10,323 (3.4)	2,458 (3.9)	–2.8
≥4	5,880 (1.9)	3,096 (1.9)	0.2	5,826 (1.9)	1,430 (2.3)	–2.5
Number of pulmonologist visits[c]						
0	284,660 (94.3)	151,350 (94.1)	1.1	284,446 (94.3)	58,608 (94)	1.4
1	7,138 (2.4)	3,946 (2.5)	–0.6	7,122 (2.4)	1,664 (2.7)	–2.0
2–6	5,396 (1.8)	3,078 (1.9)	–0.9	5,388 (1.8)	1,152 (1.8)	–0.5
7–11	1,396 (0.5)	765 (0.5)	–0.2	1,393 (0.5)	269 (0.4)	0.5
≥12	3,159 (1.0)	1,746 (1.1)	–0.4	3,156 (1.0)	653 (1.0)	0.0

Data are n (%) apart from age, which is reported as mean ± standard deviation.

[a]Characteristics post-weighting by fine stratification on propensity score at each calendar year, and measured any time before index date unless otherwise specified.

[b]Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.* (7).

[c]Measured in the year before index date.

COPD=chronic obstructive pulmonary disease; NAFLD=non-alcoholic fatty liver diseases; SMD=standardised mean difference; VTE=venous thromboembolic events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

Table 2. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and major adverse cardiovascular events: primary analysis

Exposure	No. of patients	Events	Person-years	Incidence rate (95% CI)[a]	Hazard Ratio (95% CI)	p-value	NNH
Sleep apnoea main analysis (as-treated)							
Clopidogrel	160,886	2,882	131,287	21.9 (21.2–22.8)	1.00 (reference)	Reference	Reference
Ticagrelor	301,749	8,358	277,356	30.1 (29.5–30.8)	1.27 (1.21–1.32)	<0.001	122
Prasugrel	62,346	1,637	64,150	25.5 (24.3–26.8)	1.00 (reference)	Reference	Reference
Ticagrelor	301,505	8,353	277,168	30.1 (29.5–30.8)	1.13 (1.08–1.20)	<0.001	217
MACE main analysis (as-treated)							
Clopidogrel	160,886	40,411	105,928	381.5 (377.8–385.2)	1.00 (reference)	Reference	Reference
Ticagrelor	301,749	69,567	227,532	305.7 (303.4–308.0)	0.84 (0.83–0.85)	<0.001	/
Prasugrel	62,346	15,050	51,843	290.2 (285.7–295.0)	1.00 (reference)	Reference	Reference
Ticagrelor	301,505	69,485	227,380	305.6 (303.3–307.9)	0.99 (0.97–1.00)	0.126	65

[a]Per 1000 person-years.

CI=confidence interval; MACE=major adverse cardiovascular events; NNH=number of patients exposed for one year needed to harm.

Table 3. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and major adverse cardiovascular events: sensitivity analyses

Exposure	No of patients	Events	Person-years	Incidence rate (95% CI)[a]	Hazard Ratio (95% CI)	p-value	NNH
Sleep apnoea: sensitivity analyses							
Modified intention-to-treat with a 1-year follow-up							
Clopidogrel	160,886	3,557	142,395	25.0 (24.2–25.8)	1.00 (reference)	Reference	Reference
Ticagrelor	301,749	8,216	256,436	32.0 (31.4–32.7)	1.27 (1.22–1.32)	<0.001	142
Prasugrel	62,346	1,542	54,467	28.3 (26.9–29.8)	1.00 (reference)	Reference	Reference
Ticagrelor	301,505	8,211	256,249	32.0 (31.4–32.7)	1.13 (1.07–1.19)	<0.001	268
Modified intention-to-treat with a 2-year follow-up							
Clopidogrel	160,886	5,295	265,307	20.0 (19.4–20.5)	1.00 (reference)	Reference	Reference
Ticagrelor	301,749	10,931	455,511	24.0 (23.5–24.5)	1.17 (1.14–1.21)	<0.001	248
Prasugrel	62,346	2,138	97,168	22.0 (21.1–23.0)	1.00 (reference)	Reference	Reference
Ticagrelor	301,505	10,925	455,193	24.0 (23.6–24.5)	1.09 (1.04–1.14)	<0.001	501
As-treated, post-matching on propensity score							
Clopidogrel	114,729	1,832	93,755	19.5 (18.7–20.5)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	2,727	103,498	26.3 (25.4–27.4)	1.27 (1.19–1.34)	<0.001	147

Prasugrel	57,439	1,659	60,755	27.3 (26.0–28.7)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	1,663	56,525	29.4 (28.0–30.9)	1.06 (0.99–1.13)	0.112	473
As-treated, sensitive outcome definition							
Clopidogrel	160,886	5,917	118,615	49.9 (48.6–51.2)	1.00 (reference)	Reference	Reference
Ticagrelor	301,749	16,517	253,411	65.2 (64.2–66.2)	1.20 (1.17–1.24)	<0.001	65
Prasugrel	62,346	3,258	58,892	55.3 (53.4–57.3)	1.00 (reference)	Reference	Reference
Ticagrelor	301,505	16,511	253,248	65.2 (64.2–66.2)	1.13 (1.09–1.17)	<0.001	101
MACE: sensitivity analyses							
Modified intention-to-treat with a 1-year follow-up							
Clopidogrel	160,886	44,659	115,653	386.1 (382.6–389.7)	1.00 (reference)	Reference	/
Ticagrelor	301,749	70,393	215,063	327.3 (324.9–329.7)	0.84 (0.83–0.85)	<0.001	/
Prasugrel	62,346	14,957	45,488	328.8 (323.6–334.1)	1.00 (reference)	Reference	/
Ticagrelor	301,505	70,304	214,914	327.1 (324.7–330.0)	0.98 (0.97–1.00)	0.065	/
Modified intention-to-treat with a 2-year follow-up							
Clopidogrel	160,886	52,027	207,952	250.2 (248.0–252.3)	1.00 (reference)	Reference	/
Ticagrelor	301,749	79,294	372,843	212.7 (211.2–214.2)	0.82 (0.81–0.83)	<0.001	/
Prasugrel	62,346	16,627	79,007	210.5 (207.3–213.7)	1.00 (reference)	Reference	Reference

Ticagrelor	301,505	79,183	372,598	212.5 (211.0–214.0)	1.00 (0.98–1.02)	0.828	485
As-treated, post-matching on propensity score							
Clopidogrel	114,729	30,424	75,405	403.4 (399.0–408.0)	1.00 (reference)	Reference	/
Ticagrelor	114,729	27,962	84,275	331.8 (327.9–335.7)	0.85 (0.83–0.86)	<0.001	/
Prasugrel	57,439	13,352	49,413	270.2 (265.6–274.8)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	13,185	46,257	285.0 (280.2–289.9)	1.01 (0.99–1.04)	0.386	67

[a]Per 1000 person-years.

CI=confidence interval; MACE=major adverse cardiovascular events; NNH=number of patients exposed for one year needed to harm.

REFERENCES

1. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289-367.
2. Storey RF, Bliden KP, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol* 2010;56:185-93.
3. Gaubert M, Laine M, Richard T, et al. Effect of ticagrelor-related dyspnea on compliance with therapy in acute coronary syndrome patients. *Int J Cardiol* 2014;173:120-1.
4. Lombardi N, Lenti MC, Matucci R, et al. Ticagrelor-related dyspnea: an underestimated and poorly managed event? *Int J Cardiol* 2015;179:238-9.
5. Giannoni A, Emdin M, Passino C. Cheyne-Stokes respiration, chemoreflex, and ticagrelor-related dyspnea. *N Engl J Med* 2016;375:1004-6.
6. Cattaneo MF Elena M. Why does ticagrelor induce dyspnea? *Thromb Haemost* 2017;108:1031-6.
7. Jullian-Desayes I, Revol B, Chareyre E, et al. Impact of concomitant medications on obstructive sleep apnoea. *Br J Clin Pharmacol* 2017;83:688-708.
8. Revol B, Jullian-Desayes I, Tamisier R, et al. Ticagrelor and central sleep apnea. *J Am Coll Cardiol* 2018;71:2378-9.
9. Paboeuf C, Priou P, Meslier N, et al. Ticagrelor-associated shift from obstructive to central sleep apnea: a case report. *J Clin Sleep Med* 2019;15:1179-82.
10. Puel V, Théophile H, Godard I, et al. Ticagrelor and central sleep apnoea: impact of withdrawal and reintroduction. *Br J Clin Pharmacol* 2019;85:1855-8.
11. Meurin P, Ben Driss A, Defrance C, et al. Central sleep apnea after acute coronary syndrome and association with ticagrelor use. *Sleep Med* 2021;80:39-45.
12. Tzeng WS, Klein CF, Roth RH, et al. Central sleep apnea in patients with coronary heart disease taking P2Y12 inhibitors. *J Cardiovasc Pharmacol* 2024;83:126-30.

13. Sabatine MS, Hiatt WR, Goto S, et al. No significant relationship between ticagrelor and sleep apnea in large, randomized, blinded trials. *JACC Cardiovasc Interv* 2020;13:1012-4.
14. Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primer* 2015;1:15015.
15. Khayat R, Jarjoura D, Porter K, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J* 2015;36:1463-9.
16. Cowie MR, Linz D, Redline S, et al. Sleep disordered breathing and cardiovascular disease: JACC State-of-the-Art review. *J Am Coll Cardiol* 2021;78:608-24.
17. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive Sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;144:e56-67.
18. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
19. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ* 2018;363:k3532.
20. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017;26:954-62.
21. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique 2017;65:S149-67.
22. de Germay S, Conte C, Micallef J, et al. Performing pharmacoepidemiological studies using the French health insurance data warehouse (SNDS): how to translate guidelines into practice. *Therapie* 2023;78:691-703.

23. Jabagi MJ, Bertrand M, Botton J, et al. Stroke, myocardial infarction, and pulmonary embolism after bivalent booster. *N Engl J Med* 2023;388:1431-2.
24. Lassalle M, Zureik M, Dray-Spira R. Proton pump inhibitor use and risk of serious infections in young children. *JAMA Pediatr* 2023;177:1028-38.
25. Roland N, Neumann A, Hoisnard L, et al. Use of progestogens and the risk of intracranial meningioma: national case-control study. *BMJ* 2024;384:e078078.
26. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20.
27. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167:492-9.
28. Pépin JL, Bailly S, Rinder P, et al. Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis. *Chest.* 2022;161:1657-65.
29. Pépin JL, Tamisier R, Benjafield AV, et al. CPAP resumption after a first termination and impact on all-cause mortality in France. *Eur Respir J* 2023;63:2301171.
30. Desai RJ, Rothman KJ, Bateman BT, et al. A propensity-score-based fine stratification approach for confounding adjustment when exposure is infrequent. *Epidemiol* 2017;28:249-57.
31. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019;367:l5657.
32. Jambon-Barbara C, Revol B, Hlavaty A, et al. Signal detection of drugs associated with obstructive and central sleep apnoea. *Sleep Med* 2024;124:315-22.
33. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;38:1228-34.
34. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107.
35. Pépin JL, Eastwood P, Eckert DJ. Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. *Eur Respir J* 2022;59:2101788.
36. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687-98.

37. Desai R. Propensity score fine stratification SAS macro. https://doi.org/10.7910/DVN/U8JLCW, Harvard Dataverse, V5.
38. Giannoni A, Borrelli C, Gentile F, et al. Central apnoeas and ticagrelor-related dyspnoea in patients with acute coronary syndrome. *Eur Heart J Cardiovasc Pharmacother* 2021;7:180-8.
39. Tubek S, Niewinski P, Langner-Hetmanczuk A, et al. The effects of P2Y12 adenosine receptors' inhibitors on central and peripheral chemoreflexes. *Front Physiol* 2023;14:1214893.
40. Doshi P. Doubts over landmark heart drug trial: ticagrelor PLATO study. *BMJ* 2024;387:q2550.
41. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
42. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: multicenter randomized PRAGUE-18 study. *Circulation* 2016;134:1603-12.
43. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 2019;381:1524-34.
44. Krüger N, Krefting J, Kessler T, et al. Ticagrelor vs prasugrel for acute coronary syndrome in routine care. *JAMA Netw Open* 2024;7:e2448389.
45. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720-826.
46. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;145:e18-114.
47. Angiolillo DJ, Cao D, Sartori S, et al. Dyspnea-related ticagrelor discontinuation after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2023;16:2514-24.
48. Lee M, Byun S, Lim S, et al. Dual antiplatelet therapy de-escalation in stabilized myocardial infarction with high ischemic risk: post hoc analysis of the TALOS-AMI randomized clinical trial. *JAMA Cardiol* 2024;9:125-33.

2. Use of Bisphosphonates and the Risk of Skin Ulcer: A National Cohort Study Using Data from the French Health Care Claims Database

Une précédente étude de disproportionnalité sur la base mondiale de pharmacovigilance de l'OMS, Vigibase®, ayant pour objectif l'identification de nouveaux signaux de pharmacovigilance de médicaments induisant des ulcères cutanés a retrouvé un large signal pour la classe des biphosphonates (106). Malgré de nombreux effets indésirables très bien décrits, il n'existe que de rares séries de cas qui relient la classe des biphosphonates aux affections cutanées, alors qu'un rationnel pharmacologique existe (138,139). A notre connaissance, aucune étude de pharmacoépidémiologie n'a été conduite à l'heure actuelle pour évaluer ce signal.

Cependant, la réalisation d'une étude de cohorte pour évaluer le profil de sécurité des biphosphonates est particulièrement complexe, en effet, il n'existe pas de comparateurs actifs pertinents ayant la même indication et la même place dans la stratégie thérapeutique. C'est pourquoi, nous avons réalisé un *Prior Event Rate Ratio*, qui permet de prendre en compte le risque de survenue d'ulcères cutanés chez les patients avant même l'introduction du traitement pour limiter le risque de facteurs de confusion résiduels (140,141).

Drug Safety
https://doi.org/10.1007/s40264-023-01336-x

ORIGINAL RESEARCH ARTICLE

Use of Bisphosphonates and the Risk of Skin Ulcer: A National Cohort Study Using Data from the French Health Care Claims Database

Clément Jambon-Barbara[1] · Claire Bernardeau[1] · Julien Bezin[2,3] · Matthieu Roustit[4,5] · Sophie Blaise[4,6] · Jean-Luc Cracowski[1,4] · Charles Khouri[1,4,5,7]

Accepted: 3 July 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Abstract

Introduction Previous pre-clinical and pharmacovigilance disproportionality analyses highlighted a safety signal of cutaneous ulcer with bisphosphonate use. Therefore, our objective is to evaluate this risk and assess whether unmeasured confounding factors could explain this association.

Methods This study is a population-based cohort study from a representative sample (1/97th) of the French health insurance claims database: Echantillon Généraliste des Bénéficiaires (EGB) from 2006 to 2019. To limit the impact of our study design and methodological choices on any association between skin ulceration and exposure to bisphosphonates, we used several methods: a Cox proportional hazards analysis and a prior event rate ratio (PERR) analysis, using two propensity matched control groups, and either the first episode of incident ulceration or multiple event-time outcomes.

Results There were 7402 individuals newly exposed to bisphosphonates matched to 29,605 unexposed individuals on propensity score. The primary outcome was skin ulcer occurrence assessed by at least 2 deliveries of wound dressing during the period of one month. Among 6911 individuals newly exposed to bisphosphonates and 28,072 unexposed individuals with no previous skin ulcer, the Cox regression yielded a hazard ratio (HR) of 1.40 (95% CI 1.26–1.56) for newly exposed individuals. Among 7402 exposed and 29,605 unexposed individuals, the PERR analysis found a non-significant HR of 1.03 (95% CI 0.87–1.24). Results were similar on the different sensitivity analyses.

Conclusion No association between bisphosphonate and skin ulcers was found in the French population. The association observed in previous pharmacovigilance studies and in the Cox regression analysis is likely due to unmeasured confounding factors.

✉ Charles Khouri
ckhouri@chu-grenoble.fr

1 Pharmacovigilance Department, Grenoble Alpes University Hospital, 38043 Grenoble, France

2 University Bordeaux, INSERM, BPH, Team AHeaD, U1219, 33000 Bordeaux, France

3 Clinical Pharmacology Unit, CHU de Bordeaux, 33000 Bordeaux, France

4 University Grenoble Alpes, Inserm U1300, HP2, 38000 Grenoble, France

5 University Grenoble Alpes, Inserm CIC1406, Grenoble Alpes University Hospital, 38000 Grenoble, France

6 Department of Vascular Medicine, Grenoble Alpes University Hospital, University Grenoble Alpes, 38000 Grenoble, France

7 Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France

Key Points

In the general French population, bisphosphonate exposure is not associated with a higher risk of skin ulcers.

Discrepant results between the commonly used Cox model and the PERR analysis point to the presence of unmeasured and/or unknown residual confounding factors.

Our study highlights the importance in pharmacoepidemiologic studies of conducting several complementary analyses to avoid a conclusion of false associations.

Published online: 02 August 2023

1 Introduction

Chronic skin wounds are mainly venous leg ulcers, pressure ulcers and diabetic foot ulcers and are currently a major public health concern [1–4]. In the USA, it is estimated that at least 4.5 million people have chronic wounds of which 25–50% are not fully cured at 6 months despite optimal treatment. A previous study from the French reimbursement database retrieved 667,194 patients with a skin ulcer [1, 5]. They negatively affect quality of life (pain and social unease) and represent a substantial economic burden to health care systems [6–8]. Several factors have been implicated in the skin ulcer pathogenesis such as infection, vasculitis, stasis, ulcerating skin diseases, cancer, undernutrition, etc. [9] Among them, cutaneous microvascular dysfunction plays a key role in the pathophysiology of skin ulcers, whatever their aetiology (pressure, vascular or diabetic ulcers) [10].

In this context, our team performed a pharmacovigilance disproportionality analysis on the WHO pharmacovigilance database VigiBase® to identify any signals of drugs associated with higher than expected reporting of skin ulcers [11]. This study identified most drug classes already known to increase the risk of skin ulcers (e.g., methotrexate, tyrosine kinases inhibitors, hydroxycarbamide, etc.). Furthermore, these analyses generated disproportionality signals for some recently marketed drugs (e.g., afatinib, ibrutinib), and also for older drugs such as digoxin, bisphosphonates or COX-2-inhibitors [12].

Despite numerous well-described adverse events reported in the literature, there are only a few case reports relating bisphosphonates to cutaneous reactions notwithstanding the pharmacological plausibility [11, 13]. Indeed, there is increasing evidence that bisphosphonates, especially zoledronic acid, inhibit cell migration and angiogenesis through inhibition of the EGFR/Akt/PI3K pathway and VEGF, and induce apoptosis of fibroblasts and vascular endothelial cells [14–17]. To our knowledge, no previous study has explored the association between bisphosphonates and skin ulcers despite a potentially large impact on the population. However, answering this research question using health databases introduces challenging issues. In a classical Cox proportional hazard analysis, the selection of control groups for drugs used as first-line treatment with no real alternatives is faced with the difficulty of accounting for unmeasured confounding factors. The prior event rate ratio (PERR) method solves this problem by considering individual patient risk factors of skin ulceration before drug exposure.

The main objective of this study was therefore to evaluate the risk of skin ulceration linked to bisphosphonate exposure, in the French population, using different approaches to assess the impact of the study design and of methodological choices on the results [18, 19].

2 Methods

2.1 Data Source

This cohort study was conducted using data extracted from the "Echantillon Généraliste des Bénéficiaires (EGB)" a random representative sample (to the 1/97th) of the French population covered by the national health insurance scheme, and contains data from 660,000 individuals [20]. The EGB has been extensively used and validated for pharmacoepidemiology research [21–23]. The patients are representative in age, sex and health care expenditure of the general population. The database contains anonymised individual patient data. It is linked to the hospital discharge summary database (Programme de Médicalization des Systèmes d'Information, PMSI) that contains the following hospital data: dates of entry and discharge, diagnosis coded using ICD-10 (International Classification of Diseases, 10th revision), codes of the main medical procedures. The EGB also contain reimbursement of outpatient care data (delivery date, CIP codes, ATC codes) [22, 24, 25]. For each eligible patient, demographic data (age, sex, date of death, etc.) and registration as having a long-term condition are available (extracted from ICD-10 codes, date of beginning and end of disease).

2.2 Study Population

The cohort comprised all beneficiaries present in the EGB in 2006, affiliated throughout the study period to the general public health insurance scheme (88% of the patients included in the database) with no bisphosphonates reimbursement before 2008. Index date was defined as first biphosphonate dispensing for exposed patients and matched date for unexposed patients. Patients were followed from 2 years before index date, that is pre-exposition period, until the date of death, 31st December 2019 or 2 years after index date (whichever came first), i.e., the post-exposition period. We identified the exposed group from this source cohort as individuals who received a first prescription for an oral bisphosphonate with no dispensing before 1st January 2008 (i.e., new users). A propensity score was used to match patients using greedy matching with a calliper width of 0.2 standard deviation of the logit at a ratio of up to 1:4 (i.e., 1 exposed patient matched to 4 unexposed patients). We constructed the time conditional propensity score with conditional logistic regression stratified by exposure set to predict the probability of receiving a bisphosphonate compared with no use of bisphosphonate using known and identifiable risk factors for skin ulcers [1, 26–29]. The covariates used for the propensity score were sex, age, peripheral vascular disease, urinary incontinence, faecal incontinence,

number of hospitalisations during the year prior to the index date (approximation of health care consumption), diabetes, thrombosis, high blood pressure, hyperlipidaemia, smoking status, obesity and corticoid consumption in the two years before the index date as a categorical variable (no consumption; less than 30 days of cumulative consumption; between 30 and 90 days of cumulative consumption; more than 90 days of cumulative consumption). The codes used for all diseases have previously been validated by French institutions [30–32] and are presented in the Supplementary Material (Table S1).

2.3 Drug Exposure Definition

Bisphosphonate exposure was defined as the first supply of at least one box of bisphosphonates during the study period, with no supply between 1st January 2006 and 1st January 2008. We selected oral bisphosphonates alone or in association and we excluded patients with a cancer, keeping only those with an osteoporosis indication. All codes for bisphosphonate identification are presented in the Supplementary Material (Table S1).

2.4 Outcomes

We identified skin ulcer in the EGB using a list of wound dressings supplied using the List of products and services ("Liste des Produits et Prestations—LPP") codes, i.e., at least 2 deliveries of wound dressing during the period of one month. The list of dressings included hydrocolloid, foam, alginate, hydrogel, fibre, and active carbon dressings, as well as dressings containing hyaluronic acid, or petroleum jelly, those with interfaces and adhesive dressings. The LPP codes are presented in the Supplementary Material (Table S1 to S2). We identified venous, diabetic and pressure ulcers through an algorithm previously validated by the French Health Insurance [5, 29, 31, 33] (Fig. 1). Firsty, we identified any use of an anti-bedsore mattress, cushion, or compression bandage supply by LPP codes; and hospitalisation for orthopaedic surgery or realisation of an echo-Doppler by the medical procedure codes ("Classification Commune des Actes Médicaux") presented in the Supplementary Material (Table S1 and S3 to S5). Then, we defined an episode of cutaneous ulcer if there were at least two deliveries of dressings over the period of one month and if the delivery was not associated with an orthopaedic surgery procedure in the 30 days preceding the delivery of dressings. We defined 60 days or more without a dressing delivery as being the end

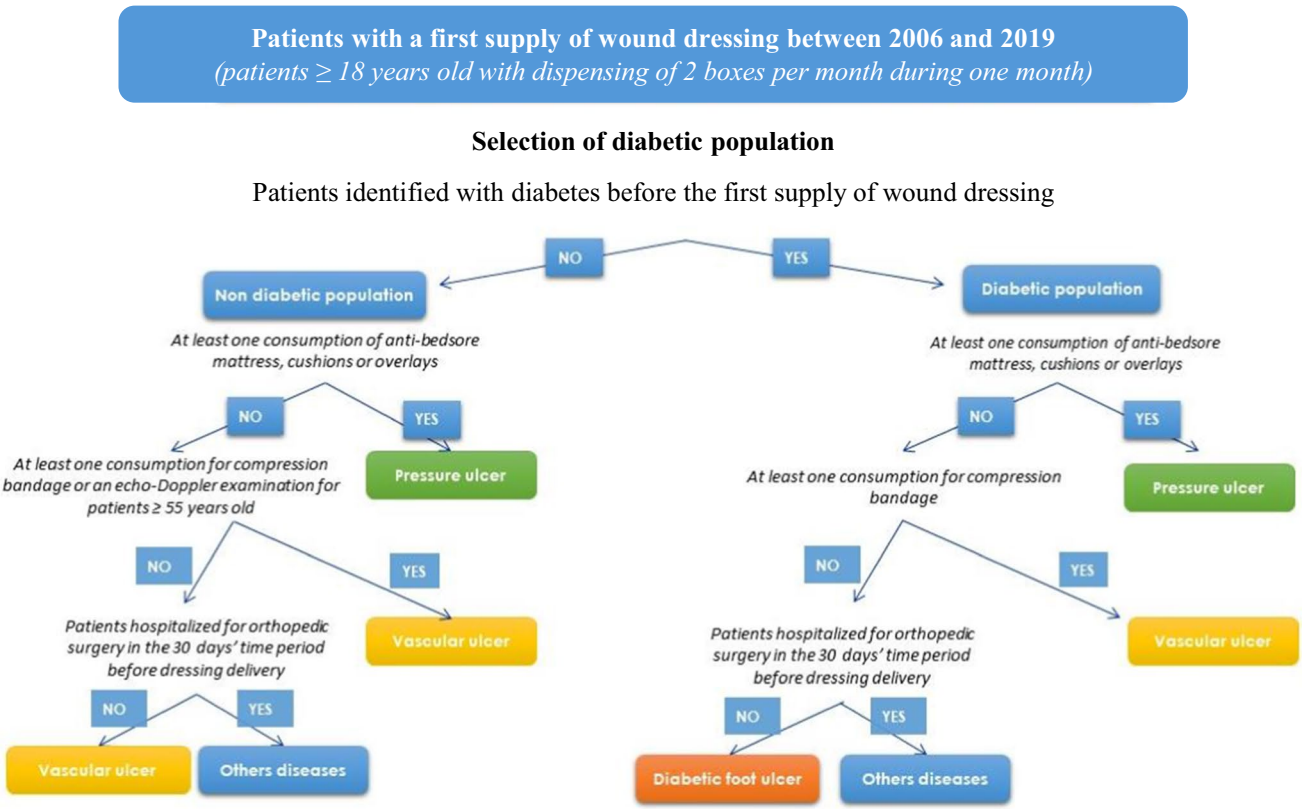


Fig. 1 Selection algorithm for vascular, pressure and diabetic foot ulcers

of an episode of cutaneous ulcer and for each patient we counted the number of episodes of skin ulcer as well as the mean duration of an episode.

To appraise the performances of the algorithm, we identified all hospitalisations of patients in the year before and after each episode of cutaneous ulcers and used ICD-10 codes of vascular, diabetic and pressure ulcers to assess their concordance with the defined types from the algorithm. All codes for ICD-10 skin ulcer identification are presented in the Supplementary Material (Table S6). From the 3769 patients with a skin ulcer, 343 were hospitalised in the year around dressing supply and were included in this concordance analysis. It shows a high similarity between hospitalisation in the year before or after skin ulcer identification and what we found with the algorithm, except for diabetic foot ulcer, which could be explain by their identification at the end of the algorithm (exclusion diagnosis). Results from this concordance analysis between the dressing supply algorithm and hospitalisation codes are summarised in the Supplementary Material (Table S7).

2.5 Study Design

An overview of the analysis strategy used in our study is shown in Fig. 2.

- Cox proportional hazards analysis

We defined the index date for the exposed group as the first supply of bisphosphonate and for the unexposed group as the index date of the exposed individual they were matched to. We excluded individuals who had an occurrence of skin ulcer before this index date. We performed Cox proportional hazards modelling to estimate the hazard ratio (HR) and the 95% confidence intervals (95% CIs) for the risk of skin ulcers associated with bisphosphonate exposure. We considered the first occurrence of skin ulcer after the index date for the first-event model, or all skin ulcers occurring in the two years from the index date for the multiple event-time outcomes model. We censored the follow-up at the date of death, the date of first skin ulcer (only for first-event cohort), on 31st December 2019 or 2 years after the index date, whichever came first.

- Prior event rate ratio (PERR)

The PERR analysis was proposed to reduce bias due to unmeasured confounding factors in survival analyses (Fig. 3) [34–36]. We defined the index date in the same way as in the Cox proportional hazards analysis. The method relies on a before and after design and is based upon the assumption that the difference between exposed and unexposed patients' prior exposure reflects the combined effect of confounders independently of any impact of the drug exposition. The prior-exposure period was the two years before the index date and the post-exposure was the two years after the index date for both groups. Therefore, it provides an estimate of the effect of drug exposition adjusted for known and unknown confounders. We did the same analyses as with the Cox design: first-event and multiple event-time outcomes. We censored the follow-up at the date of death, the date of first skin ulcer (only for first event cohort), on 31st December 2019 or 2 years after index date, whichever came first. We estimated 95% CIs by bootstrapping.

- Control groups

Two control groups were used in both analyses: (1) we individually matched the exposed patients (using a 1:4 ratio) by propensity score (detailed in study population) with unexposed patients who had never received a bisphosphonate supply at the index date; or (2) we individually matched the exposed patients to patients who would be exposed in at least

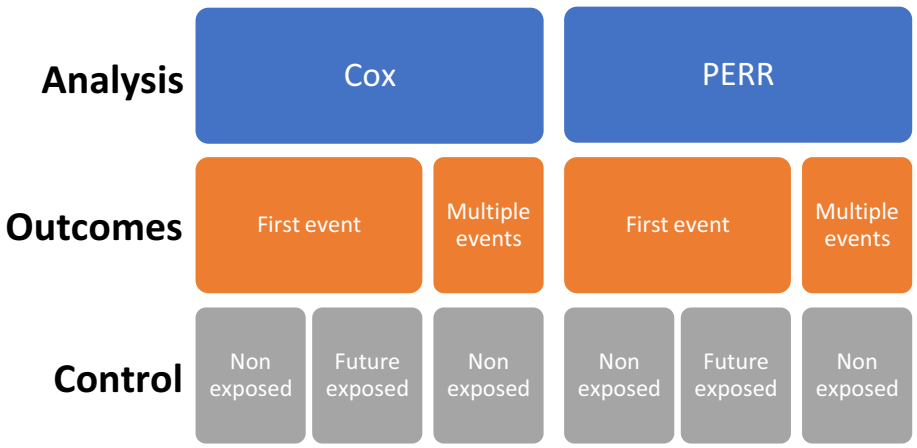


Fig. 2. Overview of analysis strategy used. *Cox* Cox proportional hazards analysis, *PERR* prior event rate ratio analysis

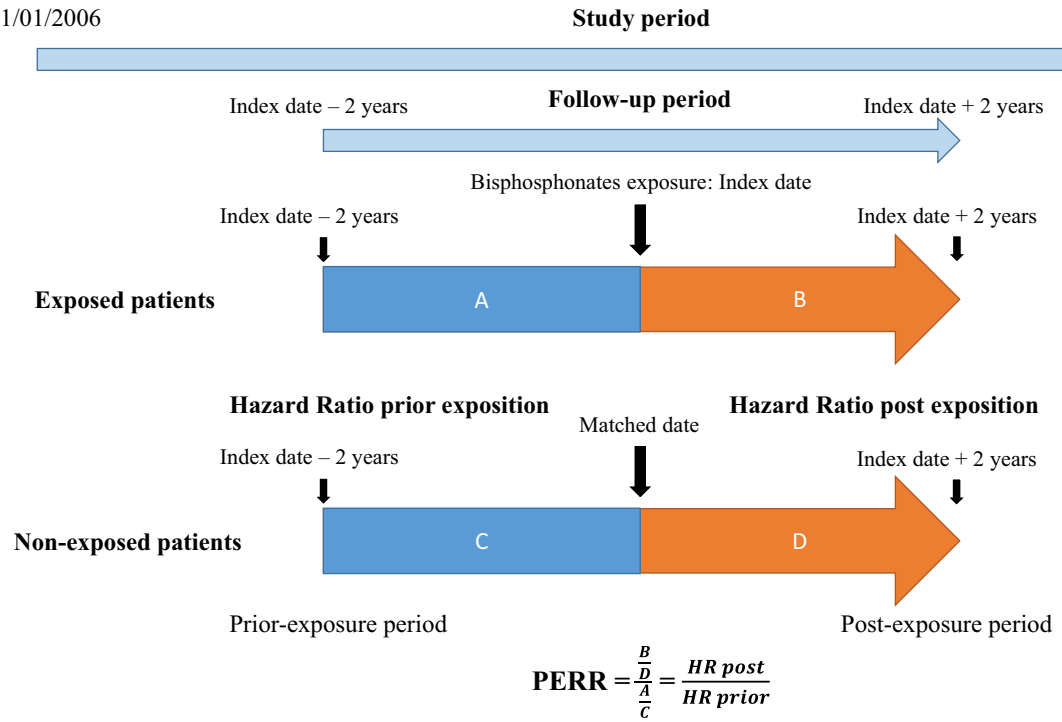


Fig. 3 Prior event rate ratio adjustment method. The prior-exposure period is the time before the index date (bisphosphonate supply date for exposed cohort and matched date for unexposed patients); the post-exposure period means the time after bisphosphonate exposure. *HR* hazard ratio, *PERR* prior event rate ratio

2 years in the future (Supplementary Material Figure S1). Patients who would be exposed after at least 2 years are the most similar we can achieve to exposed patients for the factors associated with the initiation of bisphosphonates. Consequently, this should greatly reduce protopathic bias. To compose this contemporary second control group, we used a second propensity score and matched exposed patients (in a ratio of 1:4) with return of the controls to the pool after each match. Therefore, on this second cohort, a subject who is control at time T for a first exposed patient, could be control at time $T + 1$ month for a second patient and could be in the exposed group at time $T + 2$ years.

2.6 Statistical Analysis

All statistical analyses were performed with SAS EG® (SAS Institute, Cary, NC, USA), 7.13 and R, version 4.2.1 (R Foundation).

2.6.1 Principle Analyses

We calculated descriptive summary characteristics for the study population by exposure status. We used standardised mean difference (SMD) instead of the *p* value to assess if our matching was efficient because of the large number of patients. An absolute SMD of ≤ 10% indicates a negligible difference in potential confounders and balanced matched cohorts [37].

As suggested by a reviewer, we also tested the difference of exposure to vasodilators (PDE5 inhibitors, endothelin receptor antagonists, prostacyclin analogues and calcium channel blockers) between exposed and control groups.

For the first event analysis, we considered the first occurrence of skin ulcer within 2 years before the index date (for PERR only) and similarly within 2 years after (for Cox and the PERR analyses). On the PERR cohort, we used Cox proportional hazards modelling to estimate the HR for skin ulcer in individuals receiving bisphosphonates prior to the index date (HRpre) and post-index date (HRpost), we obtained the PERR HR from the ratio of these two HRs ($HR_{PERR}=\frac{HRpost}{HRpre}$) (Fig. 3) [38]. We obtained 95% CIs by bootstrapping each HR one thousand times. On the Cox cohort, we used Cox proportional hazards modelling to estimate the HR and 95% CIs for skin ulcer in individuals receiving bisphosphonates.

2.6.2 Sensitivity Analyses

We did the same two analyses on the Cox and the PERR cohorts with the second control group: future-exposed patients.

For the multiple-event time outcome analysis, we did not censor at the onset of the first event, instead we followed all patients for 2 years before and after the index date, and counted every event that occurred during this time [39]. For the multiple-event-time outcome analysis, we used the ratio of event-free time area under the curve (AUC) with the bootstrap technique presented in the R package proposed by Claggett et al [39].

Finally, on the advice of the reviewer, we did an analysis on the Cox and the PERR cohorts with a lag time of one-month pre- and post-index date.

3 Results

3.1 Population Characteristics

In the French Healthcare EGB database, 474,536 patients initially met the eligibility criteria. We subsequently excluded 9202 patients because of a history of bisphosphonate supply between 2006 and 2008 (prevalent user patients). Finally, we excluded patients aged < 18 years or with a history of cancer before the index date or with a fracture in the year before index date. Overall, 7402 patients exposed to bisphosphonates were matched on propensity score to 29,605 unexposed patients and comprised our study cohort for the PERR analysis (Fig. 4). After exclusion of prevalent skin ulcer, for the Cox analysis, 6922 patients exposed to bisphosphonates were matched to 28,112 unexposed patients.

Our second cohort with future exposed patients as the control group comprised 7741 exposed patients and 30,513

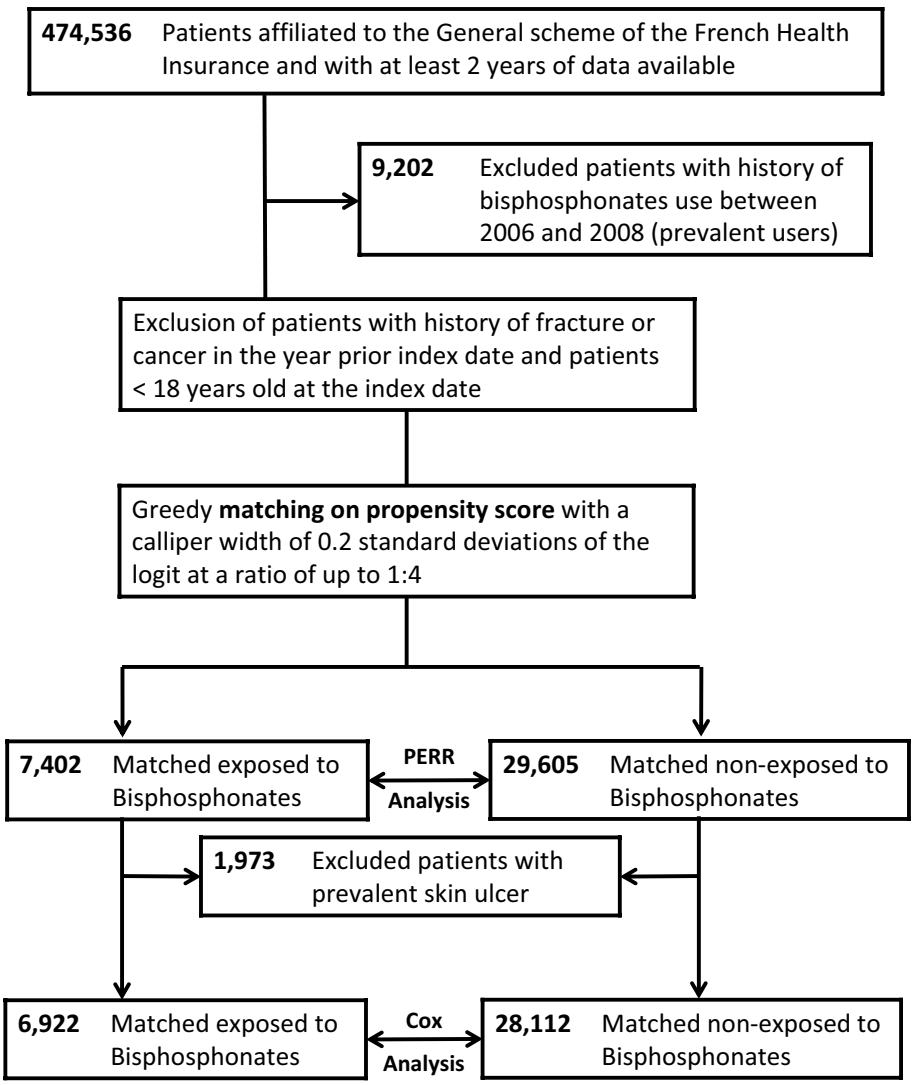


Fig. 4 Flow chart of the study. *PERR* prior event rate ratio

Table 1 Baseline and post-matching characteristics on the PERR cohort

Characteristic	Baseline (n = 465,334)		Post-matching on propensity score (n = 37,007)		
	Users of bisphosphonates (n = 11,689)[a]	Nonusers of bisphosphonates (n = 453,645)[b]	Users of bisphosphonates (n = 7402)[c]	Nonusers of bisphosphonates (n = 29,605)[c]	SMD, %
Male	2009 (17.2)	227,090 (50.1)	1200 (16.2)	4,209 (14.2)	− 9.16
Age, years (mean ± SD)	68.4 ± 12.1	40.1 ± 22.2	67.3 ± 12.1	68.2 ± 14.0	− 6.59
PVD	219 (1.87)	1157 (0.26)	120 (1.62)	504 (1.70)	0.42
Urinary incontinence	173 (1.48)	856 (0.19)	98 (1.32)	446 (1.51)	− 0.84
Faecal incontinence	13 (0.11)	111 (0.02)	5 (0.07)	100 (0.34)	− 1.24
Diabetes	1375 (11.8)	20,567 (4.53)	845 (11.4)	3316 (11.2)	0.65
Thrombosis	127 (1.09)	966 (0.21)	60 (0.81)	308 (1.04)	− 1.05
Hypertension	4202 (36.0)	39,597 (8.73)	2348 (31.7)	9362 (31.6)	0.20
Hyperlipidaemia	3291 (28.2)	25,295 (5.58)	1866 (25.2)	7447 (25.2)	0.12
Tobacco use	1082 (9.26)	10,533 (2.32)	575 (7.77)	2041 (6.89)	3.34
Obesity	686 (5.87)	6406 (1.41)	368 (4.97)	1432 (4.84)	0.60
Hospitalisations[d]	1.76 ± 5.27	0.28 ± 1.91	0.74 ± 2.53	0.55 ± 5.13	4.50
Corticosteroids[e]	4876 (41.7)	109,124 (24.1)	2895 (39.1)	10,664 (36.0)	6.37
≤ 30 days use	274 (2.34)	20,476 (4.51)	173 (2.34)	734 (2.48)	− 0.65
31–90 days use	2442 (20.9)	70,058 (15.4)	1506 (20.4)	5984 (20.2)	0.33
> 90 days use	2160 (18.5)	18,590 (4.10)	1216 (16.4)	3946 (13.3)	8.37

Data are given as n (%) unless otherwise specified

PERR prior event rate ratio, *PVD* periphery vascular disease

[a]Characteristics at first bisphosphonate dispensing date

[b]Characteristics at 01/01/2008

[c]Characteristics at index date

[d]Number of hospitalisations in the year preceding index date (mean ± SD)

[e]Cumulative corticoids use assessed by defined daily dose (DDD) in the 2 years preceding index date

controls for the PERR analysis, and 7233 exposed patients and 29,003 controls after exclusion of prevalent skin ulcer, for the Cox analysis.

Characteristics of exposed and unexposed subjects are summarised in Table 1 and Table S8 at baseline and post-matching on propensity score for the PERR and the Cox cohorts, respectively. Characteristics of exposed and unexposed subjects on the future exposed cohorts are summarised in Table S9. The SMD between the PERR and the Cox cohort are summarised in Table S10. We found almost no difference of vasodilator use between exposed and unexposed individuals with a standardised mean difference of 0.91%.

Skin ulcer characteristics, such as type of ulcer, mean number of occurrences per patient and mean duration until end of dressings supply are presented in Table 2.

Among patients exposed to bisphosphonates and unexposed patients, 3769 (10.2%) had at least one skin ulcer during the study period, 937 (12.7%) exposed patients and 2832 (9.6%) unexposed patients. Prior to the index date, 480 (6.5%) exposed patients and 1493 (5.0%) unexposed patients presented a skin ulcer. Post-index date, 572 (7.7%) exposed patients and 1728 (5.8%) unexposed patients presented a skin ulcer (Table 2).

3.2 Cox Proportional Hazards Analysis

3.2.1 Principle Analysis

The Cox proportional hazards analysis including only incident skin ulcers (exclusion of patients with a skin ulcer prior the index date) revealed a significant association between bisphosphonate exposure and skin ulcers with a HR = 1.40 (95% CI 1.26–1.56) (Fig. 5).

3.2.2 Sensitivity Analyses

The same analysis on the second control group (patients with a future exposition to bisphosphonates) also suggested a significantly higher risk of skin ulcer in the exposed group, but lower than the principle analysis with a HR = 1.25 (95% CI 1.13–1.38).

The Multiple Event-Time Outcomes analysis gave similar results, with a HR = 1.45 (95% CI 1.27–1.62).

Table 2 Number of patients with a skin ulcer and its type by bisphosphonate exposure

	PERR analysis						Cox analysis	
	Exposed group (n = 7402)			Unexposed group (n = 29,605)			Exposed	Unexposed
	Pre-exposure	Post-exposure	Total	Pre-index date	Post-index date	Total	(n = 6922)	(n = 28,112)
Skin ulcers	480 (6.5)	572 (7.7)	937 (12.7)	1493 (5.0)	1728 (5.8)	2832 (9.6)	457 (6.6)	1339 (4.8)
Pressure[a]	64 (13.3)	102 (17.8)	145 (15.5)	247 (16.5)	285 (16.5)	448 (15.8)	81 (17.7)	201 (15.0)
Vascular[a]	370 (77.1)	397 (69.4)	688 (73.4)	1086 (72.8)	1228 (71.1)	2064 (72.9)	318 (69.6)	978 (73.0)
Diabetic[a]	46 (9.6)	73 (12.8)	104 (11.1)	160 (10.7)	215 (12.4)	320 (11.3)	58 (12.7)	160 (12.0)
Number of skin ulcers	1.66 ± 1.06	1.59 ± 1.00	1.44 ± 0.84	1.67 ± 1.02	1.56 ± 0.97	1.44 ± 0.84	1.21 ± 0.51	1.19 ± 0.47
Duration, days	67 ± 138	52 ± 59	57 ± 104	66 ± 131	54 ± 62	57 ± 102	47 ± 44	47 ± 50

Data are given as *n* (%) unless otherwise specified. Number and duration are presented among patients with a skin ulcer as mean ± SD. The total column is defined by the first occurrence of skin ulcer, i.e., a patient with a skin ulcer pre- and post-index date will only count in the total for his/her prior skin ulcer

PERR prior event rate ratio

[a]Percentages are expressed among total skin ulcers for each column

Finally, with a lag time of one month, we found similar results, with a HR = 1.37 (95% CI = [1.23–1.53].

3.3 Prior Event Rate Ratio Analysis

3.3.1 Principle Analysis

Using the PERR design, we found no significant association between bisphosphonate exposure and skin ulcers in the original cohort with a HR PERR = 1.03 (95% CI 0.87–1.24) (HR pre = 1.30 [95% CI 1.17–1.44] and HR post = 1.34 [95% CI 1.22–1.47]).

3.3.2 Sensitivity Analysis

On the second control group, PERR analysis showed no significant association, with a HR = 0.89 (95% CI 0.76–1.06).

The PERR analysis on the Multiple Event-Time Outcomes cohort found a HR = 1.11 (95% CI 0.96–1.30).

Finally, with a lag time of one month, we found similar results, with a HR = 1.03 (95% CI = [0.86–1.23].

4 Discussion

In this study, while exploring the risk of skin ulceration associated with bisphosphonate exposure in a cohort comprising a random sample of the French population, we found a significant risk of cutaneous ulcer using a Cox proportional hazard model. However, this association became non-significant when using pre-exposure events to adjust the results for confounding using a PERR analysis. This situation is similar to another study exploring the impact of proton pump inhibitor exposure on the risk of pneumonia hospitalisation for which there were large discrepancies between Cox and PERR analyses [38]. In the Cox analysis, even after matching with a propensity score, using a second control group comprising future exposed patients and taking into consideration the multiplicity of events, it is still difficult to manage unmeasured confounding. This is particularly true for drugs such as bisphosphonates that do not have therapeutic alternatives for the same indication, which makes it problematic to select a relevant active control group.

Other pharmacoepidemiologic studies assessing the benefit or risk associated with bisphosphonate exposure usually selected control groups with simple matching on different covariates such as sex, age and the most common comorbidities [40–42]. Based on our results, we could hypothesise that these estimates could have been different using designs such as a PERR analysis. The method is based on a before-and-after design and assumes that differences in outcomes between exposed and unexposed patients before receiving

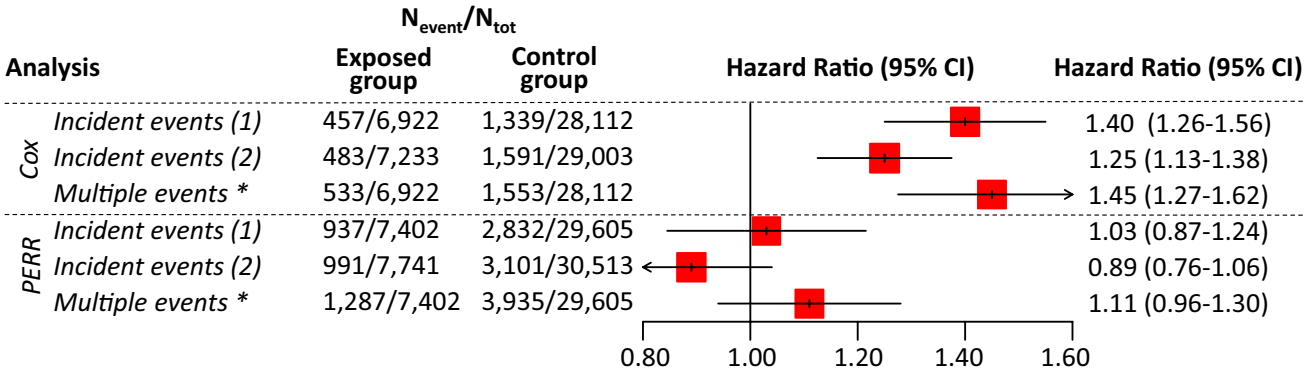


Fig. 5 Forest plot presenting the results of the 6 different analyses assessing the risk of skin ulcer after bisphosphonate exposure. *CI* confidence interval, *PERR* prior event rate ratio. (1) Non-exposed control group; (2) future exposed control group. *N* event: total number of events; N tot: total number of patients. *AUCs ratio

treatment reflect the combined effect of confounding factors independent of any effect of the study drug [34, 36, 43–47]. Yu et al and Rodgers et al studied its performance and found that the PERR method could significantly reduce bias due to unmeasured confounding factors compared with the standard Cox model, and obtained results close to those of randomised clinical trials [34, 44]. This method therefore seems an interesting way to reduce unmeasured confounders, but can only be applied to recurrent events. Moreover, several hypotheses are assumed: (1) the absence of influence of the occurrence of an event during the pre-treatment period on the choice of the treatment of interest. This hypothesis can be assumed to be valid in our study and for other studies assessing the risk of potential adverse effects that have not yet been described; (2) the presence of unmeasured confounding factors fixed in time; (3) the absence of a major interaction between the start of treatment and the unmeasured confounding factors.

Furthermore, given that the probability of a patient presenting the outcome is undoubtedly affected by the occurrence or not of the event previously and so by the number of occurrences of this event, we performed a multiple event-time outcomes analysis. We found no other study using a PERR design in combination with multiple event analysis. Our results obtained with this method were close to those of the first-event analyses, but the number of episodes of skin ulcer per patient was small and we might expect a greater difference when studying highly recurrent events.

This study also underlines the need to use multiple methods and designs when exploring an association using observational data. Recent studies have even demonstrated that thousands of sensitivity analyses can be performed to assess the robustness of pharmacoepidemiologic findings [19]. It is also worth noting that even if the safety signal detected by a disproportionality analysis conducted in the WHO pharmacovigilance database was considered robust (i.e., the signal was positive for all types of ulcers) and plausible from a pharmacological point of view, it has to be confirmed through pharmacoepidemiological studies [11]. Meta-research studies have indeed found that results of pharmacovigilance disproportionality analyses, aimed at detecting signals, are often insufficiently robust, selectively reported and over interpreted [48, 49].

This study has several strengths. First, to our knowledge, this is the first pharmacoepidemiologic study assessing the risk of skin ulcer due to bisphosphonate use, no clinical trials or meta-analyses have studied this research question. Second, the use of the French EGB database allowed us to obtain high quality data and sufficient statistical power [20, 22]. All outpatient supplies or health expenses of individuals covered by the French General Health Insurance scheme are registered in the database. In addition, the possibility of linking the data to the PMSI makes it possible to obtain quality information on patients' hospital stays. The EGB database represents a random sample of 1/97th of the French population covered by the general health insurance scheme. Thus, a selection bias seems unlikely. Identification of cutaneous ulcers was realised according to a validated algorithm [5, 29]. Our propensity score matching appears robust with standardised differences all below 10%. The use of a novel statistical method to assess the association between bisphosphonate exposure and the risk of skin ulcer limited unknown residual confounding factors. Our concordance analysis showed that the identification algorithm we used is quite robust with a good concordance between what we found with the French Health Insurance's algorithm and the diagnoses recorded at hospital discharge in the year, except for diabetic foot ulcers. This exception for diabetic foot ulcers could be explained by a clear ICD-10 diagnosis code for this condition and identification by exclusion with the algorithm, i.e., in patients with diabetes we considered a skin ulcer to be a diabetic foot ulcer if it was not classified as a pressure,

vascular or linked to surgery. Overall, the use of the algorithm instead of ICD-10 diagnosis codes seems a good compromise to identify a large number of ulcers and not just the most serious ones requiring hospitalisation. Finally, multiple time-event outcome and sensitivity analyses on another control group reinforce the validity of our results.

Notwithstanding, the use of the EGB database and PERR analysis presented some limitations. The main difficulty was to choose a comparator group. Bisphosphonates are the reference treatment for osteoporosis. Alternative therapeutic drugs are only prescribed in cases of therapeutic failure, so the patients are not at all similar in clinical terms. Thus, the absence of an active comparator group implies a risk of non-representativeness of the control group for confounding factors not included in the propensity score. We assessed this limitation by conducting sensitivity analysis on another control group comprising future-exposed subjects. Even after matching for known confounders, there may still be unmeasured or time-dependant confounders that bias the results of the study. The PERR analysis should limit this bias. Second, the EGB contains all data on prescribed medical supplies but patients buying OTC drugs and dressings, or self-medicating with products prescribed and supplied previously would not be identified in the database. In the case of bisphosphonates, in France all forms require a prescription so this limitation is unlikely. Moreover, some essential data required for drug evaluation studies are not available in the health insurance databases. This includes, medication adherence, only the dispensation of drugs can be seen in the database, not what was consumed by the patient. Socioeconomic data such as level of education, income level, socio-professional categories are not included, nor is information about lifestyle (smoking status, alcohol consumption, BMI, physical activity, etc.), which must be approximated by using specific identification algorithms [30, 31]. No clinical information (clinical examination by a physician, analytical laboratory results or medical imaging) is available in the EGB. Finally, PERR analysis is a strong method to limit confounding biases but one of its drawbacks is that it does not account for time-dependent confounding factors. For this reason, we limited our analysis to a time interval of 2 years around the index date.

5 Conclusion

This study suggests that in the general French population, bisphosphonate exposure is not associated with a higher risk of skin ulcers. Nevertheless, the discrepant results between the commonly used Cox model and the PERR analysis point to the presence of unmeasured and/or unknown residual confounding factors. Our study highlights the importance in pharmacoepidemiologic studies of conducting several analyses using complementary statistical methods to avoid a conclusion of false associations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-023-01336-x.

Acknowledgements We thank Alison Foote (an independent medical writer based in Grenoble France) for editing the manuscript.

Declarations

Funding This work was supported by CHUGA (Centre Hospitalier Universitaire Grenoble Alpes). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval Neither committee approval nor informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority (CNIL) agreement.

Consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions CJB, CB, JB, MR, SB, JLC, CK contributed to the study conception and design. Material preparation, data collection and analysis were performed by CJB, CB, CK. CJB, CB, JB, MR, SB, JLC, CK interpreted the data. CJB developed the manuscript and CB, JB, MR, SB, JLC, CK critically revised the article's intellectual content. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are not publicly available, publicly sharing EGB data is forbidden by law according to The French national data protection agency (Commission Nationale de l'Informatique et des Libertés, CNIL); regulatory decisions AT/CPZ/SVT/JB/DP/CR05222O of June 14, 2005 and DP/CR071761 of August 28, 2007. To request data access please contact The National Institute for Health Data (Institut National des Données de Santé, INDS).Clément Jambon-Barbara and Charles Khouri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Code availability The custom code will be made available to applicants upon reasonable request.

References

1. Falanga V, Isseroff RR, Soulika AM, et al. Chronic wounds. Nat Rev Dis Primer. 2022;8:50. https://doi.org/10.1038/s41572-022-00377-3.
2. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen Off Publ Wound Health Soc Eur Tissue Repair Soc. 2009;17:763–71. https://doi.org/10.1111/j.1524-475X.2009.00543.x.
3. Sen CK. Human wound and its burden: updated 2020 compendium of estimates. Adv Wound Care. 2021;10:281–92. https://doi.org/10.1089/wound.2021.0026.

4. Olsson M, Järbrink K, Divakar U, et al. The humanistic and economic burden of chronic wounds: a systematic review. Wound Repair Regen Off Publ Wound Health Soc Eur Tissue Repair Soc. 2019;27:114–25. https://doi.org/10.1111/wrr.12683.
5. Rames O, Sebo S, Pécault R et al (2015) Plaies chroniques en France: Prévalence, Caractéristiques et Évolution. Améliorer l'organisatoin de la prise en charge en sortie d'hospitalisation. Caisse National d'Assurance Maladie
6. Rice JB, Desai U, Cummings AKG, et al. Burden of venous leg ulcers in the United States. J Med Econ. 2014;17:347–56. https://doi.org/10.3111/13696998.2014.903258.
7. Rice JB, Desai U, Cummings AKG, et al. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. 2014;37:651–8. https://doi.org/10.2337/dc13-2176.
8. Hall J, Buckley HL, Lamb KA, et al. Point prevalence of complex wounds in a defined United Kingdom population. Wound Repair Regen Off Publ Wound Health Soc Eur Tissue Repair Soc. 2014;22:694–700. https://doi.org/10.1111/wrr.12230.
9. Mekkes JR, Loots MAM, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148:388–401. https://doi.org/10.1046/j.1365-2133.2003.05222.x.
10. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care. 2015;4:560–82. https://doi.org/10.1089/wound.2015.0635.
11. Duron D, Blaise S, Cracowski J-L, et al. Drug-induced skin ulcers: a disproportionality analysis from the WHO pharmacovigilance database. J Am Acad Dermatol. 2021;85:229–32. https://doi.org/10.1016/j.jaad.2020.08.013.
12. Cracowski J-L, Roustit M. Human skin microcirculation. Compr Physiol. 2020;10:1105–54. https://doi.org/10.1002/cphy.c190008.
13. Papapetrou PD. Bisphosphonate-associated adverse events. Horm Athens Greece. 2009;8:96–110. https://doi.org/10.14310/horm.2002.1226.
14. Wang Q, Liu J, Guo T, et al. Epidermal growth factor reverses the inhibitory effects of the bisphosphonate, zoledronic acid, on human oral keratinocytes and human vascular endothelial cells in vitro via the epidermal growth factor receptor (EGFR)/Akt/phosphoinositide 3-kinase (PI3K) signaling pathway. Med Sci Monit Int Med J Exp Clin Res. 2019;25:700–10. https://doi.org/10.12659/MSM.911579.
15. Gao S-Y, Zheng G-S, Wang L, et al. Zoledronate suppressed angiogenesis and osteogenesis by inhibiting osteoclasts formation and secretion of PDGF-BB. PLoS ONE. 2017;12:e0179248. https://doi.org/10.1371/journal.pone.0179248.
16. Jung J, Park JS, Righesso L, et al. Effects of an oral bisphosphonate and three intravenous bisphosphonates on several cell types in vitro. Clin Oral Investig. 2018;22:2527–34. https://doi.org/10.1007/s00784-018-2349-6.
17. Lang M, Zhou Z, Shi L, et al. Influence of zoledronic acid on proliferation, migration, and apoptosis of vascular endothelial cells. Br J Oral Maxillofac Surg. 2016;54:889–93. https://doi.org/10.1016/j.bjoms.2016.05.030.
18. Wagenmakers E-J, Sarafoglou A, Aczel B. One statistical analysis must not rule them all. Nature. 2022;605:423–5. https://doi.org/10.1038/d41586-022-01332-8.
19. Wang SV, Sreedhara SK, Bessette LG, Schneeweiss S. Understanding variation in the results of real-world evidence studies that seem to address the same question. J Clin Epidemiol. 2022;151:161–70. https://doi.org/10.1016/j.jclinepi.2022.08.012.
20. Moulis G, Lapeyre-Mestre M, Palmaro A, et al. French health insurance databases: what interest for medical research? Rev Med Interne. 2015;36:411–7. https://doi.org/10.1016/j.revmed.2014.11.009.
21. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017;65(Suppl 4):S149–67. https://doi.org/10.1016/j.respe.2017.05.004.
22. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26:954–62. https://doi.org/10.1002/pds.4233.
23. De Roquefeuil L, Studer A, Neumann A, Merlière Y. L'échantillon généraliste de bénéficiaires: représentativité, portée et limites. Prat Organ Soins. 2009;40:213–23. https://doi.org/10.3917/pos.403.0213.
24. Quantin C, Bouzelat H, Allaert FA, et al. Automatic record hash coding and linkage for epidemiological follow-up data confidentiality. Methods Inf Med. 1998;37:271–7.
25. Tuppin P, de Roquefeuil L, Weill A, et al. French national health insurance information system and the permanent beneficiaries sample. Rev Epidemiol Sante Publique. 2010;58:286–90. https://doi.org/10.1016/j.respe.2010.04.005.
26. Baumgarten M, Margolis D, Berlin JA, et al. Risk factors for pressure ulcers among elderly hip fracture patients. Wound Repair Regen Off Publ Wound Health Soc Eur Tissue Repair Soc. 2003;11:96–103. https://doi.org/10.1046/j.1524-475x.2003.11204.x.
27. Baumgarten M, Margolis DJ, Localio AR, et al. Extrinsic risk factors for pressure ulcers early in the hospital stay: a nested case-control study. J Gerontol A Biol Sci Med Sci. 2008;63:408–13. https://doi.org/10.1093/gerona/63.4.408.
28. Margolis DJ, Kantor J, Santanna J, et al. Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. Arch Dermatol. 2000;136:1531–5. https://doi.org/10.1001/archderm.136.12.1531.
29. Perez J (2020) Risque d'ulcère du pied diabétique et utilisation des inhibiteurs de la cyclooxygénase 2 : une étude cas-témoins nichée dans l'Echantillon Généraliste des Bénéficiaires (EGB)
30. Quantin C (2015) Etude des algorithmes de définition de pathologies dans le Système Nationale d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM). Caisse National d'Assurance Maladie
31. Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur. 2021;8: 100158. https://doi.org/10.1016/j.lanepe.2021.100158.
32. Géodes-Santé publique France—Indicateurs: cartes, données et graphiques. https://geodes.santepubliquefrance.fr/#view=map2&c=indicator. Accessed 25 Oct 2022.
33. Fuentes S, Cosson E, Mandereau-Bruno L, et al. Identifying diabetes cases in health administrative databases: a validation study based on a large French cohort. Int J Public Health. 2019;64:441–50. https://doi.org/10.1007/s00038-018-1186-3.
34. Yu M, Xie D, Wang X, et al. Prior event rate ratio adjustment: numerical studies of a statistical method to address unrecognized confounding in observational studies. Pharmacoepidemiol Drug Saf. 2012;21(Suppl 2):60–8. https://doi.org/10.1002/pds.3235.
35. Uddin MJ, Groenwold RHH, van Staa TP, et al. Performance of prior event rate ratio adjustment method in pharmacoepidemiology: a simulation study. Pharmacoepidemiol Drug Saf. 2015;24:468–77. https://doi.org/10.1002/pds.3724.
36. Tannen RL, Weiner MG, Xie D. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. BMJ. 2009;338: b81. https://doi.org/10.1136/bmj.b81.

37. Lip GYH, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost. 2016;116:975–86. https://doi.org/10.1160/TH16-05-0403.
38. Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. BMJ. 2016;355: i5813. https://doi.org/10.1136/bmj.i5813.
39. Claggett BL, McCaw ZR, Tian L, et al. Quantifying treatment effects in trials with multiple event-time outcomes. NEJM Evid. 2022;1:EVIDoa2200047. https://doi.org/10.1056/EVIDoa2200047.
40. Cardwell CR, Abnet CC, Veal P, et al. Exposure to oral bisphosphonates and risk of cancer. Int J Cancer. 2012;131:E717-725. https://doi.org/10.1002/ijc.27389.
41. Chlebowski RT, Chen Z, Cauley JA, et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28:3582–90. https://doi.org/10.1200/JCO.2010.28.2095.
42. Vestergaard P, Fischer L, Mele M, et al. Use of bisphosphonates and risk of breast cancer. Calcif Tissue Int. 2011;88:255–62. https://doi.org/10.1007/s00223-011-9463-7.
43. Alemayehu D, Alvir JMJ, Jones B, Willke RJ. Statistical issues with the analysis of nonrandomized studies in comparative effectiveness research. J Manag Care Pharm JMCP. 2011;17:S22–6. https://doi.org/10.18553/jmcp.2011.17.s9-a.S22.
44. Rodgers LR, Dennis JM, Shields BM, et al. Prior event rate ratio adjustment produced estimates consistent with randomized trial: a diabetes case study. J Clin Epidemiol. 2020;122:78–86. https://doi.org/10.1016/j.jclinepi.2020.03.007.
45. Lin NX, Henley WE. Prior event rate ratio adjustment for hidden confounding in observational studies of treatment effectiveness: a pairwise Cox likelihood approach. Stat Med. 2016;35:5149–69. https://doi.org/10.1002/sim.7051.
46. Uddin MJ, Groenwold RHH, Ali MS, et al. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. Int J Clin Pharm. 2016;38:714–23. https://doi.org/10.1007/s11096-016-0299-0.
47. Streeter AJ, Lin NX, Crathorne L, et al. Adjusting for unmeasured confounding in nonrandomized longitudinal studies: a methodological review. J Clin Epidemiol. 2017;87:23–34. https://doi.org/10.1016/j.jclinepi.2017.04.022.
48. Mouffak A, Lepelley M, Revol B, et al. High prevalence of spin was found in pharmacovigilance studies using disproportionality analyses to detect safety signals: a meta-epidemiological study. J Clin Epidemiol. 2021;138:73–9. https://doi.org/10.1016/j.jclinepi.2021.06.022.
49. Khouri C, Revol B, Lepelley M, et al. A meta-epidemiological study found lack of transparency and poor reporting of disproportionality analyses for signal detection in pharmacovigilance databases. J Clin Epidemiol. 2021;139:191–8. https://doi.org/10.1016/j.jclinepi.2021.07.014.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

3. Second- and Third-generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study

Au-delà des médicaments coupe-faim amphétaminiques et des drogues récréatives comme la méthamphétamine, le dasatinib est de plus suspecté d'induire des HTAP (7,114,142,143). Le dasatinib fait partie de la classe médicamenteuse des inhibiteurs de tyrosine kinase BCR-ABL, utilisée dans le traitement de la leucémie myéloïde chronique. Parmi les médicaments de cette classe, plusieurs séries de cas et analyses de disproportionnalité supportent l'association entre HTAP et le ITK BCR-ABL de seconde (nilotinib, dasatinib et bosutinib), et troisième génération (ponatinib), Figure 12 (115,144). L'imatinib, ITK BCR-ABL de première génération, n'a par contre jamais été associé à l'HTAP, et a même été testé comme traitement potentiel (145).

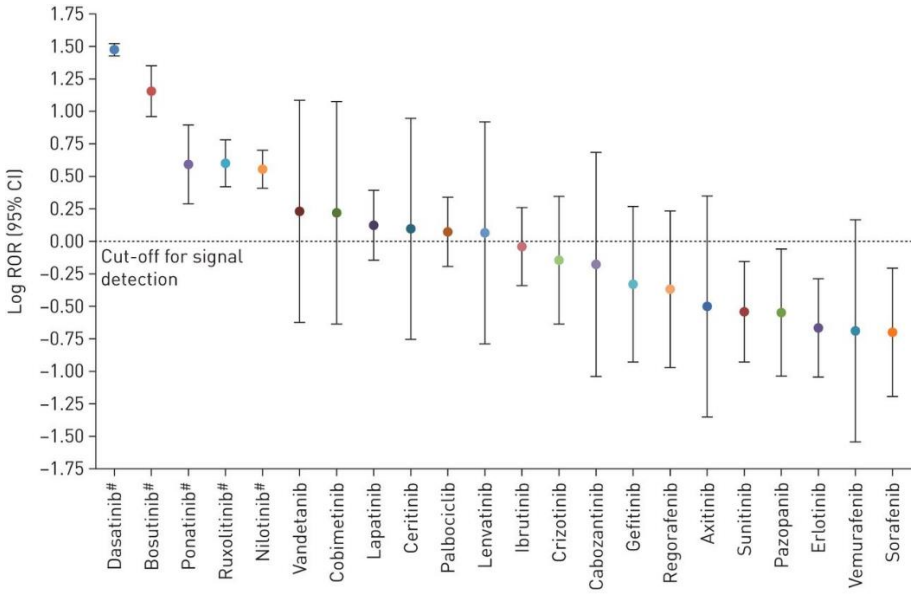


Figure 12. Forest plot des Reporting Odds Ratio (ROR) du couple ITK-HTAP. Extrait de (Cornet et al., European Respiratory Journal 2019) (115).

L'objectif de ce travail étant l'évaluation du profil de sécurité de médicaments apparus sur le marché après le contrôle (imatinib, première génération), le schéma d'étude le plus adéquat était le *Prevalent New-User Design* (146,147).

Second- and Third-generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study

Running title: PAH Risk with BCR-ABL TKI: Cohort study

Clément Jambon-Barbara [1,2], Samy Suissa [3,4], Sophie Dell'Aniello [3], Alex Hlavaty [1,2], Jean-Luc Cracowski [1,2], Marie-Camille Chaumais [5,6,7], Marc Humbert [5,8,9], David Montani [5,8,9], Charles Khouri [1,2,10]

[1] Grenoble Alpes University Hospital, Pharmacovigilance Unit, F-38000 Grenoble, France.
[2] Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, F-38000 Grenoble, France.
[3] Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada.
[4] Department of Epidemiology, Biostatistics and Occupational Health and Department of Medicine, McGill University, Montreal, Quebec, Canada.
[5] INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France.
[6] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Pharmacy, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.
[7] Université Paris-Saclay, Faculty of Pharmacy, Saclay, France.
[8] Université Paris-Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France.
[9] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Centre, Hôpital Bicêtre, DMU 5 Thorinno, Le Kremlin-Bicêtre, France.
[10] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000 Grenoble, France.

Corresponding author: Charles Khouri and Clément Jambon-Barbara, Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
Tel: +33 4 76 76 51 45
Fax: +33 4 76 76 56 55
E-mail: ckhouri@chu-grenoble.fr & cjambonbarbara@chu-grenoble.fr

ABSTRACT

Background: BCR-ABL tyrosine kinase inhibitors (TKI) have been increasingly linked to pulmonary arterial hypertension (PAH) since 2009, although supporting evidence is limited. Objective was to evaluate the risk of PAH associated with second- and third-generations BCR-ABL TKI, compared with imatinib in adults.

Methods: We conducted a prevalent new-user study within a population-based cohort constituted from the French national healthcare database between 2008 and 2022. Hazard ratios (HR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models, stratified by exposure-set to account for time effect. Incidence rates (IR) and corresponding 95% CIs were calculated using the Poisson distribution. Patients were followed from their cohort inclusion to occurrence of the primary outcome (i.e. new onset of PAH), switch to another BCR-ABL TKI, death from any cause, end of registration within the database or end of the study period, whichever came first.

Results: 5,644 dasatinib, 4,668 nilotinib, 1,756 bosutinib and 1,019 ponatinib new-users were each matched with up to 15 imatinib users on time conditional propensity score and on duration of prior imatinib use (prevalent users). Dasatinib was associated with a 20-fold increased risk of PAH compared with imatinib (946 *versus* 20 events per million persons per year; HR 20.80, 95%CI 7.08–61.07). Four PAH cases were identified after bosutinib exposure, corresponding to an IR of 982 (95%CI 267–2,514), *versus* none in the matched imatinib group. All four cases occurred on patients previously exposed to dasatinib. One case of PAH were observed with both nilotinib and ponatinib, without an increased PAH risk compared to imatinib.

Conclusion: Dasatinib is associated with an elevated risk of PAH, while bosutinib exposure may aggravate or trigger a recurrence of PAH in patients with prior dasatinib use. Whether bosutinib may trigger PAH without pre-exposure to dasatinib remains to be further explored.

CLINICAL PERSPECTIVE

What is new?

- Dasatinib exposure is associated with an elevated risk of pulmonary arterial hypertension (PAH).
- PAH after bosutinib exposure were only identified in patients previously exposed to dasatinib. Whether bosutinib may trigger PAH without pre-exposure to dasatinib remains to be further explored.
- Despite similar number of exposed patients with dasatinib, no increased risk of PAH after nilotinib exposure have been identified. The number of exposed patients is insufficient to assess the risk of PAH with ponatinib and asciminib.

What are the clinical implications?

- These findings should alert clinicians to the importance of monitoring the occurrence of PAH in chronic myeloid leukaemia patients treated with BCR-ABL tyrosine kinase inhibitor (TKI).
- Drug withdrawal and switch to another BCR-ABL TKI, notably nilotinib, for the treatment of chronic myeloid leukaemia in patients with PAH associated to dasatinib, may be a safer alternative than bosutinib.
- Some dasatinib or bosutinib exposed patients develop PAH that improves after drug withdrawal and do not require a specific treatment.

1. INTRODUCTION

Pulmonary arterial hypertension (PAH), corresponding to group one of the clinical classification of pulmonary hypertension, is a rare and incurable disease with a prevalence ranging from 15 to 55 and an incidence from 2.5 to 6 cases per million persons per year (1,2). PAH has a poor prognosis despite a significant improvement in long term median survival from 2.8 years in the 1980s to six years currently (2,3). Most common symptoms are non-specific including progressive breathlessness, fatigue, syncope, and signs of right heart failure. Among the multiple identified causes of PAH (e.g. idiopathic, heritable, associated with conditions like connective tissue disease, drugs and toxins or human immunodeficiency virus (HIV) infection), drugs associated PAH account for approximatively 10% of cases in large registry series (4,5). Beyond, amphetamine like appetite suppressants and recreational drugs such as methamphetamine, dasatinib have been increasingly linked to PAH since 2009 (6–9).

Dasatinib is a second-generation BCR-ABL tyrosine kinase inhibitors (BCR-ABL TKI) used to treat chronic myeloid leukaemia. Among the drug class, several recent case reports and pharmacovigilance analyses also support potential associations with other second-generation (nilotinib, bosutinib) and third-generation BCR-ABL TKI (ponatinib) (10–13). On the other hand, the first-generation BCR-ABL TKI (imatinib) has never been associated with PAH and was even tested as a potential treatment for PAH (14).

Preclinical data have shown that dasatinib exaggerates pre-existing PH after monocrotaline or sugen hypoxia exposure, compared to DMSO and imatinib (15). Furthermore, dasatinib has been shown to induce apoptosis of pulmonary endothelial cells, facilitate vasoconstriction of the human pulmonary artery, promote endothelial-mesenchymal transition and reduce cAbl kinase activity (16,17). cAbl deficiency also decrease the effect of the bone morphogenetic protein 9, a ligand encoded by *GDF2* whose loss is associated with PAH (18). Overall, while preclinical experiments and case series support a potential association with some of these drugs,

no observational study using routinely collected data have been conducted yet to estimate the risk of PAH associated with exposure to these drugs.

The primary objective of this study was to conduct a population-based cohort study, using the French Healthcare database, to evaluate the risk of PAH associated with exposure to each single second- and third- generation BCR-ABL TKI compared with first-generation imatinib.

2. METHODS

The reporting of this cohort study complies with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) and RECORD-PE statements **(Supplementary Material–Strobe Checklist)** (19,20). According to data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or organisation (public or private; for-profit or non-profit), can access anonymised SNDS data to do a study, research, or an evaluation of public interest, upon authorisation from the French Data Protection Office. Codes used to perform the analyses are available on demand of the corresponding author. The study cohort was formed using a prevalent new-user design with time-conditional propensity score matching, a design that emulates a clinical trial (21,22). The use of this design was driven by the objective of the study, which was to assess the risk of PAH associated with second or third-lines of chronic myeloid leukaemia treatment in comparison to the first-line (imatinib).

2.1.Data Source

The data source was derived from the French healthcare database, namely "Système National des Données de Santé (SNDS)". The SNDS covers over 99% of the population residing in France and contains information on demographic data, health care encounters visits, drug and medical devices dispensing, chronic medical conditions and is linked to the hospital discharge database, including hospitalisations diagnoses, date and duration, procedures, diagnostic-related groups and cause of death (23). It is currently one of the largest healthcare databases in the world, thus allowing the study of rare diseases and related pharmacoepidemiologic studies (24–28).

This study was conducted exclusively using anonymized data in the SNDS, with not informed consent required, under the French Data Protection Supervisory Authority (CNIL) agreement.

2.2.Study Population

2.2.1. Base cohort

First, we formed a base cohort of newly treated patients, defined as all patients aged 18 years or older receiving a first dispensing for any BCR-ABL TKI between January 01, 2008 and December 31, 2022. The date of this first dispensing defined base cohort entry. The BCR-ABL TKI treatments included the first-generation imatinib and second- and third-generations dasatinib, nilotinib, bosutinib, ponatinib, and asciminib (denoted DNBPA) (**Figure 1A**). Subjects with missing data on sex, date of birth, a previous diagnosis of PAH, a BCR-ABL TKI dispensing before January 01, 2008 or with fewer than 365 consecutive days of healthcare coverage before the date of base cohort entry were excluded.

2.2.2. *The prevalent new-user approach*

Time zero, or index date, was therefore defined as first DNBPA dispensing for the exposed group, and the corresponding date with same time since cohort entry for the imatinib group. Within the base cohort, each new-user of DNBPA generated an exposure-set of all subjects with the same year of index date and the same duration of imatinib exposure since base cohort entry (**Figure 1B**). The first exposure-set included exclusively the incident new-users of DNBPA, namely those whose first treatment was not imatinib, and those initiating treatment with imatinib. For this first exposure-set, a propensity score of treatment initiation with DNBPA was computed using covariate information measured at index date. For the subsequent exposure sets that included prevalent new-users (second-, third-, fourth-, or fifth- treatment line), namely those who initiated treatment with DNBPA after having first received imatinib, the exposure-set included all subjects continuing to receive a new prescription of first-generation imatinib at the same time since base cohort entry. For these prevalent new-users, time-conditional

propensity scores (TCPS) were computed using logistic regression, conditional on the exposure-set (i.e. duration of imatinib exposure prior treatment of interest), as a function of every covariate measured at the index date (see covariates below). Within each exposure-set, an DNBPA exposed patient with TCPS falling outside of the imatinib patients' TCPS range was excluded to confirm the positivity assumption. Subsequently, each new user of DNBPA was matched using a variable sequential ratio matching with up to 15 imatinib users, without replacement, within their exposure-set (i.e. same imatinib exposure duration since cohort entry) and with the same calendar year, the same exposure status (prevalent or incident), age on the range of ± 1 year and the closest TCPS value (within a calliper of 0.2 times the standard deviation).

Patients meeting these criteria were followed with an as-started approach, that is, until a first-ever PAH diagnosis, switch to another BCR-ABL TKI, death from any cause, end of registration within the database or end of the study period, whichever came first (**Figure 1C**).

2.3.Outcome

The primary outcome was the first PAH diagnosis. Given previous studies have shown that some TKI associated PAH may improve spontaneously without the need of PAH specific treatments, we defined our primary outcome by an hospitalisation for PAH (10th revision of the International Classification of Diseases (ICD-10) code I27.0) associated with at least 2 right heart catheterization (RHC) procedure 1 year before or after this hospitalisation (29). In addition, to avoid chronic thromboembolic pulmonary hypertension (CTEPH) misclassification, there was to be no CTEPH-specific procedures at any time. Date of the outcome was defined as the first hospitalisation or first RHC, whichever occurred first. All clinical codes used are presented in Supplementary Material Tables S1 (specific treatment codes) and S2 (right heart catheterization and CTEPH specific procedures codes).

189

190 *2.4.Covariates*

191 We considered a wide range of potential confounders measured at or before index date to
192 estimate the TCPS. Age and sex were retrieved at index date; at any time before index date, we
193 retrieved history of: chronic obstructive pulmonary disease (COPD), hypertension, heart
194 failure, diabetes, venous thromboembolic events (i.e. pulmonary embolism, phlebitis and
195 thrombophlebitis, other venous embolism and thrombosis), active dialysis, interstitial lung
196 diseases, lung transplant, lung cancer and PAH associated conditions (systemic scleroderma,
197 portal hypertension, HIV positive, sickle cell disease, congenital heart disease). The number of
198 hospitalizations and pulmonologist visits in the year before index date were used as an
199 approximation of healthcare consumption. Lastly, exposure to drugs associated with PAH
200 (possible or definite association) as defined by the 2022 ESC/ERS Guidelines: benfluorex,
201 dexfenfluramine, fenfluramine, cyclophosphamide, mitomycin C, diazoxide, sofosbuvir,
202 interferons alpha and beta, leflunomide, phenylpropanolamine, carfilzomib, trichloroethylene
203 (1) were also considered in the year before index date. As certain drugs were withdrawn from
204 the market before study start, or were not identifiable in the database (e.g. drugs reserved for
205 hospital use), we did not include: dexfenfluramine, fenfluramine, diazoxide, interferons alpha
206 and beta, phenylpropanolamine, carfilzomib, and trichloroethylene. All clinical codes used are
207 presented in Supplementary Material Table S3.

208

209 *2.5.Statistical Analysis*

210 All analyses were conducted for dasatinib, nilotinib, bosutinib, ponatinib, and asciminib
211 separately, using the matched imatinib users as comparator for each. Descriptive statistics for
212 quantitative parameters (mean and standard deviation or median and percentiles 25th and 75th)
213 and qualitative parameters (number of patients and percentage) were used to summarize

214 characteristics for the study population by exposure status. Characteristics of patients initiating
215 DNBPA were compared with matched imatinib users using standardized mean difference
216 (SMD) (imatinib users were weighted by the inverse of the number of controls to account for
217 the number of matched imatinib users per DNBPA new user). An absolute SMD ≤ 10%
218 indicates a negligible difference in potential known confounders and balanced matched cohorts
219 (30,31). Incidence rates (IR) and corresponding 95% confidence intervals (CI) of PAH were
220 calculated using the Poisson distribution and cumulative incidence functions were estimated
221 using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of PAH onset comparing
222 DNBPA versus imatinib users was estimated using a Cox proportional hazards regression
223 model, stratified by exposure-set to account for time effect. Finally, the number needed to harm
224 (NNH) over one year was estimated using the rate difference as a clinically more
225 understandable measure of impact (32,33).
226 Several sensitivity analyses were performed. First, the exposure window was modified to an
227 as-treated definition, i.e. patients were considered exposed from the first dispensing to the end
228 of the study period, a BCR-ABL TKI switch or the end of the drug coverage duration that is the
229 last drug dispensing plus 45 days. Second, incident and prevalent patients were analysed
230 independently to ensure that results were consistent between patients switching from imatinib
231 and patients starting directly with a second-line one. Third, PAH outcome definition was
232 modified to improve its specificity by adding the need of a PAH-approved treatment dispensing
233 6 months before or any time after hospitalisation but only requiring one RHC (34). Fourth, to
234 assess the impact of outcome misclassification we used the vibration of effect framework to
235 vary outcome classification according to estimated sensitivity and specificity (see
236 supplementary methods for a detailed information of this analysis). Lastly, to improve the
237 similarity between BCR-ABL TKI users, we have selected only the first matched imatinib user,
238 that is equivalent to a 1:1 propensity score matched cohort.

All statistical analyses were conducted with SAS EG® (SAS Institute, Cary, NC, USA), 8.3.7, and R, version 4.4.0 (R Foundation).

2.6.Role of the Funding source

This study was funded by the AGIRADOM (grant APMC 2023) and by the Grenoble Alpes University (PhD funding). The funders had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication. CJB and CK have full access to all data and all authors have full access to the statistical reports and tables in the study. CJB and CK take responsibility for the integrity of the data and the accuracy of the data analysis.

3. RESULTS

Among the 83,092,244 patients present in the SNDS between 2008 and 2022, the base cohort included 27,616 patients and 38,379 different treatment lines (i.e. each patient could be exposed to several treatment lines during the study period). A total of 23,477 (85.0%) patients were exposed to imatinib, 6,407 (23.2%) to dasatinib, 5,212 (18.9%) to nilotinib, 1,941 (7.0%) to bosutinib, 1,225 (4.4%) exposed to ponatinib and 117 (0.4%) to asciminib (not included in our study given the small number of patients exposed) (**Figure 2**). From the 27,616 patients of the base cohort, 22,605 (81.8%) had imatinib as their first-line BCR-ABL TKI, from whom 17,087 (75.6%) remained only on imatinib, and 3,662 (16.2%) switched for dasatinib, 1,216 (5.4%) for nilotinib, 526 (2.3%) for bosutinib, 114 (0.5%) for ponatinib, and none for asciminib. Among those who did not get exposed to imatinib as first-line, 3,004 (10.9%) were exposed to nilotinib, 1,565 (5.7%) to dasatinib, 246 (0.9%) to bosutinib, 196 (0.7%) to ponatinib, and none to asciminib (Supplementary Material Figure S1).

After TCPS matching and applying the positivity assumption, 5,644 dasatinib, 4,668 nilotinib, 1,756 bosutinib and 1,019 ponatinib new-users were matched to 20,065, 16,438, 9,491, and 6,452 imatinib users respectively (**Figure 2**, and for a detailed description of the number of controls per exposed patient, see Supplementary Material Table S4). Among them, 68.5% of patients were prevalent new users of dasatinib, 46.8% of nilotinib, 76.2% of bosutinib, and 55.6% of ponatinib, with a mean imatinib treatment duration since base cohort entry of 508 days for dasatinib, 507 days for nilotinib, 580 days for bosutinib, and 386 days for ponatinib. Median (interquartile range) of follow-up were 877 (271 to 2,120) and 1,054 (312 to 2,473), 1,064 (327 to 2,341) and 1,069 (336 to 2,323), 619 (195 to 1,275) and 615 (227 to 1,362), and 536 (213 to 1,299) and 686 (277 to 1,479) days for dasatinib and imatinib, nilotinib and imatinib, bosutinib and imatinib, and ponatinib and imatinib respectively. The baseline characteristics of dasatinib new users and matched imatinib users are presented in **Table 1**, and

see Supplementary Material Tables S5 to S7 for other cohorts. The groups were well-balanced across all covariates, as indicated by the SMD < 10% (see Supplementary Material Figures S2 to S5 for TCPS distribution pre- and post-matching).

In the dasatinib cohort, we identified 20 cases of PAH in the dasatinib group and 4 cases in the imatinib group, corresponding to incidence rates (IR) of 945.7 (95% CI 577.6 to 1,460.5), and 20.3 (95% CI 1.9 to 79.7) per million persons per year, respectively. Compared with imatinib use, dasatinib was associated with an increased risk of PAH with a HR of 20.80 (95% CI 7.08 to 61.07) and with a NNH of 1 case of PAH per 1,081 (95%CI 746 to 1,961) patients exposed for one year (**Table 2** & **Figure 3**). All sensitivity analyses (as-treated analysis, incident and prevalent status distinction, PAH specific definition and control group refinement) were consistent with the main analysis (**Table 3**). Characteristics of dasatinib users presenting PAH are described in supplementary material (Table S8 and Table S9 for PAH specific and sensitive definitions respectively).

In the nilotinib cohort, there was a single PAH case in nilotinib users, and two cases in the matched imatinib group, corresponding to IR of 55.2 (1.4 to 307.7) and 11.7 (0.1 to 80.2) respectively. Compared to imatinib use, nilotinib was not associated with an increased PAH risk with a HR of 1.16 (95%CI 0.10 to 12.9) (**Table 2**).

In the bosutinib cohort, there were 4 cases of PAH in bosutinib users and none in the matched imatinib group, corresponding to an IR of 981.7 (95% CI 267.5 to 2,513.5) and 0.0 (95% CI 0.0 to 158.9) respectively, and a NNH of 1,019 (95%CI 515 to 49,736) patients exposed for one year (**Table 2**). All four PAH cases occurred during bosutinib exposure as second or third treatment-line therapy on patients previously exposed to dasatinib as, and two of these patients had been hospitalised in the year prior to bosutinib initiation for cardiac or pulmonary conditions.

In the ponatinib cohort, one case of PAH was retrieved both in ponatinib and in imatinib users, corresponding to IR of 443.3 (11.2 to 2,469.7) and 4.1 (0.0 to 236.2) respectively. Compared to imatinib use, ponatinib was not associated with an increased PAH risk with a HR of 6.56 (95%CI 0.40 to 107.00) (**Table 2**).

All results retrieved with the specific outcome definition are presented in Supplementary Material Table S10, and vibration of effect framework analysis is presented in Supplementary Material Figure S6 to S9.

4. DISCUSSION

In this population-based cohort study of patients exposed to BCR-ABL TKI, dasatinib use was associated with an increased risk for PAH compared to imatinib users. Bosutinib use may also be associated with an increased risk for PAH or an increased risk of PAH aggravation after dasatinib exposure. This study constitutes the first retrospective cohort study aiming to assess causal links between exposure to suspected drugs and onset of PAH and demonstrates the feasibility of using routinely collected data to assess iatrogenic signals of PAH, opening new avenues in the field.

Causally attributing the onset of a PAH to drug exposure is extremely challenging, given the long and variable delay in onset of disease (e.g. sometimes years after exposure), the latency between first symptoms and diagnosis by right heart catheterization, frequent multiple and variable exposures, especially for BCR-ABL TKI, and the large proportion of non-drug-induced and idiopathic forms of PAH. Thus, populational data allowing to quantify risk of events in users of a given drug are crucial to assess safety signals identified by clinical and/or pre-clinical studies. While dasatinib is already considered as a definite cause of PAH since the 6th World Symposium on Pulmonary Hypertension in 2018 (7), the evidence base is only constituted by cases series, pharmacovigilance disproportionality analyses and preclinical evidence (7,13,35–40). Our results are therefore consistent with and reinforce these previous evidences but also adds substantial knowledge on the topic, notably by quantifying the relative (HR) and absolute (NNH) risk of PAH after dasatinib and bosutinib exposure. Moreover, an in-depth review of the PAH cases retrieved with both algorithms under dasatinib exposure showed that patients were overall in better health, younger, and more importantly with no PAH-associated condition or drugs, which reinforces the hypothesis of PAH induced solely by dasatinib exposure. In addition, cardiologic and respiratory characteristics of dasatinib users

presenting PAH were similar to those of users without PAH, which strengthens our confidence in the identification of PAH cases and the absence of misclassification of type 2, or type 3 PH. Our findings support the hypothesis that bosutinib may worsen or trigger a recurrence of PAH initially induced by dasatinib. This observation aligns with most of previously reported cases in the literature, where patients with pre-existing dasatinib-induced PAH experienced a relapse within 12 months after a direct switch to bosutinib (41–45). Yet, two recent case-reports described new onset of PAH after exposure to bosutinib in patients without pulmonary or cardiovascular symptoms during exposure to dasatinib (46,47). Whether exposure to dasatinib still have a role in the pathophysiology of these PAH remains therefore to be further elucidated. In our study, the low number of patients exposed to bosutinib without prior dasatinib exposure prevents us to conclude as an absence of PAH risk although we did not observe any PAH cases in this specific subpopulation. Our results also suggest the absence or very low risk of PAH following nilotinib exposure and the low number of exposed patients prevents us to any conclusion for ponatinib, while also flagged as a potential trigger of PAH by the World Symposium on Pulmonary Hypertension (2). However, given the limited number of exposed patients in France, ongoing vigilance is warranted, highlighting the need of collaborative initiatives to further investigate these associations.

Although we included the entire French population, our study suffers from a lack of power and very few events were identified using our definition of PAH. After considering comments from editors and reviewers, we decided to use a definition of PAH outcomes not requiring PAH-specific drugs, despite lower specificity in validation studies (34,48). This choice was made because some PAH associated with TKI may improve spontaneously without the need for specific PAH treatment, and because this result gives figures more consistent with the French PH registry. While this definition of PAH found 20 cases of PAH in dasatinib users versus 7 using the specific validated definition of PAH, fewer cases were identified in the overall French

356 healthcare database (9,486 versus 9,931). These results highlight the need to develop and
357 validate complementary algorithms specific to PAH aetiologies, or to merge electronic medical
358 records with hospital data warehouses to enable direct identification of PAH from medical
359 records. (49).
360 We also encourage other researchers to replicate our findings and conduct meta-analyses to get
361 more precise estimates and further investigate the risk of PAH associated with bosutinib
362 exposure. The development of database networks, common data models, and methods for
363 federated analyses will allow in the near future to perform collaborative international
364 observational studies powered to explore rare diseases associated with rare exposures (50,51).
365 This study has several strengths. First, to our knowledge, it is the first population-level study
366 assessing the risk of PAH after BCR-ABL TKI exposure. Second, we assembled a large
367 representative cohort of every patient who was dispensed a BCR-ABL TKI in France between
368 2008 and 2022. We matched almost all dasatinib, nilotinib, bosutinib, and ponatinib users to
369 imatinib users reducing selection bias. Matching was based on duration of imatinib exposure,
370 time-conditional propensity score, calendar year, age and incident/prevalent status to enhance
371 comparability. The use of a prevalent new-user design allowed inclusion of all patients exposed
372 to any BCR-ABL TKI treatment, even in second- or third-line therapies, which is essential
373 given that most patients in France receive imatinib initially (21,22). Our TCPS matching
374 appears robust with SMD all below 10%. Additionally, using an active comparator (i.e.
375 imatinib) helps minimize unmeasured confounders and time-related bias (52,53). Third, we
376 used a PAH outcome definition validated within our healthcare database (34).
377 Nonetheless, some limitations should be considered. Firstly, the lack of data on RHC results is
378 a major limitation to the identification of PAH, and misclassification of some PAH cases may
379 have occurred. Yet, we performed two sensitivity analyses using a specific outcome definition
380 previously validated and used a vibration of effect framework to assess the impact of

misclassification of the results; both analyses yielding consistent results. Moreover, we extracted all cases of PAH reported in the French PH registry in patients exposed to BCR-ABL TKI during the study period (n=47) (5). In the French healthcare database, before matching, and regardless of the date of PAH occurrence, from 2007 to December 2022 we identified consistent number of PAH (n=61) using the main outcome definition. Second, despite matching on TCPS for multiple known confounders, residual confounding may persist, especially due to lack of sociodemographic data and data on the severity/evolution of CML. To minimize this issue and to approximate the likelihood to be diagnosed for a PAH, we used the number of hospitalizations and pulmonologist visits in the year prior index date. Third, to explore the influence of prior treatment lines on our causal contrast of interest, we conducted separate subgroup analyses on prevalent or incident users, finding consistent results that reinforce the robustness of the merged results from our prevalent new-user design.

5. CONCLUSION

This study suggests that in French chronic myeloid leukaemia patients treated by BCR-ABL TKI, dasatinib is associated with an elevated risk of PAH, while bosutinib exposure may aggravate or trigger a recurrence of PAH in patients with pre-existing dasatinib-associated PAH. Whether bosutinib may trigger PAH without pre-exposure to dasatinib remains to be further explored. Replicating this study in other countries and databases is essential to enhance the power and precision of these findings.

DISCLOSURE STATEMENTS

Contributors: All authors conceived and designed the study and acquired, analysed, or interpreted the data. CJB, JLC, AH, MCC, MH, DM and CK reviewed the clinical identification codes. CJB conducted the statistical analyses and wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. CK obtained the funding. CK is the guarantor. The corresponding authors (CJB and CK) attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by the AGIRADOM (grant APMC 2023) and by the Grenoble Alpes University (PhD funding). The funders had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication. CJB and CK have full access to all data and all authors have full access to the statistical reports and tables in the study. CJB and CK take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CJB, SD, AH, JLC, MCC, and CK have no competing interests. SS reports the following activities: payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events made to him as speaking fees from CSL Behring, and Covispharma; payments made to him for participation on Advisory Board Committee Meetings from Boehringer-Ingelheim Intl, Novartis, and Panalgo. MH reports the following activities: grants or contracts from Gossamer, and Merck to his institution; consulting fees as payments made to him from 35 Pharma, Aerovate, AOP Orphan, Chiesi, Ferrer, Gossamer, Inhibikase, Janssen, Keros, Liquidia, Merck, Morphic, Novartis, Regeneron, Respira, Roivant, and United Therapeutics; payment or honoraria for

lectures, presentations, speakers bureaus, manuscript writing or educational events made to him from Merck; payments made to him for participation on a Data Safety Monitoring Board or Advisory Board from 35 Pharma, Aerovate, Janssen, Inhibikase, Keros, Merck, Novartis, and United Therapeutics. DM reports the following activities: grants or contracts from Acceleron, Janssen, and Merck MSD to his institution; consulting fees as steering committee in pulmonary hypertension from Acceleron, Merck MSD, Janssen, and Ferrer; payment or honoraria as speaker at conferences from Bayer, Janssen, Boerhinger, Chiesi, GSK, Ferrer, Merck MSD.

Data sharing: According to data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or organisation (public or private; for-profit or non-profit), can access anonymised SNDS data to do a study, research, or an evaluation of public interest, upon authorisation from the French Data Protection Office (See https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html). Codes used to perform the analyses are available on demand of the corresponding author.

6. REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618–731.

2. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024 Aug 29;2401324.

3. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018 Mar 14;360:j5492.

4. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest. 2010 Feb;137(2):376–87.

5. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary Arterial Hypertension in France: Results from a National Registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023–30.

6. Correale M, Tricarico L, Grazioli D, Formica ES, Petrucci R, Persichella P, et al. Drug-Induced Pulmonary Arterial Hypertension: Mechanisms and Clinical Management. Cardiovasc Drugs Ther. 2019 Dec;33(6):725–38.

7. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan;53(1):1801913.

8. Mattei D, Feola M, Orzan F, Mordini N, Rapezzi D, Gallamini A. Reversible dasatinib-induced pulmonary arterial hypertension and right ventricle failure in a previously allografted CML patient. Bone Marrow Transplant. 2009 Jun;43(12):967–8.

9. Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. Leuk Res. 2009 Jun;33(6):861–4.

10. Quilot FM, Georges M, Favrolt N, Beltramo G, Foignot C, Grandvuillemin A, et al. Pulmonary hypertension associated with ponatinib therapy. Eur Respir J. 2016 Feb;47(2):676–9.

11. Hickey PM, Thompson AAR, Charalampopoulos A, Elliot CA, Hamilton N, Kiely DG, et al. Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. Eur Respir J. 2016;48(5):1514–6.

12. Zakrzewski D, Seferynska I, Warzocha K, Hryniewiecki T. Elevation of pulmonary artery pressure as a complication of nilotinib therapy for chronic myeloid leukemia. Int J Hematol. 2012 Jul;96(1):132–5.

13. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, et al. Pulmonary Arterial Hypertension associated with Protein Kinase Inhibitors: A pharmacovigilance-pharmacodynamic study. Eur Respir J. 2019 Mar 7;

14. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013 Mar 12;127(10):1128–38.

15. Guignabert C, Phan C, Seferian A, Huertas A, Tu L, Thuillet R, et al. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. J Clin Invest. 2016 Aug 2;126(9):3207–18.

16. Le Vely B, Phan C, Berrebeh N, Thuillet R, Ottaviani M, Chelgham MK, et al. Loss of cAbl Tyrosine Kinase in Pulmonary Arterial Hypertension Causes Dysfunction of Vascular Endothelial Cells. Am J Respir Cell Mol Biol. 2022 Aug;67(2):215–26.

17. Ribeuz HL, Willer ASM, Chevalier B, Sancho M, Masson B, Eyries M, et al. Role of KCNK3 Dysfunction in Dasatinib-associated Pulmonary Arterial Hypertension and Endothelial Cell Dysfunction. Am J Respir Cell Mol Biol. 2024 Jul;71(1):95–109.

18. Grynblat J, Bogaard HJ, Eyries M, Meyrignac O, Savale L, Jaïs X, et al. Pulmonary vascular phenotype identified in patients with GDF2 (BMP9) or BMP10 variants: an international multicentre study. Eur Respir J. 2024 Apr;63(4):2301634.

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007 Oct 20;335(7624):806–8.

20. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ. 2018 Nov 14;k3532.

21. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiol Drug Saf. 2017 Apr;26(4):459–68.

22. Suissa S, Dell'Aniello S, Renoux C. The Prevalent New-user Design for Studies With no Active Comparator: The Example of Statins and Cancer. Epidemiol Camb Mass. 2023 Sep 1;34(5):681–9.

23. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954–62.

24. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, De Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev DÉpidémiologie Santé Publique. 2017 Oct;65:S149–67.

25. de Germay S, Conte C, Micallef J, Bouquet E, Chouchana L, Lafaurie M, et al. Performing pharmacoepidemiological studies using the French health insurance data warehouse (SNDS): How to translate guidelines into practice. Therapie. 2023 Jan 28;S0040-5957(23)00026-4.

26. Jabagi MJ, Bertrand M, Botton J, Le Vu S, Weill A, Dray-Spira R, et al. Stroke, Myocardial Infarction, and Pulmonary Embolism after Bivalent Booster. N Engl J Med. 2023 Apr 13;388(15):1431–2.

27. Lassalle M, Zureik M, Dray-Spira R. Proton Pump Inhibitor Use and Risk of Serious Infections in Young Children. JAMA Pediatr. 2023 Oct 1;177(10):1028–38.

516 28. Roland N, Neumann A, Hoisnard L, Duranteau L, Froelich S, Zureik M, et al. Use of progestogens
517 and the risk of intracranial meningioma: national case-control study. BMJ. 2024 Mar
518 27;384:e078078.

519 29. Weatherald J, Chaumais MC, Savale L, Jaïs X, Seferian A, Canuet M, et al. Long-term outcomes of
520 dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J. 2017
521 Jul;50(1):1700217.

522 30. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable
523 Between Two Groups in Observational Research. Commun Stat - Simul Comput. 2009 May
524 14;38(6):1228–34.

525 31. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between
526 treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083–
527 107.

528 32. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the
529 consequences of treatment. N Engl J Med. 1988 Jun 30;318(26):1728–33.

530 33. Suissa S. Calculation of number needed to treat. N Engl J Med. 2009 Jul 23;361(4):424–5.

531 34. Jambon-Barbara C, Hlavaty A, Bernardeau C, Bouvaist H, Chaumais MC, Humbert M, et al.
532 Development and validation of a code-based algorithm using in-hospital medical records to
533 identify patients with pulmonary arterial hypertension in the French Healthcare Database. ERJ
534 Open Res. 2024 Jan 1;00109–2024.

535 35. Weatherald J, Bondeelle L, Chaumais MC, Guignabert C, Savale L, Jaïs X, et al. Pulmonary
536 complications of Bcr-Abl tyrosine kinase inhibitors. Eur Respir J. 2020 Oct;56(4):2000279.

537 36. Weatherald J, Chaumais MC, Montani D. Pulmonary arterial hypertension induced by tyrosine
538 kinase inhibitors. Curr Opin Pulm Med. 2017;23(5):392–7.

539 37. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, et al. Pulmonary arterial
540 hypertension in patients treated by dasatinib. Circulation. 2012 May 1;125(17):2128–37.

541 38. Orlikow E, Weatherald J, Hirani N. Dasatinib-Induced Pulmonary Arterial Hypertension. Can J
542 Cardiol. 2019 Nov;35(11):1604.e1-1604.e3.

543 39. Hlavaty A, Roustit M, Montani D, Chaumais MC, Guignabert C, Humbert M, et al. Identifying new
544 drugs associated with pulmonary arterial hypertension: A WHO pharmacovigilance database
545 disproportionality analysis. Br J Clin Pharmacol. 2022 Dec;88(12):5227–37.

546 40. McGee M, Whitehead N, Martin J, Collins N. Drug-associated pulmonary arterial hypertension.
547 Clin Toxicol Phila Pa. 2018 Sep;56(9):801–9.

548 41. Hickey PM, Thompson AAR, Charalampopoulos A, Elliot CA, Hamilton N, Kiely DG, et al. Bosutinib
549 therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. Eur
550 Respir J. 2016 Nov;48(5):1514–6.

551 42. Riou M, Seferian A, Savale L, Chaumais MC, Guignabert C, Canuet M, et al. Deterioration of
552 pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. Eur
553 Respir J. 2016 Nov;48(5):1517–9.

554 43. Seegobin K, Babbar A, Ferreira J, Lyons B, Cury J, Seeram V. A case of worsening pulmonary
555 arterial hypertension and pleural effusions by bosutinib after prior treatment with dasatinib.
556 Pulm Circ. 2017;7(4):808–12.

557 44. Takatsuka I, Hirata H, Takahashi T, Dohtan S, Oka S, Sakamoto N, et al. Successful treatment with
558 nilotinib after bosutinib-induced pulmonary arterial hypertension recurrence following dasatinib
559 in chronic myeloid leukemia in chronic phase. Leuk Res Rep. 2022;17:100312.

560 45. Parthvi R, Gibbons W. Pulmonary Arterial Hypertension Worsened by Bosutinib in Patient With
561 Previous Dasatinib Treatment. Am J Ther. 2020 Sep 16;28(6):e704–6.

562 46. Ivan J, Esnaud R, Orvain C, Khouri C, Chaumais MC, Humbert M, et al. Reversible pulmonary
563 arterial hypertension induced by bosutinib: a case report. ERJ Open Res. 2024 Nov 14;00943–
564 2024.

565 47. Yo S, Thenganatt J, Lipton J, Granton J. Incident pulmonary arterial hypertension associated with
566 Bosutinib. Pulm Circ. 2020;10(3):2045894020936913.

567 48. Gillmeyer KR, Lee MM, Link AP, Klings ES, Rinne ST, Wiener RS. Accuracy of Algorithms to Identify
568 Pulmonary Arterial Hypertension in Administrative Data. Chest. 2019 Apr;155(4):680–8.

569 49. Kogan E, Didden EM, Lee E, Nnewihe A, Stamatiadis D, Mataraso S, et al. A machine learning
570 approach to identifying patients with pulmonary hypertension using real-world electronic health
571 records. Int J Cardiol. 2023 Mar;374:95–9.

572 50. EMA. European Medicines Agency. 2022 [cited 2022 Nov 3]. Initiation of DARWIN EU®
573 Coordination Centre advances integration real-world evidence into assessment medicines in the
574 EU. Available from: https://www.ema.europa.eu/en/news/initiation-darwin-eur-coordination-
575 centre-advances-integration-real-world-evidence-assessment

576 51. Gedeborg R, Igl W, Svennblad B, Wilén P, Delcoigne B, Michaëlsson K, et al. Federated analyses
577 of multiple data sources in drug safety studies. Pharmacoepidemiol Drug Saf. 2023
578 Mar;32(3):279–86.

579 52. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational
580 studies. Nat Rev Rheumatol. 2015 Jul;11(7):437–41.

581 53. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug
582 Saf. 2020 Sep;29(9):1101–10.

583

584

585 **7. TABLES**

Table 1. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for dasatinib versus imatinib cohort

Characteristic	Dasatinib users	Imatinib users	SMD (%)
Number of patients	5,644	20,065	/
Weighted number of patients	5,644	5,644	/
Female	2,486 (44)	2,452 (43.4)	1.2
Age, years (mean ± SD)	59.6 ± 15.2	59.6 ± 8.0	- 0.1
Imatinib exposure *	150 (0 – 450)	150 (0 – 450)	Matching variable
Prevalent user status	3,867 (68.5)	3,867 (68.5)	Matching variable
Calendar year			
2008	114 (2.0)	114 (2.0)	Matching variable
2009	239 (4.2)	239 (4.2)	Matching variable
2010	266 (4.7)	266 (4.7)	Matching variable
2011	328 (5.8)	328 (5.8)	Matching variable
2012	323 (5.7)	323 (5.7)	Matching variable
2013	373 (6.6)	373 (6.6)	Matching variable
2014	402 (7.1)	402 (7.1)	Matching variable
2015	390 (6.9)	390 (6.9)	Matching variable
2016	474 (8.4)	474 (8.4)	Matching variable
2017	488 (8.7)	488 (8.7)	Matching variable
2018	451 (8.0)	451 (8.0)	Matching variable
2019	458 (8.1)	458 (8.1)	Matching variable
2020	406 (7.2)	406 (7.2)	Matching variable
2021	465 (8.2)	465 (8.2)	Matching variable
2022	467 (8.3)	467 (8.3)	Matching variable
Comorbidities			
COPD	216 (3.8)	238 (4.2)	- 2.0
Hypertension	3,032 (53.7)	3088 (54.7)	- 2.0
Heart Failure	309 (5.5)	321 (5.7)	- 0.9
Diabetes	1,001 (17.7)	1026 (18.2)	- 1.2
VTE	317 (5.6)	337 (6.0)	- 1.5
Dialysis	23 (0.4)	21 (0.4)	0.5
Interstitial lung diseases	40 (0.7)	43 (0.8)	- 0.6
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	45 (0.8)	54 (1.0)	- 1.8
PAH associated conditions			
Systemic Scleroderma	8 (0.1)	5 (0.1)	1.3
Portal Hypertension	10 (0.2)	10 (0.2)	0.1
HIV positive	17 (0.3)	22 (0.4)	- 1.6
Sickle cell disease	7 (0.1)	8 (0.1)	- 0.3
Congenital heart disease	7 (0.1)	5 (0.1)	0.9
Drugs associated with PAH (possible and definite association) †			
Benfluorex	1 (0.0)	1 (0.0)	0.1
Cyclophosphamide	3 (0.1)	6 (0.1)	- 2.1
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	1 (0.0)	0 (0.0)	1.9
Leflunomide	0 (0.0)	0 (0.0)	- 1.1

Number of hospitalizations ‡			
0	2,126 (37.7)	2055 (36.4)	2.6
1	1,459 (25.9)	1475 (26.1)	- 0.6
2	841 (14.9)	896 (15.9)	- 2.7
3	403 (7.1)	401 (7.1)	0.1
≥ 4	815 (14.4)	817 (14.5)	- 0.1
Number of pulmonologist visits ‡			
0	5,190 (92.0)	5144 (91.1)	3.0
1	136 (2.4)	143 (2.5)	- 0.9
2-6	142 (2.5)	167 (3.0)	- 2.7
7-11	45 (0.8)	57 (1.0)	- 2.3
≥ 12	131 (2.3)	132 (2.3)	- 0.1

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a dasatinib user with 10 controls, will have a weight of 0.1.
Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
TCPS: Time Conditional Propensity Score.
SMD: Standardized Mean Differences.
* Duration of imatinib exposure since base cohort entry, days, median (IQR).
† Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (1).
‡ Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
PAH: Pulmonary Arterial Hypertension.
HIV: Human Immunodeficiency Virus.

586

Table 2. Incidence rates, hazard ratios and number needed to harm for PAH: primary analysis

Exposure	No of patients	No of events	Person-years	Incidence rate (95%CI) *	Hazard Ratio (95%CI)	NNH (95%CI) †
Main analysis (as-started)						
Imatinib	20,065	4	85,334	20.3 (1.9 to 79.7)	1.00 (reference)	Reference
Dasatinib	5,644	20	21,149	945.7 (577.6 to 1,460.5)	**20.80 (7.08 to 61.07)**	1,081 (746 to 1,961)
Imatinib	16,438	2	63,949	11.7 (0.1 to 80.2)	1.00 (reference)	Reference
Nilotinib	4,668	1	18,108	55.2 (1.4 to 307.7)	1.16 (0.10 to 12.86)	22,991 (6,454 to NA)
Imatinib	9,491	0	23,214	0.0 (0.0 to 158.9)	/	Reference
Bosutinib	1,756	4	4,074	981.7 (267.5 to 2,513.5)	/	1,019 (515 to 49,736)
Imatinib	6,452	1	16,208	4.1 (0.0 to 236.2)	1.00 (reference)	/
Ponatinib	1,019	1	2,256	443.3 (11.2 to 2,469.7)	6.56 (0.40 to 107.00)	/

PAH: pulmonary arterial hypertension; No: Number; CI: confidence interval; NNH: number of patients exposed for one year needed to harm; RHC: right heart catheterization; NA: not applicable.

* Per million person-years.

† 95%CI estimated from the 95%CI of the risk difference.

Table 3. Incidence rates, hazard ratios and number needed to harm for PAH: sensitivity analyses

Exposure	No of patients	No of events	Person-years	Incidence rate (95%CI) *	Hazard Ratio (95%CI)	NNH (95%CI) †
As-treated:						
Imatinib	20,065	3	54,645	28.1 (2.1 to 118.4)	1.00 (reference)	Reference
Dasatinib	5,644	19	15,211	1,249.1 (752.0 to 1,950.6)	**22.78 (6.72 to 77.18)**	819 (561 to 1,520)
Imatinib	16,438	1	44,644	11.2 (0.0 to 104.7)	/	/
Nilotinib	4,668	0	14,122	0.0 (0.0 to 261.2)	/	/
Imatinib	9,491	0	18,055	0.0 (0.0 to 204.3)	/	Reference
Bosutinib	1,756	4	3,214	1,244.6 (339.1 to 3,186.6)	/	804 (406 to 38,986)
Imatinib	6,452	1	12,798	5.2 (0.0 to 299.1)	1.00 (reference)	Reference
Ponatinib	1,019	1	1,540	649.4 (16.4 to 3,618.2)	8.34 (0.52 to 133.89)	1,552 (522 to NA)
Only incident users (i.e. no prior exposure to imatinib):						
Imatinib	8,398	0	35,026	0.0 (0.0 to 105.3)	/	Reference
Dasatinib	1,777	5	7,568	660.7 (214.5 to 1,541.9)	/	1,514 (807 to 12,231)
Imatinib	9,014	0	30,664	0.0 (0.0 to 120.3)	/	Reference
Nilotinib	2,483	1	10,380	96.3 (2.4 to 536.8)	/	10,380 (3,507 to NA)
Imatinib	3,729	0	7,667	0.0 (0.0 to 481.1)	/	Reference
Bosutinib	418	1	911	1097.5 (27.8 to 6,114.7)	/	911 (308 to NA)
Imatinib	3,345	1	7,627	8.7 (0.0 to 501.9)	/	/
Ponatinib	452	0	942	0.0 (0.0 to 3,916.2)	/	/
Only prevalent users (i.e. prior exposure to imatinib):						
Imatinib	11,667	4	50,308	34.5 (3.3 to 135.1)	1.00 (reference)	Reference
Dasatinib	3,867	15	13,581	1,104.5 (618.2 to 1,821.6)	**15.24 (5.03 to 46.15)**	935 (613 to 1,965)
Imatinib	7,424	2	33,285	22.5 (0.2 to 154.2)	/	/
Nilotinib	2,185	0	7,729	0.0 (0.0 to 477.3)	/	/
Imatinib	5,762	0	15,547	0.0 (0.0 to 237.3)	/	Reference
Bosutinib	1,338	3	3,163	948.3 (195.6 to 2,771.4)	/	1,054 (495 to NA)
Imatinib	3,107	0	8,582	0.0 (0.0 to 429.9)	/	Reference
Ponatinib	567	1	1,314	761.0 (19.3 to 4,240.1)	/	1,314 (444 to NA)
Specific outcome definition (i.e. PAH treatment dispensing but only one RHC):						
Imatinib	20,065	3	85,336	8.6 (0.1 to 59.8)	1.00 (reference)	Reference

Dasatinib	5,644	7	21,164	330.7 (133.0 to 681.5)	**10.16 (2.61 to 39.55)**	3,104 (1,761 to 13,092)
Imatinib	16,438	1	63,951	3.9 (0.0 to 65.6)	/	/
Nilotinib	4,668	0	18,109	0.0 (0.0 to 203.7)	/	/
Imatinib	9,491	0	23,214	0.0 (0.0 to 158.9)	/	Reference
Bosutinib	1,756	2	4,079	490.4 (59.4 to 1,771.4)	/	2,039 (855 to NA)
Imatinib	6,452	0	16,211	0.0 (0.0 to 227.6)	/	/
Ponatinib	1,019	0	2,260	0.0 (0.0 to 1,632.5)	/	/
1:1 Matching						
Imatinib	5,644	2	24,342	82.2 (10.0 to 296.8)	1.00 (reference)	Reference
Dasatinib	5,644	20	21,144	945.9 (577.8 to 1,460.9)	**11.94 (2.78 to 51.31)**	1,158 (773 to 2,304)
Imatinib	4,668	1	19,627	51.0 (1.3 to 283.9)	1.00 (reference)	Reference
Nilotinib	4,668	1	18,108	55.2 (1.4 to 307.7)	0.93 (0.06 to 14.91)	234,033 (6,599 to NA)
Imatinib	1,756	0	4,222	0.0 (0.0 to 873.7)	/	Reference
Bosutinib	1,756	4	4,073	982.0 (267.6 to 2,514.3)	/	1,018 (514 to 49,721)
Imatinib	1,019	1	2,525	396.1 (10.0 to 2,206.9)	1.00 (reference)	Reference
Ponatinib	1,019	1	2,257	443.2 (11.2 to 2,469.1)	0.94 (0.06 to 15.11)	21,244 (825 to NA)

PAH: pulmonary arterial hypertension; No: Number; CI: confidence interval; NNH: number of patients exposed for one year needed to harm; RHC: right heart catheterization; NA: not applicable.
* Per million person-years.
† 95%CI estimated from the 95%CI of the risk difference.

8. FIGURES

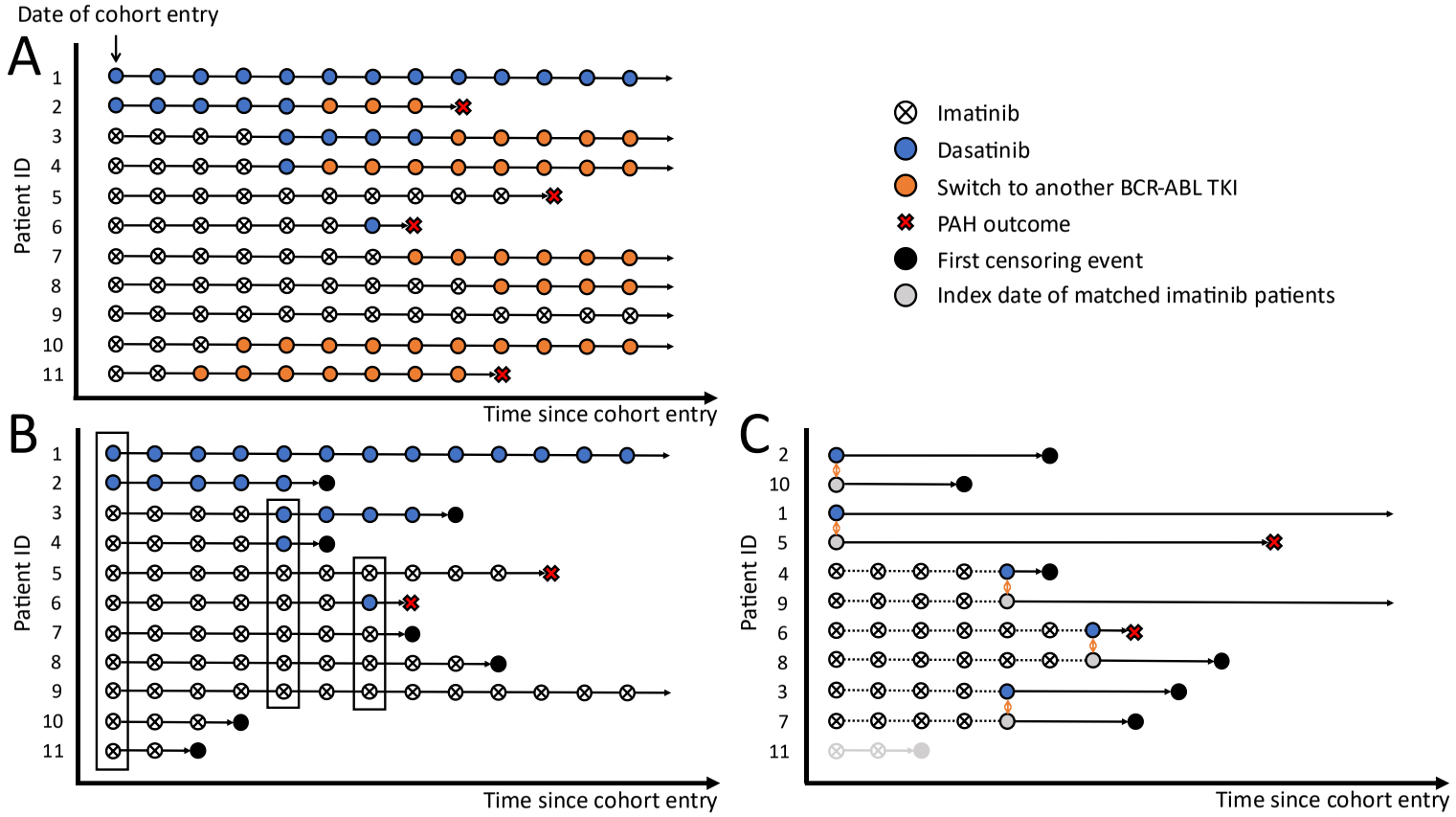


Figure 1. Prevalent new-user study design: example of population identification for dasatinib. A: Base cohort of every patient treated with BCR-ABL TKI before matching presenting individual level prescription of BCR-ABL TKI in a given year, B: Exposure-sets identification, C: Matching of dasatinib users on time conditional propensity score as up to 1:15 to imatinib users within the same exposure-set. Patient shaded-out (patient 11) was not matched. BCR-ABL TKI: BCR-ABL tyrosine kinase inhibitors; PAH: pulmonary arterial hypertension.

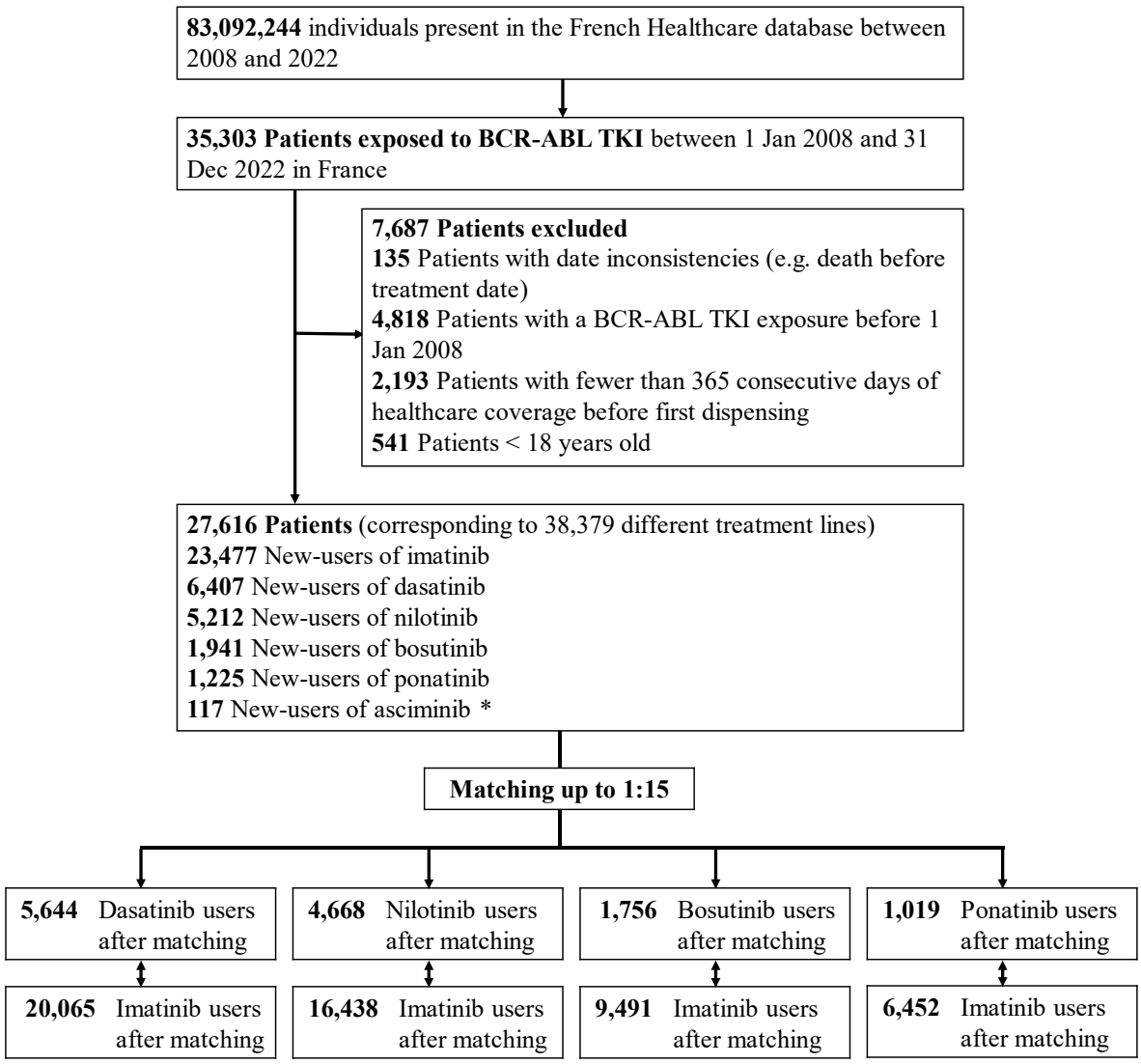


Figure 2. Study flowchart for study cohorts of dasatinib, nilotinib, bosutinib, ponatinib, and asciminib users versus imatinib users in the French healthcare database. An individual can represent multiple matching opportunities (multiple treatment lines); thus, number of treatment lines (38,379) exceed number of patients (27,616). TKI: tyrosine kinase inhibitors. *Asciminib users were not included in the analysis given the low number of patients.

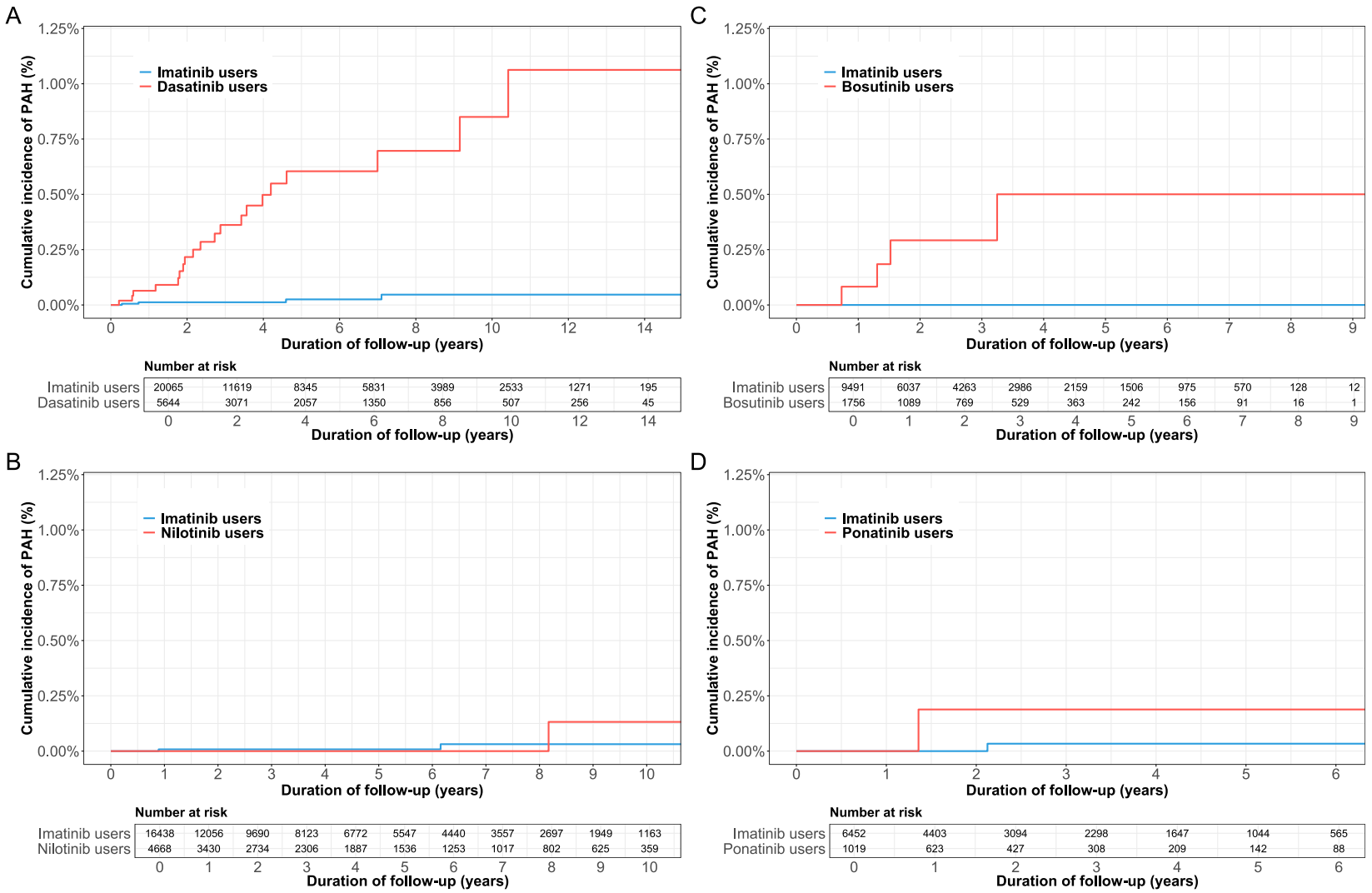


Figure 3. Cumulative incidence of pulmonary arterial hypertension (PAH) events among users of dasatinib (A), nilotinib (B), bosutinib (C), and ponatinib (D) and their matched users of imatinib.

4. Conclusion de la partie

Ces travaux ont démontré l'importance d'adapter le schéma d'étude et la méthodologie à la question de recherche et aux spécificités de la pathologie et du traitement d'intérêts. En effet, nous avons évalué des signaux de pharmacovigilance dans nos trois pathologies d'intérêts, et avons dû utiliser des méthodes spécifiques pour chacune d'elles.

Nous avons tout d'abord conduit une étude de cohorte classique dans le SNDS pour identifier le potentiel surrisque d'apnées du sommeil après l'exposition au ticagrelor. Nous avons conduit de nombreuses analyses de sensibilité pour juger de la robustesse de nos résultats et tenter de s'affranchir au maximum des biais. Nous concluons à un surrisque d'apnées du sommeil suite à l'exposition au ticagrelor, comparativement au clopidogrel et au prasugrel. Cependant, nous n'avons pas étudié si ce surrisque avaient un impact clinique important en diminuant l'efficacité du ticagrelor dans la prévention secondaire cardiovasculaire. Nous prévoyons de réaliser une analyse de médiation pour évaluer l'impact du surrisque d'apnées du sommeil sur la survenue d'événements cardiovasculaires majeurs.

Ensuite, nous avons étudié l'association entre l'exposition aux biphosphonates et le risque d'ulcères cutanés. Les biphosphonates n'ayant pas de comparateur actif pertinent, c'est-à-dire un médicament ayant la même indication et la même place dans la stratégie thérapeutique, nous avons réalisé une analyse en *Prior Event Rate Ratio* pour essayer de limiter au maximum la confusion non mesurée entre les deux groupes. Nous avons trouvé des résultats discordants entre l'analyse de Cox classique sur notre cohorte apparié sur un score de propension et l'analyse en *Prior Event Rate Ratio*, soulignant la probable présence de facteurs de confusion résiduelles. Au final, nous concluons à l'absence de surrisque d'ulcères cutanés avec l'exposition aux biphosphonates et le signal retrouvé était probablement dû à du bais et à l'absence de comparabilité entre les deux groupes.

Finalement, nous nous sommes intéressés au risque d'HTAP suite à l'exposition aux ITK BCR-ABL de seconde et troisième génération. Nous avions un contrôle actif particulièrement intéressant, l'ITK BCR-ABL de première génération imatinib, qui a la même indication et la même place dans la stratégie thérapeutique et dont on sait qu'il n'induit pas d'HTAP. Etant donnée la nature des traitements d'intérêts, première versus deuxième et troisième générations, si nous utilisions une cohorte classique de nouveaux utilisateurs, nous allions perdre tous les patients qui étaient exposés à l'imatinib et qui ont switch avec l'arrivée des autres générations. Pour palier à ce problème, nous avons décidé de réaliser l'étude selon un schéma en *Prevalent New-User Design*, c'est-à-dire que nous incluons tous les patients (incidents ou prévalents de l'exposition) mais avec le même historique d'exposition au moment du switch. Par exemple un patient exposé 1 an à l'imatinib puis qui switch pour le dasatinib sera apparié à un patient exposé également 1 an à l'imatinib mais qui reste sous imatinib. Au total, nous concluons au surrisque d'HTAP après l'exposition au dasatinib et à une possible aggravation ou déclenchement d'une récurrence d'HTAP chez des patients avec une HTAP induite par le dasatinib préexistante. Enfin, nous concluons à une absence de surrisque suite à l'exposition au nilotinib. Savoir si le bosutinib ne peut que déclencher une HTAP préexistante ou s'il peut en créer *de novo* nécessitent d'être encore exploré.

PARTIE 5 – DISCUSSION ET PERSPECTIVES

1. Detection and evaluation of drug-associated pulmonary arterial hypertension

Ces différents travaux nous ont permis d'apprécier l'importance de l'approche multimodale dans l'évaluation du profil de sécurité médicamenteux. Dans cette discussion, nous nous concentrerons sur une de ces trois pathologies : l'HTAP, et développerons les perspectives pour l'étude de ses causes iatrogènes. Cette discussion est applicable cependant à l'ensemble des études concernant la sécurité du médicament. En effet, il est important d'avoir une approche multiple en se basant sur les données issues des études pré-cliniques, des essais cliniques, des bases de notification spontanées de pharmacovigilance, et des études observationnelles sur des bases de données médico-administratives. Avec le développement des outils connectés (comme les montres par exemple), et de la tokenisation, il apparait possible de chaîner les informations d'un patient à travers toutes les différentes bases de données pour obtenir un phénotypage fin des cas identifiés.

Detection and Evaluation of Drug-associated Pulmonary Arterial Hypertension

Clément Jambon-Barbara[1,2], Alex Hlavaty[1,2], Julien Grynblat[3,], Fabrice Antigny[3,], Marie-Camille Chaumais[3,4], Marc Humbert[3], Jean-Luc Cracowski[1,2], David Montani[3], Charles Khouri[1,2]

[1] Univ. Grenoble-Alpes, Pharmacovigilance Unit, Grenoble-Alpes University Hospital, 38000 Grenoble, France;

[2] Univ. Grenoble-Alpes, HP2 Laboratory, Inserm U1300, 38000 Grenoble, France.

[3]Université Paris-Saclay, INSERM, UMR_S 999, Hypertension Pulmonaire : Physiopathologie and Innovation Thérapeutique (HPPIT), AP-HP, Hôpital Bicêtre, Hôpital Marie Lannelongue (Groupe Hospitalier Paris Saint Joseph), ERN-LUNG, FHU André Cournand, Le Plessis robinson, France.[4] Université Paris-Saclay, Faculty of Pharmacy, Orsay, France

Corresponding author: Charles Khouri, Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
Tel: +33 4 76 76 51 45
Fax: +33 4 76 76 56 55
E-mail: ckhouri@chu-grenoble.fr

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

The growing number of drugs suspected to induce and/or aggravate PAH

Pulmonary arterial hypertension (PAH) is a form of precapillary pulmonary hypertension (PH) defined at right heart catheterization, by a mean pulmonary arterial pressure (mPAP) > 20 mmHg, a pulmonary vascular resistance (PVR) > 2 WU and a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg [1]. The estimated prevalence of PAH in adults is about 15–55 cases per million people, with an annual incidence of 2.4–6 per million people [2,3]. PAH can be idiopathic, familial/heritable, associated with connective tissue disease, congenital heart disease, portal hypertension, human immunodeficiency virus infection, schistosomiasis, or associated with exposure to drugs or toxins [1,3]. The proportion of drug- and toxin-associated PAH varies greatly from country to country depending on the drugs on the market, the availability and societal/cultural penchant for abusive consumption of illicit substances, the level of exposure in the population, the awareness of healthcare professionals evaluating these patients, and the proper reporting and identification of the cases [4]. For example, it was estimated that 1 person over 500 exposed to aminorex and 1 over 154 exposed to dasatinib developed PAH, thus dramatically increasing the background risk of this disease in exposed individuals [5,6]. In the REVEAL registry, 5.3% of patients with WHO group 1 PAH were considered to have drug-associated PAH, and 9.5% in the French national registry; furthermore, around half of patients were considered to have idiopathic PAH, while exposure to certain unsuspected drugs or substances probably played a role in the development of the disease [7,8]. The number and type of drugs potentially implicated in the onset or aggravation of PAH have been steadily increasing since the Evian World Symposium on PH in 1998, which drew up a list of nine drugs considered to be possibly, probably or certainly associated with PAH [9]. The updates of the 7th World Symposium of PH now

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

classify 25 drugs or drug classes as definitely or probably associated with PAH (**Table 1**) [1]. However, only 9 of these drugs are currently considered to be definitively associated with PAH, whereas some, such as St John's wort or L-tryptophan, have been suspected for decades. These figures underline the indubitably complex process of causal assessment between drug exposure and PAH, which involve synthesizing, sometimes conflicting, individual, populational and mechanistic information's from multiple sources [10–13]. Nevertheless, in past few years, the improvement in our knowledge of drug-associated PAH, the identification of many unknown associations, and the advent of innovative methods and data sources to explore drug harms has prompted us to review the current state of the field and its perspectives. Our aim is therefore to offer readers a fresh look at the advantages, limitations and complementarity of data sources for identifying drug-associated PAH, and to provide ideas for optimizing their usefulness in generating robust evidences.

The need for a disease model of drug-associated PAH

Beyond the scarcity of the disease, one of the main challenges in identifying drug-associated PAH stems from the lack of understanding of the pharmacological and pathophysiological mechanisms leading to PAH, preventing us from defining a clear disease model. The complex network of mechanisms leading to structural and functional changes in the pulmonary vascular bed of PAH patients is indeed still only partially understood. Nevertheless, dysfunctions in the pulmonary endothelium, vascular smooth muscle, and the inflammatory and immune systems are the three main driving factors [14]. Endothelial cells regulate the flow of fluid, proteins, and blood cells across the vessel wall into parenchymal tissue, maintain vascular tone and integrity as well as exert anti-

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

thrombotic and anti-inflammatory effects on the vascular bed and are suspected to be the primary dysfunctional process in PAH [15,16]. Pharmacological knowledge of drugs suspected to be associated with PAH, and preclinical experiments suggest that endothelial dysfunction is probably the main factor leading to drug-associated PAH, while drugs can probably act on all three driving factors *via* different mechanisms that have already been thoroughly described (see refs [17–19] for a review of drug-associated PAH mechanisms) (**Table 2**). Whether certain drugs can independently trigger the cascade of events leading to PAH or whether they act only as "second hits" in patients at risk, or exacerbate pre-existing PAH, remains an open question [20]. Yet accumulated knowledge of drug-associated PAH mainly supports the "second-hit" hypothesis, with a high prevalence of underlying risk or genetic factors of PAH, such as BMPR2 mutation in amphetamine users, and a relatively short duration between the start of drug intake and the first symptoms and diagnosis [21]. However, some drugs, such as benfluorex, present a specific profile with a median time to onset of several years, and a predominance of valvular heart diseases early on, which might suggest that it could act earlier on pathogenesis. Other drugs, such as selective serotonin reuptake inhibitors (SSRI), were also suspected to aggravate the disease in PAH patients, and the ELEVATE-2 trial have demonstrated that exposure to rodatristat, a tryptophan hydroxylase-1 (enzyme involved in the synthesis of serotonin [22]) inhibitor, during 24 weeks, resulted in significant increase in PVR and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and worsened right atrial pressure, mPAP, stroke volume, and cardiac index [23,24].

Drug-associated PAH can, therefore, be conceptualized in the same way as drug-induced cancer with drugs described as initiators (i.e. able to cause the first clone of neoplastic cells) and promoters (i.e. drug that accelerates the progression or growth of premalignant

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

or subclinical disease) [25]. In fact, some authors suggest that PAH and cancer share common features, such as hyperproliferation, resistance to apoptosis, and metabolic reprogramming, which has led to the exploration of therapies already tested in the treatment of malignant tumors [26,27].

We could, therefore, hypothesize that at least two disease models of drug-associated PAH may exist, with some drugs initiating the process of PAH with a very long delay between exposure and first symptoms (i.e. initiators), and some other exacerbating a latent disease (i.e. promoters). The definition of disease models is essential to identify data sources with suitable follow-up, and to design studies capable of detecting suspect drugs. For example, during a meeting between the Food and Drug Administration and the National Cancer Institute in 2014, the median follow-up of 2 to 5 years of North American claims databases was identified as an important challenge impairing the exploration of some drug-cancer associations [28]. This need of identifying suit-to-purpose data sources have recently driven the release of a metadata catalogue of real-world healthcare data sources by the European Medicine Agency to help investigators in this task [29]. Preclinical experiments therefore play an essential role in gaining a better understanding of the pathophysiological mechanisms involved in exposure to known or suspected drugs, but also in improving our ability to detect new drugs associated with PAH.

The importance and limitations of pre-clinical experiments

Rodent models are important for understanding the mechanisms of experimental PH and testing for the potential efficacy or detrimental impact of drugs. For example in rats, intraperitoneal administration of mitomycin C successfully reproduced pulmonary veno-occlusive disease allowing to support the role of the drug in triggering the disease [51]. Conversely, dexfenfluramine, dasatinib or rodatristat were found to paradoxically

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

protect or reverse PH in monocrotaline and Sugen hypoxia rats [74,75]. These observations illustrate that rodent studies are imperfect models of human PAH and that great caution is needed in the interpretation of experimental data and their translation to human disease [74]. The choice of model may thus depend on the mechanism, metabolization, dosage, and route of administration of the drug under study, and specific "second hit" models may be required for some of them. However, the choice of the optimal model is still unclear, and a systematic evaluation of the impact of drugs on a panel of rodent models is advisable.

Yet, cellular models, particularly of endothelial toxicity or smooth muscle cell models, can provide additional information. For example, exposure to dasatinib has been shown to reduce the expression and function of the outward potassium channel subfamily K member 3 (KCNK3), contributing to pulmonary artery constriction and dysfunction of human pulmonary artery smooth muscle cells and pulmonary endothelial cells [44]. Contrarywise, numerous paradoxical findings have been observed with in vitro models. Activation of SUR1 and SUR2 have been shown to lead to the relaxation of human and rodent pulmonary arteries, and reduce the severity of experimental PH, while diazoxide, a SUR1 activator, has been associated with the occurrence of PH in children treated for neonatal hypoglycaemia [1,60,76]. Moreover, proteasome inhibitors, carfilzomib and bortezomib, were suggested as potential therapeutic strategies or as a promising way to improve PAH therapy in vitro [38,57].

Yet rodent and cellular models are still limited in their applicability to humans as they do not replicate all the spectrum of the disease, and are susceptible to strain and sex differences [74]. Moreover, exploration of the impact of drugs in these models is further limited by the lack (or a different) metabolization, by the irrelevance of dose used

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

compared to human plasma concentration and by the difficulty to reproduce the duration of exposure.

Prospective biobanking of drug-associated PAH lung tissues?

The creation of biobanks containing blood samples, DNA, and lung tissue from patients who have developed drug-associated PAH represents a unique opportunity to better understand pathophysiological mechanisms and identifying individual risk factors that contribute to the development of PAH. Indeed, lung transplantation is currently the only long-term curative treatment for PAH. Access to lung tissue from patients who have undergone transplantation for PAH has led to significant discoveries, including insights into endothelial cell dysfunction, the hyper-proliferative phenotype of pulmonary artery smooth muscle cells, and the imbalance between pro- and anti-proliferative pathways within the transforming growth factor beta family, among others [77]. Furthermore, histological examination of explanted tissues can aid in confirming a PAH diagnosis, including specific forms such as pulmonary veno-occlusive disease (PVOD) [78].

Interestingly, there are limited histological descriptions available for cases of drug- and toxin-associated PAH, despite the potential for such studies to enhance our understanding of the disease's underlying mechanisms and potentially implicate specific drugs. This was exemplified in the study by Zamanian et al., which identified intravascular deposits of microcrystalline cellulose in the vessels of patients with methamphetamine-induced PAH, and in Garcia-Dorado et al. work, which revealed the direct vascular toxicity of toxic rapeseed oil [47,79]. Notably, Perros et al. demonstrated in patients with PVOD induced by mitomycin C that disruptions in general control nonderepressible 2 (GCN2)

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

signalling led to a decrease in SMAD 1, 5, and 8 expression, without affecting BMPR-II, providing further insights into the disease mechanism [51].

The scarcity of data on drug-associated PAH lung histology can be attributed to several factors. Many drugs suspected or known to induce PAH are used in oncology or haematology, where the underlying malignancy often contraindicates lung transplant listing [80,81]. Some historical case studies of drug-associated PAH histology were based on lung biopsies [1,3]; however, this hazardous procedure is clearly not recommended in PH guidelines [1,3]. As right-heart catheterization is the gold-standard procedure to diagnose PAH, it has recently been suggested that this procedure could provide a valuable source of primary cells. In fact, Ventetuolo et al. showed that sustained culture and characterization of pulmonary artery endothelial cells collected from right-heart catheterization is feasible [82]. Additionally, it is worth-noting that drug withdrawal may improve clinical and haemodynamic outcomes—supporting drug-related causation [6,41,62]. Therefore, post-mortem analysis remains the primary avenue for studying the lungs of patients with drug and toxin-associated PAH, though practitioners and families may be reluctant to pursue it.

The pivotal role of case reports and pulmonary hypertension registries

Case reports whether coming from isolated observations, registries, or pharmacovigilance spontaneous reporting systems are cornerstone in generating new hypotheses about (rare) drug-induced diseases. The vast majority of new safety signals published in the literature, underlying communication or drug labelling changes by drug agencies are still coming from clinical case analysis [83–85]. A thorough description of the diagnosis, and evolution of these patients is therefore crucial to be able to judge the level of plausibility of the association (i.e. intrinsic causality) in each single patient,

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

including a diagnosis based on right hear catheterization and exclusion of other etiologies. Prospective registries systematically collecting data are therefore useful in rare diseases in order to improve the quality and reliability of the information gathered and allow integrating data on patient characteristics, dosage, comorbidities. Additionally, they enable early signal detection through continuous statistical analyses and regular data updates. Yet, given the absence of a disease model and the heterogeneous features of drug-associated PAH, the definition of a suggestive or index case (i.e. a well-documented case with an unusual "striking" feature) is highly complex.

Box 1. Difficulties in defining index cases in drug-associated PAH

The following specificities of drug-associated PAH reduce our ability to determine the role of drugs from anecdotal cases:

- No improvement of symptoms are observed after drug withdrawal for many drugs, such as fenfluramine derivatives; moreover, it can be challenging to discern between improvement after drug withdrawal and efficacy of PAH-approved medications initiated at the time of PAH diagnosis, as recommended in guidelines [18].
- Besides uncommon cases of reversible PAH after drug withdrawal, there are no clinical, biological or haemodynamic features suggestive of drug-induced PAH.
- Additional genetic or clinical risk factors may be present in patients with drug-associated PAH, making it difficult to distinguish between incidental onset of idiopathic/heritable PAH and drug-associated PAH in a susceptible patient [34,86].
- Plausible temporal association is extremely variable from month to years and the latency between the first unspecific symptoms, such as dyspnoea, to diagnosis could also take years, making it difficult to assess the patient's medication history [19,87].
- No drug rechallenges due to the severity of the disease.
- The lack of specificity of first symptoms, such as dyspnoea, further delay the diagnosis of PAH (e.g. 21.1% of patients in the REVEAL registry had symptoms for

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

more than 2 years before diagnosis), making it difficult to relate exposure to first symptoms [8].

- Right heart catheterization is not always performed, notably in frail patients with poor prognosis such as in the case of solid cancers or haematological malignancies, impairing the detection, definition (pre- or post-capillary PH), classification, and proper assessment of the role of these drugs.

We must emphasize the difficulty to identify some exposure, notably illicit substance ones. In fact, Zamanian et al. identified exposure to (meth)amphetamine using a comprehensive questionnaire that included routine and slang terms, and methamphetamine-associated PAH was defined in the case of significant exposure (i.e. characterized as more than three episodes of use reported per week for greater than 3 months [31]) to methamphetamine [47]. Defining the criteria for a definite case of drug-associated PAH and developing the capacity to identify all pharmacological and non-pharmacological exposures (e.g. recreative drugs, occupational, pollution…) at the onset of first symptoms in PAH patients are the next steps to improve our understanding of drug-associated PAH. To achieve this, the development of secure, integrative data warehouses is essential, enabling the consolidation of clinical, biological, radiological, environmental, genetic, and histological data from patients (see reference [88] for an overview of Clinical Research Data Warehouse). Moreover, the emergence of artificial intelligence models coupled with near real-time analyses of self-reported data and data from wearables and implanted devices that could detect trends, both in improvement and in deterioration, could be a way to detect aggravation of symptoms in PAH patients [89]. These longitudinal data coupled with methods allowing to distinguish between the natural evolution of the disease and unexpected break in its progression, such as difference-in-difference designs, may represent valuable source of information to uncover new triggers, including drugs and toxins [90]. Nevertheless, those valuable data

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

should be interpreted with caution, and only as an additional argument as trend detection do not causally imply a drug-induced relationship and could just reflect the natural progression of the underlying disease.

Overall, given the heterogeneous presentation of drug and toxin-associated PAH and the high likelihood of idiopathic/heritable disease, evidences derived from population-level data are mandatory for validating signals identified in individual patients.

The rise in the use of pharmacovigilance adverse event reporting systems

Mining pharmacovigilance adverse event reporting systems to identify more than expected reports of drug-associated PAH (the so-called disproportionality analyses) have been an important source of evidence in recent years [35,56,60,64,91,92]. Pharmacovigilance systems around the world are collecting individual case safety reports of suspected adverse drug reactions spontaneously reported by healthcare professionals and patients or generated within active surveillance activities [93]. Disproportionality analyses are statistical methods that aim at highlighting a plausible association between drug(s) and adverse event(s) by comparing the number of observed cases recording both the drug and the event of interest with the number of cases that would be expected in the absence of any association between these specific drug and event, based on the underlying drug and event rates within the same database. These analyses generate a signal of disproportionate reporting when the statistic significantly exceeds a predefined threshold. However, because of the lack of exposure and longitudinal data, the unquantified under- and selective reporting of adverse events, signal of disproportionate reporting cannot be interpreted in themselves as conclusive scientific evidence of a causal relationship between a drug and an adverse event [94,95]. Nevertheless, these reporting systems have the advantage and particularity of being

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

physician- and patient-centered, based mostly on the voluntary nature of reporting, and having a high power for detecting rare adverse drug reactions [96]. Disproportionality analyses combined with case-by-case analyses, when properly planned, performed, and reported, offer a decent way to generate new signals of drug-induced diseases [94,95]. Background rate of events estimated from populational data (e.g. claims database) could also be used to perform hybrid designs called observed-to-expected analyses. Moreover, new developments in the field, including merging data with drug pharmacodynamics properties, clustering adverse events to identify iatrogenic syndromes, or developing text mining approaches to extract unstructured information on verbatims may allow better phenotyping of drug-associated PAH patients and exploring pharmacological mechanisms implicated [43,97]. Predicting the risk of PAH based on pharmacological, biochemical or proteomic data for newly marketed drugs could reinforce post-marketing safety surveillance. For instance, given the chemical structure and pharmacological activity of solriamfetol, a theoretical risk of PAH has been identified. The inclusion of a specific warning in the French recommendations for the assessment and management of residual somnolence in obstructive sleep apnea-hypopnea syndrome has helped to communicate and raise awareness of this plausible risk among pulmonologists and PH expert centers [98].

However, in most cases, robust epidemiological evidence is required to quantify the risk and definitively establish a causal relationship between a drug and PAH.

Is there a place for mining clinical trials?

Clinical trials are the primary source of safety data about newly marketed drugs in humans, but they can only properly estimate the incidence of frequent adverse events [99]. These clinical trials are largely underpowered to detect rare adverse drug reactions,

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

such as PAH. This limitation is further impaired by heterogenous reporting and coding practices (e.g. PH instead of PAH), and the frequent insufficient duration of follow-up. However, in certain situations where the baseline risk of PAH is high in the exposed population, an increase in the risk of PH and/or PAH could be identified in meta-analyses of clinical trials [35,100]. Clinical trials may notably be long enough to identify aggravation of disease in PAH or disease onset in drugs used at very high-risk patients, notably for promoter ones. The development of living meta-analyses with automatization of data extraction and analysis and grouping drugs by pharmacological properties and indications, may be a way to detect early signals of drug-associated PAH that could be following marketing authorization. For example, the metaPreg project provides, through a semi-automated synthesis process (study search, selection, extraction, etc.) and an online open-access platform (www.metaPreg.org), real-time evidence syntheses about risk of drugs during pregnancy [101]. Additionally, tokenization (i.e. a novel approach that permits anonymous patient-level linkage across different healthcare databases [102]) may allow for long-term follow-up of patients after clinical trial completion, and broader access to individual patient data could facilitate more accurate phenotyping of identified cases.

Generation of evidence from pharmacoepidemiologic studies

Prospective pharmacoepidemiologic studies have been the most striking and convincing studies in the field of drug-associated PAH, allowing to demonstrate the association between appetite-suppressant drugs and PAH and to quantify this risk in exposed patients [31]. Yet, the huge human efforts to collect data on cases and controls, patient exposure, the need for international collaboration, and the financial burden of that kind of study make it extremely challenging to plan and undertake. Yet, the advent of claims

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

databases describing medication dispensing or prescription and clinical events in large populations, the rapid increase of computational capacities, and methodological expertise make retrospective pharmacoepidemiology studies the most useful and robust data source for confirming safety signals [103]. Moreover, public or private claims databases are becoming more and more interoperable, with the development and adoption of common data models making it possible to conduct analyses on federated databases that leverage data from hundred million of patients. The FDA, for example, routinely uses a network of claims data to provide evidence about drug safety with its Sentinel System Program [104]. The European Medicine Agency has, in the same way, launched the Data Analysis and Real World Interrogation Network (DARWIN EU®) initiative that allows to perform observational studies in several European countries using a common protocol [105]. These large individual-level databases are particularly useful for studying rare events, but necessitate to accurately identify PAH patients using available data. Numerous algorithms have been purposefully developed and validated in recent years, and they enable PAH patients to be identified with sufficient specificity and sensitivity [106–108]. Beyond inferential studies such as cohorts that allow to assess already identified signals, numerous designs could also be used to mine these databases and detect new signals. Classical case-control studies can, of course, be used but also newer designs, such as TreeScan-based statistic or sequence symmetry analyses, designs devised to generate signals using routinely collected data [109]. Recent methodological development accounting for time-varying exposure and confounding factors, or accounting for treatment sequences such as prevalent new-user design or multiple cohort approaches may allow to assess diseases with long latency periods and prolonged and variable exposures over time in a time-dependent manner [110,111].

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

These methodological developments, in parallel with the definition of disease models, must now be undertaken to identify the most suitable methods according to the role of the drugs (i.e. initiators or promoters), to define when a drug can plausibly be the cause of PAH, and to define the corresponding lag times in order to limit reverse causality and detection bias, and account for residual effects of drugs. These drivers, coupled with opportunities to merge claims data with in-hospital electronic health records, PAH registries and genetic data, will allow us to perform more comprehensive drug–PAH association studies in the future and to adjust on confounders missing in claims databases.

Box 2. The need of defining a new classification of drug-associated PAH

The classification of the level of plausibility of drug-associated PAH proposed during the 7th World Symposium of PH is cornerstone to inform scientific societies guidelines and clinicians on potential drugs when classifying a PH case. Drugs are classified as definitely associated with PAH (i.e. drugs with data based on outbreaks, epidemiological case-control studies or large multicentre series) or possibly associated with PAH (i.e. multiple case series or cases with drugs with similar mechanisms of action)[1]. Yet, the level of evidence provided by a single case or a series of cases is highly heterogeneous, as well as the robustness of epidemiological studies. Moreover, these criteria do not take into account the diversity of evidence and criteria that have been explored and that can be used to assess a causal link between drugs and adverse events in general, and PAH more specifically [17,18,30]. The most widely used and best-known criteria for the evaluation of the causal nature of an association were first proposed by Sir Austin Bradford Hill [112]. Through nine criteria (i.e. strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) they allow to consider the evidence from diverse sources of data or study designs. Adapting these widely used criteria and defining what is suggestive at clinical, pre-clinical, and populational level in each criterion may help to better inform about the level of evidence underlying the classification and to identify gap in knowledge about drug-associated PAH [113].

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

In conclusion, integration of evidence from multiple data sources and improvement in our ability to mine them will, in the near future, allow us to better understand the causal role of drugs in triggering PAH and to identify individuals at risk. Moreover, the definition of disease model, index cases and specific criteria to assess causal role of drugs associated with PAH will allow to assess the robustness of the evidence generated by these methods.

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

Figure Legend

Figure 1. Perspective in the assessment of signals of drug-associated PAH. Bradford Hill criteria for causal assessment of associations between drugs and adverse events that can be informed by each data source/method are indicated

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

Table 1. Drugs and toxins associated with PAH

Definite association	Possible association
Aminorex	Alkylating agents [a]
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C [a]	Direct-acting antiviral agents against hepatitis C virus
Toxic rapeseed oil	(sofosbuvir)
	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Lefunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene) [a]
	St John's wort

[a] PAH with features of venous (pulmonary veno-occlusive disease)/capillary (pulmonary capillary haemangiomatosis) involvement.

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

Table 2. Evidences on main drug-associated PAH

Drugs	Range of time to onset	Improvement after withdrawal	Hypothesized pathophysiological mechanism	Reproduction of disease in pre-clinical experiments	Data sources	Main references
Drugs definitely associated with PAH						
Aminorex	6 months First symptoms: weeks	Yes	Indirect serotonin agonist Serotonin may be an important growth factor for pulmonary artery smooth muscle cells	No: aminorex did not induce PH in the calf or in the pig	Case report	[18,30–33]
Benfluorex	Median duration of exposure: 30 months Median time to onset: 108 months	No	Same active metabolite as fenfluramine: norfenfluramine Indirect serotonin agonist Serotonin may be an important growth factor for pulmonary artery smooth muscle cells Valvopathy		Case report Registry PV reporting systems	[18,30,31,34]
Carfilzomib	Median: 6.5 months	Yes	Unknown mechanism of action	No: identified as potential treatment for PAH	Case report Meta-analysis PV reporting systems	[30,35–38]
Dasatinib	1 month to 7 years Median range: 34 months	Yes, but heterogeneous	Smooth muscle hyperplasia and endothelial dysfunction Injure pulmonary vasculature Generating mitochondrial oxidative stress Reduce the expression and function of KCNK3	Yes, in rat	Case report Registry PV reporting systems	[6,18,30,39–44]
Dexfenfluramine	Interval between dyspnoea and drug intake: 49 months	Yes	Indirect serotonin agonist: increase level of circulating serotonin Serotonin may be an important growth factor for pulmonary artery smooth muscle cells Strike a sensitive balance in how lung tissue deals with oxygen availability Effect in pulmonary smooth muscle cells	No: impact on lung homeostasis and vascular dynamics. But: protect the rat lung vasculature	Case report Epidemiological studies PV reporting systems	[18,30,31]
Fenfluramine	Interval between dyspnoea and drug intake: 49 months	Yes	Indirect serotonin agonist: increase level of circulating serotonin Serotonin may be an important growth factor for pulmonary artery smooth muscle cells Effect in pulmonary smooth muscle cells	Yes: impact on lung homeostasis and vascular dynamics	Case report Epidemiological studies	[18,30,31,33,45,46]
Methamphetamines	Median exposure: 60 months	Yes	Molecular structure is similar to that of aminorex, fenfluramine Release dopamine, norepinephrine, and serotonin Generating mitochondrial oxidative stress Pulmonary vascular remodelling and intravascular collections of microcrystalline celluloses	Yes: mitochondrial oxidative stress in hypoxic mice after amphetamine.	Pre-clinical Case report Prospective cohort	[18,47–50]

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

Mitomycin C	Median: 8.5 months First symptoms: 5 months	No, except for 1 patient after bosentan therapy	Pulmonary veno-occlusive disease Dose-dependent depletion of pulmonary GCN2 content Decreased smad1/5/8 signalling	Yes, in rat: PH with pulmonary arterial and venous remodeling	Case report Registry PV reporting systems	[18,51–54]
Drugs possibly associated with PAH						
Alkylating agents	In disproportionality analysis: Median time to onset from 66 to 275 days	In disproportionality analysis: only few patients recovered	Pulmonary veno-occlusive disease	Yes	Case report Registry PV reporting systems	[18,30,55]
Bevacizumab	In disproportionality analysis: Median: 1 year	In disproportionality analysis: 3 out of 13 patients have recovered or are recovering	Unknown mechanism of action VEGF inhibition induces PH in animal models		Case report PV reporting systems	[30,56]
Bortezomib	Median: 6.5 months	Yes	Unknown mechanism of action	No: identified as potential treatment for hypoxia induced-PAH	Case report Meta-analysis PV reporting systems	[30,35,56,57]
Bosutinib	First symptoms: 4 months	Yes	Smooth muscle hyperplasia and endothelial dysfunction Injure pulmonary vasculature Generating mitochondrial oxidative stress	Yes	Case report Registry PV reporting systems	[18,30,42,43,56,58,59]
Diazoxide	Range: 2-317 days Median: 1 month	Yes: rapid improvements	Stimulates the pancreatic β-cell KATP channels and the smooth muscle KATP channels, but not the cardiac KATP channels	No	Case report PV reporting systems	[56,60,61]
Sofosbuvir	In disproportionality analysis: Median: 123 days	In disproportionality analysis: 6 out of 17 patients have recovered or are recovering	Unknown mechanism of action Possible exacerbation of an underlying tendency to PAH.		Case report PV reporting systems	[18,30,56]
Interferons-α and -β	Mean treatment duration: 7.7 months Range to PAH diagnosis: 59-117 months	Yes	Endothelial injury Promoting the expression of endothelin-1 and precipitating changes in pulmonary vascular resistance	Yes, in sheep: stimulation of thromboxane cascade resulting in PAH	Case report PV reporting systems	[18,30,56,62,63]

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

Leflunomide	Median: 32 months	No	Endothelial injury Role in either pathogenesis or at least exacerbation of undiagnosed pre-existing PAH associated with connective tissue disease Inhibition of prostaglandin E2 production		Case report PV reporting systems	[30,56,64,65]
Phenylpropanolamine			Indirect serotonin agonist Serotonin may be an important growth factor for pulmonary artery smooth muscle cells		Case report	[30]
Ponatinib	In disproportionality analysis: Median: 58 days	Partial	Unknown mechanism of action Common pathway with dasatinib	Yes Damage to pulmonary circulation	Case report Registry PV reporting systems	[18,30,42,43,56,66]
New safety signal not yet classified						
Trastuzumab-Emtansine	Median treatment duration: 28 months Median time to diagnosis: 43 months	Yes: significant clinical improvement	Emtansine could induce apoptosis of HER2-expressing endothelial cells in distal small pulmonary vessels Inappropriate processing via pathways normally involved in immune complex clearance		Clinical trial Registry PV analysis	[67–72]
Rodatristat			Paradoxically reduce peripheral serotonin	Yes, contradictory: protect or reverse PH	Clinical trial	[24,73]

PH: pulmonary hypertension; PV: pharmacovigilance; PAH: pulmonary arterial hypertension.

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

References

1. Kovacs, G. *et al.* (2024) Definition, classification and diagnosis of pulmonary hypertension. *Eur. Respir. J.* DOI: 10.1183/13993003.01324-2024
2. Hoeper, M.M. *et al.* (2016) A global view of pulmonary hypertension. *Lancet Respir. Med.* 4, 306–322
3. Humbert, M. *et al.* (2023) 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur. Respir. J.* 61, 2200879
4. Swinnen, K. *et al.* (2019) Learning from registries in pulmonary arterial hypertension: pitfalls and recommendations. *Eur. Respir. Rev.* 28, 190050
5. Hatano, S. and Strasser, T., eds. (1975) *Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15-17 October 1973*, World Health Organization ; distributed by Q Corporation]
6. Montani, D. *et al.* (2012) Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* 125, 2128–2137
7. Humbert, M. *et al.* (2006) Pulmonary Arterial Hypertension in France: Results from a National Registry. *Am. J. Respir. Crit. Care Med.* 173, 1023–1030
8. Badesch, D.B. *et al.* (2010) Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 137, 376–387
9. Rich, S. *et al.* Executive summary from the World Symposium on Primary Pulmonary Hypertension (Evian, France, September 6–10, 1998). The World Health Organization publication via the Internet. at <http://www.who.int/ncd/cvd/pph.html>
10. Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products
11. Guideline on good pharmacovigilance practices (GVP) - Module IX – Signal management (Rev 1)
12. Hill, A.B. (1965) The Environment and Disease: Association or Causation? *Proc. R. Soc. Med.* 58, 295–300
13. Bégaud, B. and Jones, J.K. (2021) Assessing Causality from Case Reports. In *Textbook of Pharmacoepidemiology*, pp. 246–256, John Wiley & Sons, Ltd
14. Humbert, M. *et al.* (2019) Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur. Respir. J.* 53, 1801887
15. Bousseau, S. *et al.* (2023) Pathophysiology and new advances in pulmonary hypertension. *BMJ Med.* 2, e000137
16. Evans, C.E. *et al.* (2021) Endothelial cells in the pathogenesis of pulmonary arterial hypertension. *Eur. Respir. J.* 58, 2003957
17. Correale, M. *et al.* (2019) Drug-Induced Pulmonary Arterial Hypertension: Mechanisms and Clinical Management. *Cardiovasc. Drugs Ther.* 33, 725–738
18. Orcholski, M.E. *et al.* (2018) Drug-induced pulmonary arterial hypertension: a primer for clinicians and scientists. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 314, L967–L983
19. De Jesus Perez, V.A. (2017) Drug-Induced Pulmonary Hypertension: The First 50 Years. *Adv. Pulm. Hypertens.* 15, 133–137
20. Humbert, M. *et al.* (2002) BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. *Eur. Respir. J.* 20, 518–523
21. Jaliawala, H.A. *et al.* (2022) A second hit? Pulmonary arterial hypertension, BMPR2 mutation, and exposure to prescription amphetamines. *Pulm. Circ.* 12, e12053
22. Hale, M.W. *et al.* (2011) Development by environment interactions controlling tryptophan hydroxylase expression. *J. Chem. Neuroanat.* 41, 219–226
23. Sadoughi, A. *et al.* (2013) Use of selective serotonin reuptake inhibitors and outcomes in pulmonary arterial hypertension. *Chest* 144, 531–541

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

24. Sitbon, O. *et al.* (2024) Safety and efficacy of rodatristat ethyl for the treatment of pulmonary arterial hypertension (ELEVATE-2): a dose-ranging, randomised, multicentre, phase 2b trial. *Lancet Respir. Med.* DOI: 10.1016/S2213-2600(24)00226-1
25. Pottegård, A. *et al.* (2018) Considerations for Pharmacoepidemiological Studies of Drug–Cancer Associations. *Basic Clin. Pharmacol. Toxicol.* 122, 451–459
26. Prins, K.W. *et al.* (2019) Repurposing Medications for Treatment of Pulmonary Arterial Hypertension: What's Old Is New Again. *J. Am. Heart Assoc.* 8, e011343
27. Guignabert, C. *et al.* (2013) Pathogenesis of pulmonary arterial hypertension: lessons from cancer. *Eur. Respir. Rev. Off. J. Eur. Respir. Soc.* 22, 543–551
28. Pinheiro, S.P. *et al.* (2016) Challenges in evaluating cancer as a clinical outcome in postapproval studies of drug safety. *Ann. Epidemiol.* 26, 735–740
29. Pajouheshnia, R. *et al.* (2024) Metadata for Data dIscoverability aNd Study rEplicability in obseRVAtional Studies (MINERVA): Development and Pilot of a Metadata List and Catalogue in Europe. *Pharmacoepidemiol. Drug Saf.* 33, e5871
30. McGee, M. *et al.* (2018) Drug-associated pulmonary arterial hypertension. *Clin. Toxicol. Phila. Pa* 56, 801–809
31. Abenhaim, L. *et al.* (1996) Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N. Engl. J. Med.* 335, 609–616
32. Byrne-Quinn, E. and Grover, R.F. (1972) Aminorex (Menocil) and amphetamine: acute and chronic effects on pulmonary and systemic haemodynamics in the calf. *Thorax* 27, 127–131
33. Mlczoch, J. *et al.* (1979) Long term effects of the anorectic agent fenfluramine alone and in combination with aminorex on pulmonary and systemic circulation in the pig. *Basic Res. Cardiol.* 74, 313–320
34. Savale, L. *et al.* (2012) Pulmonary hypertension associated with benfluorex exposure. *Eur. Respir. J.* 40, 1164–1172
35. Grynblat, J. *et al.* (2024) Characteristics and outcomes of patients developing pulmonary hypertension associated with proteasome inhibitors. *Eur. Respir. J.* 63, 2302158
36. Efentakis, P. *et al.* (2020) Investigating the Vascular Toxicity Outcomes of the Irreversible Proteasome Inhibitor Carfilzomib. *Int. J. Mol. Sci.* 21
37. McGregor, P.-C. *et al.* (2021) Carfilzomib-induced pulmonary hypertension with associated right ventricular dysfunction: A case report. *SAGE Open Med. Case Rep.* 9, 2050313X21994031
38. Wang, X. *et al.* (2016) Carfilzomib reverses pulmonary arterial hypertension. *Cardiovasc. Res.* 110, 188–199
39. Guignabert, C. *et al.* (2016) Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. *J. Clin. Invest.* 126, 3207–3218
40. Baumgart, B. *et al.* (2017) In vitro and in vivo evaluation of dasatinib and imatinib on physiological parameters of pulmonary arterial hypertension. *Cancer Chemother. Pharmacol.* 79, 711–723
41. Weatherald, J. *et al.* (2017) Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. *Eur. Respir. J.* 50, 1700217
42. Weatherald, J. *et al.* (2020) Pulmonary complications of Bcr-Abl tyrosine kinase inhibitors. *Eur. Respir. J.* 56, 2000279
43. Cornet, L. *et al.* (2019) Pulmonary arterial hypertension associated with protein kinase inhibitors: a pharmacovigilance–pharmacodynamic study. *Eur. Respir. J.* 53, 1802472

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

44. Ribeuz, H.L. *et al.* (2024) Role of KCNK3 Dysfunction in Dasatinib-associated Pulmonary Arterial Hypertension and Endothelial Cell Dysfunction. *Am. J. Respir. Cell Mol. Biol.* 71, 95–109
45. Connolly, H.M. *et al.* (1997) Valvular heart disease associated with fenfluramine-phentermine. *N. Engl. J. Med.* 337, 581–588
46. Douglas, J.G. *et al.* (1981) Pulmonary hypertension and fenfluramine. *Br. Med. J. Clin. Res. Ed* 283, 881–883
47. Zamanian, R.T. *et al.* (2018) Features and Outcomes of Methamphetamine-associated Pulmonary Arterial Hypertension. *Am. J. Respir. Crit. Care Med.* 197, 788–800
48. Ramirez, R.L. *et al.* (2018) Methamphetamine and the risk of pulmonary arterial hypertension. *Curr. Opin. Pulm. Med.* 24, 416–424
49. Kolaitis, N.A. *et al.* (2021) Clinical Differences and Outcomes between Methamphetamine-associated and Idiopathic Pulmonary Arterial Hypertension in the Pulmonary Hypertension Association Registry. *Ann. Am. Thorac. Soc.* 18, 613–622
50. Ramirez, R.L. *et al.* (2021) Pulmonary Arterial Hypertension Secondary to Drugs and Toxins. *Clin. Chest Med.* 42, 19–38
51. Perros, F. *et al.* (2015) Mitomycin-Induced Pulmonary Veno-Occlusive Disease: Evidence From Human Disease and Animal Models. *Circulation* 132, 834–847
52. Certain, M.-C. *et al.* (2021) Characteristics and Long-term Outcomes of Pulmonary Venoocclusive Disease Induced by Mitomycin C. *Chest* 159, 1197–1207
53. Kunadu, A. *et al.* (2021) Mitomycin induced pulmonary veno-occlusive disease. *Respir. Med. Case Rep.* 34, 101437
54. Zhang, C. *et al.* (2021) Mitomycin C induces pulmonary vascular endothelial-to-mesenchymal transition and pulmonary veno-occlusive disease via Smad3-dependent pathway in rats. *Br. J. Pharmacol.* 178, 217–235
55. Ranchoux, B. *et al.* (2015) Chemotherapy-induced pulmonary hypertension: role of alkylating agents. *Am. J. Pathol.* 185, 356–371
56. Hlavaty, A. *et al.* (2022) Identifying new drugs associated with pulmonary arterial hypertension: A WHO pharmacovigilance database disproportionality analysis. *Br. J. Clin. Pharmacol.* 88, 5227–5237
57. Kim, S.-Y. *et al.* (2012) Bortezomib alleviates experimental pulmonary arterial hypertension. *Am. J. Respir. Cell Mol. Biol.* 47, 698–708
58. Hickey, P.M. *et al.* (2016) Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. *Eur. Respir. J.* 48, 1514–1516
59. Ivan, J. *et al.* (2024) Reversible pulmonary arterial hypertension induced by bosutinib: a case report. *ERJ Open Res.* DOI: 10.1183/23120541.00943-2024
60. Montani, D. *et al.* (2023) Pulmonary hypertension associated with diazoxide: the SUR1 paradox. *ERJ Open Res.* 9, 00350–02023
61. Sullivan, R.T. *et al.* (2021) Diazoxide-associated pulmonary hypertension in a patient with noncompaction cardiomyopathy. *Pulm. Circ.* 11, 2045894020987117
62. Savale, L. *et al.* (2014) Pulmonary arterial hypertension in patients treated with interferon. *Eur. Respir. J.* 44, 1627–1634
63. George, P.M. *et al.* (2012) Endothelin-1 as a mediator and potential biomarker for interferon induced pulmonary toxicity. *Pulm. Circ.* 2, 501–504
64. Lacoste Palasset, T. *et al.* (2021) Association between Leflunomide and Pulmonary Hypertension. *Ann. Am. Thorac. Soc.* DOI: 10.1513/AnnalsATS.202008-913OC
65. Coirier, V. *et al.* (2018) Pulmonary arterial hypertension in four patients treated by leflunomide. *Jt. Bone Spine Rev. Rhum.* DOI: 10.1016/j.jbspin.2017.12.014
66. Quilot, F.-M. *et al.* (2016) Pulmonary hypertension associated with ponatinib therapy. *Eur. Respir. J.* 47, 676–679

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

67. Krop, I.E. *et al.* (2010) Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 28, 2698–2704
68. Kwon, Y. *et al.* (2016) Telangiectasia and Pulmonary Arterial Hypertension Following Treatment With Trastuzumab Emtansine: A Case Report. *Chest* 149, e103-105
69. Umoru, G. *et al.* (2020) Pulmonary arterial hypertension in breast cancer patients on HER2-targeted therapy: a review of FDA Adverse Events Reporting System data. *ERJ Open Res.* 6, 00199–02020
70. Montani, D. *et al.* (2021) Screening for pulmonary arterial hypertension in adults carrying a BMPR2 mutation. *Eur. Respir. J.* 58, 2004229
71. Taylor, R.P. and Lindorfer, M.A. (2024) Antibody-drug conjugate adverse effects can be understood and addressed based on immune complex clearance mechanisms. *Blood* 144, 137–144
72. Poisson, C. *et al.* (2024) Pulmonary hypertension associated with Trastuzumab-Emtansine: an analysis of French PH registry and WHO pharmacovigilance database. *Chest* DOI: 10.1016/j.chest.2024.11.006
73. Condon, D.F. *et al.* (2022) Novel Mechanisms Targeted by Drug Trials in Pulmonary Arterial Hypertension. *Chest* 161, 1060–1072
74. Bonnet, S. *et al.* (2017) Translating Research into Improved Patient Care in Pulmonary Arterial Hypertension. *Am. J. Respir. Crit. Care Med.* 195, 583–595
75. Aiello, R.J. *et al.* (2017) Tryptophan hydroxylase 1 Inhibition Impacts Pulmonary Vascular Remodeling in Two Rat Models of Pulmonary Hypertension. *J. Pharmacol. Exp. Ther.* 360, 267–279
76. Le Ribeuz, H. *et al.* (2022) Involvement of SUR2/Kir6.1 channel in the physiopathology of pulmonary arterial hypertension. *Front. Cardiovasc. Med.* 9, 1066047
77. Guignabert, C. *et al.* (2024) Pathology and pathobiology of pulmonary hypertension: current insights and future directions. *Eur. Respir. J.* 64, 2401095
78. Hagenburg, J. *et al.* (2021) Pulmonary hypertension associated with busulfan. *Pulm. Circ.* 11, 20458940211030170
79. Garcia-Dorado, D. *et al.* (1983) An epidemic of pulmonary hypertension after toxic rapeseed oil ingestion in Spain. *J. Am. Coll. Cardiol.* 1, 1216–1222
80. Leard, L.E. *et al.* (2021) Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. *J. Heart Lung Transplant. Off. Publ. Int. Soc. Heart Transplant.* 40, 1349–1379
81. Savale, L. *et al.* (2024) Transplantation, bridging, and support technologies in pulmonary hypertension. *Eur. Respir. J.* 64, 2401193
82. Ventetuolo, C.E. *et al.* (2020) Culture of pulmonary artery endothelial cells from pulmonary artery catheter balloon tips: considerations for use in pulmonary vascular disease. *Eur. Respir. J.* 55, 1901313
83. Croteau, D. *et al.* (2022) Sources of Evidence Triggering and Supporting Safety-Related Labeling Changes: A 10-Year Longitudinal Assessment of 22 New Molecular Entities Approved in 2008 by the US Food and Drug Administration. *Drug Saf.* 45, 169–180
84. Tau, N. *et al.* (2019) Association Between Data Sources and US Food and Drug Administration Drug Safety Communications. *JAMA Intern. Med.* 179, 1590
85. Sartori, D. *et al.* (2023) Signals of Adverse Drug Reactions Communicated by Pharmacovigilance Stakeholders: A Scoping Review of the Global Literature. *Drug Saf.* 46, 109–120
86. Weatherald, J. *et al.* (2024) Phenotypes in Pulmonary Hypertension. *Eur. Respir. J.* DOI: 10.1183/13993003.01633-2023

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

87. Didden, E. *et al.* (2023) Time to diagnosis of pulmonary hypertension and diagnostic burden: A retrospective analysis of nationwide US healthcare data. *Pulm. Circ.* 13, e12188
88. Gagalova, K.K. *et al.* (2020) What You Need to Know Before Implementing a Clinical Research Data Warehouse: Comparative Review of Integrated Data Repositories in Health Care Institutions. *JMIR Form. Res.* 4, e17687
89. Williams, G.J. *et al.* (2023) Wearable technology and the cardiovascular system: the future of patient assessment. *Lancet Digit. Health* 5, e467–e476
90. Wing, C. *et al.* (2018) Designing Difference in Difference Studies: Best Practices for Public Health Policy Research. *Annu. Rev. Public Health* 39, 453–469
91. Mouillot, P. *et al.* (2024) Characteristics and outcomes of gemcitabine-associated pulmonary hypertension. *ERJ Open Res.* 10, 00654–02023
92. Khouri, C. *et al.* (2021) Investigating the association between ALK receptor tyrosine kinase inhibitors and pulmonary arterial hypertension: a disproportionality analysis from the WHO pharmacovigilance database. *Eur. Respir. J.* 58, 2101576
93. Raschi, E. *et al.* (2019) Evolving Roles of Spontaneous Reporting Systems to Assess and Monitor Drug Safety. In *Pharmacovigilance* (S. Kothari, C. et al., eds), IntechOpen
94. Fusaroli, M. *et al.* (2024) The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement. *Drug Saf.* DOI: 10.1007/s40264-024-01421-9
95. Fusaroli, M. *et al.* (2024) The REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Explanation and Elaboration. *Drug Saf.* DOI: 10.1007/s40264-024-01423-7
96. Lacroix, C. *et al.* (2020) Pharmacovigilance and drug-induced rare diseases: Strengths of the French Network of Regional Pharmacovigilance Centres. *Therapies* 75, 207–213
97. Norén, G.N. *et al.* (2021) Consensus clustering for case series identification and adverse event profiles in pharmacovigilance. *Artif. Intell. Med.* 122, 102199
98. Barateau, L. *et al.* (2024) Guidelines for the assessment and management of residual sleepiness in obstructive apnea-hypopnea syndrome: Endorsed by the French Sleep Research and Medicine Society (SFRMS) and the French Speaking Society of Respiratory Diseases (SPLF). *Respir. Med. Res.* 86, 101105
99. Cracowski, J.-L. *et al.* (2024) Assessing the benefit-risk balance of drugs. Some lessons from the COVID pandemic. *Expert Opin. Drug Saf.* DOI: 10.1080/14740338.2024.2368811
100. Price, L.C. *et al.* (2024) Reversible carfilzomib-induced pulmonary arterial hypertension: don't take your eyes off the ball! *Eur. Respir. J.* 64, 2401087
101. Picot, C. *et al.* (2023) Risk of drug use during pregnancy: master protocol for living systematic reviews and meta-analyses performed in the metaPreg project. *Syst. Rev.* 12, 101
102. Zhuang, Y. *et al.* (2023) Self-sovereign identity empowered non-fungible patient tokenization for health information exchange using blockchain technology. *Comput. Biol. Med.* 157, 106778
103. Corrigan-Curay, J. *et al.* (2018) Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness. *JAMA* 320, 867
104. Desai, R.J. *et al.* (2024) The FDA Sentinel Real World Evidence Data Enterprise (RWE-DE). *Pharmacoepidemiol. Drug Saf.* 33, e70028
105. Data Analysis and Real World Interrogation Network (DARWIN EU®).[Online]. Available: https://www.darwin-eu.org/. [Accessed: 14-Oct-2024]

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

106. Gillmeyer, K.R. *et al.* (2019) Accuracy of Algorithms to Identify Pulmonary Arterial Hypertension in Administrative Data. *Chest* 155, 680–688
107. Gillmeyer, K.R. *et al.* (2021) Development and Validation of Algorithms to Identify Pulmonary Arterial Hypertension in Administrative Data. *Chest* 159, 1986–1994
108. Jambon-Barbara, C. *et al.* (2024) Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in a French healthcare database. *ERJ Open Res.* 10, 00109–02024
109. Arnaud, M. *et al.* (2017) Methods for safety signal detection in healthcare databases: a literature review. *Expert Opin. Drug Saf.* 16, 721–732
110. Suissa, S. *et al.* (2017) Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol. Drug Saf.* 26, 459–468
111. Hernán, M.A. *et al.* (2022) Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA* 328, 2446
112. Hill, A.B. (1965) THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proc. R. Soc. Med.* 58, 295–300
113. Budhram, B. *et al.* (2024) Moving the needle on proteasome inhibitor-induced pulmonary arterial hypertension: a definite maybe. *Eur. Respir. J.* 63, 2400946

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

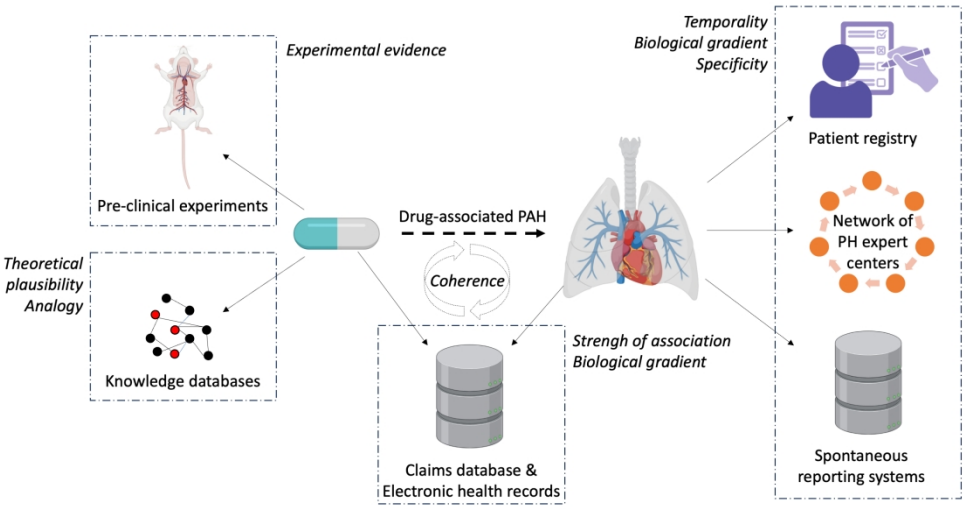


Figure 1. Perspective in the assessment of signals of drug-associated PAH. Bradford Hill criteria for causal assessment of associations between drugs and adverse events that can be informed by each data source/method are indicated

359x190mm (212 x 212 DPI)

AJRCCM Articles in Press. Published June 12, 2025 as 10.1164/rccm.202411-2339PP
Copyright © 2025 by the American Thoracic Society

CONCLUSION

A travers ces travaux nous avons exploré l'ensemble du déroulement de la détection jusqu'à l'évaluation de signaux de sécurité médicamenteux. Nous avons pris l'exemple de trois pathologies vasculaires et respiratoires avec des physiopathologies, des durées d'apparition et des incidences dans la population très différentes pour balayer un maximum de cas que nous pouvons retrouver dans les études sur la sécurité du médicament. De plus, ces pathologies s'intègrent parfaitement dans le scope de notre laboratoire de recherche HP2, dédié à l'étude de l'hypoxie intermittente (induite par l'apnée du sommeil) et de la microcirculation (ulcères cutanés et HTAP).

Le développement et la validation d'algorithmes d'identification de ces pathologies permet la réalisation de futures études de pharmacoépidémiologie dans le domaine. Nous sommes en train de réaliser le développement et la validation d'algorithmes d'identification spécifiques en fonction de l'étiologie de l'HTAP et le développement et la validation d'un algorithme spécifique et un sensible pour l'identification des apnées du sommeil.

Nous concluons sur l'importance d'adapter le schéma d'étude et la méthodologie en fonction de la question de recherche, du profil physiopathologique et de la fonction de risque de la pathologie d'intérêt, ainsi de la place du traitement d'intérêt dans la prise en charge thérapeutique.

REFERENCES

1. Perros F, Günther S, Ranchoux B, Godinas L, Antigny F, Chaumais MC, et al. Mitomycin-Induced Pulmonary Veno-Occlusive Disease: Evidence From Human Disease and Animal Models. Circulation. 1 sept 2015;132(9):834-47.

2. Bonnet S, Provencher S, Guignabert C, Perros F, Boucherat O, Schermuly RT, et al. Translating Research into Improved Patient Care in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 1 mars 2017;195(5):583-95.

3. Aiello RJ, Bourassa PA, Zhang Q, Dubins J, Goldberg DR, De Lombaert S, et al. Tryptophan hydroxylase 1 Inhibition Impacts Pulmonary Vascular Remodeling in Two Rat Models of Pulmonary Hypertension. J Pharmacol Exp Ther. févr 2017;360(2):267-79.

4. Ribeuz HL, Willer ASM, Chevalier B, Sancho M, Masson B, Eyries M, et al. Role of KCNK3 Dysfunction in Dasatinib-associated Pulmonary Arterial Hypertension and Endothelial Cell Dysfunction. Am J Respir Cell Mol Biol. juill 2024;71(1):95-109.

5. Le Ribeuz H, Masson B, Dutheil M, Boët A, Beauvais A, Sabourin J, et al. Involvement of SUR2/Kir6.1 channel in the physiopathology of pulmonary arterial hypertension. Front Cardiovasc Med. 2022;9:1066047.

6. Montani D, Antigny F, Jutant EM, Chaumais MC, Le Ribeuz H, Grynblat J, et al. Pulmonary hypertension associated with diazoxide: the SUR1 paradox. ERJ Open Res. nov 2023;9(6):00350-2023.

7. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 29 août 2024;2401324.

8. Lineberry N, Berlin JA, Mansi B, Glasser S, Berkwits M, Klem C, et al. Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective. BMJ. 3 oct 2016;355:i5078.

9. Ioannidis JPA, Evans SJW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 16 nov 2004;141(10):781-8.

10. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. août 2010;63(8):834-40.

11. Junqueira DR, Zorzela L, Golder S, Loke Y, Gagnier JJ, Julious SA, et al. CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. BMJ. 24 avr 2023;381:e073725.

12. Zhou Y, Ke C, Jiang Q, Shahin S, Snapinn S. Choosing Appropriate Metrics to Evaluate Adverse Events in Safety Evaluation. Ther Innov Regul Sci. mai 2015;49(3):398-404.

13. Siddiqui O. Statistical methods to analyze adverse events data of randomized clinical trials. J Biopharm Stat. sept 2009;19(5):889-99.

14. Huang Q, Wang W, Zheng L, Shi YX, Ge L, Zeng XT, et al. Suboptimal practices in harm reporting: a meta-epidemiological study on metrics, recurrence, and exposure duration in clinical trials. J Clin Epidemiol. juin 2025;182:111755.

15. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA. 26 mai 2004;291(20):2457-65.

16. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. BMJ. 2 avr 2005;330(7494):753.

17. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med. 12 nov 2009;361(20):1963-71.

18. Dwan K, Gamble C, Williamson PR, Kirkham JJ, Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PloS One. 2013;8(7):e66844.

19. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K, et al. Harms are assessed inconsistently and reported inadequately part 1: systematic adverse events. J Clin Epidemiol. sept 2019;113:20-7.

20. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K, et al. Harms are assessed inconsistently and reported inadequately Part 2: nonsystematic adverse events. J Clin Epidemiol. sept 2019;113:11-9.

21. Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. BMJ. 3 janv 2012;344:d7202.

22. Golder S, Loke YK, Wright K, Norman G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. PLoS Med. sept 2016;13(9):e1002127.

23. Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol. janv 2004;57(1):86-92.

24. Zink RC, Marchenko O, Sanchez-Kam M, Ma H, Jiang Q. Sources of Safety Data and Statistical Strategies for Design and Analysis: Clinical Trials. Ther Innov Regul Sci. mars 2018;52(2):141-58.

25. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 22 avr 1971;284(15):878-81.

26. Bouvenot G, Vray M. Essais cliniques : théorie, pratique et critique (4° éd.). Lavoisier. 2006.

27. Cracowski JL, Molimard M, Richard V, Roustit M, Khouri C. Assessing the benefit-risk balance of drugs. Some lessons from the COVID pandemic. Expert Opin Drug Saf. 19 juin 2024;1-9.

28. Meyler L. Side effects of drugs. Elsevier. Amsterdam; 1952.

29. Wallerstein RO, Condit PK, Kasper CK, Brown JW, Morrison FR. Statewide study of chloramphenicol therapy and fatal aplastic anemia. JAMA. 16 juin 1969;208(11):2045-50.

30. Lenz W. Malformations caused by drugs in pregnancy. Am J Dis Child 1960. août 1966;112(2):99-106.

31. Postigo R, Brosch S, Slattery J, van Haren A, Dogné JM, Kurz X, et al. EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection. Drug Saf. juill 2018;41(7):665-75.

32. Center for Drug Evaluation and Research. FDA Adverse Event Reporting System (FAERS) Database. FDA [Internet]. 16 oct 2024 [cité 17 juin 2025]; Disponible sur: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers-database

33. Uppsala Monitoring Centre. The WHO global database [Internet]. [cité 17 juin 2025]. Disponible sur: https://who-umc.org/vigibase-search-services/about-vigibase/

34. van Puijenbroek EP, Bate A, Leufkens HGM, Lindquist M, Orre R, Egberts ACG. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11(1):3-10.

35. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. Br J Clin Pharmacol. déc 2011;72(6):905-8.

36. Poluzzi E, Raschi E, Piccinni C, Ponti FD, Poluzzi E, Raschi E, et al. Data Mining Techniques in Pharmacovigilance: Analysis of the Publicly Accessible FDA Adverse Event Reporting System (AERS). In: Data Mining Applications in Engineering and Medicine [Internet]. IntechOpen; 2012 [cité 17 juin 2025]. Disponible sur: https://www.intechopen.com/chapters/38579

37. Wisniewski AFZ, Bate A, Bousquet C, Brueckner A, Candore G, Juhlin K, et al. Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Saf. juin 2016;39(6):469-90.

38. Hasegawa S, Matsui T, Hane Y, Abe J, Hatahira H, Motooka Y, et al. Thromboembolic adverse event study of combined estrogen-progestin preparations using Japanese Adverse Drug Event Report database. PloS One. 2017;12(7):e0182045.

39. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 6 juill 1998;54(4):315-21.

40. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002;25(6):381-92.

41. Xiao C, Li Y, Baytas IM, Zhou J, Wang F. An MCEM Framework for Drug Safety Signal Detection and Combination from Heterogeneous Real World Evidence. Sci Rep. 29 janv 2018;8(1):1806.

42. Pham M, Cheng F, Ramachandran K. A Comparison Study of Algorithms to Detect Drug–Adverse Event Associations: Frequentist, Bayesian, and Machine-Learning Approaches. Drug Saf. juin 2019;42(6):743-50.

43. Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug-drug interaction surveillance. Stat Med. 20 juill 2008;27(16):3057-70.

44. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res. févr 2013;22(1):57-69.

45. Jambon-Barbara C, Revol B, Hlavaty A, Joyeux-Faure M, Borel JC, Cracowski JL, et al. Signal detection of drugs associated with obstructive and central sleep apnoea. Sleep Med. déc 2024;124:315-22.

46. Weber J. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. Adv Inflamm Res. 1984;6:1.

47. Mouly S, Roustit M, Bagheri H, Perault-Pochat MC, Molimard M, Bordet R. The French Levothyrox® crisis: We did the best we could but…. Therapie. juin 2019;74(3):431-5.

48. Tubert-Bitter P, Haramburu F, Begaud B, Chaslerie A, Abraham E, Hagry C. Spontaneous reporting of adverse drug reactions: who reports and what? Pharmacoepidemiol Drug Saf. sept 1998;7(5):323-9.

49. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of Safety Alerts on Measures of Disproportionality in Spontaneous Reporting Databases: The Notoriety Bias. Drug Saf. 2007;30(10):891-8.

50. Faillie JL. Case–non-case studies: Principle, methods, bias and interpretation. Therapies. avr 2019;74(2):225-32.

51. Bate A, Lindquist M, Edwards IR. The application of knowledge discovery in databases to post-marketing drug safety: example of the WHO database. Fundam Clin Pharmacol. avr 2008;22(2):127-40.

52. Haramburu F, Bégaud B, Moride Y. Temporal trends in spontaneous reporting of unlabelled adverse drug reactions. Br J Clin Pharmacol. sept 1997;44(3):299-301.

53. Moride Y, Haramburu F, Requejo AA, Bégaud B. Under-reporting of adverse drug reactions in general practice. Br J Clin Pharmacol. févr 1997;43(2):177-81.

54. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;29(5):385-96.

55. Raschi E, Poluzzi E, Salvo F, Pariente A, De Ponti F, Marchesini G, et al. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: What a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutr Metab Cardiovasc Dis. juin 2018;28(6):533-42.

56. Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Explanation and Elaboration. Drug Saf. juin 2024;47(6):585-99.

57. Fusaroli M, Salvo F, Begaud B, AlShammari TM, Bate A, Battini V, et al. The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement. Drug Saf. juin 2024;47(6):575-84.

58. Strom BL. What Is Pharmacoepidemiology? In: Pharmacoepidemiology [Internet]. John Wiley & Sons, Ltd; 2019. p. 1-26. Disponible sur: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119413431.ch1

59. Lee JA, Draper PA, Weatherall M. PRIMARY MEDICAL CARE. 3. PRESCRIBING IN THREE ENGLISH TOWNS. Milbank Mem Fund Q. avr 1965;43:285-90.

60. Muller C. Medical review of prescribing. J Chronic Dis. 1 juill 1965;18(7):689-96.

61. Meade TW. Prescribing of chloramphenicol in general practice. Br Med J. 18 mars 1967;1(5541):671-4.

62. ICH M14 guideline on general principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines - Scientific guideline | European Medicines Agency (EMA) [Internet]. 2024 [cité 21 juin 2025]. Disponible sur: https://www.ema.europa.eu/en/ich-m14-guideline-general-principles-plan-design-analysis-pharmacoepidemiological-studies-utilize-real-world-data-safety-assessment-medicines-scientific-guideline

63. Fonarow GC. Randomization-There Is No Substitute. JAMA Cardiol. 1 sept 2016;1(6):633-5.

64. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JPA. Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey. BMJ. 8 févr 2016;352:i493.

65. Fanaroff AC, Califf RM, Harrington RA, Granger CB, McMurray JJV, Patel MR, et al. Randomized Trials Versus Common Sense and Clinical Observation: JACC Review Topic of the Week. J Am Coll Cardiol. 4 août 2020;76(5):580-9.

66. Concato J, Corrigan-Curay J. Real-World Evidence - Where Are We Now? N Engl J Med. 5 mai 2022;386(18):1680-2.

67. Burns L, Roux NL, Kalesnik-Orszulak R, Christian J, Hukkelhoven M, Rockhold F, et al. Real-World Evidence for Regulatory Decision-Making: Guidance From Around the World. Clin Ther. mars 2022;44(3):420-37.

68. Dahabreh IJ, Bibbins-Domingo K. Causal Inference About the Effects of Interventions From Observational Studies in Medical Journals. JAMA. 4 juin 2024;331(21):1845-53.

69. Cucherat M, Demarcq O, Chassany O, Le Jeunne C, Borget I, Collignon C, et al. Attentes méthodologiques pour la démonstration de l'efficacité des produits de santé par les études observationnelles. Therapies. oct 2024;S0040595724001689.

70. Desai RJ, Wang SV, Sreedhara SK, Zabotka L, Khosrow-Khavar F, Nelson JC, et al. Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center. BMJ. 12 févr 2024;384:e076460.

71. Quantin C. Etude des algorithmes de définition de pathologies dans le Système Nationale d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) [Internet]. Caisse National d'Assurance Maladie; 2015 août p. 272. Disponible sur: https://assurance-maladie.ameli.fr/sites/default/files/2014_etude-algorithmes-definition-pathologies-partie-1_cartographie.pdf

72. Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur. sept 2021;8:100158.

73. Hoisnard L, Pina Vegas L, Dray-Spira R, Weill A, Zureik M, Sbidian E. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. Ann Rheum Dis. févr 2023;82(2):182-8.

74. Hansford HJ, Cashin AG, Jones MD, Swanson SA, Islam N, Douglas SRG, et al. Reporting of Observational Studies Explicitly Aiming to Emulate Randomized Trials: A Systematic Review. JAMA Netw Open. 5 sept 2023;6(9):e2336023.

75. Hernán MA, Dahabreh IJ, Dickerman BA, Swanson SA. The Target Trial Framework for Causal Inference From Observational Data: Why and When Is It Helpful? Ann Intern Med. 18 févr 2025;

76. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Math Model. 1 janv 1986;7(9):1393-512.

77. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 28 juill 2016;375(4):311-22.

78. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. nov 2016;79:70-5.

79. Hernán MA, Sterne JAC, Higgins JPT, Shrier I, Hernández-Díaz S. A Structural Description of Biases That Generate Immortal Time. Epidemiol Camb Mass. 1 janv 2025;36(1):107-14.

80. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 15 févr 2008;167(4):492-9.

81. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. sept 2020;29(9):1101-10.

82. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41-55.

83. Rubin DB. Causal Inference Using Potential Outcomes: Design, Modeling, Decisions. J Am Stat Assoc. 1 mars 2005;100(469):322-31.

84. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. mars 2006;98(3):253-9.

85. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol. mai 2006;59(5):437-47.

86. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ. 23 oct 2019;367:l5657.

87. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primer. 25 juin 2015;1:15015.

88. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. août 2019;7(8):687-98.

89. Cowie MR, Linz D, Redline S, Somers VK, Simonds AK. Sleep Disordered Breathing and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 10 août 2021;78(6):608-24.

90. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, et al. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 20 juill 2021;144(3):e56-67.

91. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 15 oct 2013;188(8):996-1004.

92. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. janv 2017;49(1):1600959.

93. Gaisl T, Haile SR, Thiel S, Osswald M, Kohler M. Efficacy of pharmacotherapy for OSA in adults: A systematic review and network meta-analysis. Sleep Med Rev. août 2019;46:74-86.

94. Jullian-Desayes I, Revol B, Chareyre E, Camus P, Villier C, Borel JC, et al. Impact of concomitant medications on obstructive sleep apnoea. Br J Clin Pharmacol. avr 2017;83(4):688-708.

95. Revol B, Jullian-Desayes I, Tamisier R, Puel V, Mallaret M, Joyeux-Faure M, et al. Ticagrelor and Central Sleep Apnea. J Am Coll Cardiol. 22 mai 2018;71(20):2378-9.

96. Falanga V, Isseroff RR, Soulika AM, Romanelli M, Margolis D, Kapp S, et al. Chronic wounds. Nat Rev Dis Primer. 21 juill 2022;8(1):50.

97. Haute Autorité de Santé [Internet]. 2022 [cité 11 févr 2022]. Les pansements : Indications et utilisations recommandées - Fiche BUTS. Disponible sur: https://www.has-sante.fr/jcms/r_1438004/fr/les-pansements-indications-et-utilisations-recommandees-fiche-buts

98. Améliorer la prise en charge des plaies chroniques | L'Assurance Maladie [Internet]. 2022 [cité 11 févr 2022]. Disponible sur: https://assurance-maladie.ameli.fr/etudes-et-donnees/2015-prise-en-charge-plaies-chroniques-parcours-soins

99. Rames O, Sebo S, Pécault R, Agamaliyev E, Tuppin P, Rodde Dunet MH, et al. Plaies chroniques en France : Prévalence, Caractéristiques et Évolution. Améliorer l'organisatoin de la prise en charge en sortie d'hospitalisation [Internet]. Caisse National d'Assurance Maladie; 2015 mars. Disponible sur: https://assurance-maladie.ameli.fr/etudes-et-donnees/2015-prise-en-charge-plaies-chroniques-parcours-soins

100. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen Off Publ Wound Heal Soc Eur Tissue Repair Soc. déc 2009;17(6):763-71.

101. Sen CK. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. Adv Wound Care. mai 2021;10(5):281-92.

102. Perez J. Risque d'ulcère du pied diabétique et utilisation des inhibiteurs de la cyclooxygénase 2 : une étude cas-témoins nichée dans l'Echantillon Généraliste des Bénéficiaires (EGB) [Internet]. 2020. Disponible sur: https://dumas.ccsd.cnrs.fr/dumas-03245999

103. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound Healing: A Cellular Perspective. Physiol Rev. 1 janv 2019;99(1):665-706.

104. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet Lond Engl. 12 nov 2005;366(9498):1736-43.

105. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med. 3 déc 2014;6(265):265sr6.

106. Duron D, Blaise S, Cracowski JL, Roustit M, Khouri C. Drug-induced skin ulcers: A disproportionality analysis from the WHO pharmacovigilance database. J Am Acad Dermatol. juill 2021;85(1):229-32.

107. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. janv 2019;53(1):1801913.

108. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 11 oct 2022;43(38):3618-731.

109. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. janv 2023;61(1):2200879.

110. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulm Circ. 2021;11(1):2045894020977300.

111. GBD 2021 Pulmonary Arterial Hypertension Collaborators. Global, regional, and national burden of pulmonary arterial hypertension, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Respir Med. 18 oct 2024;S2213-2600(24)00295-9.

112. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol. oct 2017;14(10):603-14.

113. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 29 août 1996;335(9):609-16.

114. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation. 1 mai 2012;125(17):2128-37.

115. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, et al. Pulmonary arterial hypertension associated with protein kinase inhibitors: a pharmacovigilance-pharmacodynamic study. Eur Respir J. mai 2019;53(5):1802472.

116. Hlavaty A, Roustit M, Montani D, Chaumais M, Guignabert C, Humbert M, et al. Identifying new drugs associated with pulmonary arterial hypertension: A WHO pharmacovigilance database disproportionality analysis. Br J Clin Pharmacol. déc 2022;88(12):5227-37.

117. Poisson C, Hlavaty A, Favrolt N, Chaumais MC, Grynblat J, Jutant EM, et al. Pulmonary hypertension associated with Trastuzumab-Emtansine: an analysis of French PH registry and WHO pharmacovigilance database. Chest. 19 nov 2024;S0012-3692(24)05562-4.

118. Grynblat J, Khouri C, Hlavaty A, Jaïs X, Savale L, Chaumais MC, et al. Characteristics and outcomes of patients developing pulmonary hypertension associated with proteasome inhibitors. Eur Respir J. juin 2024;63(6):2302158.

119. Rich S, Rubin L, Abenhail L. Executive summary from the World Symposium on Primary Pulmonary Hypertension (Evian, France, September 6–10, 1998). The World Health Organization publication via the Internet. Disponible sur: http://www.who.int/ncd/cvd/pph.html

120. Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products.

121. Guideline on good pharmacovigilance practices (GVP) - Module IX – Signal management (Rev 1).

122. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. mai 1965;58(5):295-300.

123. Bégaud B, Jones JK. Assessing Causality from Case Reports. In: Textbook of Pharmacoepidemiology [Internet]. John Wiley & Sons, Ltd; 2021 [cité 20 août 2024]. p. 246-56. Disponible sur: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119701101.ch14

124. Rodríguez AJ, Nerlekar N, Ebeling PR. Cardiac adverse events in bisphosphonate and teriparatide users: An international pharmacovigilance study. Bone. 2023;168:116647.

125. Arnaud M, Bégaud B, Thurin N, Moore N, Pariente A, Salvo F. Methods for safety signal detection in healthcare databases: a literature review. Expert Opin Drug Saf. juin 2017;16(6):721-32.

126. Lai ECC, Pratt N, Hsieh CY, Lin SJ, Pottegård A, Roughead EE, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. Eur J Epidemiol. juill 2017;32(7):567-82.

127. Maura G, Billionnet C, Coste J, Weill A, Neumann A, Pariente A. Non-bleeding Adverse Events with the Use of Direct Oral Anticoagulants: A Sequence Symmetry Analysis. Drug Saf. 1 sept 2018;41(9):881-97.

128. King CE, Pratt NL, Craig N, Thai L, Wilson M, Nandapalan N, et al. Detecting Medicine Safety Signals Using Prescription Sequence Symmetry Analysis of a National Prescribing Data Set. Drug Saf. août 2020;43(8):787-95.

129. Rames O, Sebo S, Pécault R, Agamaliyev E, Tuppin P, Rodde Dunet MH, et al. Plaies chroniques en France : Prévalence, Caractéristiques et Évolution. Améliorer l'organisatoin de la prise en charge en sortie d'hospitalisation [Internet]. Caisse National d'Assurance Maladie; 2015 mars. Disponible sur: https://assurance-maladie.ameli.fr/etudes-et-donnees/2015-prise-en-charge-plaies-chroniques-parcours-soins

130. Gillmeyer KR, Lee MM, Link AP, Klings ES, Rinne ST, Wiener RS. Accuracy of Algorithms to Identify Pulmonary Arterial Hypertension in Administrative Data: A Systematic Review. Chest. avr 2019;155(4):680-8.

131. Gillmeyer KR, Nunez ER, Rinne ST, Qian SX, Klings ES, Wiener RS. Development and Validation of Algorithms to Identify Pulmonary Arterial Hypertension in Administrative Data. Chest. mai 2021;159(5):1986-94.

132. Pépin JL, Bailly S, Rinder P, Adler D, Benjafield AV, Lavergne F, et al. Relationship Between CPAP Termination and All-Cause Mortality: A French Nationwide Database Analysis. Chest. juin 2022;161(6):1657-65.

133. Pépin JL, Tamisier R, Benjafield AV, Rinder P, Lavergne F, Josseran A, et al. CPAP Resumption After a First Termination and Impact on All-Cause Mortality in France. Eur Respir J. 22 déc 2023;2301171.

134. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 7 avr 2021;42(14):1289-367.

135. Paboeuf C, Priou P, Meslier N, Roulaud F, Trzepizur W, Gagnadoux F. Ticagrelor-Associated Shift From Obstructive to Central Sleep Apnea: A Case Report. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 15 août 2019;15(8):1179-82.

136. Puel V, Théophile H, Godard I, Raymond N, Miremont-Salamé G, Gosse P, et al. Ticagrelor and central sleep apnoea: Impact of withdrawal and reintroduction. Br J Clin Pharmacol. août 2019;85(8):1855-8.

137. Meurin P, Ben Driss A, Defrance C, Dumaine R, Weber H, Renaud N, et al. Central sleep apnea after acute coronary syndrome and association with ticagrelor use. Sleep Med. avr 2021;80:39-45.

138. Wang Q, Liu J, Guo T, Liu D, Pan J. Epidermal Growth Factor Reverses the Inhibitory Effects of the Bisphosphonate, Zoledronic Acid, on Human Oral Keratinocytes and Human Vascular Endothelial Cells In Vitro via the Epidermal Growth Factor Receptor (EGFR)/Akt/Phosphoinositide 3-Kinase (PI3K) Signaling Pathway. Med Sci Monit Int Med J Exp Clin Res. 24 janv 2019;25:700-10.

139. Gao SY, Zheng GS, Wang L, Liang YJ, Zhang SE, Lao XM, et al. Zoledronate suppressed angiogenesis and osteogenesis by inhibiting osteoclasts formation and secretion of PDGF-BB. PloS One. 2017;12(6):e0179248.

140. Tannen RL, Weiner MG, Xie D. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. BMJ. 27 janv 2009;338:b81.

141. Yu M, Xie D, Wang X, Weiner MG, Tannen RL. Prior event rate ratio adjustment: numerical studies of a statistical method to address unrecognized confounding in observational studies. Pharmacoepidemiol Drug Saf. mai 2012;21 Suppl 2:60-8.

142. Mattei D, Feola M, Orzan F, Mordini N, Rapezzi D, Gallamini A. Reversible dasatinib-induced pulmonary arterial hypertension and right ventricle failure in a previously allografted CML patient. Bone Marrow Transplant. juin 2009;43(12):967-8.

143. Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. Leuk Res. juin 2009;33(6):861-4.

144. Quilot FM, Georges M, Favrolt N, Beltramo G, Foignot C, Grandvuillemin A, et al. Pulmonary hypertension associated with ponatinib therapy. Eur Respir J. févr 2016;47(2):676-9.

145. Hoeper MM, Barst RJ, Bourge RC, Feldman J, Frost AE, Galié N, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 12 mars 2013;127(10):1128-38.

146. Suissa S, Moodie EEM, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiol Drug Saf. avr 2017;26(4):459-68.

147. Suissa S, Dell'Aniello S, Renoux C. The Prevalent New-user Design for Studies With no Active Comparator: The Example of Statins and Cancer. Epidemiol Camb Mass. 1 sept 2023;34(5):681-9.

ANNEXES 1 – AUTRES TRAVAUX EN RELATION AVEC LA THESE

1. Understanding the variability of pharmaco-epidemiological studies assessing the risk of appendicitis with mRNA COVID-19 vaccines

Check for updates

Received: 19 July 2022 | Revised: 30 September 2022 | Accepted: 26 October 2022

DOI: 10.1002/pds.5560

COMMENTARY

WILEY

Understanding the variability of pharmaco-epidemiological studies assessing the risk of appendicitis with mRNA COVID-19 vaccines

Clement Jambon-Barbara[1,2] | Claire Bernardeau[1,2] | Jean-Luc Cracowski[1,2] | Charles Khouri[1,2,3]

[1]Pharmacovigilance Department, Grenoble Alpes University Hospital, Grenoble, France

[2]Univ. Grenoble Alpes, Inserm U1300, HP2, Grenoble, France

[3]Univ. Grenoble Alpes, Inserm CIC1406, Grenoble Alpes University Hospital, F-38000, Grenoble, France

Correspondence
Charles Khouri, Pharmacovigilance department, Université Grenoble Alpes and Grenoble Alpes University Hospital. Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France.
Email: ckhouri@chu-grenoble.fr

Key Points

- Results of cohort studies evaluating the risk of appendicitis after mRNA COVID-19 vaccines are heterogeneous.
- Our analysis suggests that the discrepancies between results of these studies is mainly linked to the choice of control groups.
- Selection of comparator group was particularly difficult with COVID-19 vaccines given the large proportion of population exposed, often by using the same vaccine platform.
- Using self-controlled design could be an interesting option to addresses these issues.
- Sensitivity analyses are crucial to assess the degree of variability in the results of a study according to methodological choices.

1 | INTRODUCTION

Whether mRNA COVID vaccines could increase the risk of appendicitis has been raised from the phase 3 clinical trial of BNT162b2 in which the rate of appendicitis disproportionately affected vaccinated volunteers.[1] The US Food and Drug Administration advisory committee thus enjoined for further signal detection efforts in adding appendicitis as an adverse effect of special interest.[2] This signal has then been assessed in three large nationwide cohort studies who provided very discrepant results.[3–5] Whether three large pharmaco-epidemiological studies can produce widely discrepant results in using the same design for a relatively simple outcome deserve to be explored.

Clement Jambon-Barbara and Claire Bernardeau are co-first authors.

2 | METHOD

We extracted study characteristics and incidence rates of appendicitis from the three studies.

We then performed a random-effect meta-analysis of incidence rate of appendicitis in control and vaccinated groups and of incidence rate ratio (IRR) in vaccinated compared to nonvaccinated groups. Statistical analysis was performed with R (version 4.1.1).

3 | RESULTS

The main methodological characteristics of these studies are described in Table 1. All these studies assessed the risk of appendicitis 21 days after vaccination using a cohort design. However, outcomes definitions and appendicitis identification were slightly different due

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2022 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons Ltd.

TABLE 1 Synthesis of main methodological characteristics of pharmacoepidemiological studies assessing the risk of appendicitis after mRNA COVID-19 vaccines

	Study design	Follow-up time	Inclusion criteria	Exclusion criteria	Outcome definition	Exposure definition	End of follow-up
Barda N et al. NEJM 2021[3]	Cohort study on Clalit Health Services (CHS) database (a 52% representative sample of Israeli population) with matching 1:1 on baseline variables. Unvaccinated patients matched on a given day could become vaccinated on a future date and newly eligible for inclusion as a vaccinated person	42 days (21 days after each dose)	-16 years or older -Continuous membership in the CHS during one full year -No previous SARS-CoV-2 infection -No contact with the healthcare system in previous 7 days	-Previous diagnosis of appendicitis -Long term care facility residents -Persons confined to their homes for medical reasons -Health care workers -Persons for whom data on BMI or residential area were missing	ICD-9 diagnosis codes: -540: Acute appendicitis -541: Unspecified appendicitis -542: Other appendicitis ICD-9 procedure code: -47: Operation on appendix	A dose of BNT162b2 vaccine	Earliest of one of the following: -Documentation of the appendicitis -21 days after a vaccine dose -May 24, 2021 -Death -Diagnosis of SARS-COV2 infection in either vaccinated or unvaccinated patient will end the follow-up for both
Klein N and al. JAMA. 2021[5]	Cohort study composed of only vaccinated patients present in the 8 data-contributing health plans, representing 3% of the US population. Comparison of appendicitis incidence during a risk interval of days 1 to 21 after vaccination with appendicitis incidence for those who were concurrently (same calendar day) in comparison interval (22 to 42 days after their most recent COVID-19 vaccination)	42 days (21 days after each dose)	-12 years or older -Present in one of the eight data-contributing health plans -BNT162b2 or mRNA-1273 vaccination	None	ICD-10 codes: -K35: Acute appendicitis -K36: Other appendicitis -K37: Unspecified appendicitis -K38.8: Other specified diseases of appendix	A dose of BNT162b2 or mRNA-1273 vaccine	Earliest of one of the following: -21 days after a vaccine dose -June 26, 2021
Kildegaard H et al. JAMA Internal Medicine. 2022[4]	Cohort study on Danish nationwide registers. Evaluation of the risk of appendicitis during the 21 days following vaccine dose. Reference group is unvaccinated patients matched on weighting to adjust for potential confounders. Individuals with previous appendicicitis or appendicectomy were excluded	42 days (21 days after each dose)	-12 years or older -BNT162b2 or mRNA-1273 vaccination	-Previous appendicitis or appendectomy -Individuals immunized with non-mRNA COVID-19 vaccines -Individuals with PCR-confirmed SARS-CoV-2 before study inclusion	ICD-10 codes: -K35: Acute appendicitis -K36: Other appendicitis -K37: Unspecified appendicitis Appendectomy diagnosis code in Danish Pathology Register (SNOMED codes)	A dose of BNT162b2 or mRNA-1273 vaccine	Earliest of one of the following: -21 days after a vaccine dose -Occurrence of the appendicitis -November 30, 2021 -Death -SARS-COV2 infection -Immunization against COVID-19 for unvaccinated patients

10991557, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5560 by CHU Grenoble Alpes, Wiley Online Library on [28/04/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

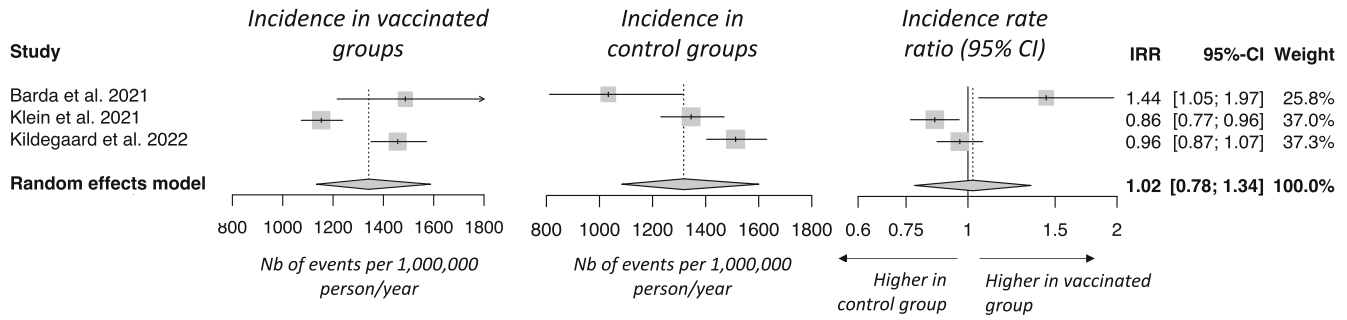


FIGURE 1 Forest plot of Incidence Rate of appendicitis in vaccinated and control groups, and Incidence Rate Ratio of appendicitis with mRNA COVID vaccines compared to nonvaccinated.

to different coding systems (ICD-9 or ICD-10) and selective inclusion of appendectomies. More importantly, the choice of the comparator group and matching/weighting procedures were highly heterogeneous between studies (Table 1).

The results of the meta-analysis assessing the risk of appendicitis was IRR = 1.02 (95% CI 0.78, 1.34), with a large heterogeneity (I^2 = 80%) (Figure 1). The incidence of appendicitis in vaccinated groups was highly similar for two studies (Barda et al and Kildegaard et al.) with an incidence of 1487 (95% CI 1216, 1818) and 1456 (95% CI 1350, 1571) cases per 1 000 000 person years respectively. The incidence of appendicitis was inferior in the Klein et al. study, probably because of the noninclusion of appendicectomies. However, the incidence of appendicitis was more heterogeneous in control groups notably for Barda et al. and Kildegaard et al. with an incidence of 1033 (95% CI 811, 1315) and 1512 (95% CI 1404, 1630) per 1 000 000 person years, respectively. This large discrepancy in incidence rate in control groups explain the discrepant results of these two studies, IRR = 1.44 (95% CI 1.05, 1.97) for Barda et al. and 0.96 (95% CI 0.87, 1.07) for Kildegaard et al.

4 | DISCUSSION

The case of appendicitis well illustrate the range of options available to pharmacoepidemiological researchers when designing a study.[6] Multitudes of methods are possible which all have their pros and cons, making the evaluation of a safety signal on the basis of these results challenging. The result of the meta-analysis of these three studies is in favor of an absence of risk of appendicitis 21 days after mRNA COVID-19 vaccination but with a strong heterogeneity, making the unique role of sampling variance unlikely. Heterogeneity between observational studies addressing the same research question may occur from differences in data sources, set of inclusion/exclusion criteria, confounders, duration of baseline assessment, date of entry in the cohort, outcome and exposure risk algorithm and analytical strategies…[7,8] Our analysis suggests that the discrepancies between results of these studies is mainly linked to the choice of control groups. Comparator selection is cornerstone in observational studies to limit confounding by indication, leading to an imbalance between treatment groups in the baseline level of risk for the outcome of interest. Use of active-comparator and new-user design in cohort studies is currently one of the best option for increasing comparability of measured and unmeasured confounding factors between groups before further statistical adjustment and to account for time-related bias (i.e. 'depletion of the susceptible' and immortal time bias).[9,10]

The choice of a suited comparator group was particularly difficult for studies assessing adverse events risks after COVID-19 vaccines given that, in western countries, a large proportion of the population have been vaccinated, often by using the same vaccine platform (i.e. mRNA COVID-19 vaccines), thus no active-comparator group could be found and nonvaccinated vanished rapidly. Moreover, given the dynamic nature of the pandemic most of the control and vaccinated individuals have been infected by the SARS-CoV2 making it difficult to distinguish between the role of the vaccine or the virus.

To deal with these difficulties and increase the comparability between groups Klein et al, used post vaccinated patients as comparator. Whether this strategy may increase global mean comparability of patient's characteristics, it do not ensure individual similarity of baseline risk of appendicitis between exposed and control groups. One of the main methodological solution, that have not been used to assess the risk of appendicitis after COVID-19 vaccination, is to use self-controlled designs. Indeed, case only designs such as self-controlled case series are particularly adapted to repeated intermittent drug exposure with risk periods immediately following drug use.[11] Given the difficulty to identify nonvaccinated-noninfected groups for which the exchangeability assumption could be reasonably met, these designs could be a relevant alternative. They have, for example, been recently successfully used to assess the risk of arterial and venous thromboembolic events with mRNA or adenoviral based COVID vaccines.[12–14]

These results further stress the importance of conducting sensitivity analyses in pharmaco-epidemiological studies, which make it possible to assess the degree of variability in the results of a study according to the methodological choices made. Such sensitivity analyses must ideally be formalized a priori rationale to aid decision-maker assessment and increase the utility of the findings.[15] Yet, recent studies have demonstrated that conducting hundreds or thousands of sensitivity analyses to evaluate the influence of design and

10991557, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5560 by CHU Grenoble Alpes, Wiley Online Library on [28/04/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

analysis choices for studies conducted in healthcare database is becoming feasible and could be one of the future direction to appraise the robustness of pharmacoepidemiological results.[7]

CONFLICT OF INTEREST

The author have no conflict of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in related articles.

ORCID

Charles Khouri https://orcid.org/0000-0002-8427-8573

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615. doi:10.1056/NEJMoa2034577
2. Research C for BE and COVID-19 Vaccine Safety Surveillance 2022. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance.
3. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a Nationwide setting. *N Engl J Med*. 2021;385:NEJMoa2110475. doi:10.1056/NEJMoa2110475
4. Kildegaard H, Ladebo L, Andersen JH, et al. Risk of appendicitis after mRNA COVID-19 vaccination in a Danish population. *JAMA Intern Med*. 2022;182:684-686. doi:10.1001/jamainternmed.2022.1222
5. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326:1390-1399. doi:10.1001/jama.2021.15072
6. *Pharmacoepidemiology*. 6th ed. Wiley https://www.wiley.com/en-us/Pharmacoepidemiology%2C+6th+Edition-p-9781119413417; 2022.
7. Wang SV, Sreedhara SK, Bessette LG, Schneeweiss S. Understanding variation in the results of real-world evidence studies that address the same question. *J Clin Epidemiol*. 2022;S0895-4356(22):212-218. doi:10.1016/j.jclinepi.2022.08.012
8. Patel CJ, Burford B, Ioannidis JPA. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. *J Clin Epidemiol*. 2015;68:1046-1058. doi:10.1016/j.jclinepi.2015.05.029
9. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11:437-441. doi:10.1038/nrrheum.2015.30
10. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2020;29:1101-1110. doi:10.1002/pds.5083
11. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *BMJ*. 2016;354:i4515. doi:10.1136/bmj.i4515
12. Botton J, Jabagi MJ, Bertrand M, et al. Risk for myocardial infarction, stroke, and pulmonary embolism following COVID-19 vaccines in adults younger than 75 years in France. *Ann Intern Med*. 2022;175:1250-1257. doi:10.7326/M22-0988
13. Jabagi MJ, Botton J, Bertrand M, et al. Myocardial infarction, stroke, and pulmonary embolism after BNT162b2 mRNA COVID-19 vaccine in people aged 75 years or older. *JAMA*. 2022;327:80-82. doi:10.1001/jama.2021.21699
14. Ghebremichael-Weldeselassie Y, Jabagi MJ, Botton J, et al. A modified self-controlled case series method for event-dependent exposures and high event-related mortality, with application to COVID-19 vaccine safety. *Stat Med*. 2022;41:1735-1750. doi:10.1002/sim.9325
15. Wang SV, Pinheiro S, Hua W, et al. STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies. *BMJ*. 2021;372:m4856. doi:10.1136/bmj.m4856

How to cite this article: Jambon-Barbara C, Bernardeau C, Cracowski J-L, Khouri C. Understanding the variability of pharmaco-epidemiological studies assessing the risk of appendicitis with mRNA COVID-19 vaccines. *Pharmacoepidemiol Drug Saf*. 2023;32(1):87-90. doi:10.1002/pds.5560

10991557, 2023, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/pds.5560 by CHU Grenoble Alpes , Wiley Online Library on [28/04/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2. Regional Heterogeneity of the Results of Glucagon-Like Peptide 1 Receptor Agonist Trials in Type 2 Diabetes: A Reanalysis of Individual Participant Data

Diabetes Care
American Diabetes Association

Regional Heterogeneity of the Results of Glucagon-Like Peptide 1 Receptor Agonist Trials in Type 2 Diabetes: A Reanalysis of Individual Participant Data

Ariane Jullien, Clément Jambon-Barbara, Jean-Luc Cracowski, Brian L. Claggett, Anne-Laure Borel, Charles Khouri, and Matthieu Roustit

Diabetes Care 2024;47(11):1–9 | https://doi.org/10.2337/dca24-0034

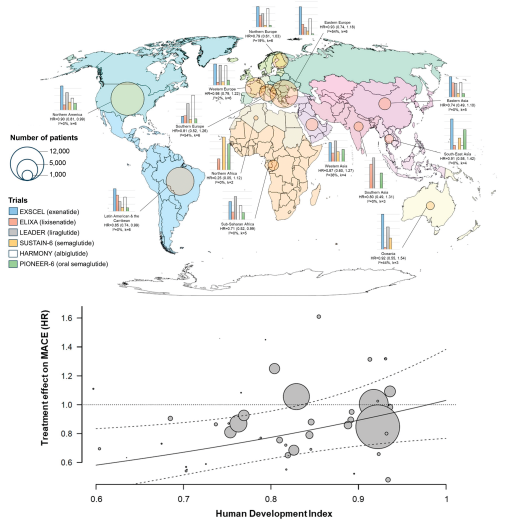
Exploratory subgroup analyses of international trials have suggested geographic heterogeneity in the efficacy of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes.
Are these geographic variations real or coincidental?

Methods

- Individual participant data GLP-1RAs versus placebo from pivotal randomized controlled trials comparing any GLP-1Ra vs placebo in type 2 diabetes were used to calculate hazard ratios (HRs) for major cardiovascular events (MACE), sub-grouped by region.
- We conducted a meta-analysis with meta-regressions to assess the potential influence of predetermined variables of interest on treatment effect.

Results

- 6 trials including 45,426 patients
- Baseline risk of cardiovascular events ranged from 2.9 to 7.4 per 100 patient-years across regions, **but treatment effect did not significantly vary**.
- A **higher baseline risk and lower development status were associated with a greater benefit of these drugs**.



ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HARMONY, Effect of Albiglutide on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; PIONEER-6, Peptide Innovation for Early Diabetes Treatment.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Exploratory, subgroup analyses have suggested geographic heterogeneity in the efficacy of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes.
- **What is the specific question we wanted to answer?**
  Are these geographic variations real or coincidental?
- **What did we find?**
  We reanalyzed individual participant data from pivotal trials by region. Baseline risk of cardiovascular events ranged from 2.9 to 7.4 per 100 patient-years across regions, but treatment effect did not vary significantly. However, meta-regressions showed associations between baseline risk and indexes of development status and GLP-1RA efficacy.
- **What are the implications of our finding?**
  This study does not suggest regional heterogeneity of GLP-1RA efficacy in cardiovascular events. However, a higher baseline risk and lower development status are associated with a greater benefit of these drugs.

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

Regional Heterogeneity of the Results of Glucagon-Like Peptide 1 Receptor Agonist Trials in Type 2 Diabetes: A Reanalysis of Individual Participant Data

Ariane Jullien,[1] *Clément Jambon-Barbara,*[1,2] *Jean-Luc Cracowski,*[1,2] *Brian L. Claggett,*[3] *Anne-Laure Borel,*[2,4] *Charles Khouri,*[1,2] *and Matthieu Roustit*[1,2]

https://doi.org/10.2337/dca24-0034

OBJECTIVE

Multiregional trials are designed under the assumption that treatment effect applies to the entire target population, yet several factors may introduce geographic heterogeneity in treatment effect. We explored whether such variations exist in trials assessing the efficacy of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in major cardiovascular events (MACE) in type 2 diabetes.

RESEARCH DESIGN AND METHODS

A systematic search of Medline and the Cochrane Library was conducted from inception until 30 June 2020. We included international randomized controlled trials comparing any GLP-1RA versus placebo, with MACE as a primary end point. Individual participant data were subsequently requested from the sponsor or through data sharing platforms. For each trial, we calculated hazard ratios (HRs) and their 95% CIs for MACE, subgrouped by region. We then performed a random-effects meta-analysis and conducted meta-regressions to assess the influence of predetermined variables of interest on treatment effect.

RESULTS

We included six trials including 45,426 patients. Baseline risk of MACE ranged from 2.9 per 100 patient-years in Southern Asia to 7.4 per 100 patient-years in Sub-Saharan Africa. HRs for MACE ranged between 0.25 (95% CI 0.05, 1.12) in Northern Africa to 0.98 (0.79, 1.22) in Western Europe. There was no significant subgroup difference across regions (P = 0.70). Baseline risk of MACE and indexes of development status (i.e., Human Development Index, gross domestic product) were independently associated with GLP-1RA efficacy.

CONCLUSIONS

This study does not suggest any regional heterogeneity of GLP-1RA efficacy in MACE. However, a higher baseline risk and lower development status were associated with a greater benefit of these drugs.

Major adverse cardiovascular events (MACE) are considered the leading cause of death in patients with type 2 diabetes (1,2). While most oral glucose-lowering drugs have shown efficacy in controlling chronic hyperglycemia, some glucagon-like peptide 1

[1]*INSERM, CIC1406, University of Grenoble Alpes, Grenoble, France*
[2]*INSERM, U1300, HP2, University of Grenoble Alpes, Grenoble, France*
[3]*Cardiovascular Division, Brigham and Women's Hospital, Boston, MA*
[4]*Endocrinology Diabetology & Nutrition Department, Grenoble Alpes University Hospital, Grenoble, France*

Corresponding author: Matthieu Roustit, mroustit@chu-grenoble.fr

Received 31 May 2024 and accepted 6 August 2024

This article contains supplementary material online at https://doi.org/10.2337/figshare.26528158.

© 2024 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/journals/pages/license.

ORIGINAL ARTICLE

Downloaded from http://diabetesjournals.org/care/article-pdf/47/9/1616/dca240034.pdf by INSERM DISC IST user on 30 August 2024

receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is) have also demonstrated efficacy in reducing cardiovascular events or even all-cause mortality (3,4). However, there have been some discrepancies in the results among the various large randomized controlled trials assessing the effect of these agents on MACE. The American Diabetes Association has reported that causes of variability in the efficacy of current therapies against diabetes are multifactorial (5).

Among these factors, geographic variations in clinical trials are a well-known phenomenon. Although large, multiregional trials are designed under the assumption that the benefit of the treatment applies to the entire target population, several factors may introduce heterogeneity in the treatment effect, including genetic variations (6); differences in lifestyle, diet, health care systems and medical practices (7,8); and socioeconomic factors (9). To explore whether geographic variations existed in trials assessing the efficacy of GLP-1RAs and SGLT2is, we previously conducted a subgroup meta-analysis including 25,725 patients, which revealed a greater benefit on MACE in trial subgroups from Latin America, Africa, and Asia compared with those from Europe and North America (10), while the latter represents the largest market share. Yet, interpretation of these results should be done with caution. First, there was great heterogeneity in the definition of regions across trials. Second, we could not explain whether these differences were attributed to development status or other causes since data per region were not available. Finally, due to the limited number of trials and the exploratory nature of subgroup analyses, the geographic variations in treatment effect that we observed may be due solely to chance (7,8).

Considering the widespread use of these drugs and their impact on public health, it is essential to understand whether these geographic variations are real or coincidental. Thus, the objective of this work was to address this issue through a reanalysis of individual patient data (IPD) from large randomized controlled trials. The primary aim of this study was to assess whether there is significant heterogeneity in the efficacy of GLP-1RAs in cardiovascular outcomes according to the region of patient inclusion. We further explored the sources of heterogeneity in GLP-1RA trials.

RESEARCH DESIGN AND METHODS

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guideline (11,12). The protocol and systematic search strategy were published before the study started (PROSPERO registry no. CRD42019120221). The protocol is available on Open Science Framework (https://osf.io/yxdbm).

Search Strategy

We searched all double-blind randomized controlled trials comparing any GLP-1RA with placebo, in addition to existing antidiabetic and/or cardiovascular treatment, in patients with type 2 diabetes. The search was conducted in Medline and the Cochrane Library from inception to 30 June 2020, with no restriction regarding the publication period. Language restrictions included studies published in English or French. Additional searches of unpublished trials through registries (i.e., ClinicalTrials.gov) were conducted.

Trials were deemed eligible if the primary efficacy end point was MACE validated by an adjudication committee. Moreover, only international multicenter trials with a subgroup analysis according to the country or region were selected.

Access to IPD

To homogenize the definition of regions and outcomes across trials meeting our eligibility criteria, we requested access to IPD directly from the sponsor or through data sharing platforms (Yale Open Data Access Project, Vivli, and Clinical Study Data Request). Since identification of the country could lead to a breach of confidentiality regarding personal data, countries for which 15 patients or fewer were included in a single trial were not provided or were already pooled by region before data were shared.

Definition of the Regions

We used the United Nations (UN) classification to define 14 regions in six continents: Africa (Northern Africa, Sub-Saharan Africa), Latin America and the Caribbean, Northern America, Asia (Central Asia, Eastern Asia, Southeastern Asia, Southern Asia, Western Asia), Europe (Eastern Europe, Northern Europe, Southern Europe, Western Europe), and Oceania. The list of countries corresponding to each UN region is provided in Supplementary Table 1.

For each region, we calculated the weighted Human Development Index (HDI) from the UN and gross domestic product (GDP) from the Organization for Economic Cooperation and Development as indexes of development. They were averaged for each country over the study period (inclusion and follow-up) and weighted by the number of patients included per country.

Outcomes

The main outcome was MACE, defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke. Additional outcomes were death from any cause, death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, transient ischemic attack, coronary revascularization procedure, and hospitalization for cardiovascular causes. The following variables were extracted from each trial: characteristics of the study (authors, year of publication, regions, number of participants by country, follow-up duration, study design), characteristics of the participants at baseline (age, sex, race/ethnicity, BMI, heart rate, systolic and diastolic blood pressure, HbA_{1c}, fasting glucose, duration of diabetes, retinopathy, neuropathy, estimated glomerular filtration rate, total cholesterol, HDL and LDL cholesterol, triglycerides, current smoking, hypertension, coronary artery disease, peripheral artery disease, cerebrovascular disease, heart failure, myocardial infarction), and concomitant medications at baseline (insulin, metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors, SGLT2is, GLP-1RAs, thiazolidinediones, antiplatelet agents, ACE inhibitors, angiotensin receptor antagonists, β-blockers, statins, and diuretics).

Data Collection

Data were extracted from eligible published articles and from the statistical reports of each trial reanalysis (see details below). Data entry was performed by one investigator and double-checked by a second investigator. Discrepancies were discussed with a third investigator.

Risk of Bias

We assessed the risk of bias of included studies by using the Cochrane Collaboration's risk-of-bias tool for randomized trials (13).

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

Data Analysis

We reanalyzed each trial and calculated hazard ratios (HRs) and their 95% CIs for all outcomes (MACE, stroke, myocardial infarction, cardiovascular death) within each region. We also synthesized all covariates by region. Baseline risk of MACE was estimated by calculating the incidence of primary events per 100 patient-years of follow-up in the placebo arms.

We then estimated the effect of antidiabetics on each outcome per region by performing a hierarchical random-effects meta-analysis, including a random intercept to account for differences in trials, subgrouped by region. $P < 0.05$ for the test of subgroup differences was considered significant, as previously done in our preliminary assessment (10).

Meta-regressions were performed to assess the potential influence of predetermined variables of interest on treatment effect for the primary outcome. Given the intrinsic correlation between baseline risk of MACE and patient characteristics and background treatment, we used two different approaches. The first approach consisted of testing the baseline risk of MACE first, to which we added one by one the region, HDI, and GDP in a multivariate meta-regression model to assess whether heterogeneity in treatment effect could be related to regional or socioeconomic factors. Given the correlation between baseline risk in the control arm and treatment effect and the potential influence of regression toward the mean, we also performed the meta-regression using a Bayesian framework, with weakly informative priors (14,15). In the second approach, baseline characteristics of patients, comorbidities, and cardiovascular and/or glucose-lowering drugs at baseline were all tested in univariate meta-regressions. Covariates associated with $P < 0.1$ were subsequently included in a multivariate meta-regression model (after selecting noncorrelated covariates [Pearson $r < 0.6$] with <10% of missing data) to which we added the region, as well as weighted HDI and GDP, keeping a random intercept per trial. Given the differences in baseline risk of MACE across regions, we replicated all analyses using absolute risk differences (ARDs) and their 95% CIs as post hoc sensitivity analyses. All statistical analyses were performed using the metafor, meta, and brms packages of R statistical software (version 3.2.4).

RESULTS

Trial and Patient Characteristics

We identified seven eligible trials and had full access to IPD for six of them (Supplementary Fig. 1 and Supplementary Table 2). We could not obtain the data for dulaglutide (Researching Cardiovascular Events With a Weekly Incretin in Diabetes [REWIND] trial [NCT01394952]).

These trials enrolled 46,103 patients in 59 different countries. Data were missing for 673 patients (including 672 for the Exenatide Study of Cardiovascular Event Lowering [EXSCEL] trial) and for three regions of the Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] trial; thus, HRs could not be computed because of an insufficient number of events. For all trials, the risk of bias was considered low for all domains except selective outcome reporting for EXSCEL due to the aforementioned missing data for some patients (Supplementary Table 3). Baseline characteristics of the population of each included trial are described in Supplementary Table 4. HRs for the primary outcome ranged from 0.73 (95% CI 0.57, 0.94) for semaglutide (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6]) to 1.02 (0.89, 1.17) for lixisenatide (ELIXA trial). Baseline risk of MACE ranged from 3.60 per 100 patient-years (Peptide Innovation for Early Diabetes Treatment [PIONEER-6] trial) to 6.31 per 100 patient-years (ELIXA trial). The results of the random-effects meta-analysis of aggregated data were in favor of a significant effect of GLP-R1As on MACE compared with placebo, whether expressed as a relative (HR 0.87 [0.79, 0.96], I^2 = 55%) or an absolute (ARD −0.01 [95% CI −0.02, −0.01], I^2 = 38%) treatment effect (Supplementary Fig. 2).

Geographic Variations in the Results of GLP-1RA Trials

Subgroup analysis per geographic region was reported in the original publication for five trials. For all of them, the *P* value for the interaction test was not significant, and all trials used different regions for these subgroup analyses (Supplementary Table 5). In addition, the definition of geographic regions was highly heterogeneous, with the same country being associated with up to four different regions (Fig. 1).

Baseline characteristics of the patients per region, after standardization according to the UN definition, are presented in Table 1. Baseline risk of MACE ranged from 2.9 (first and third quartiles 2.9–3.1) per 100 patient-years in Southern Asia to 7.4 (4.6–9.8) per 100 patient-years in Sub-Saharan Africa. Background medications also varied across regions (Supplementary Fig. 3). For example, the proportion of patients treated with insulin ranged from 31.8% in Southern Asia to 68.5% in Northern Africa; and the proportion treated with sulfonylureas ranged from 24.1% in Western Europe to 73.4% in Southern Asia (Table 1 and Supplementary Fig. 3).

Among each clinical trial, reanalysis of IPD showed no major heterogeneity in the efficacy of GLP-1RAs in MACE when subgrouping by UN region (I^2 range 0–9%) (Supplementary Figs. 4 and 5). For each trial, the relationship between relative treatment effect and the number of patients included, by region, is shown in Supplementary Fig. 6.

Figure 2 shows a world map representing the number of patients included in the trials, the number of trials conducted in each region, and the HR for MACE in each region. Overall, there were no subgroup differences between regions in the hierarchical random-effects meta-analysis for HR (*P* for interaction = 0.70) and ARD (*P* = 0.51) (Supplementary Fig. 7). Restricting subgroups to continents did not change the results (*P* = 0.52 for HR and *P* = 0.24 for ARD) (Supplementary Fig. 8). Results for each component of the composite outcome (stroke, myocardial infarction, and cardiovascular death) were similar, with no significant subgroup differences among regions (*P* = 0.78, 0.66, and 0.76, respectively) (Supplementary Figs. 9–11).

Meta-Regressions

Baseline risk of MACE was significantly associated with the efficacy of GLP-1RAs in MACE whether expressed as HR (β = −0.093 [95% CI −0.175, −0.011], *P* = 0.025) (Fig. 3*A*) or as ARD (β = −0.005 [−0.009, −0.002], *P* = 0.003). The association was consistent when using the Bayesian meta-regression model for both estimates (β = −0.041 [−0.083, 0.002] for HR and −0.006 [−0.002, 0.004] for ARD). In a multivariate model adding regional and sociodemographic factors to baseline risk, we found a significant association for weighted HDI (β = 0.930 [0.118, 1.742], *P* = 0.025) (Fig. 3*B*) and GDP (β = 0.004 [0.000, 0.008], *P* = 0.041)

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

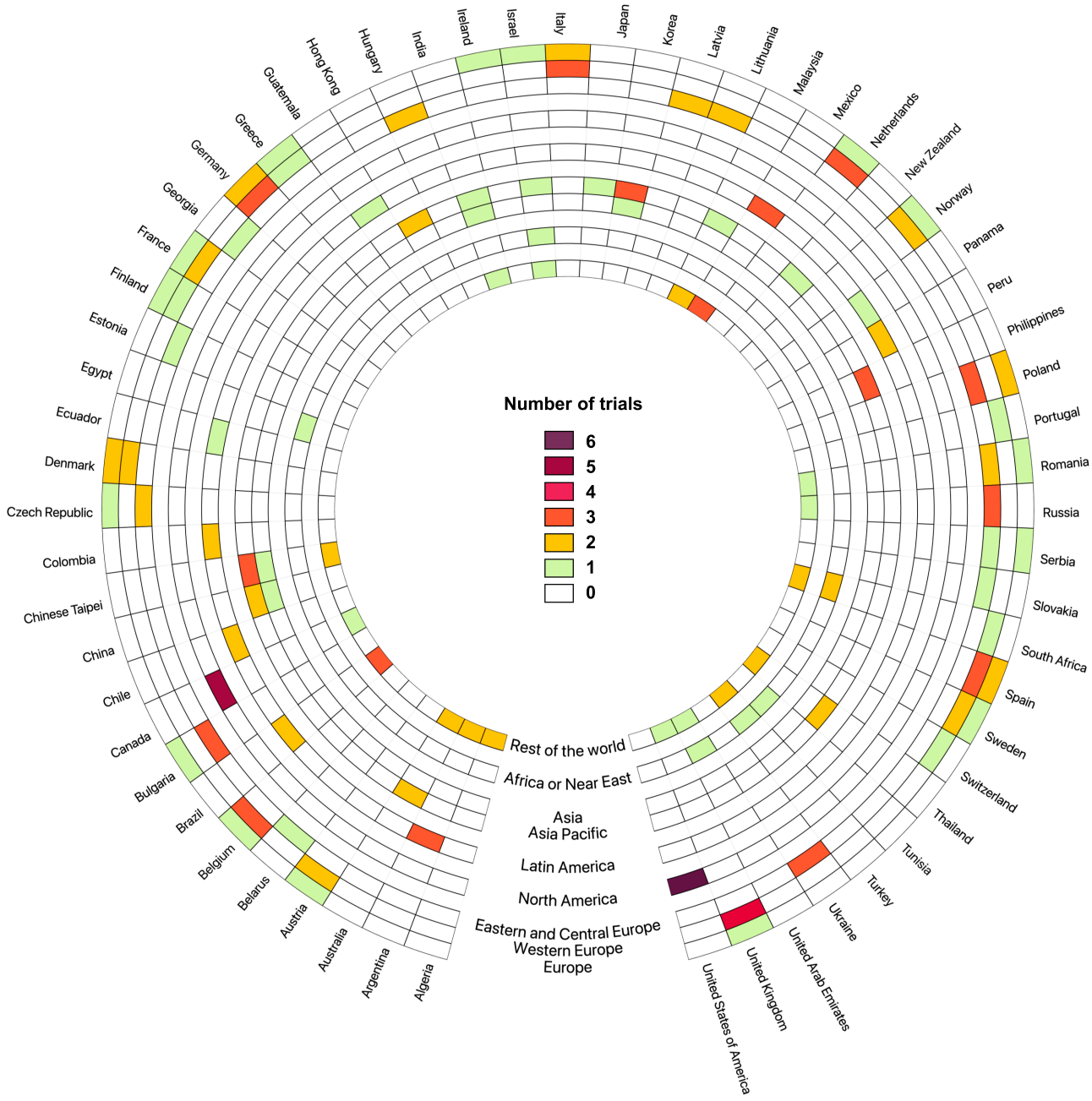


Figure 1—Region to which each country belongs, as reported in the trial. The color represents the number of trials that included patients in each country, from white (no trial) to dark purple (six trials).

(Fig. 3*C*) but not region (P = 0.225). The results were consistent using ARD as the estimate of treatment effect (Supplementary Table 6).

In our second approach, univariate meta-regressions on HRs showed associations between treatment effect on MACE and HbA_{1c}; BMI; creatinine level; history of hypertension, coronary artery disease, and myocardial infarction; and treatment by glinides and diuretics (all $P < 0.1$) (Supplementary Table 7). Using ARDs as estimates, systolic blood pressure, cholesterol, coronary artery disease, myocardial infarction, and treatment by glinides were associated with treatment effect on MACE (Supplementary Table 8). After selecting among highly correlated covariates and excluding diuretics and BMI at baseline because of a higher rate of missing data, HbA_{1c}, hypertension, and history of myocardial infarction were selected for inclusion in the final multivariate model using HRs, and history of myocardial infarction, cholesterol, and systolic blood pressure were selected using ARD estimates. Higher HbA_{1c} levels and a higher proportion of patients with prior myocardial infarction were the two variables that remained significantly associated with treatment efficacy in this model using HRs but not ARDs. The region, HDI, and GDP were not significantly associated with treatment effect on MACE (Supplementary Tables 9 and 10).

CONCLUSIONS

This reanalysis of large, multiregional, randomized controlled trials does not suggest regional heterogeneity in the treatment effect of GLP-1RAs on MACE. Similarly, there was no significant association between

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

Table 1—Baseline characteristics of the patients per region

Characteristic	Region												
	Northern Africa	Sub-Saharan Africa	Latin America and Caribbean	Northern America	Eastern Asia	Southern Asia	Southeastern Asia	Western Asia	Eastern Europe	Northern Europe	Southern Europe	Western Europe	Oceania
Patients, *n*	202	1,183	8,335	11,676	1,570	919	867	1,604	8,314	2,663	3,010	4,405	678
Trials, *n*	3	5	6	6	6	3	5	5	6	6	6	6	4
Baseline risk, events/100 patient-years, median (Q1–Q3)	4.1 (2.1–6.9)	7.4 (4.6–9.8)	3.5 (2.3–4.0)	4.9 (3.9–7.0)	4.0 (2.9–4.2)	2.9 (2.9–3.1)	4.3 (3.4–4.8)	5.5 (3.7–6.2)	3.8 (3.4–4.9)	4.9 (3.2–7.2)	3.9 (2.9–5.6)	3.9 (3.8–4.0)	4.1 (2.9–4.5)
GDP, USD	12,011	12,478	16,714	54,737	39,097	5,199	16,649	30,789	24,070	42,821	33,159	47,964	45,427
HDI	0.735	0.694	0.776	0.921	0.774	0.608	0.753	0.852	0.826	0.913	0.875	0.932	0.932
Male sex,	62.4	64.1	58.4	68.1	71.1	75.2	59.7	71.5	55.1	74.6	74	73	75.8
Age, years	63.7 ± 6.3	61.3 ± 7.6	61.9 ± 8.6	64.1 ± 8.0	61.3 ± 8.1	59.8 ± 7.2	59.9 ± 7.4	61.8 ± 7.0	61.6 ± 7.7	64.6 ± 8.4	64.5 ± 7.9	65.2 ± 7.9	64.2 ± 7.3
Race/ethnicity													
Asian	0	19.2	0.5	2.8	100	99.8	100	3.5	0.1	0.9	0.1	1.9	8.4
Black or African American	0	22.4	4.6	14.3	0	0.1	0	0.1	0	0.1	0.1	0.7	0.8
White	100	21.6	72.4	80.8	0	0.1	0	96.2	99.9	98.9	99.5	97	89.1
Other	0	36.8	22.5	2.1	0	0	0	0.2	0	0.1	0.3	0.4	1.7
Diabetes duration, years	12.7 ± 7.5	12.9 ± 8.4	12.8 ± 8.5	13.9 ± 9.0	13.8 ± 8.1	10.7 ± 6.8	12.3 ± 7.9	12.8 ± 7.8	11.0 ± 7.2	11.8 ± 7.8	13.9 ± 8.6	13.2 ± 8.1	14.5 ± 8.0
Retinopathy	31.2	13.8	15.2	14.6	31.1	16.4	20.3	21.8	25.9	23.2	20.9	17.3	23.2
Neuropathy	6.5	19.2	24.3	27.2	11.8	2.3	11.4	14.6	33.3	22.3	11.6	34.7	22.2
BMI, kg/m^2	30.0 ± 4.8	30.8 ± 6.1	30.1 ± 5.2	34.3 ± 6.8	26.6 ± 3.6	26.3 ± 3.9	27.8 ± 4.8	31.7 ± 5.7	33.1 ± 5.4	31.2 ± 5.3	31.3 ± 5.0	32.8 ± 5.8	33.5 ± 6.0
HbA_{1c}, %	8.6 ± 1.6	8.8 ± 1.6	8.5 ± 1.4	8.4 ± 1.3	8.4 ± 1.2	8.6 ± 1.6	8.5 ± 1.35	8.4 ± 1.3	8.3 ± 1.2	8.1 ± 1.1	8.2 ± 1.2	8.1 ± 1.1	8.4 ± 1.1
SBP, mmHg	136.5 ± 17.6	134.5 ± 21.0	132.7 ± 20.8	129.3 ± 22.7	131.6 ± 16.4	128.2 ± 13.3	132.5 ± 20.3	134.2 ± 17.1	135.8 ± 15.6	137.3 ± 20.2	137.1 ± 18.2	138.7 ± 20.2	131.8 ± 26.0
DBP, mmHg	77.5 ± 9.9	78.6 ± 12.1	77.3 ± 11.5	73.3 ± 13.4	76.4 ± 10.2	77.1 ± 7.9	75.9 ± 12.0	76.3 ± 10.1	80.0 ± 9.8	78.4 ± 11.9	75.8 ± 10.1	77.6 ± 11.8	73.6 ± 15.4
LDL-C, mg/dL	74.3 ± 28.5	90.5 ± 33.1	86.5 ± 33.5	72.3 ± 30.4	76.5 ± 28.2	62.6 ± 23.7	90.0 ± 32.8	81.1 ± 30.2	95.3 ± 37.8	77.6 ± 31.8	80.0 ± 31.0	92.4 ± 64.6	71.4 ± 28.7
eGFR, mL/min/1.73 m^2	82.4 ± 20.3	85.4 ± 29.3	77.5 ± 24.7	75.1 ± 24.6	79.7 ± 24.7	80.9 ± 23.4	71.1 ± 24.7	84.6 ± 24.1	79.8 ± 22.6	78.8 ± 23.6	81.2 ± 24.2	76.8 ± 23.5	76.0 ± 22.4
Current smoker,	4.1	16.6	8.8	13.3	23.2	19.2	7.3	28.2	11.9	17.7	17.2	19.8	9.4
Heart failure (NYHA 2–3)	8.4	10.1	10.4	13.9	10.4	11	10.6	10.4	38.1	23.7	15.2	16.9	6.5
Coronary artery disease*	69.4	59.7	47.4	66.1	62.7	66.3	52.5	66.5	53	67.3	69.4	58.8	69.2
Myocardial infarction	31.5	37.1	28.9	35.4	22.9	22.7	23.4	35.2	32.8	43.6	40.7	32.4	36.2
Prior stroke or TIA	11.6	12.3	14.5	17.6	21.8	10.2	19.5	13	25	21.1	22.7	19.4	16.8
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	13.5	19.5	24.5	28.3	24.7	21.8	35.2	15.2	37.6	20.2	19.8	24	23.7
Hypertension, %	78	86.3	73.3	89.2	76.5	68	78	83.2	92.1	80.7	84	87.3	86.4
Peripheral artery disease	16.5	11.5	25.1	11.1	5.1	6.4	15	5.6	18.4	9.9	19.9	22.7	12.6
Insulin therapy,	68.5	47.8	46.2	48.8	51	31.8	45.6	51.9	44.9	46.3	54.3	54.6	53.5
Diabetes medications													
Metformin	74.8	86.3	77.2	66.6	70.5	79.9	76	80.3	74.1	77.4	79.2	74.5	79.4
Sulfonylurea	28.2	44.6	36.2	39.4	45.4	73.4	46.4	31.8	42.7	25.7	28.4	24.1	45.2
DPP-4 inhibitor	0	1.2	4.4	8.4	18.2	0.3	6.3	8.9	5.9	10.5	12.5	13.7	3.1
SGLT2i	0	0	0.6	2.6	2.2	2	1.5	2.3	1.1	2.6	6.9	4.5	0.3
Cardiovascular medications, %													
β-Blocker	55.9	51.5	52.9	61.7	55.2	58.6	47.1	64.8	71.5	69.9	64.4	64.5	47.8
CCB	29.9	35.9	20.3	28.2	36.1	19.6	38.7	27	35.5	36.8	31.4	33.1	29.8
ACE inhibitor	40.9	56.7	40.2	53.8	27.1	35.4	33.3	53.3	62.7	55.8	50	52.1	50.2
ARB	52	21.7	37.7	26.4	47.5	32.7	40.7	30.8	29.3	29.7	36.6	31.4	37.9
Diuretic	14.7	50.6	34	44.5	20.3	28.9	20.7	29.6	51.3	40.4	42.1	48	28
Statin	84.3	82.4	71.3	81.1	76.8	85.5	78.7	80.7	72.8	86	84.4	77.5	79.7
Antiplatelet agent	84.2	79.2	74.7	76.7	79.8	81.3	72.2	83.8	74.5	76.4	84.2	69.5	72.8

Data are % or mean ± SD unless otherwise indicated. ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; LDL-C, LDL cholesterol; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischemic attack; USD, U.S. dollars. *Coronary artery disease includes any of the following: myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or at least 50% stenosis of coronary artery on angiography.

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

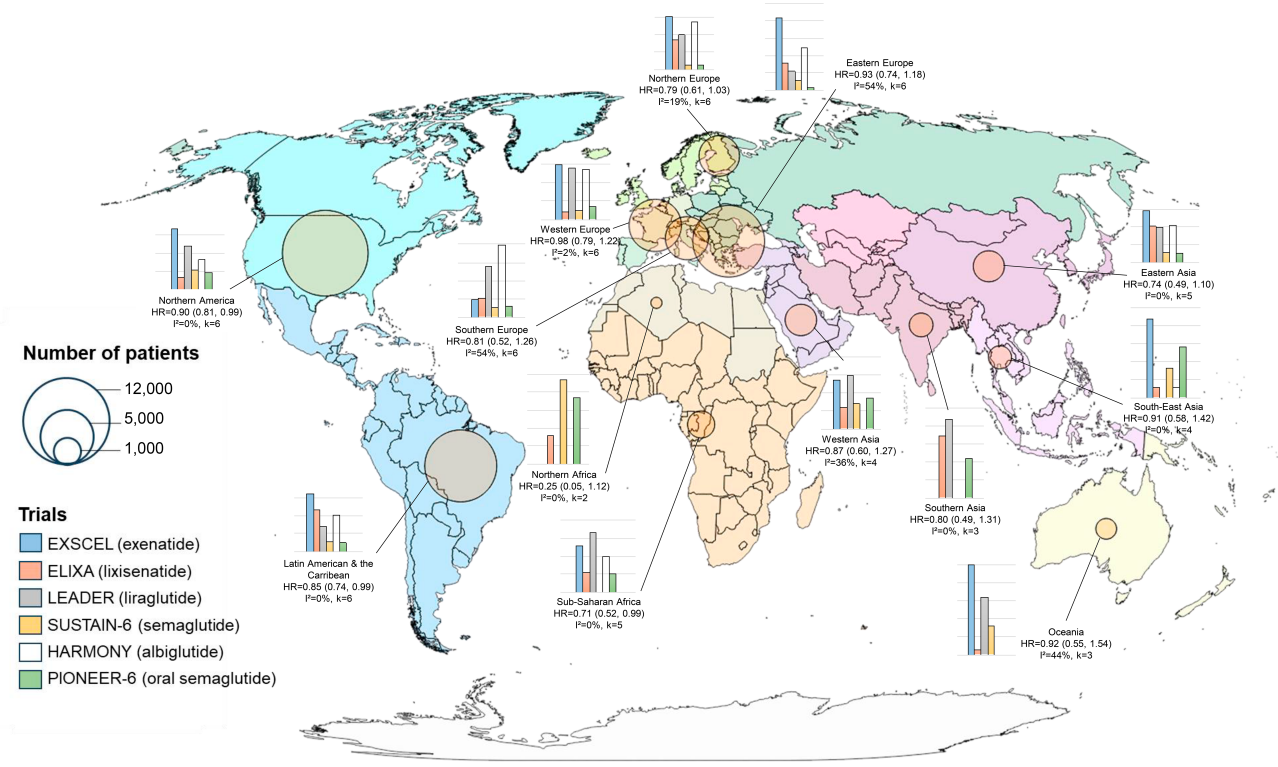


Figure 2—Effect of GLP-1RAs on MACE across the various UN regions. The size of the circles is proportional to the number of patients included per region. Histograms represent the proportion of patients from each trial in each region. Efficacy is expressed as the HR with its 95% CI. Heterogeneity within each region is expressed with the I^2 statistic, and *k* represents the number of trials per region included in the meta-analyses.

race/ethnicity and treatment efficacy. However, baseline risk, estimated by the incidence of cardiovascular events in the placebo arm, and indexes of development status (HDI and GDP) were significantly and independently associated with GLP-1RA efficacy.

More than 10 meta-analyses have explored the heterogeneity in treatment effect of GLP-1RAs based on subgroup analyses (recently reviewed by Young et al. [16]). The main strengths of our study are its focus on geographic heterogeneity and reliance on IPD of six out of seven eligible pivotal trials. This permitted us to standardize the definitions of continents and regions and to collect covariates for these regions. This step is key to study geographic variations in trials given the substantial heterogeneity in the definition of the regions in the original articles. For example, patients from Israel were included in four of the six trials, each time in a different region. Beyond the great variability of the countries included in the different regions, the choice of the regions included in subgroup analyses was also different for each trial, making comparisons and subgroup meta-analyses difficult to interpret. This may explain the discrepancy with our previous subgroup meta-analysis in which observed regional differences in the treatment effect of GLP-1RAs and SGLT2is on MACE were probably due to chance (10). A weakness of the current study is that we could not include data from SGLT2i trials, although we initially intended to explore their heterogeneity as well. Indeed, out of four drugs and five eligible trials, we only had access to IPD for canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS] and Study of the Effects of Canagliflozin [JNJ-28431754] on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus [CANVAS-R] trials [NCT01032629 and NCT01989754, respectively]). We therefore decided to restrict the scope of our study to GLP1-RAs. In addition, the time needed to obtain full access to data from all sponsors, and the time required to analyze these data, means that there is a long period between the end of the literature search and the end of the study, with the risk that the study may no longer be up to date. Finally, another limitation is that most sponsors granted us access through specific platforms, meaning that all databases could not be merged. Therefore, we had to reanalyze all the data using standardized definitions of regions and outcomes and then meta-analyze those results. While the possibility of accessing individual trial data is to be welcomed, more flexibility in the reuse of such data would be a real asset to open science (17).

Not having access to IPD may introduce a disclosure bias. Although probably limited by not having data for only one trial, this bias might be accentuated by the fact that we only selected studies exploring and reporting regional heterogeneity in a subgroup analysis. Indeed, a sponsor might omit publishing such an analysis if it does not appear favorable. We thus checked all the trials screened in our study, and none were excluded for this reason.

Another limitation is that we decided to restrict our search to trials with cardiovascular events as the primary outcome, which may reduce the power of our study. However, we felt that trials with cardiovascular events as secondary end points would be more likely to include different populations, which would have increased heterogeneity, or to be smaller trials based, for example, on a surrogate

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

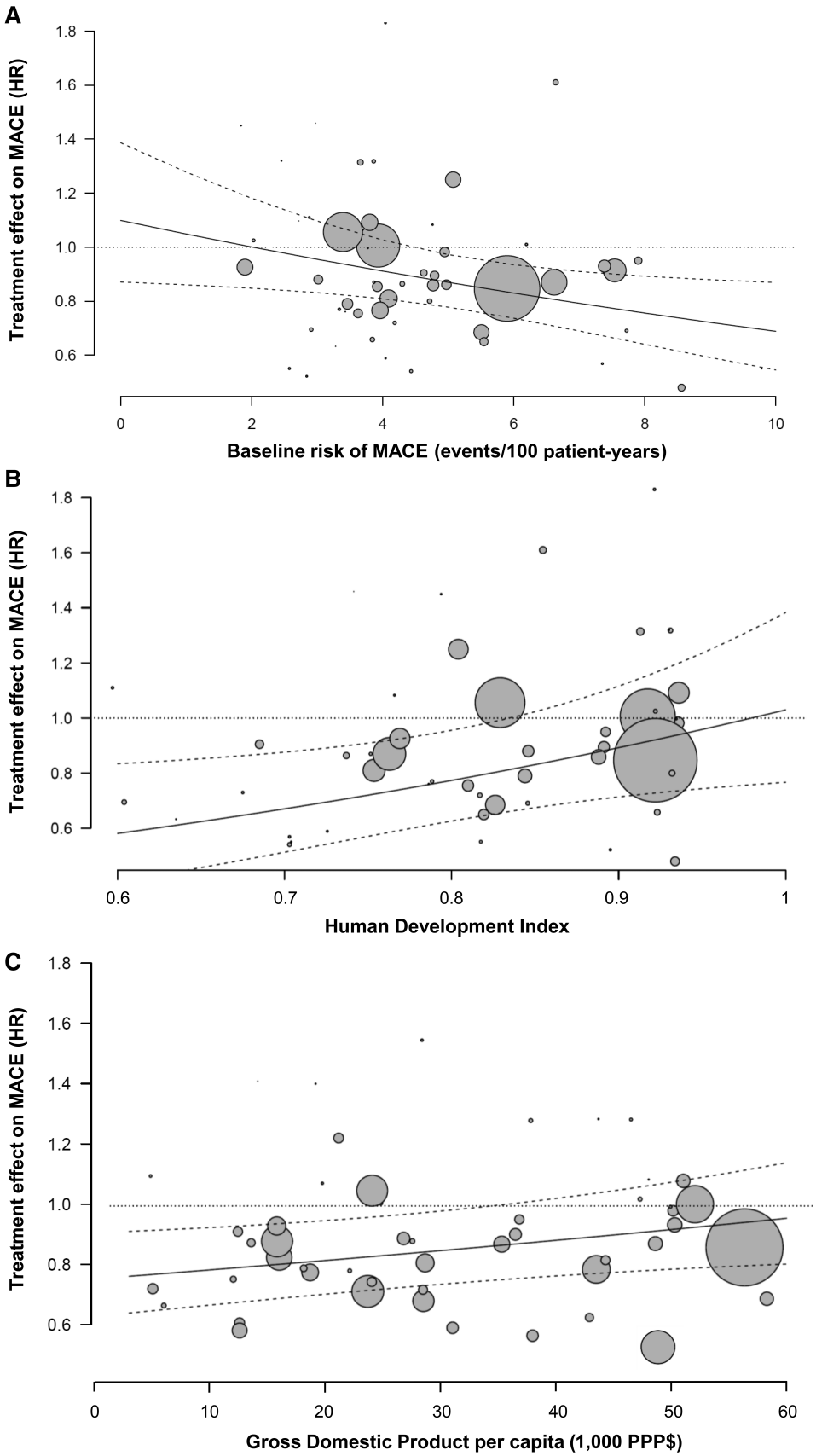


Figure 3—Meta-regressions between treatment effect on MACE expressed as HR and baseline risk of MACE estimated by the number of events in the placebo arm (*A*), HDI (*B*), and GDP per capita expressed as purchasing power parity dollars (PPP$) (*C*).

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

outcome. The small number of patients per region then would have made the HR calculation problematic. Finally, as discussed above, accessing IPD is time consuming, making the inclusion of a large number of trials unfeasible.

There was a significant, negative association between baseline risk, estimated by the event rate in the placebo arms, and relative treatment effect, suggesting that patients at higher risk benefit the most from GLP-1RAs. When conducting multivariate meta-regressions, higher HbA_{1c} levels and a higher proportion of patients with a history of myocardial infarction were both significantly and independently associated with GLP-1RAs' relative effect on cardiovascular outcomes. Such findings have been inconsistently reported in subgroup analyses of previous meta-analyses (16). Similarly, previous subgroup analyses have shown an influence of race/ethnicity on treatment effect, suggesting a greater benefit on GLP-1RA on MACE in Asian patients (18). Although we have included almost all of the same trials in our analysis, we did not observe such an association, which highlights the frailty of these exploratory findings when the number of trials is limited. Although reanalysis of IPD allowed us to increase the number of subgroups in our meta-regressions (one per region per trial), the low number of trials remains a weakness, providing relatively low statistical power for multivariate meta-regressions. This probably explains why the two approaches we used do not provide consistent findings.

Another key factor underlying geographic variations is development status. Our study suggests a significant association between the relative treatment effect and HDI and GDP, independently of basal risk. This is consistent with a meta-epidemiological review by Panagiotou et al. (9) of 139 meta-analyses with mortality as the main outcome. The authors regrouped 1,297 clinical trials and found that the treatment effects were more favorable in developing countries vs higher income countries.

Despite identical inclusion and exclusion criteria within a trial, we observed differences in baseline risk among the different regions, as reflected by differences in comorbidities and background treatments. This may be explained by various factors, including genetic diversity, environment, and dietary and lifestyle habits. Differences in health care systems may also explain these differences as patients referred to centers participating in trials and the choice of whether to include them in a trial may vary from one region to another, thus contributing to incongruency in patient characteristics at inclusion (8).

The exploration of geographic variations in the results of clinical trials is important to both clinicians and policymakers. Whether these variations are due to chance or reflect true differences in treatment effect should be comprehensively studied to understand whether results of a trial apply to the target population. From a regulatory point of view, this has become particularly challenging in the era of global drug development and led the International Conference on Harmonization to issue a guidance several years ago that describes the general principles for planning and designing multiregional trials (19). This guidance recommends a structured exploration to examine the consistency of treatment effects across regions by performing covariate-adjusted analysis or testing treatment-by-region interaction. The latter was done by five of the six trials we included, but this approach presents limitations. Indeed, most trials are not adequately powered to detect an interaction. Therefore, if not significant, one cannot exclude a real heterogeneity. If significant, however, the findings remain exploratory and may be due to chance, which challenges the usefulness of such explorations. Furthermore, the lack of standardization in the definition of regions (all the trials included in our meta-analysis had a different definition) make it difficult to interpret.

In conclusion, this reanalysis of pivotal trials assessing the efficacy of GLP-1RAs in MACE does not suggest regional heterogeneity. However, a greater benefit of these drugs was associated with a higher baseline risk and lower development status.

Acknowledgments. The authors thank the sponsors and platforms and data repositories for sharing data, including Novo Nordisk SA for sharing and providing data from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), PIONEER-6, and SUSTAIN-6 trials; Sanofi and Clinical Study Data Request for sharing data from the ELIXA trial and Jiankang Liu and Prof. Marc A. Pfeffer (Brigham and Women's Hospital and Harvard Medical School) for helping in their analysis; GlaxoSmithKline and Clinical Study Data Request for sharing and providing data from the HARMONY (Effect of Albiglutide on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus) trial; AstraZeneca for data that has been made available through Vivli, Inc (EXSCEL trial); and Janssen Research & Development LLC and Yale University Open Data Access Project (YODA project no. 2019-4025) for sharing and providing data from the CANVAS and CANVAS-R trials. The authors also thank Max Albert Remon Torres, Elsa Revel, and Alex Hlavaty for providing help in data collection and analysis.

The interpretation and reporting of research using these data are solely the responsibility of the authors and do not necessarily represent the official views of the Yale University Open Data Access Project or Janssen Research & Development. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this article.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.J., C.J.-B., and B.L.C. contributed to the data acquisition and analysis. A.J., C.K., and M.R. drafted the manuscript. J.-L.C. and A.-L.B. reviewed the manuscript critically for important intellectual content. J.-L.C., A.-L.B., C.K., and M.R. contributed to the data interpretation. C.K. and M.R. contributed to the study conception and design. All authors approved the final version of the manuscript. M.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Steven E. Kahn and Jennifer B. Green.

References

1. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403–469

2. Emerging Risk Factors Collaboration. Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation. Lancet Diabetes Endocrinol 2023;11:731–742

3. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA 2018;319:1580–1591

4. Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. BMJ 2023;381:e074068

5. American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl):1–2

6. Moon MK, Hur KY, Ko SH, et al.; Committee of Clinical Practice Guidelines of the Korean Diabetes Association. Combination Therapy of

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

oral hypoglycemic agents in patients with type 2 diabetes mellitus. Diabetes Metab J 2017;41:357–366
7. Yusuf S, Wittes J. Interpreting geographic variations in results of randomized, controlled trials. N Engl J Med 2016;375:2263–2271
8. Pocock S, Calvo G, Marrugat J, et al. International differences in treatment effect: do they really exist and why? Eur Heart J 2013;34:1846–1852
9. Panagiotou OA, Contopoulos-Ioannidis DG, Ioannidis JPA. Comparative effect sizes in randomised trials from less developed and more developed countries: meta-epidemiological assessment. BMJ 2013;346:f707
10. Roustit M, Khouri C, Boussageon R. Geographic variations in controlled trials. N Engl J Med 2017;376:1196–1197
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700
12. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–784
13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898
14. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity–subgroups, meta-regression, bias, and bias-adjustment. Med Decis Making 2013;33:618–640
15. Arends LR, Hoes AW, Lubsen J, Grobbee DE, Stijnen T. Baseline risk as predictor of treatment benefit: three clinical meta-re-analyses. Statist Med 2000;19:3497–3518
16. Young KG, McInnes EH, Massey RJ, et al.; ADA/EASD PDMI. Treatment effect heterogeneity following type 2 diabetes treatment with GLP1-receptor agonists and SGLT2-inhibitors: a systematic review. Commun Med 2023;3:1–20
17. Mansmann U, Locher C, Prasser F, et al. Implementing clinical trial data sharing requires training a new generation of biomedical researchers. Nat Med 2023;29:298–301
18. Lee MMY, Ghouri N, McGuire DK, Rutter MK, Sattar N. Meta-analyses of results from randomized outcome trials comparing cardiovascular effects of SGLT2is and GLP-1RAs in Asian versus White patients with and without type 2 diabetes. Diabetes Care 2021;44:1236–1241
19. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. General Principles for Planning and Design of Multi-Regional Clinical Trials: E17. Final version 16 November 2017. Accessed 20 August 2024. Available from: https://database.ich.org/sites/default/files/E17EWG_Step4_2017_1116.pdf

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dca24-0034/779916/dca240034.pdf by INSERM DISC IST user on 30 August 2024

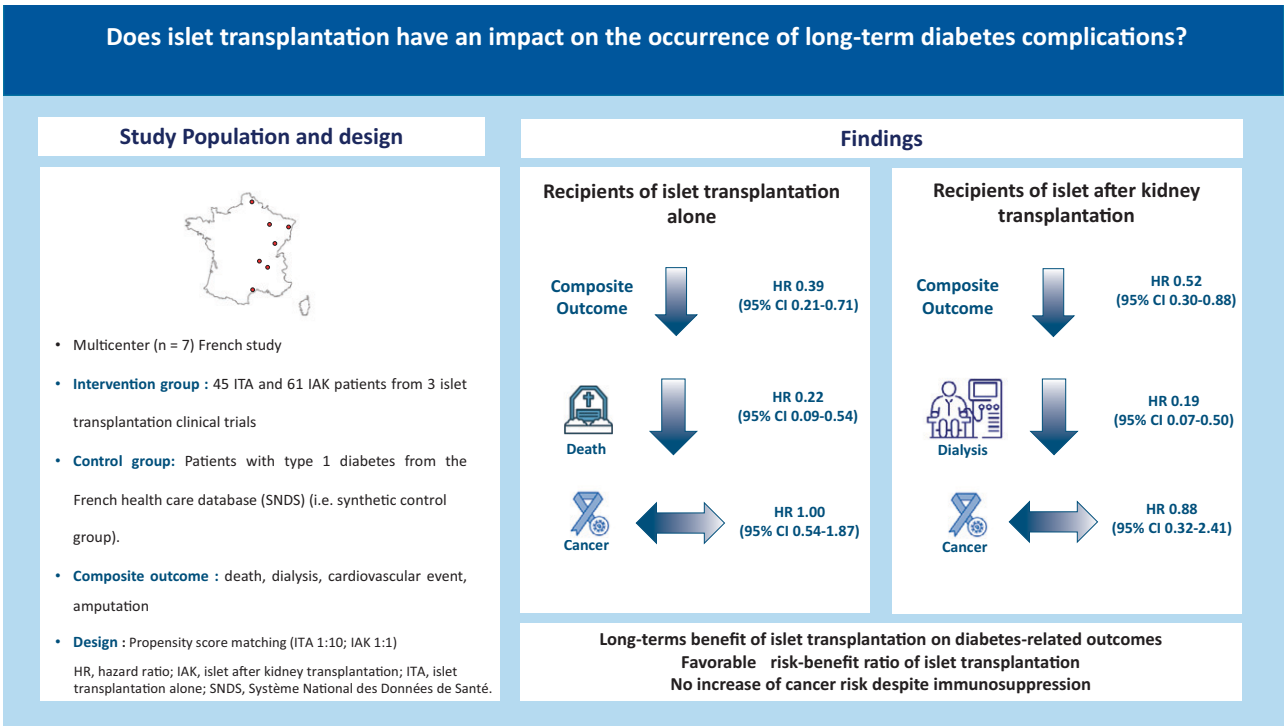
3. Impact of islet transplantation on diabetic complications and mortality in patients living with type 1 diabetes

Diabetes Care
American Diabetes Association

Impact of Islet Transplantation on Diabetes Complications and Mortality in Patients Living With Type 1 Diabetes

Quentin Perrier, Clément Jambon-Barbara, Laurence Kessler, Orianne Villard, Fanny Buron, Bruno Guerci, Sophie Borot, Matthieu Roustit, Ekaterine Berishvilli, Luc Rakotoarisoa, Marie-Christine Vantyghem, Emmanuel Morelon, Eric Renard, Camille Besch, Thierry Berney, Pierre-Yves Benhamou, and Sandrine Lablanche, on behalf of the GRAGIL Network

Diabetes Care 2025;48(6):1–9 | https://doi.org/10.2337/dc25-0059



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Islet transplantation (IT) is a minimally invasive technique used to improve glycemic control and quality of life, prevent severe hypoglycemia, and achieve insulin independence, but comparative information with patients not receiving IT is currently lacking.
- **What is the specific question we wanted to answer?**
  What are the long-term benefits and risks of IT on diabetes-related complications and cancers induced by immunosuppressive treatment compared with patients with type 1 diabetes treated with insulin?
- **What did we find?**
  IT is associated with a lower risk of diabetes complications, mainly mortality reduction in IT recipients and return to dialysis in IT after kidney transplant recipients, without differences in cancer risk.
- **What are the implications of our findings?**
  IT offers long-term benefits for type 1 diabetes complications, with a favorable risk-benefit ratio.

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

Impact of Islet Transplantation on Diabetes Complications and Mortality in Patients Living With Type 1 Diabetes

https://doi.org/10.2337/dc25-0059

Quentin Perrier,[1] Clément Jambon-Barbara,[2] Laurence Kessler,[3] Orianne Villard,[4] Fanny Buron,[5] Bruno Guerci,[6] Sophie Borot,[7] Matthieu Roustit,[8] Ekaterine Berishvilli,[9] Luc Rakotoarisoa,[3] Marie-Christine Vantyghem,[10] Emmanuel Morelon,[5] Eric Renard,[4] Camille Besch,[3] Thierry Berney,[5,9] Pierre-Yves Benhamou,[11] and Sandrine Lablanche,[11] on behalf of the GRAGIL Network*

[1]Univ. Grenoble Alpes, INSERM U1055, Department of Pharmacy, Grenoble Alpes University Hospital, LBFA, Grenoble, France
[2]Univ. Grenoble Alpes, INSERM U1300, Pharmacovigilance Unit, Grenoble Alpes University Hospital, HP2, Grenoble, France
[3]Univ. Strasbourg, INSERM UMR 1260, Department of Endocrinology and Diabetology, University Hospital of Strasbourg, Regenerative nanomedicine federation of translational medicine, Strasbourg, France
[4]Univ. Montpellier, INSERM U1191, CNRS UMR5203, Department of Endocrinology and Diabetes, University Hospital of Montpellier, Montpellier, France
[5]Univ. Lyon, Department of Nephrology, Immunology and Transplantation, Hospices Civils de Lyon, Lyon, France
[6]Univ. Lorraine, Department of Endocrinology, Diabetology and Nutrition, Brabois Adult Hospital, Nancy, France
[7]Univ. Besançon, Department of Endocrinology, Besançon University Hospital, Besançon, France
[8]Univ. Grenoble Alpes, INSERM U1300, CIC1406, Grenoble Alpes University Hospital, HP2, Grenoble, France
[9]Univ. Geneva, Cell isolation and transplantation center, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland
[10]Univ. Lille, INSERM UMR 1190, Department of Endocrinology, Diabetology, Metabolism and Nutrition, University Hospital of Lille, Translational research in diabetes, Lille, France
[11]Univ. Grenoble Alpes, INSERM U1055, Department of Diabetology, Endocrinology and Nutrition, Grenoble Alpes University Hospital, LBFA, Grenoble, France

Corresponding author: Quentin Perrier, qperrier@chu-grenoble.fr

Received 8 January 2025 and accepted 26 March 2025

This article contains supplementary material online at https://doi.org/10.2337/figshare.28672787.

Q.P. and C.J.B. contributed equally.

*A complete list of the members of GRAGIL Network is provided in the Supplementary Material online.

© 2025 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at https://www.diabetesjournals.org/journals/pages/license.

OBJECTIVE

This study aimed to evaluate the impact of islet transplantation (IT) on diabetes complications, death, and cancer incidence.

RESEARCH DESIGN AND METHODS

This retrospective, multicenter, cohort study included patients from three IT clinical trials (intervention group) and from the French health insurance claims database Système National des Données de Santé (SNDS) (control group). Two cohorts of IT recipients were analyzed: IT recipients after kidney transplantation (IAK) and IT recipients alone (ITA). They were matched with patients living with type 1 diabetes (T1D) from the SNDS using a propensity score. The primary outcome was a composite criterion including death, dialysis, amputation, nonfatal stroke, nonfatal myocardial infarction, and transient ischemic attack. The secondary outcome was cancer. Hazard ratio (HRs) and *P* values were obtained using Cox proportional hazards analysis and log-rank test, respectively.

RESULTS

The study included 61 ITA recipients matched to 610 T1D control patients and 45 IAK recipients matched to 45 T1D control patients over a median follow-up period >10 years. Compared with T1D control patients, ITA and IAK recipients had a lower composite outcome risk (HR 0.39 [95% CI 0.21–0.71; $P = 0.002$] and 0.52 [0.30–0.88; $P = 0.014$], respectively) that seemed driven by reduced mortality (0.22 [0.09–0.54]; $P < 0.001$) for ITA and reduced dialysis (0.19 [0.07–0.50]; $P < 0.001$) for IAK. Both groups showed no significant changes in cancer risk.

CONCLUSIONS

This study suggests long-term benefits of IT on diabetes-related outcomes. Furthermore, despite the use of immunosuppressive drugs following IT, we observed no significant increase in the risk of cancer. Altogether, these findings highlight a favorable risk-benefit ratio of IT in treating patients with unstable T1D.

Despite intensive insulin therapy, people living with type 1 diabetes (T1D) still have a high risk of microvascular and macrovascular complications (1,2). Islet transplantation (IT) is a minimally invasive technique used to improve glycemic control, prevent severe hypoglycemia, improve quality of life, and achieve insulin independence, with the rate of insulin independence varying based on center

ORIGINAL ARTICLE

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

experience and transplantation strategy (3–5). Based on these results, IT is now considered a therapeutic option for people living with unstable T1D (islet transplantation alone [ITA]) and people living with T1D and functional kidney graft (islet after kidney transplantation [IAK]), especially in European countries (6).

If IT metabolic outcomes are well described, as well as the long-term impacts of IT on recipients' mortality and diabetes complications or return to dialysis, comparative information with patients not undergoing IT is poorly described. Indeed, when considering mortality among IT recipients, data from the Collaborative Islet Transplant Registry (CITR) indicated a 5-year survival probability of 97.7% (7). The Groupe Rhin Rhône Alpes Genève pour la transplantation d'îlots de Langerhans (GRAGIL) group observed a 10-year survival probability of 86.4% (5), while the Edmonton group reported a 20-year survival probability of 75% (8). Recently, a study conducted in Miami, Florida, involving 49 IT recipients demonstrated that IT does not increase mortality related to long-term immunosuppressant use compared with patients with type 1 diabetes (T1D) not transplanted (9). However, this conclusion was based on epidemiological data from national diabetes registries spanning different periods without matched patient data. The rate of cancer incidence was 13.6% at 10 years (5) and remained stable at 20 years (8), with a predominance of skin cancers (33%).

Regarding kidney function, the most recent studies (10,11) indicated that following IAK, an initial decline in glomerular filtration rate (GFR) was observed (-10 to -20 mL/min). However, kidney function subsequently recovered and, in the best cases, either continued to improve, remained stable, or showed a decline similar to that seen in healthy individuals (-1 to -2 mL/min/year). Finally, for the benefits of IAK, a few comparative studies are available. In a cohort followed for 3 years, Fiorina and colleagues (12,13) demonstrated an improvement in cardiovascular function and kidney graft survival in the IAK group compared with the kidney-transplanted group without IT. Another recent study focusing on IAK recipients showed that IAK improves patient-graft survival based on a composite end point that associated graft failure with return to dialysis, kidney retransplantation, and death compared with patients with kidney graft and T1D but without IT (14).

Therefore, further investigation is needed to determine the long-term benefits of IT based on overall diabetes-related complications. The objective of this study was to evaluate the impact of IT on diabetes complications such as death, dialysis, amputation, myocardial infarction, stroke, transient ischemic attack, return to dialysis for IAK, and immunosuppressive treatment complications such as cancer.

RESEARCH DESIGN AND METHODS

This multicenter cohort study complied with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies (15). The protocol was published online before the study started (Open Science Framework registry, https://osf.io/c25pv/).

Data Source

The study was conducted from the individualized data of patients from databases built following the previously published GRAGIL trial and Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy for Type 1 Diabetes's Treatment (TRIMECO) (ClinicalTrials.gov identifiers: NCT00639600, NCT00321256, and NCT01148680) (16–18) and data extracted from the French health insurance claims database Système National des Données de Santé (SNDS). SNDS covers the entire population of France (67 million residents), of which 87% are covered by the national health insurance general scheme. Each person is identified by a unique, anonymous number. Since 2006, SNDS has recorded information on all outpatient care (including drugs, imaging, and laboratory tests) and inpatient care (including medical diagnoses, ICD-10 codes, and procedures performed as coded according to the Common Classification of Medical Procedures). The health expenses for patients with long-term disease, such as cancer, diabetes, and their related complications, are fully reimbursed, and their diagnoses are registered according to ICD-10 coding. SNDS has been extensively used and described, and all codes used for characteristic identification have been previously described (19–21).

Study Population

Our experimental cohort was composed of two subgroups: a group of all clinical trial patients with a kidney transplant before IT (IAK cohort) and a group of all other clinical trial patients (ITA cohort). The initial sample for the experimental group (i.e., clinical trial patients) consisted of all IT recipients in the GRAGIL trial, TRIMECO with its extension, and Swiss IT recipients (estimated n = 150). However, due to a regulatory issue, we were not able to obtain data from the Swiss IT recipients, so the final experimental cohort was composed of 106 IT recipients with 45 IAK and 61 ITA recipients transplanted between 1999 and 2016.

Our nonexposed cohort was composed of a synthetic control group identified from the SNDS. First, we identified every patient with T1D with at least 5 years of insulin use before inclusion, no reimbursement for oral antidiabetic drugs, and a follow-up of up to 10 years. As the SNDS includes data from 1 January 2006 through 31 December 2022, we included patients between 1 January 2011 and 31 December 2012 to ensure a minimum diabetes duration and follow-up. Second, we selected patients $>$18 years old at the inclusion date. Third, we divided our cohort of patients with T1D into two distinct cohorts: *1*) patients with T1D without a kidney transplant and *2*) patients with T1D with a kidney transplant. Fourth, we excluded patients with fewer than two hospitalizations for diabetes or diabetes complications in the year preceding inclusion (i.e., proxy for diabetes severity) for the group without kidney transplant. We excluded patients with $<$3 years between kidney transplant and the inclusion date for the group with kidney transplant. Fifth, to ensure that patients in our control group were not in the experimental group, we excluded every patient with the same sex, birth month, birth year, and death status (dead or alive) on 31 December 2022. A flow diagram of the SNDS patient selection and timeline for the selection of the control group are presented in Supplementary Figs. 1 and 2.

Finally, for both cohorts, each patient included in the experimental group was

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

matched using greedy matching on propensity score with a caliper width of 0.2 SDs of the logit at a ratio of up to 1:10 (i.e., 1 experimental group patient matched to 10 synthetic control group patients) for the ITA cohort and 1:1 for the IAK cohort. We constructed the propensity score with conditional logistic regression stratified by an IT set to predict the probability of receiving IT compared with no IT using known and identifiable risk factors for diabetes severity. The covariates used for the propensity score were sex, age, history (in the 5 years prior to the index date) of dialysis, amputation, stroke, transient ischemic attack, and myocardial infarction. Codes used for covariate identification are presented in Supplementary Table 1.

Outcome Definitions

The primary outcome was defined as the first occurrence of a composite criterion composed of various events: death, dialysis, amputation, nonfatal stroke, nonfatal myocardial infarction, or transient ischemic attack. The secondary outcome was defined as the first occurrence of a cancer: breast cancer, colorectal cancer, pulmonary cancer, prostate cancer, or other classified cancer (e.g., skin cancer). Codes used for event identification are presented in Supplementary Table 2.

Ethical Obligation

All patients had previously given their consent for the retrospective use of their hospital care data. This study obtained ethical approval from a local ethics committee (CERGA-Avis-2013-15). For patients included in the synthetic control group from the SNDS, no informed consent was required because only anonymous data were used under the French Data Protection Supervisory Authority agreement.

Statistical Analyses

We calculated descriptive summary characteristics for the study population by exposure status for quantitative parameters (mean and SD or median and 25th to 75th percentiles) and qualitative parameters (number and percentage of patients), and normality was graphically assessed. We used standardized mean difference (SMD) instead of the *P* value to assess whether our matching was efficient because of the large number of patients. An absolute SMD $\leq$10% indicated a negligible difference in potential confounders and balanced matched cohorts (22). We compared the occurrence of events between groups using a survival analysis (log-rank test). As a sensitivity analysis, we conducted a Cox proportional hazards analysis in both propensity score–matched cohorts (Supplementary Table 3) to assess the robustness of the method. We estimated the hazard ratio (HR) and 95% CI for each end point in individuals with IT. Patients with missing data on sociodemographic variables were excluded. All statistical analyses were performed using SAS Enterprise Guide version 7.13 or higher (SAS Institute, Cary, NC), R version 4.2.1 or higher (R Foundation for Statistical Computing), and PASS version 15 (NCSS, LLC, Kaysville, UT).

Data and Resource Availability

According to data protection and French regulations, the authors cannot publicly release the data from the SNDS. However, any person or organization (public or private, for-profit, or nonprofit) can access anonymized SNDS data to perform a study, research, or an evaluation of public interest upon authorization from the French Data Protection Office (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html).

RESULTS

Description of Population and Matching Parameters

The experimental group was composed of two distinct populations: a first population of 61 ITA recipients with a median duration of T1D of 31.6 (25th–75th percentile 24.5–39.3) years and a median follow-up after IT of 10.4 (8.7–13.6) years and a second population of 45 IAK recipients with a median duration of T1D of 32.6 (26.9–40.9) years, a median follow-up after IT of 13.4 (8.2–17.4) years, and a median delay between kidney and IT of 3.9 (2.6–6.4) years (kidney transplantation occurred between 1990 and 2011). Detailed anthropometric data and preexisting T1D-related complications (before IT for the experimental group or before inclusion for the control group) are compiled in Table 1. Overall, 61 ITA recipients were matched on propensity score to 610 control patients from the synthetic group, achieving a satisfactory level of global matching (absolute SMD $<$10%) except for stroke history (SMD $-$11.4%) in disfavor of the control group (i.e., there were more patients with a history of stroke in the control group). Forty-five IAK recipients were matched on propensity score to 45 control patients, with a median delay between kidney transplantation and inclusion of 3.72 (3.00–4.51) years and a lower matching quality compared with ITA (three absolute SMDs $>$10% for transient ischemic attack, age, and myocardial infarction [10.8%, 30.2%, and 26.2%, respectively]) in disfavor of the IAK group (i.e., there were more patients with the presence of the characteristic in the intervention group). SMD distributions at baseline and postmatching for the two groups are presented in Supplementary Fig. 3*A* and *B*.

Positive Impact of ITA on Mortality Without a Significant Increase in Cancer Risk

ITA recipients exhibited a significantly lower occurrence of the primary outcome compared with control patients without IT (HR 0.39 [95% CI 0.21–0.71]; $P = 0.002$) (Table 2 and Fig. 1*A*). This difference was predominantly driven by a significant reduction in mortality among ITA recipients (0.22 [0.09–0.54]; $P < 0.001$) (Fig. 2). There was no statistical difference regarding macrovascular complications, including stroke, myocardial infarction, transient ischemic attack, or amputation ($P > 0.05$) (Table 2), or in cancer outcome between the two groups (1.00 [0.54–1.87]; $P = 1$) (Fig. 2). Kaplan-Meier survival curves for all subcriteria in the ITA group are presented in Supplementary Figs. 4–13.

Positive Impact of IAK on Dialysis Occurrence After IT Without a Significant Increase in Cancer Risk

IAK recipients exhibited a significantly lower occurrence of the primary outcome compared with control patients with kidney transplant alone (HR 0.52 [95% CI 0.30–0.88]; $P = 0.014$) (Table 2 and Fig. 1*B*). This difference was predominantly driven by significantly less dialysis among IAK recipients (0.19 [0.07–0.50]; $P < 0.001$) (Fig. 2). IAK recipients statistically exhibited a higher occurrence of myocardial infarction compared with patients with kidney transplant alone (4.24 [1.18–15.2]; $P = 0.016$) (Table 2). There

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

Table 1—Baseline and postmatching characteristics of patients

	Baseline (n = 6,310)			Postmatching (n = 671)		
Characteristic	Experimental group	Synthetic control group	SMD (%)	Experimental group	Synthetic control group	SMD (%)
Patients with ITA, n	61	6,249		61	610	
Male sex	31 (50.8)	3,480 (55.7)	9.7	31 (50.8)	296 (48.5)	−4.6
Age, years (mean ± SD)	50.1 ± 10.5	42.5 ± 11.4	72.0	50.1 ± 10.5	49.2 ± 9.2	8.9
Dialysis	0 (0.00)	461 (7.37)	28.4	0 (0.00)	0 (0.00)	0.0
Amputation	1 (1.64)	330 (5.28)	28.7	1 (1.64)	10 (1.64)	0.0
Stroke	3 (4.92)	123 (1.97)	13.6	3 (4.92)	45 (7.38)	−11.4
Transient ischemic attack	0 (0.00)	44 (0.70)	8.5	0 (0.00)	0 (0.00)	0.0
Myocardial infarction	6 (9.84)	137 (2.19)	25.7	6 (9.84)	67 (11.0)	−3.9
	Baseline (n = 244)			Postmatching (n = 90)		
Patients with IAK, n	45	199		45	45	
Male	28 (62.2)	107 (53.8)	−17.2	28 (62.2)	26 (57.8)	−9.1
Age, years (mean ± SD)	45.2 ± 9.0	49.8 ± 8.9	−51.6	45.2 ± 9.0	42.4 ± 11.2	30.2
Dialysis	25 (55.6)	171 (85.9)	−61.1	25 (55.6)	25 (55.6)	0.0
Amputation	5 (11.1)	20 (10.1)	3.4	5 (11.1)	6 (13.3)	−7.1
Stroke	3 (6.67)	3 (1.50)	20.7	3 (6.67)	3 (6.67)	0.0
Transient ischemic attack	2 (4.44)	1 (0.50)	19.1	2 (4.44)	1 (2.22)	10.8
Myocardial infarction	6 (13.3)	5 (2.51)	31.8	6 (13.3)	2 (4.44)	26.2

Data are n (%) unless otherwise indicated. IAK, Islet after kidney transplantation; ITA, islet transplantation alone; SMD, standardized mean difference.

was no statistical difference in cancer outcome between the two groups (0.88 [0.32–2.41]; P = 0.80) (Fig. 2). Kaplan-Meier survival curves for all subcriteria of the IAK group are presented in Supplementary Figs. 14–23.

CONCLUSIONS

The findings of this study shed light on the long-term impact of ITA and IAK for people living with unstable T1D and those with T1D and kidney transplant and provide comprehensive insights into the long-term benefits (>10 years) and potential risks associated with ITA and IAK. It is important to highlight that these positive results for IT were achieved without long-term insulin independence. Indeed, <5% of patients in the GRAGIL trials (5) remained insulin independent 10 years after islet infusion (although 50% had a functional graft), while 59% of patients in the TRIMECO (18) remained insulin independent 1 year after islet infusion (with 85% having a functional graft).

Regarding the population of patients undergoing ITA, numerous studies have demonstrated improvements in metabolic parameters (reduction in glycemic variability, decrease in HbA_{1c} levels), prevention of severe hypoglycemia, and enhancement of quality of life (3,4,16–18). Unfortunately, there are limited comparative data on the impact of ITA on serious diabetes-related complications such as death, cardiovascular complications, amputation, and dialysis. Only Lemos et al. (9) reported a trend of no increased risk with ITA compared with historical data from the Pittsburgh Epidemiology of Diabetes Complications and the Allegheny County T1D registry cohort. One of the notable observations from our study was the significant reduction in the composite end point frequency among patients who underwent ITA compared with those who did not. Although the benefit on the composite outcome seemed to be driven by the reduction of mortality, this interpretation should be made with caution due to the limited number of events. Furthermore, our study suggests that there is no significant difference on cardiovascular events (myocardial infarction, stroke, transient ischemic attack) and lower-limb amputation associated with IT in ITA population.

Nakamura et al. (23) reported a cancer incidence of 43% (3 of 7) among IT recipients compared with 4% (1 of 26) in patients treated with multiple daily injections of insulin over the same period. The higher cancer prevalence observed in this study (vs. 13% previously published [5,8] and >20% observed in our cohort) can likely be attributed to the small sample size. Moreover, the increased risk reported in this study was observed in nonmatched patients who did not share comparable characteristics. Matching was performed based on age, C-peptide negativity, and baseline creatinine levels but not on the presence of unstable T1D. In our cohort, the absence of a significant increase in the risk of cancer following ITA is a noteworthy finding, considering the use of immunosuppressive regimens previously described (induction with thymoglobulin or interleukin-2 inhibitor and maintenance with calcineurin inhibitor, mammalian target of rapamycin inhibitor, or mycophenolate acid) (16–18). While immunosuppressive treatment is known to carry oncogenic risks, the current study provides reassurance regarding the safety profile of ITA in this regard. It should be noted that the median follow-up period of this cohort of >10 years may not be sufficient to detect certain cancers that emerge years after transplantation but remains compatible with the delay in cancer development reported in the literature. The literature indicates an increased risk of cancer (mostly liver, pancreatic, colorectal, endometrial, and kidney) in mostly patients with type 2 diabetes but also in patients with T1D compared with individuals without diabetes (24,25). Taken together, these studies could suggest that the risk of cancer in patients with diabetes is related to glycemic control (as it is present regardless the types of diabetes). Based on these data, we hypothesize that the better glycemic control offered by ITA (already well demonstrated for patients included in our

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

Table 2—Outcomes for the ITA and IAK groups

	ITA								IAK							
	Experimental group (n = 61)			Synthetic control group (n = 610)			Statistical test		Experimental group (n = 45)			Synthetic control group (n = 45)			Statistical test	
	Events n (%)	Person-years, n	Incidence rate*	Events, n (%)	Person-years, n	Incidence rate*	Log-rank P	HR† (95% CI)	Events n (%)	Person-years, n	Incidence rate*	Events, n (%)	Person-years, n	Incidence rate*	Log-rank P	HR† (95% CI)
Outcome																
Composite	15 (24.6)	652	2.30 (1.29–3.60)	265 (42.1)	5,532	4.79 (4.23–5.38)	0.002	0.39 (0.21–0.71)	32 (71.1)	464	6.89 (4.71–9.48)	33 (73.3)	284	11.60 (7.99–15.88)	0.014	0.52 (0.30–0.88)
Death	8 (13.1)	692	1.16 (0.50–2.09)	208 (34.1)	5,843	3.56 (3.09–4.06)	< 0.001	0.22 (0.09–0.54)	16 (35.6)	592	2.70 (1.54–4.18)	17 (37.8)	440	3.86 (2.25–5.90)	0.50	0.78 (0.38–1.61)
Dialysis	7 (11.5)	664	1.05 (0.42–1.97)	53 (8.69)	5,660	0.94 (0.70–1.20)	0.92	1.05 (0.45–2.44)	8 (17.8)	531	1.51 (0.65–2.71)	21 (46.7)	314	6.70 (4.14–9.85)	< 0.001	0.19 (0.07–0.50)
Stroke	4 (6.56)	682	0.59 (0.16–1.29)	39 (6.39)	5,697	0.68 (0.49–0.92)	0.58	0.72 (0.22–2.33)	4 (8.89)	584	0.68 (0.19–1.50)	3 (6.67)	411	0.73 (0.15–1.76)	0.74	1.29 (0.29–5.78)
Myocardial infarction	5 (8.20)	671	0.75 (0.24–1.53)	26 (4.26)	5,763	0.45 (0.29–0.64)	0.46	1.49 (0.52–4.27)	15 (33.3)	475	3.16 (1.77–4.95)	3 (6.67)	428	0.70 (0.14–1.69)	0.016	4.24 (1.18–15.2)
Transient ischemic attack	0 (0.00)	692	—	7 (1.15)	5,805	0.12 (0.05–0.22)	0.38	—	1 (2.22)	577	0.17 (0.00–0.64)	0 (0.00)	440	—	0.31	—
Amputation	0 (0.00)	692	—	33 (5.41)	5,718	0.58 (0.40–0.79)	0.056	—	3 (6.67)	573	0.52 (0.11–1.26)	8 (17.8)	400	2.00 (0.86–3.61)	0.10	0.35 (0.09–1.32)
Cancers																
Any	13 (21.3)	629	2.07 (1.10–3.33)	103 (16.9)	5,451	1.89 (1.54–2.27)	1	1.00 (0.54–1.87)	10 (22.2)	534	1.87 (0.90–3.20)	8 (17.8)	415	1.93 (0.83–3.47)	0.80	0.88 (0.32–2.41)
Breast	2 (3.28)	680	0.29 (0.04–0.82)	13 (2.13)	5,771	0.23 (0.12–0.36)	0.58	1.51 (0.34–6.72)	1 (2.22)	590	0.17 (0.00–0.63)	1 (2.22)	431	0.23 (0.01–0.86)	0.32	—
Colorectal	0 (0.00)	692	—	7 (1.15)	5,805	0.12 (0.05–0.22)	0.39	—	1 (2.22)	592	0.17 (0.00–0.62)	0 (0.00)	440	—	1	—
Pulmonary	0 (0.00)	692	—	20 (3.28)	5,814	0.34 (0.21–0.51)	0.15	—	0 (0.00)	592	—	2 (4.44)	440	0.45 (0.06–1.27)	0.16	—
Prostate	1 (1.64)	689	0.15 (0.00–0.54)	9 (1.48)	5,778	0.16 (0.07–0.27)	0.99	1.01 (0.13–7.98)	1 (2.22)	588	0.17 (0.00–0.63)	1 (2.22)	434	0.23 (0.01–0.85)	0.32	—
Other	11 (18.0)	643	1.71 (0.85–2.86)	71 (11.6)	5,603	1.27 (0.99–1.58)	0.63	1.18 (0.59–2.37)	7 (15.6)	541	1.29 (0.52–2.41)	5 (11.1)	430	1.16 (0.38–2.38)	0.50	1.48 (0.47–4.68)

*Per 100 persons per year (95% CI). †Obtained by Cox proportional hazards analysis. IAK, islet after kidney; ITA, islet transplantation alone; Testlog-rank, log-rank statistical analysis.

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc25005 9.pdf by guest on 28 April 2025

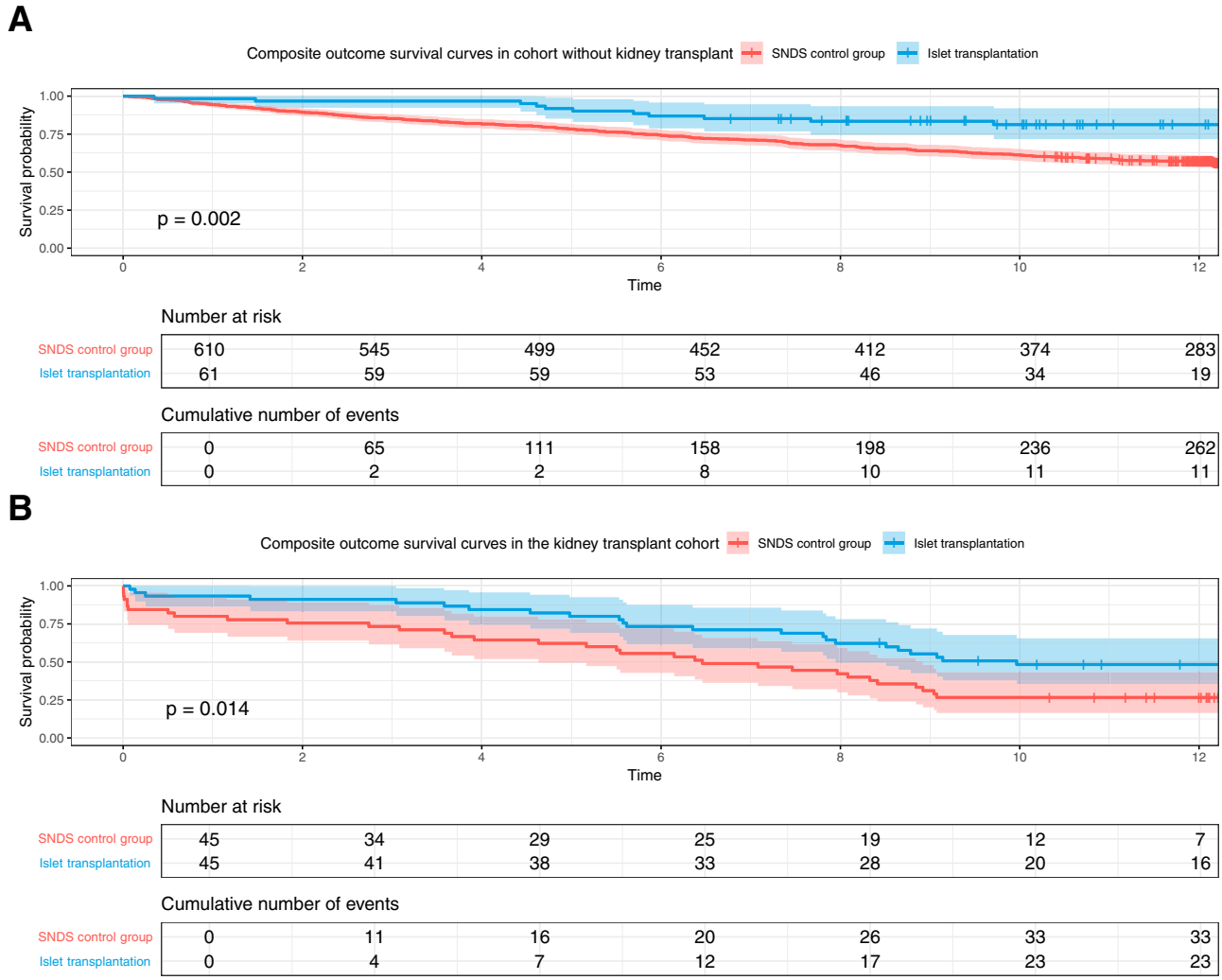


Figure 1—Kaplan-Meier survival curves of the primary composite outcome in the ITA (*A*) and IAK (*B*) groups. Time is given in years.

study [16–18]) may counterbalance the oncogenic risk associated with immunosuppressive treatment used after IT and provide similar oncogenic risk as patients with poorly controlled T1D.

In our study, we observed a significant reduction in the composite end point incidence rate among patients who underwent IAK compared with those with kidney transplant alone. This reduction suggests the potential of IAK to improve long-term outcomes and seems particularly driven by the reduced risk of dialysis (81%). This benefit of IAK on dialysis risk could also be linked to the eligibility criteria for IAK (GFR >50 mL/min) in the experimental group. However, our results are consistent with those of other studies (4,26–28). Several teams have demonstrated stabilization of kidney function at 5 and 10 years after IAK (4,26–28), a positive impact of IT on kidney graft survival (13). Recently, Maanaoui et al. (29) showed a positive impact of IAK on a composite primary end point for patient-graft survival (graft failure with return to dialysis, kidney retransplantation, or death) in 40 IAK recipients with T1D matched on biological and clinical parameters with 80 patients with T1D with kidney transplantation alone. Altogether, these data demonstrate the positive impact of IT of kidney graft function.

Although patients with T1D and kidney transplant received a new immunosuppressive induction at the time of IT, which could increase their oncogenic risk, our study suggests an absence of oncogenic risk in IAK recipients compared with patients with T1D solely transplanted with a kidney. Previous data (30,31) have suggested that the decline in kidney function increases the risk of cancer. IAK is now well known to preserve kidney graft function in selected patients (4,26–28). The absence of oncogenic risk could be linked both to the improvement of glycemic control and the preservation of the kidney graft following IT. However, the data from our study suggest an increased risk of myocardial infarction in the IAK population. This finding contradicts several studies that have demonstrated improvements in cardiovascular function (12) and intima-media thickness (32) and a decrease in coronary calcifications (33). The poorer quality matching of patients between the IAK and control groups, due to a smaller sample size for matching, was done in disfavor of the IAK group for two criteria, age and history of myocardial infarction, which are known risk factors for myocardial infarction (34). This mismatching of patients may therefore contribute to a statistically significant but clinically unverified signal.

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

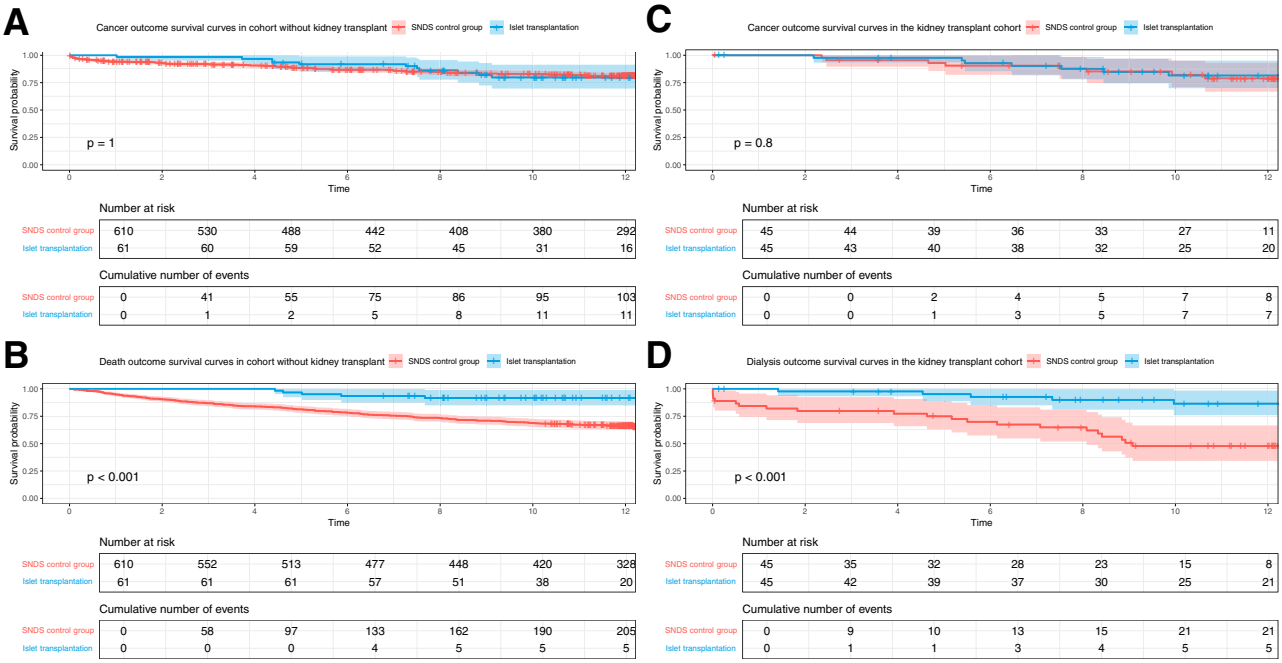


Figure 2—Kaplan-Meier survival curves of the secondary cancer (*A*) and death (*B*) outcomes in the ITA group and the secondary cancer (*C*) and dialysis (*D*) outcomes in the IAK group. Time is given in years.

Nonetheless, special attention should be paid to the evolution of cardiovascular complications for this population of patients.

Automated insulin delivery (AID) therapy is now standard of care for patients living with T1D. One study assessed the effectiveness and safety of a closed-loop hybrid system (Diabeloop Generation 1, DBLG1) in seven patients with highly unstable T1D and potential candidates for IT and showed glycemic stabilization benefits (35). Another study demonstrated the utility of a closed-loop system (Control IQ) in 72 patients selected because of a history of severe hypoglycemia or hypoglycemia unawareness (36). This therapy offers the advantage of avoiding the invasive procedure associated with IT (which now typically involves only minor complications) and the use of immunosuppressants (with data from our study suggesting no increased oncogenic risk, though infection risks and other adverse effects have not been studied). Additionally, the cost is likely lower, as the long-term costs of IT are still under investigation (37). AID therapy could, therefore, serve as a bridge (for patients who accept it) before considering ITA (38). It is important to note that the decision should be made jointly by the patient and physician, weighing the benefits and risks of both therapeutic approaches. Currently, AID data in patients living with T1D and kidney transplant are not available, with IT remaining the most validated option for these patients as they are already receiving immunosuppressive maintenance due to their kidney transplant.

Limitations

Several limitations in our study should be noted. First, a randomized trial with such a long follow-up was hardly feasible, which is the reason why we opted for an external control design. However, the latter does not guarantee between-group comparability. We have built the control group using a national health care database covering almost the entire French population, which is a strength of this study, but some key variables are missing, including metabolic data, laboratory results (e.g., HbA_{1c}, GFR), and sociodemographic data (e.g., BMI, tobacco consumption, exercise). Moreover, although a better cancer classification would have been invaluable information, notably for skin cancers, there is no specific cancer identification algorithm validated in the SNDS to date. Therefore, we decided to reproduce what was already done and studied in the literature (i.e., breast, colorectal, pulmonary, and prostate cancers) and classified other cancers as "other." As we could not better classify cancer type in the control group, we applied the same classification in the experimental group to avoid a possible misclassification. We partially addressed this limitation with the use of proxies to approximate these missing variables (e.g., two hospitalizations for diabetes complications in the year prior to inclusion as a proxy of unstable diabetes). With the emergence of several T1D cohorts, access to metabolic data could provide a new, comprehensive understanding of patient outcomes.

Second, dates of inclusion and follow-up times were not identical between the two groups as the SNDS starting point was 2006 and the first patient included in the intervention group was in 1999. As best we could, we restricted our control group to have contemporary patients with a sufficient history of diabetes (5 years) and at least 10 years of follow-up (i.e., inclusion between 2011 and 2012). However, with the median duration of diabetes in the intervention group was 31.6 (ITA) and 32.6 (IAK) years, we can assume that the intervention group patients were probably in a more advanced diabetes stage than the control patients, which might underestimate the observed IT effect. Similarly, for the IAK analysis, the matching was not optimal (as shown by large SMDs) and led to imbalance of prognostic factors

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

between groups, which seemed in favor of the control group and, thus, potentially underestimated the observed benefit of IT.

Third, the study cohorts were small, with <100 patients in experimental groups. Thus, the number of observed events were low, and we cannot exclude a lack of power to detect an excess risk of cancer. Moreover, even with a low statistical power, we were able to identify a significantly lower risk of the primary composite outcome, which strengthens the hypothesis of a genuinely favorable benefit of IT on the risk of diabetes complications or mortality. In the present situation, use of a synthetic control group permitted us to compare the patients who received an IT during clinical trials with patients with T1D with ongoing insulin therapy, the main strength of which is the possibility of matching patients on several risk factors to include and compare them as close as possible on known and measurable risk factors (39). Nevertheless, like every observational study, use of an external control group is subject to biases and unmeasurable residual confounding on every factor, a limit largely discussed before (39).

Fourth, we did not match patients on their cancer history due to a lack of available data; thus, we recommend cautious interpretation of the secondary outcome results. Moreover, in the experimental group, patients with a history of neoplasia in the previous 5 years could not be included, whereas we did not have this exclusion criterion in the control group, possibly selecting patients at higher risk of relapse in the control group. The absence of an excess risk of cancer, although statistically significant, needs to be assessed more thoroughly in a study that considers matching on this criterion. Another common complication of immunosuppressive treatments is the risk of infection. We could not study this due to the lack of a validated algorithm to obtain comprehensive data in the SNDS. Moreover, the absence of accurate data on the day-to-day immunosuppressive regimen in the SNDS made it difficult to draw any conclusions at this stage. Therefore, this study does not provide insight into this type of complication and would necessitate further investigation.

Finally, all patients in the experimental group (IT) were transplanted as part of clinical trials, with strict inclusion/exclusion criteria (i.e., neoplasia history, basal GFR, HLA hyperimmunization) and close monitoring. Now that this therapy is part of standard care, it would be valuable to investigate whether real-world data from newly transplanted patients confirm these findings.

Conclusion

In conclusion, this externally controlled study suggests a long-term benefit of ITA and IAK on a composite outcome of death, cardiovascular complications, or dialysis, with no significant increase in the risk of cancer despite the use of immunosuppressive drugs. Despite the inherent challenges and limitations, the insights gleaned from this study contribute to the growing body of evidence supporting the positive impact of IT on long-term patient outcomes. Moving forward, continued research efforts are warranted to further elucidate the mechanisms underlying the observed outcomes and to optimize the therapeutic approach for patients with T1D and unstable glucose control.

Acknowledgments. The authors thank all transplant recipients, donors, islet isolation centers, graft centers for islets/pancreata, and clinical research teams from all participating centers for help in clinical data acquisition.

Funding. This work was funded by a Grenoble Alpes University Hospital internal grant and an "Agence de la Biomédecine" graft grant.

Duality of Interest. No potential conflicts of interest relevant to the article were reported.

Author Contributions. Q.P., C.J.-B., L.K., O.V., F.B., M.R., P.-Y.B., and S.L. conceptualized the study. Q.P., L.K., O.V., F.B., B.G., S.B., L.R., and M.-C.V. acquired data. Q.P., C.J.-B., and M.R. had access to the raw data, verified the data, and performed the statistical analysis. Q.P., C.-J.B., M.R., and S.L. drafted the manuscript. All authors were involved in the islet transplantation process and reviewed the manuscript critically for important intellectual content and approved the manuscript for publication. Q.P. and S.L. are the guarantors of this work and, as such, had full access to all the data in the article and take responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Liz Selvin and Thomas Danne.

References

1. Pease A, Lo C, Earnest A, Kiriakova V, Liew D, Zoungas S. The efficacy of technology in type 1 diabetes: a systematic review, network meta-analysis, and narrative synthesis. Diabetes Technol Ther 2020;22:411–421

2. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16

3. Brennan DC, Kopetskie HA, Sayre PH, et al. Long-term follow-up of the Edmonton protocol of islet transplantation in the United States. Am J Transplant 2016;16:509–517

4. Vantyghem M-C, Chetboun M, Gmyr V, et al. Erratum. Ten-year outcome of islet alone or islet after kidney transplantation in type 1 diabetes: a prospective parallel-arm cohort study. Diabetes Care 2019;42:2042-2049. Diabetes Care 2020;43:1164–2049

5. Lablanche S, Borot S, Wojtusciszyn A, et al.; GRAGIL Network. Ten-year outcomes of islet transplantation in patients with type 1 diabetes: data from the Swiss-French GRAGIL Network. Am J Transplant 2021;21:3725–3733

6. Wojtusciszyn A, Branchereau J, Esposito L, et al.; TREPID Group. Indications for islet or pancreatic transplantation: statement of the TREPID Working Group on behalf of the Société francophone du diabète (SFD), Société francaise d'endocrinologie (SFE), Société francophone de transplantation (SFT) and Société française de néphrologie-dialyse-transplantation (SFNDT). Diabetes Metab 2019;45:224–237

7. Chetboun M, Drumez E, Ballou C, et al.; Collaborative Islet Transplant Registry (CITR) Investigators Study Group. Association between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: a retrospective, multicentre, observational cohort study in 1210 patients from the Collaborative Islet Transplant Registry. Lancet Diabetes Endocrinol 2023;11:391–401

8. Marfil-Garza BA, Imes S, Verhoeff K, et al. Pancreatic islet transplantation in type 1 diabetes: 20-year experience from a single-centre cohort in Canada. Lancet Diabetes Endocrinol 2022;10:519–532

9. Lemos JRN, Baidal DA, Ricordi C, Fuenmayor V, Alvarez A, Alejandro R. Survival after islet transplantation in subjects with type 1 diabetes: twenty-year follow-up. Diabetes Care 2021;44:e67–e68

10. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. Am J Transplant 2021;21:1477–1492

11. Rickels MR, Eggerman TL, Bayman L, et al.; Clinical Islet Transplantation Consortium. Long-term outcomes with islet-alone and islet-after-kidney transplantation for type 1 diabetes in the Clinical Islet Transplantation Consortium: the CIT-08 study. Diabetes Care 2022;45:2967–2975

12. Fiorina P, Gremizzi C, Maffi P, et al. Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients. Diabetes Care 2005;28:1358–1365

13. Fiorina P, Venturini M, Folli F, et al. Natural history of kidney graft survival, hypertrophy, and vascular function in end-stage renal disease type 1 diabetic kidney-transplanted patients: beneficial impact of pancreas and successful islet cotransplantation. Diabetes Care 2005;28:1303–1310

14. Maanaoui M, Lenain R, Foucher Y, et al.; TREPID-ABM study group. Islet-after-kidney transplantation versus kidney alone in kidney transplant recipients with type 1 diabetes (KAIAK):

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

a population-based target trial emulation in France. Lancet Diabetes Endocrinol 2024;12:716–724
15. von Elm E, Altman DG, Egger M, et al.; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–808
16. Borot S, Niclauss N, Wojtusciszyn A, et al.; GRAGIL Network. Impact of the number of infusions on 2-year results of islet-after-kidney transplantation in the GRAGIL network. Transplantation 2011;92: 1031–1038
17. Badet L, Benhamou PY, Wojtusciszyn A, et al.; GRAGIL Group. Expectations and strategies regarding islet transplantation: metabolic data from the GRAGIL 2 trial. Transplantation 2007; 84:89–96
18. Lablanche S, Vantyghem M-C, Kessler L, et al.; TRIMECO trial investigators. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol 2018;6:527–537
19. Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur 2021;8:100158
20. Hoisnard L, Pina Vegas L, Dray-Spira R, Weill A, Zureik M, Sbidian E. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. Ann Rheum Dis 2023; 82:182–188
21. Marcombes C, Penso L, Weill A, Dray-Spira R, Zureik M, Sbidian E. Persistence of second-line biologics in psoriasis after first-line biologic failure: a nationwide cohort study from the French health insurance database (SNDS). Br J Dermatol 2023; 189:561–568
22. Lip GYH, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb Haemost 2016;116:975–986
23. Nakamura T, Fujikura J, Anazawa T, et al. Long-term outcome of islet transplantation on insulin-dependent diabetes mellitus: an observational cohort study. J Diabetes Investig 2020;11:363–372
24. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123
25. Carstensen B, Read SH, Friis S, et al.; Diabetes and Cancer Research Consortium. Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals. Diabetologia 2016;59:980–988
26. Lablanche S, Borot S, Wojtusciszyn A, et al.; GRAGIL Network. Five-year metabolic, functional, and safety results of patients with type 1 diabetes transplanted with allogenic islets within the Swiss-French GRAGIL Network. Diabetes Care 2015;38: 1714–1722
27. Caiazzo R, Vantyghem M-C, Raverdi V, et al. Impact of procedure-related complications on long-term islet transplantation outcome. Transplantation 2015;99:979–984
28. Peixoto E, Vendrame F, Arnau A, et al. Ten years of preserved kidney function after islet transplant graft failure. Diabetes Care 2016;39: e209–e211
29. Maanaoui M, Lenain R, Foucher Y, et al. Islet transplantation versus insulin alone in type 1 diabetic kidney transplant recipients: a French nationwide study on behalf of the TREPID group. Transplantation 2023;107:142–142
30. Wong G, Hayen A, Chapman JR, et al. Association of CKD and cancer risk in older people. J Am Soc Nephrol 2009;20:1341–1350
31. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305
32. Danielson KK, Hatipoglu B, Kinzer K, et al. Reduction in carotid intima-media thickness after pancreatic islet transplantation in patients with type 1 diabetes. Diabetes Care 2013;36:450–456
33. Madrigal JM, Monson RS, Hatipoglu B, et al. Coronary artery calcium may stabilize following islet cell transplantation in patients with type 1 diabetes. Clin Transplant 2017;31:e13059
34. Sagris M, Antonopoulos AS, Theofilis P, et al. Risk factors profile of young and older patients with myocardial infarction. Cardiovasc Res 2022; 118:2281–2292
35. Benhamou P-Y, Lablanche S, Vambergue A, et al. The beneficial effects of closed-loop insulin delivery in patients with highly unstable type 1 diabetes eligible for islet transplantation are maintained over 6 months: an extension study of the DBLHU-WP10 trial. Diabetes Obes Metab 2022;24:956–961
36. Renard E, Joubert M, Villard O, et al.; iDCL Trial Research Group. Safety and efficacy of sustained automated insulin delivery compared with sensor and pump therapy in adults with Type 1 diabetes at high risk for hypoglycemia: a randomized controlled trial. Diabetes Care 2023; 46:2180–2187
37. Lablanche S, David-Tchouda S, Margier J, et al. Randomised, prospective, medico-economic nationwide French study of islet transplantation in patients with severely unstable type 1 diabetes: the STABILOT study protocol. BMJ Open 2017;7:e013434
38. Hussain S, Braune K, Forbes S, Senior PA. Closed-loop systems: a bridge to cell therapy for type 1 diabetes? Lancet Diabetes Endocrinol 2024;12:782–784
39. Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and external controls in clinical trials - a primer for researchers. Clin Epidemiol 2020;12: 457–467

Downloaded from http://diabetesjournals.org/care/article-pdf/doi/10.2337/dc25-0059/804106/dc250059.pdf by guest on 28 April 2025

ANNEXES 2 – SUPPLEMENTARY MATERIALS DES ARTICLES

1. Signal detection of drugs associated with obstructive and central sleep apnoea

Supplementary Material

Signal detection of drugs associated with obstructive and central sleep apnoea

C. Jambon-Barbara[1,2], B. Revol[1,2], A. Hlavaty[1,2], M. Joyeux-Faure[2], JC. Borel[2], JL Cracowski[1,2], JL. Pepin[2,3*], C. Khouri[1,2,4*]

1. Grenoble Alpes University Hospital, Pharmacovigilance Unit, F-38000 Grenoble, France

2. Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, F-38000 Grenoble, France

3. Grenoble Alpes University Hospital, EFCR Laboratory, Grenoble, France.

4. Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000 Grenoble, France.

** co-last authors*

Corresponding author: Charles Khouri, E-mail address: *ckhouri@chu-grenoble.fr*

Table of Content

Table S1. Comorbidity identification **2**

Table S2. Outcome identification codes **3**

Table S3. Outcome identification codes **3**

Table S4. Principle analysis results of the 71 detected signals for drug classes (ATC4 codes) **5**

Table S5. Results of adjusted SR using using null-sequence ratio for refined drug classes. **8**

Table S6. Results of stratified analyses for refined drug classes. **9**

Table S7. Results of the SSA for drugs at the ATC5 level in selected drug classes. **10**

Table S1. Comorbidity identification

Stroke	Hospitalization or ALD with ICD-10 diagnosis codes: I60 to I64, I67 to I69.
Heart Failure	Hospitalization or ALD with ICD-10 diagnosis codes: I50, I11.0, I13.0, I13.9, K76.1, J81.
Coronary heart disease	Hospitalization or ALD with ICD-10 diagnosis codes: I20 to I24.
Chronic respiratory disease	Hospitalization or ALD with ICD-10 diagnosis codes: J40 to J47, J96 (excluding J96.0 or J96.9), J98. At least 3 reimbursements in one year of ATC codes: R03.
Hypertension	Hospitalization or ALD with ICD-10 diagnosis codes: I10 (primary), I15 (secondary). At least 3 reimbursements in one year of ATC codes: C02AB, C02AC, C02CA, C02DC, C03, C07, C08, C09.
Diabetes	Hospitalization or ALD with ICD-10 diagnosis codes: E10, E11, E12, E13, E14. Hospitalization with ICD-10 diagnosis codes for complications: H28.0, H36.0, M14.2, G59.0, G63.2, G99.0, I79.2, M14.6. At least 3 reimbursements in one year of ATC codes: A10 (excluding A10BX06).
Obesity	Hospitalization with ICD-10 diagnosis codes: E66 (excluding E6603, E6613, E6683, E6693). Bariatric surgery CCAM codes: HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027.
Smoking status	Hospitalization or ALD with ICD-10 diagnosis codes: Z71.6, F17, T65.2, Z72.0. Reimbursement for ATC codes N06AX12, N07BA since 2014. Hospitalization with ICD-10 diagnosis codes: I73.1, J41, J42, J43, J44, T65.2 and a drug reimbursement for ATC codes: R03AC18, R03AC19, R03BB04, R03BB05, R03BB06, R03BB07, R03AL04, R03AL05, R03AK04 since 2014. Reimbursement of nicotine replacement therapy or smoking cessation consultation.

If one of the parameters was satisfied, the co-morbidity was considered to be present.
ALD: Affection de Longue Durée. ICD-10: International Classification of Diseases, 10th revision. ATC: Anatomical Therapeutic Chemical. CCAM: Classification Commune des Actes Médicaux.

Table S2. Outcome identification codes

Sleep apnoea ICD-10 code	G 47.3
PAP LPP codes	1188684, 1130897, 1189991, 1162093, 1166688, 1188767, 1124460, 1118904, 1103156, 1126660, 1118614, 1132608, 1187880, 1115455, 1192987, 1103446, 1162006, 1124112, 1106663, 1142417, 1152686, 1179248, 1129888, 1116911, 1154886, 1151250, 1102470
MAS LPP codes	2451474, 2412971, 2455325, 2497884, 2407378, 2462680
Respiratory polygraphy and poylsomnography CCAM codes	GLQP007, AMQP009, AMQP010, AMQP011, AMQP012, AMQP013, AMQP014, AMQP015

OSA: Obstructive Sleep Apnoea. CPAP: Continous Positive Airway Pressure. LPP: Liste des Produits et Prestations. MAS: Mandibular Advancement Splints. CCAM: Classification Commune des Actes Médicaux

Table S3. PAP LPP codes description

PAP LPP codes	Plain language description
1188684	CPAP, Sleep Apnoea, Non-teleobserved patient, Weekly rate 9.4
1130897	FRA-25, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 1.00
1189991	FRA-26, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.00
1162093	FRA-35, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.11
1166688	FRA-41, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 1.31
1188767	FRA-58, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.13
1124460	FRA-59, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.14
1118904	FRA-65, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.15
1103156	FRA-47, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.12
1126660	FRA-27, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 3.00
1118614	FRA-102, CPAP, Sleep Apnoea, 9.4 + Oxygenotherapy 2.16
1132608	CPAP, Sleep Apnoea, Initial phase, Weekly rate 9.INI
1187880	CPAP, Sleep Apnoea, Teleobserved patient (more than 112 hours), Weekly rate 9.TL1
1115455	CPAP, Sleep Apnoea, Teleobserved patient (between 56 and 112 hours), Weekly rate 9.TL2
1192987	CPAP, Sleep Apnoea, Teleobserved patient (less than 56 hours), Weekly rate 9.TL3
1103446	CPAP, Sleep Apnoea, Non-teleobserved patient (good compliance), Weekly rate 9.NT1
1162006	CPAP, Sleep Apnoea, Non-teleobserved patient (insufficient compliance), Weekly rate 9.NT2
1124112	CPAP, Sleep Apnoea, Non-teleobserved patient (non compliance), Weekly rate 9.NT3
1106663	CPAP, Sleep Apnoea, Patient without compliance data, Weekly rate 9.SRO
1142417	CPAP, Sleep Apnoea, Initial phase, Weekly rate 9.INI-to be associated
1152686	CPAP, Sleep Apnoea, Teleobserved patient (more than 112 hours), Weekly rate 9.TL1-to be associated
1179248	CPAP, Sleep Apnoea, Teleobserved patient (between 56 and 112 hours), Weekly rate 9.TL2-to be associated
1129888	CPAP, Sleep Apnoea, Teleobserved patient (less than 56 hours), Weekly rate 9.TL3- to be associated
1116911	CPAP, Sleep Apnoea, Non-teleobserved patient (good compliance), Weekly rate 9.NT1-to be associated
1154886	CPAP, Sleep Apnoea, Non-teleobserved patient (insufficient compliance), Weekly rate 9.NT2-to be associated
1151250	CPAP, Sleep Apnoea, Non-teleobserved patient (non compliance), Weekly rate 9.NT3-to be associated
1102470	CPAP, Sleep Apnoea, Patient without compliance data, Weekly rate 9.SRO-to be associated

PAP: Positive Airway Pressure. LPP: Liste des Produits et Prestations.

Table S4. Principle analysis results of the 71 detected signals for drug classes (ATC4 codes)

Drug class	ATC code	ATC class name	Sensitive outcome					Specific outcome					Reason for exclusion
			Mean SSA	95% CI LB	95% CI HB	N pre	N post	Mean SSA	95% CI LB	95% CI LB	N pre	N post	
Anxiolytics	N05BX	Other anxiolytics	1.225	1.082	1.393	551	674	1.211	0.949	1.543	162	194	
	N05CD	Benzodiazepine derivatives	1.335	1.133	1.578	303	404	1.250	0.926	1.691	109	134	
	N05CX	Hypnotics and sedatives in combination. excl. barbiturates	1.707	1.071	2.625	44	72	1.879	0.714	5.000	12	20	Exposure too low
Analgesics	R05DA	Opium alkaloids and derivatives	1.174	1.090	1.263	1716	2011	1.014	0.883	1.158	606	614	
	M01AX	Other antiinflammatory and antirheumatic agents. non-steroids	1.220	1.093	1.359	861	1050	1.053	0.878	1.269	291	305	Topical
Myorelaxants	M02AC	Preparations with salicylic acid derivatives	1.395	1.023	1.900	98	134	1.435	0.853	2.316	35	48	Topical
	M03BA	Carbamic acid esters	1.354	1.060	1.703	155	209	1.181	0.740	1.806	54	62	
	M03BX	Other centrally acting agents	1.175	1.070	1.291	1122	1315	1.093	0.940	1.286	392	427	
	M09AA	Quinine and derivatives	1.540	1.170	2.026	121	185	1.373	0.872	2.174	42	55	
Hormonotherapy	L02BA	Anti-estrogens	4.349	1.167	12.000	4	13	1.451	0.250	4.000	3	3	Exposure too low
Anti-infectives	J01CR	Combinations of penicillins. incl. beta-lactamase inhibitors	1.110	1.041	1.184	2222	2464	1.073	0.952	1.197	732	783	Intermittent exposure
	J01DC	Second-generation cephalosporins	1.257	1.119	1.399	685	861	1.165	0.943	1.432	233	269	Intermittent exposure
	J01DD	Third-generation cephalosporins	1.151	1.056	1.243	1448	1666	1.053	0.910	1.215	509	536	Intermittent exposure
	J01FA	Macrolides	1.220	1.127	1.315	1601	1954	1.158	1.014	1.331	532	614	Intermittent exposure
	J07CA	Bacterial and viral vaccines. combined	1.167	1.080	1.262	1468	1710	1.132	0.975	1.315	441	498	Intermittent exposure
	A07AA	Antibiotics	1.713	1.030	2.778	34	56	2.071	0.556	6.000	7	11	Exposure too low
	G01AF	Imidazole derivatives	1.316	1.122	1.518	401	525	1.520	1.111	2.054	91	137	Intermittent exposure
	P02CA	Benzimidazole derivatives	1.340	1.081	1.648	220	292	1.263	0.780	1.871	53	65	Intermittent exposure
	S02CA	Corticosteroids and antiinfectives in combination	1.171	1.053	1.295	904	1058	1.220	1.008	1.448	286	347	Risk of detection and confunding bias
Antiosteoporosis drugs	G03XC	Selective estrogen receptor modulators	2.482	1.125	4.667	14	31	1.770	0.444	5.500	7	10	Exposure too low
Antimigraine drugs	N02CA	Ergot alkaloids	1.673	1.143	2.333	60	99	2.151	0.846	5.000	11	21	Risk of detection and confunding bias
	N02CC	Selective serotonin (5HT1) agonists	1.646	1.329	2.016	196	322	1.623	1.024	2.609	43	67	Risk of detection and confunding bias
	C04AE	Ergot alkaloids	1.762	1.135	2.762	39	66	2.583	1.143	6.500	12	27	Exposure too low

Respiratory drugs and associated symptoms	R01AB	Sympathomimetics. combinations excl. corticosteroids	1.158	1.034	1.298	736	848	1.159	0.944	1.399	234	271	Risk of detection and confunding bias
	R03AC	Selective beta-2-adrenoreceptor agonists	1.460	1.357	1.573	1407	2054	1.452	1.270	1.654	507	736	Risk of detection and confunding bias
	R03AK	Adrenergics in combination with corticosteroids or other drugs. excl. anticholinergics	1.529	1.410	1.652	1265	1934	1.621	1.429	1.851	447	723	Risk of detection and confunding bias
	R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	1.393	1.189	1.622	348	484	1.580	1.204	2.074	129	202	Risk of detection and confunding bias
	R03BA	Glucocorticoids	1.257	1.159	1.364	1435	1803	1.350	1.187	1.553	473	635	Risk of detection and confunding bias
	R03BB	Anticholinergics	1.413	1.280	1.568	783	1105	1.682	1.413	2.025	276	463	Risk of detection and confunding bias
	R03DC	Leukotriene receptor antagonists	1.334	1.166	1.523	463	617	1.313	1.039	1.657	152	198	Risk of detection and confunding bias
	R06AD	Phenothiazine derivatives	1.146	1.049	1.249	1206	1380	1.192	1.013	1.398	370	441	Risk of detection and confunding bias
	R06AE	Piperazine derivatives	1.125	1.019	1.237	1062	1193	1.000	0.840	1.175	390	389	Risk of detection and confunding bias
	R05CB	Mucolytics	1.172	1.075	1.277	1274	1490	1.127	0.956	1.308	419	470	Risk of detection and confunding bias
Cardiovascular drug	B01AC	Platelet aggregation inhibitors excl. heparin	1.391	1.281	1.511	1271	1769	1.125	0.994	1.285	608	683	Risk of detection and confunding bias
	B01AF	Direct factor Xa inhibitors	1.583	1.368	1.832	366	578	1.349	1.078	1.677	198	266	Risk of detection and confunding bias
	C01BD	Antiarrhythmics. class III	1.610	1.360	1.883	328	529	1.861	1.434	2.395	129	237	Risk of detection and confunding bias
	C01DA	Organic nitrates	1.353	1.175	1.556	450	609	1.097	0.874	1.376	217	237	Risk of detection and confunding bias
	C02AC	Imidazoline receptor agonists	1.373	1.126	1.638	210	286	1.399	0.988	1.850	96	132	Risk of detection and confunding bias
	C02CA	Alpha-adrenoreceptor antagonists	1.416	1.181	1.694	253	357	1.302	1.000	1.699	130	168	Risk of detection and confunding bias
	C03BA	Sulfonamides. plain	1.356	1.078	1.704	166	223	1.244	0.895	1.667	86	106	Risk of detection and confunding bias
	C03CA	Sulfonamides. plain	1.334	1.207	1.463	925	1232	1.273	1.095	1.484	417	527	Risk of detection and confunding bias
	C07AA	Beta blocking agents. non-selective	1.461	1.232	1.745	318	463	1.290	0.963	1.675	125	160	Risk of detection and confunding bias
	C07AB	Beta blocking agents. selective	1.478	1.351	1.622	1137	1675	1.314	1.144	1.499	514	675	Risk of detection and confunding bias
	C07BB	Beta blocking agents. selective. and thiazides	1.283	1.008	1.630	154	196	1.021	0.690	1.449	79	80	Risk of detection and confunding bias
	C08CA	Dihydropyridine derivatives	1.459	1.317	1.604	1017	1479	1.302	1.129	1.510	459	597	Risk of detection and confunding bias
	C09AA	ACE inhibitors. plain	1.565	1.426	1.712	995	1550	1.379	1.197	1.592	445	612	Risk of detection and confunding bias
	C09BA	ACE inhibitors and diuretics	1.503	1.272	1.781	284	427	1.473	1.121	1.910	123	179	Risk of detection and confunding bias
	C09BB	ACE inhibitors and calcium channel blockers	1.383	1.170	1.640	300	414	1.306	0.992	1.708	140	181	Risk of detection and confunding bias
	C09CA	Angiotensin II receptor blockers (ARBs). plain	1.287	1.169	1.421	996	1280	1.149	0.995	1.320	460	526	Risk of detection and confunding bias

	C09DB	Angiotensin II receptor blockers (ARBs) and calcium channel blockers	1.375	1.135	1.639	267	366	1.194	0.932	1.562	139	165	Risk of detection and confunding bias
	N02BA	Salicylic acid and derivatives	1.214	1.073	1.369	599	727	1.224	0.989	1.493	213	259	Risk of detection and confunding bias
Other	V08AB	Watersoluble. nephrotropic. low osmolar X-ray contrast media	1.311	1.225	1.409	1890	2477	1.288	1.141	1.436	681	874	Intermittent exposure
	V08CA	Paramagnetic contrast media	1.198	1.098	1.302	1290	1545	1.143	0.992	1.317	469	534	Intermittent exposure
	A03ED	Antispasmodics in combination with other drugs	1.254	1.082	1.443	406	505	1.107	0.842	1.429	140	154	Intermittent exposure
	A06AB	Contact laxatives	1.275	1.084	1.507	305	386	1.298	0.979	1.704	112	144	Intermittent exposure
	A12CC	Magnesium	1.320	1.112	1.547	303	398	1.127	0.807	1.542	95	105	Intermittent exposure
	N07BA	Drugs used in nicotine dependence	1.217	1.036	1.434	345	417	1.210	0.919	1.566	129	155	Risk of detection and confunding bias
	N07CA	Antivertigo preparations	1.329	1.188	1.487	740	981	1.100	0.913	1.329	293	320	

Table S5. Results of adjusted SR using using null-sequence ratio for refined drug classes.

ATC	Sensitive outcome (composite OSA)					Specific outcome (CPAP)				
	Crude SR	**Null-effect SR**	**Adjusted SR**	**95%CI lower bound**	**95%CI higher bound**	**Crude SR**	**Null-effect SR**	**Adjusted SR**	**95%CI lower bound**	**95%CI higher bound**
R05DA	1.17	1.11	1.06	1.03	1.09	1.03	1.11	0.92	0.87	0.98
N05CD	1.34	1.11	1.22	1.14	1.30	1.24	1.11	1.09	0.97	1.22
N05BX	1.23	1.12	1.11	1.05	1.17	1.21	1.12	1.07	0.97	1.17
M03BA	1.35	1.10	1.19	1.09	1.30	1.16	1.10	1.03	0.87	1.22
M03BX	1.17	1.11	1.05	1.01	1.09	1.10	1.11	0.98	0.92	1.05
M09AA	1.54	1.08	1.32	1.21	1.45	1.35	1.08	1.19	0.99	1.42
N07CA	1.33	1.11	1.20	1.16	1.26	1.10	1.11	0.98	0.91	1.06

Table S6. Results of analyses stratified on sex for refined drug classes.

ATC	Female			Male		
	N prior	N post	SR (95% CI)	N prior	N post	SR (95% CI)
R05DA	709	842	1.19 (1.06-1.35)	1,007	1,169	1.16 (1.06-1.28)
N05CD	149	238	1.61 (1.29-2.03)	154	166	1.09 (0.83-1.42)
N05BX	309	365	1.19 (1.00-1.41)	242	309	1.28 (1.03-1.56)
M03BA	76	101	1.34 (0.96-1.83)	79	108	1.39 (1.00-1.88)
M03BX	498	572	1.15 (0.99-1.33)	624	743	1.19 (1.06-1.35)
M09AA	61	78	1.31 (0.88-1.84)	60	107	1.82 (1.29-2.60)
N07CA	410	524	1.28 (1.09-1.48)	330	457	1.39 (1.20-1.65)

ATC: Anatomical Therapeutic Chemical classification; N prior: number of patients with the sequence outcome→exposure; N post: number of patients with the sequence exposure→outcome; SR: Sequence Ratio; 95%CI: 95% confidence interval

Table S7. Results of the SSA for drugs at the ATC5 level in selected drug classes.

ATC5_code	SSA	95%CI_low	95%CI_high	n_pre	n_post	n_tot	Age_mean	Age_sd	Male_proportion	Diag_time_mean	Diag_time_sd
L02BG06	7,318	2,333	9,000	1	12	13	70,5	10,3	NA	167,5	103,0
B01AC24	2,538	1,720	3,690	52	129	181	60,6	10,8	78,45	138,6	107,4
C04AE51	5,535	1,714	18,000	5	20	25	48,6	17,3	56,00	140,6	113,2
A12CC05	2,209	1,410	3,476	40	85	125	52,4	16,0	49,60	184,6	108,8
C09AA04	1,597	1,407	1,817	499	792	1291	61,4	12,7	63,75	143,5	107,0
C07FB02	3,750	1,400	11,000	8	24	32	61,3	14,7	50,00	180,5	118,3
R03AK08	1,605	1,390	1,841	436	698	1134	56,7	15,9	47,35	140,6	107,8
N02CC03	1,886	1,388	2,500	95	175	270	42,6	13,4	29,26	177,7	109,3
B01AC22	2,429	1,385	4,167	25	57	82	58,4	10,3	84,15	146,9	109,2
B01AF02	1,706	1,375	2,138	169	286	455	69,6	12,5	65,05	149,3	109,8
C01BD01	1,618	1,374	1,874	326	528	854	70,1	10,8	69,44	137,1	106,5
C09BA04	1,649	1,337	2,024	192	315	507	60,8	12,2	62,72	139,9	107,4
N02CA52	3,819	1,333	9,500	7	21	28	43,7	11,3	14,29	177,1	112,9
R03AC13	1,660	1,329	2,034	182	299	481	60,7	14,4	56,13	153,4	112,9
R03AK03	1,931	1,328	2,750	62	117	179	62,9	12,7	63,13	138,7	112,8
C09AA05	1,502	1,324	1,704	498	745	1243	63,0	13,5	65,65	141,1	107,4
C07AB07	1,485	1,321	1,664	715	1061	1776	65,2	12,9	67,12	135,8	108,3
R03AC02	1,427	1,312	1,550	1216	1731	2947	52,8	21,0	52,80	153,6	108,5
C08CA04	1,565	1,301	1,856	263	409	672	62,8	14,3	50,00	141,3	108,5
C07AA05	1,615	1,301	1,961	195	314	509	50,6	14,7	44,60	153,7	105,7
R03AK06	1,462	1,295	1,635	642	934	1576	55,6	19,2	53,05	147,0	110,0
R03AK07	1,442	1,285	1,606	679	978	1657	56,1	16,1	54,44	138,7	108,9
C07AB03	1,582	1,284	1,926	183	288	471	60,6	12,8	62,21	144,4	109,9
B01AC06	1,391	1,276	1,501	1238	1715	2953	63,7	12,0	67,90	143,5	109,0
C09BB02	1,695	1,240	2,294	84	140	224	60,5	11,7	67,41	143,8	109,0
R03BB04	1,423	1,239	1,616	547	778	1325	62,7	13,0	66,19	120,4	107,1
G04BD04	1,869	1,236	2,618	58	106	164	58,7	18,7	51,83	181,4	106,4
N05CD11	1,637	1,220	2,156	103	166	269	54,8	15,0	39,03	174,6	105,4

N07CA01	1,422	1,219	1,657	364	514	878	58,9	15,0	47,15	174,5	109,6
C03CA01	1,344	1,218	1,471	914	1227	2141	67,5	13,3	60,02	143,9	108,0
C02CA06	1,481	1,198	1,848	192	282	474	65,2	13,0	55,49	142,7	108,5
C08CA13	1,360	1,195	1,558	491	665	1156	62,7	12,2	55,88	150,2	109,5
R03BA02	1,349	1,189	1,529	625	840	1465	56,0	20,0	51,81	156,4	107,2
C07AB04	1,629	1,183	2,229	79	127	206	62,5	12,1	63,11	148,9	107,8
C08CA01	1,326	1,171	1,496	589	780	1369	64,1	13,3	60,12	141,0	110,6
C09CA04	1,375	1,170	1,604	366	501	867	62,2	13,0	55,48	151,5	110,5
R03DC03	1,334	1,166	1,523	463	617	1080	49,7	20,8	47,69	140,9	111,1
J01DC02	1,329	1,165	1,504	536	709	1245	53,1	17,3	55,02	174,3	105,7
R03BA01	1,292	1,158	1,438	820	1056	1876	54,2	18,4	50,80	166,2	107,1
M01AX25	1,455	1,158	1,803	179	258	437	59,4	11,6	45,08	180,5	109,8
V08AB07	1,299	1,150	1,466	665	860	1525	58,2	14,2	58,43	151,9	110,2
J01FA10	1,278	1,149	1,414	826	1053	1879	50,7	18,4	52,53	178,9	107,1
C01DA02	1,340	1,146	1,561	446	595	1041	65,1	12,2	69,45	156,0	106,4
R05DA20	1,264	1,143	1,398	881	1112	1993	51,4	17,5	54,19	179,9	106,3
C10AA05	1,265	1,143	1,401	892	1127	2019	62,3	12,0	67,41	145,9	110,4
C07AB12	1,319	1,129	1,544	410	538	948	62,4	13,0	62,34	139,0	108,8
R03AC18	1,401	1,127	1,706	205	285	490	63,9	12,2	67,76	133,7	109,7
N07CA04	1,270	1,126	1,431	657	831	1488	56,9	15,3	43,41	171,5	105,4
G03XC01	2,482	1,125	4,667	14	31	45	62,2	8,6	13,33	190,6	117,7
C09CA03	1,345	1,123	1,582	305	410	715	63,4	12,5	58,04	156,5	110,5
R06AX26	1,471	1,121	1,873	123	179	302	53,2	15,7	49,01	167,2	106,5
R03AC03	1,302	1,121	1,540	388	502	890	61,9	16,8	54,49	130,7	108,2
A03AX58	1,239	1,113	1,386	768	948	1716	54,7	15,8	47,90	182,7	105,7
N05BA01	1,326	1,113	1,577	290	383	673	47,7	18,0	51,26	168,4	108,9
R01AD52	1,253	1,112	1,411	657	821	1478	51,0	14,8	58,19	168,4	108,1
C02AC06	1,376	1,110	1,680	184	251	435	66,1	12,6	57,93	143,5	101,9
B01AF01	1,337	1,107	1,602	246	329	575	66,2	12,6	64,00	155,6	106,9
H02AB06	1,179	1,103	1,256	2280	2685	4965	51,0	19,9	57,68	168,9	107,8
M01AB16	1,317	1,099	1,590	281	368	649	53,5	13,5	54,24	187,8	107,8
R06AD08	1,209	1,098	1,324	1022	1233	2255	49,2	19,3	51,04	178,3	105,1
J07CA02	1,213	1,098	1,330	995	1206	2201	47,7	19,3	55,97	179,2	107,4

N02CC02	2,223	1,095	4,500	19	39	58	44,9	12,3	31,03	162,7	114,0
M03BX07	1,253	1,094	1,430	502	628	1130	52,3	14,0	55,84	173,6	104,6
M01AE11	1,224	1,091	1,369	718	875	1593	47,9	16,7	53,86	175,3	106,1
R03BB01	1,308	1,090	1,545	324	422	746	65,3	15,8	53,08	130,5	110,2
N05BA12	1,195	1,087	1,314	1038	1240	2278	53,8	15,6	49,78	168,9	107,7
G03AC09	1,413	1,086	1,847	134	188	322	35,5	9,5	0,62	186,5	109,2
R06AE09	1,231	1,085	1,383	629	772	1401	52,8	16,7	51,53	163,7	108,1
R06AX29	1,204	1,083	1,340	834	1001	1835	52,2	15,5	49,16	158,9	110,1
A03ED	1,254	1,082	1,443	406	505	911	55,3	15,5	48,63	181,1	106,0
R06AX27	1,158	1,082	1,243	1741	2010	3751	50,7	20,1	53,16	167,9	108,1
N05BX03	1,225	1,082	1,393	551	674	1225	51,7	15,7	44,98	167,7	105,5
V08AB11	1,272	1,081	1,487	394	498	892	59,5	14,6	57,40	157,6	111,1
V08AB10	1,243	1,081	1,410	552	685	1237	59,4	13,4	58,45	155,0	109,5
R05CB	1,173	1,079	1,287	1323	1546	2869	51,2	20,6	55,14	179,1	104,7
J01FA06	1,248	1,078	1,429	535	666	1201	55,1	17,1	49,88	175,9	107,0
C03BA11	1,356	1,078	1,704	166	223	389	62,8	11,7	59,64	151,3	109,7
M01AE01	1,161	1,076	1,257	1669	1935	3604	49,6	18,8	56,63	179,1	106,6
A06AB58	1,276	1,076	1,519	305	387	692	57,9	12,2	53,18	171,8	107,3
C09DB02	1,474	1,074	2,027	91	132	223	60,1	12,3	65,92	129,7	111,3
N02BA01	1,216	1,074	1,384	575	699	1274	52,8	17,5	57,22	170,7	107,1
C09CA08	1,405	1,073	1,772	142	197	339	60,8	12,5	58,41	149,8	106,8
M09A	1,480	1,072	2,018	93	136	229	59,0	14,3	56,77	173,4	104,0
J01DD13	1,173	1,072	1,291	1024	1199	2223	48,3	20,9	54,84	181,8	105,5
N05CX	1,707	1,071	2,625	44	72	116	56,0	13,8	54,31	164,3	102,4
R03AC12	1,682	1,070	2,708	45	73	118	61,2	16,7	56,78	156,4	108,3
R05DA04	1,294	1,068	1,531	264	340	604	38,1	25,2	52,98	147,4	115,9
J07CA01	1,213	1,068	1,380	608	735	1343	52,4	19,2	59,49	183,2	106,9
V08CA09	1,262	1,064	1,502	305	385	690	56,4	15,1	51,30	161,2	109,9
R05DA08	1,181	1,063	1,302	1023	1204	2227	52,7	16,7	54,20	176,5	106,5
G03DB07	2,298	1,063	4,500	14	29	43	44,0	8,9	NA	182,6	108,9
V08AB09	1,272	1,063	1,506	291	369	660	58,5	14,4	54,24	168,7	111,6
R01AD01	1,153	1,062	1,255	1298	1497	2795	50,7	18,7	53,24	146,8	110,1
R06AX28	1,317	1,062	1,622	192	252	444	53,0	16,2	47,52	155,9	108,5

M03BA03	1,354	1,060	1,703	155	209	364	52,1	14,2	51,37	181,4	101,6
B01AC04	1,236	1,060	1,434	409	503	912	66,3	11,4	75,33	147,4	109,8
H02AB01	1,155	1,059	1,268	1191	1372	2563	51,2	21,1	53,10	176,0	105,6
N02CC05	1,765	1,057	2,789	35	61	96	42,3	12,5	22,92	173,9	109,5
C09BB04	1,289	1,055	1,568	198	254	452	61,8	11,7	65,71	138,4	108,3
M01AH05	1,340	1,048	1,702	145	193	338	56,0	13,3	43,49	182,7	99,5
H02AB07	1,167	1,047	1,289	862	1004	1866	55,9	16,1	51,55	175,6	107,1
V08AB05	1,243	1,046	1,462	370	460	830	59,8	14,9	58,55	156,4	111,8
C07AB02	1,596	1,043	2,310	50	78	128	59,8	13,3	60,94	158,7	109,5
N05BA11	1,227	1,042	1,440	376	459	835	52,7	15,0	45,75	171,7	105,8
P02CA05	1,288	1,042	1,571	199	256	455	38,3	22,8	48,79	177,0	105,2
N05BA08	1,163	1,042	1,301	694	805	1499	55,6	15,1	49,23	168,0	108,9
R03AL01	1,384	1,041	1,807	139	190	329	61,8	14,7	62,01	141,0	111,8
J01CR02	1,111	1,040	1,182	2220	2464	4684	52,7	20,0	60,20	172,8	107,3
C10AA01	1,244	1,038	1,478	283	353	636	61,9	12,0	60,06	154,3	109,5
J01FA07	1,226	1,036	1,449	304	372	676	45,7	23,0	48,22	181,5	105,8
G03AA07	1,350	1,036	1,723	129	172	301	33,3	11,7	2,33	176,8	106,0
M03BX05	1,137	1,033	1,253	1071	1221	2292	51,8	14,9	51,92	178,2	106,9
V08AB02	1,211	1,033	1,412	410	495	905	60,2	13,4	59,67	156,7	110,5
C09DB01	1,302	1,031	1,595	190	246	436	61,0	12,0	67,43	144,1	114,4
V08CA02	1,140	1,030	1,257	957	1089	2046	56,0	15,6	52,83	159,2	107,8
A07AA02	1,713	1,030	2,778	34	56	90	46,7	25,2	43,33	162,9	110,4
R03CC12	1,703	1,030	2,941	34	55	89	64,6	13,9	48,31	143,5	104,0
N07CA03	1,663	1,029	2,732	35	56	91	50,2	15,1	40,66	152,9	113,4
R01AB08	1,152	1,027	1,280	738	846	1584	51,0	18,1	59,22	176,6	107,6
A01AB03	1,111	1,024	1,204	1230	1364	2594	53,1	16,6	54,32	179,1	106,3
M02AC	1,395	1,023	1,900	98	134	232	53,4	13,7	50,00	181,5	107,8
M01AX17	1,284	1,023	1,574	205	261	466	52,9	13,5	54,29	184,9	107,3
R01AX10	1,168	1,022	1,326	513	600	1113	48,4	21,9	54,36	176,8	104,6
J01RA04	1,139	1,021	1,259	913	1039	1952	53,4	15,0	53,64	181,9	106,9
C07AA07	1,370	1,020	1,829	112	152	264	66,4	10,7	62,88	139,4	107,8
J01FA09	1,135	1,020	1,256	948	1074	2022	51,9	17,3	49,06	163,8	108,8
R05DA09	1,120	1,017	1,234	1094	1223	2317	52,6	17,6	53,52	180,9	106,9

V03AX	1,155	1,017	1,313	590	679	1269	51,8	18,8	37,83	176,5	107,5
N05CD06	1,242	1,016	1,497	230	285	515	55,1	14,8	45,44	169,1	105,5
R06AX13	1,202	1,011	1,412	327	391	718	51,8	19,5	46,52	171,3	106,0
S02CA06	1,158	1,010	1,310	608	704	1312	50,0	19,7	53,43	173,6	105,7
G01AF19	1,233	1,009	1,469	258	317	575	47,1	14,7	0,52	190,2	104,8
N05CF02	1,124	1,003	1,258	747	839	1586	55,8	15,5	53,97	164,8	107,5
A02BC01	1,079	1,003	1,153	2029	2187	4216	53,0	16,6	53,63	167,5	108,9
M01AB05	1,090	1,002	1,188	1223	1326	2549	52,6	14,9	53,24	179,9	103,9
C04AX21	1,375	1,000	1,911	83	112	195	63,8	13,0	61,03	156,3	106,2

ATC5_code: 5th level of the Anatomical Therapeutic Chemical classification (chemical substance).
SSA: Sequence Symmetry Analysis ratio value
95%CI_low: 95% confidence interval lower bound
95%CI_high: 95% confidence interval higher bound
n_pre: number of patients with the sequence OSA -> drug
n_post: number of patients with the sequence drug -> OSA
n_tot: total number of patients included in the SSA analysis
Age_mean: mean age of diagnosis, years
Age_sd: standard deviation of the age of diagnosis, years
Male_proportion: proportion of sex male, %
Diag_time_mean: mean time between exposure and OSA diagnosis, days
Diag_time_sd: standard deviation of the time between exposure and OSA diagnosis, days

2. Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France

Validation of in-hospital diagnosis codes in one French hospital and out-hospital algorithm to identify skin ulcers in healthcare databases in France.

ELECTRONIC SUPPLEMENTARY MATERIAL

Table of content

Table S1. Wound dressing LPP codes (n = 329) *2*

Table S2. Anti-bedsore mattress, cushions or overlays LPP codes (n = 247) *4*

Table S3. Compression bandage LPP codes (n = 238) *5*

Table S4. Orthopedic surgery CCAM codes (n = 482) *6*

Table S5. Echo Doppler CCAM codes *7*

Table S1. Wound dressing LPP codes (n = 329)

LPP Codes: hydrocolloid dressing
1322792, 1387113, 1321321, 1343788, 1396632, 1342926, 1335004, 1399518, 1323805, 1362188, 1386042, 1314261, 1344859, 1311446, 1390530, 1339090, 1385321, 1399895, 1303688, 1331383
LPP Codes: foam dressing
1351374, 1316136, 1328085, 1388590, 1344428, 1398163, 1315102, 1350653, 1304736, 1319063, 1366980, 1308094, 1314723, 1370220, 1310783, 1387188, 1301347, 1371106, 1353870, 1381642, 1347875, 1342240, 1375050, 1327370, 1353864, 1354355, 1347823, 1302996, 1375564, 1316320, 1338936, 1322065, 1327186, 1315384, 1365270, 1326502, 1311943, 1357106, 1301070, 1307692, 1326666, 1308898, 1397732, 1365755, 1370704, 1351747, 1348633, 1348679, 1374381, 1365117, 1308668, 1312760, 1319643, 1333399, 1380074, 1326560, 1303470, 1393616, 1372672, 1337026, 1370236, 1320913, 1333198, 1389112, 1392717, 1335866, 1336558, 1359097, 1364342, 1358152, 1328493, 1376990, 1314829, 1306497, 1368185, 1351262, 1396690, 1336015, 1303748, 1318030, 1315852, 1316107, 1360717, 1381576, 1306400, 1321982, 1398708, 1358399, 1349710, 1327536, 1346829, 1350509, 1392114, 1348946, 1375618, 1379378, 1322326, 1358347, 1356331, 1384238, 1378485, 1375587, 1338942, 1388319, 1378048, 1394975, 1314278, 1301525, 1307700, 1380097, 1356348, 1310620, 1383397, 1382759, 1388153, 1374932, 1319904, 1300744, 1392574, 1367501, 1379444, 1307769, 1370897, 1357336, 1376747, 1324868, 1355136, 1328748, 1363325, 1365904, 1330082, 1399263, 1356207, 1310033, 1302298, 1345942, 1370800, 1349319, 1323113, 1332968, 1340330, 1354600, 1381056, 1364974, 1368363, 1373565, 1330805, 1314284, 1342872, 1348484, 1337820, 1374694, 1356319
LPP Codes: alginates dressing
1306155, 1319040, 1319896, 1310300, 1366128, 1351871, 1316633, 1393160, 1310464, 1334737, 1395259, 1304972, 1342174, 1346597, 1372420, 1384988, 1306304, 1345830, 1330840, 1365465, 1345037, 1394521, 1316120, 1371253
LPP Codes: hydrogel dressing
1334690, 1311624, 1396939, 1305718, 1351109, 1340399, 1354154, 1355350, 1340399, 1339404, 1396891, 1328895, 1328501
LPP Codes: fibre dressing
1357833, 1347830, 1325299, 1304498, 1333695, 1305026, 1344842, 1365488, 1371388, 1393295, 1379088, 1305598, 1310346, 1327039, 1390055, 1338132, 1304742, 1355165, 1358063, 1333732, 1361800, 1331667
LPP Codes: active carbon
1346628, 1327772, 1339321, 1311469, 1309202, 1345557, 1333436
LPP codes: Dressings containing hyaluronic acid
1300299, 1369227, 1395420, 1348550, 1380950, 1360350, 1335062, 1366921, 1397790, 1335040, 1351463, 1353485
LPP Codes: dressing with interfaces
1318767, 1398281, 1310910, 1387633, 1355604, 1346002, 1372301, 1329682, 1379527, 1382825, 1344434, 1324101, 1318572, 1347102, 1316142, 1386473, 1324673, 1350564,

1331526, 1358324, 1325508, 1334252, 1368877, 1359045, 1338379, 1330254, 1342613, 1341252, 1346315, 1348410, 1343311, 1349934
LPP Codes: dressing with petroleum jelly
1366074, 1348998, 1369322, 1369078, 1314367, 1317851, 1356408
LPP Codes: adhesive dressing
1300810, 1374004, 1368015, 1347310, 1316290, 1365264, 1334619, 1375140, 1395868, 1305960, 1397749, 1330478, 1307893, 1368222, 1394751, 1332282, 1392367, 1305457, 1301130, 1337150, 1335872, 1383641, 1389320, 1300709, 1391089, 1390010, 1333962, 1387314, 1334743, 1370064, 1346769, 1362797, 1307195, 1375475, 1314166, 1329452, 1306847, 1393326, 1325550

LPP: Liste des Produits et Prestations

Table S2. Anti-bedsore mattress, cushions or overlays LPP codes (n = 247)

1221855, 1253051, 1265410, 1289942, 1277465, 1212000, 1223624, 1235478, 1286978, 1274395, 1264178, 1233002, 1206956, 1201717, 1269320, 1238778, 1299870, 1230423, 1209972, 1297002, 1244260, 1233427, 1211851, 1267969, 1262110, 1263977, 1274076, 1247518, 1249374, 1283900, 1202250, 1236911, 1256730, 1283359, 1204012, 1209908, 1264764, 1258657, 1293180, 1201433, 1231960, 1241941, 1286955, 1217003, 1247665, 1249411, 1240485, 1217658, 1296876, 1244678, 1286381, 1298734, 1287340, 1265090, 1290129, 1273438, 1277749, 1255096, 1291904, 1276951, 1213028, 1246424, 1228395, 1273875, 1245459, 1200072, 1230972, 1280562, 1201700, 1238650, 1200014, 1270180, 1226315, 1253878, 1289422, 1228857, 1204035, 1226410, 1218020, 1222429, 1270687, 1272545, 1247754, 1259177, 1223920, 1251773, 1280036, 1256546, 1223297, 1204242, 1243680, 1233143, 1259214, 1257155, 1206904, 1251460, 1229160, 1258864, 1260677, 1229785, 1231233, 1272344, 1262713, 1239022, 1294653, 1231865, 1285690, 1261725, 1224084, 1262699, 1271379, 1258730, 1245844, 1245034, 1253766, 1215808, 1204288, 1202705, 1296793, 1292789, 1217664, 1255274, 1243510, 1223452, 1289652, 1296103, 1267343, 1236710, 1278329, 1231285, 1283260, 1294570, 1204302, 1240150, 1211265, 1219462, 1294794, 1237804, 1241668, 1280065, 1283589, 1214134, 1212276, 1238554, 1224138, 1297841, 1234600, 1265166, 1295960, 1256813, 1263753, 1252689, 1220028, 1285111, 1256428, 1205425, 1225273, 1253677, 1232468, 1273065, 1236696, 1297427, 1224233, 1203290, 1293932, 1214269, 1228350, 1230624, 1225729, 1223423, 1214890, 1294506, 1213092, 1269342, 1236839, 1260602, 1222808, 1203640, 1266421, 1221536, 1251840, 1216937, 1216682, 1228917, 1259220, 1202272, 1234728, 1233433, 1249517, 1284057, 1298119, 6269097, 6274052, 6245665, 6270500, 6255592, 6276298, 6240515, 6229710, 1203633, 6255617, 6276654, 6276269, 6229778, 1279317, 1206548, 1238896, 1255506, 1263351, 1290342, 1282006, 1257296, 1283537, 1280680, 1203113, 1295374, 1254984, 1297628, 1215205, 1252815, 1218280, 1278045, 1294802, 1220034, 1224411, 1200250, 1267449, 1284927, 1250259, 1249138, 1204220, 1244900, 1237218, 1224078, 1251342, 1237017, 1227770, 1205477, 6278647, 6255563, 6276306, 6229962, 6231634, 1203679, 1233367, 1248713, 1293872

LPP: Liste des Produits et Prestations

Table S3. Compression bandage LPP codes (n = 238)

6316098, 6316112, 6316106, 6372932, 6313792, 6362715, 6313846, 6361101, 6324100, 6366311, 6332430, 6311497, 6372926, 6313817, 6363525, 6318594, 6361093, 6324092, 6376516, 6366328, 6332571, 6311505, 6372910, 6313786, 6362589, 6312485, 6361118, 6324117, 6376491, 6366305, 6330247, 6311480, 6316649, 6313770, 6313763, 6312060, 1349727, 1384853, 1349756, 1395526, 1368370, 6313800, 6363175, 6316750, 6361087, 6324086, 6376485, 6366334, 6332507, 6311511, 1316981, 1330892, 1364030, 1317489, 1328665, 1307002, 1375386, 1318052, 1397620, 1306110, 1371282, 1385025, 1324957, 6380558, 6380104, 6311468, 6312002, 6356979, 6362649, 6312657, 6324330, 6364306, 6325111, 6371677, 6381888, 6381285, 1325891, 1322208, 1330231, 1355857, 6325128, 1345971, 1395839, 6382793, 6379880, 6380564, 6311474, 6312048, 6356991, 6363554, 6318810, 6346171, 6324324, 6363927, 6371660, 6381291, 1303889, 1327826, 1329268, 1380298, 1332307, 1320103, 1352712, 1395437, 1387426, 6382801, 6330721, 1370934, 1340301, 1332508, 1389307, 1313528, 1393987, 6313591, 1311966, 1365146, 1389052, 1322384, 1334482, 1340873, 6313600, 1399180, 1317555, 1317472, 1349414, 1346143, 1395147, 1344629, 1331934, 6324235, 6332453, 1398499, 6324198, 6332588, 1377540, 1317354, 1315177, 1301117, 6339283, 6310747, 6324229, 6330129, 1331733, 6313852, 6324206, 1358330, 6344918, 6316490, 6324181, 6332499, 1321835, 6339290, 6312545, 6324175, 6330276, 1366105, 1319130, 1315220, 1344061, 1322355, 1388242, 6332559, 1349147, 6315153, 6324318, 6320585, 6332482, 1394202, 6318536, 6324293, 6320579, 6332565, 6315124, 1345362, 6324270, 6320562, 6332476, 1327217, 6320556, 6332418, 1397896, 1368587, 6332513, 1378858, 6317092, 6313272, 6324301, 6320540, 6332536, 1372689, 6317040, 6324287, 6320533, 6332520, 1325460, 6312663, 6324264, 6320527, 6332401, 1381100, 6317123, 6324258, 6320510, 6332542, 1322237, 1307309, 6312108, 6324212, 1361480, 1384451, 1374872, 1302967, 1330277, 1351173, 1340152, 1349058, 1335323, 1390977, 1378410, 1367961, 1387202, 1324791, 1324213, 1381286, 1306310, 1367412, 1338557, 1346574, 1314746, 1359714, 1312598, 1352741, 1328518, 1387030, 1326689, 1313238, 1314769, 6332447

LPP: Liste des Produits et Prestations

Table S4. Orthopedic surgery CCAM codes (n = 482)

‘QBFA007', 'QZJA011', 'EJGA002', 'QZMA001', 'QEMA013', 'PDFA001', 'EPLF002', 'HMFC004', 'EBLA003', 'QCJA001', 'AHPA009', 'QZMA004', 'NFFC004', 'PAGA011', 'NEKA020', 'EJFA002', 'QEFA008', 'ENLF001', 'QBPA001', 'NFMC003', 'QZFA011', 'ZZQP119', 'QZFA004', 'MEMC005', 'LMMA009', 'HFFC018', 'NDPA011', 'QAMA002', 'BFGA004', 'AHPC001', 'LMMA012', 'LMMA004', 'QZFA036', 'HKPA006', 'MJEC002', 'QZJA001', 'EJFA006', 'QEFA017', 'MJFA010', 'NFFC003', 'MEMC003', 'HKPA007', 'QEFA020', 'HKPA004', 'QEMA012', 'MJCA012', 'LMMC002', 'LMMA010', 'QEFA004', 'AHPA022', 'QZJA012', 'MJDC001', 'LMMA006', 'HHFA009', 'HMFA007', 'QZFA014', 'QZEA020', 'HFCC003', 'MJFA006', 'NFKA007', 'ZCJA002', 'HHFA002', 'NCCA017', 'EBGA001', 'QBFA012', 'HHFA016', 'QEJA001', 'MJMA002', 'QBFA005', 'MJFA018', 'QZJA009', 'QZFA007', 'MCCB004', 'PDFA002', 'AHPA028', 'HKPA005', 'QZJA022', 'GGJB001', 'MJFA015', 'QBFA001', 'NFKA008', 'MDCA011', 'HJFA004', 'EJGA001', 'NDPA013', 'QEFA019', 'QELH001', 'LFFA002', 'MCCA005', 'QEMA006', 'HHCA002', 'MJFA003', 'QEMA008', 'ZCQA001', 'HHFA006', 'MDCB003', 'MJEC001', 'QBFA008', 'HGFA007', 'HFCB001', 'QEKA001', 'QEMA010', 'HHFA008', 'QZEA045', 'HFMC007', 'QZFA002', 'NFFC002', 'EJGA003', 'QZJA017', 'JQGA003', 'HGSA001', 'QZFA039', 'MJCA001', 'HJFA002', 'HPFA004', 'NCCB006', 'HHFA025', 'GAFA007', 'QZJA013', 'NCCA012', 'YYYY062', 'PZMA004', 'HGFA005', 'ZCJA004', 'HHMA003', 'NEKA011', 'QEFA001', 'LMMC020', 'MDCA014', 'HGPA004', 'EZMA001', 'QZFA035', 'NJPA018', 'QEGA004', 'GGJB002', 'HGCA008', 'LFFA001', 'FCFA006', 'PAGA009', 'QZFA020', 'FCFA029', 'NBCA010', 'JQQP001', 'MJJA001', 'JKFA028', 'NHDA004', 'NEKA014', 'EJSA001', 'FCFA008', 'DELF005', 'LMMC001', 'MJJA003', 'FCFA018', 'JGFA006', 'QZJA010', 'MJPA011', 'NGCA001', 'MJPA013', 'NCCA016', 'QEMA004', 'QZJA002', 'MZFA013', 'QBFA004', 'JJFC003', 'HHFA014', 'AHCA023', 'HHSA001', 'MJJA004', 'LFAA002', 'LMMA001', 'NFJC001', 'QBFA003', 'JJFC010', 'NHMA002', 'JQGA002', 'NBCA006', 'PDFA003', 'LMMA017', 'PCCA002', 'PAGA010', 'HPPA002', 'NZFA005', 'NDPA008', 'FCFA013', 'MJPA002', 'NDPA002', 'HHFA001', 'EPLF005', 'QAGA004', 'HGCA004', 'NHFA001', 'FCFA011', 'MZEA010', 'NFKA006', 'JGFA015', 'HGCA002', 'HHFA018', 'KCFA005', 'JGFC001', 'HJFA007', 'JHFA009', 'NDPA014', 'QBFA002', 'QZFA009', 'AHLB001', 'MJPA009', 'QZJA015', 'CAFA005', 'NCCA004', 'FCFA019', 'HPPC003', 'MHDB001', 'LHFA016', 'QZJA005', 'QZJB002', 'QEKA002', 'AFLB008', 'MJFA005', 'QZJA021', 'QZEA027', 'MCCB002', 'MJEA006', 'MJFA004', 'PCPA004', 'QZMP001', 'QZFA001', 'HHFA011', 'MBCA005', 'PAFA010', 'HLFA019', 'MHFA001', 'GGPA002', 'NJCA001', 'QZFA027', 'MHFA002', 'PCCA001', 'MHDA005', 'LMGA001', 'MEMA006', 'GFFA013', 'NGFA002', 'CAMA022', 'HFCA002', 'JJFA004', 'MJPA012', 'NBGA007', 'NEKA012', 'DBKA006', 'QZEA008', 'NDGA003', 'HHFA024', 'YYYY026', 'FCFA016', 'QZMA007', 'MBCB002', 'MHJA001', 'QZJA016', 'NCCA002', 'MHPA004', 'QAJA006', 'AHPA011', 'NDPA004', 'JHJA001', 'QEFA002', 'QZJA007', 'JKFA027', 'MJFC001', 'QZMA006', 'HNFA007', 'HGLA001', 'MGFA004', 'QEGA002', 'QZJB003',

'NCCA018', 'ZZJH003', 'HDQE001', 'QAJA012', 'HJFA019', 'QEDA002', 'AHPA021', 'LMMC015', 'MCCA011', 'MGFA007', 'JCPC002', 'JHFA013', 'MJDA001', 'HHFA026', 'AHCA015', 'HHFA017', 'QZFA024', 'FCFA010', 'JKFA015', 'JDLF001', 'NEFA004', 'NJFA008', 'QZGA003', 'HHFA020', 'MHMA005', 'MJCA003', 'NFFA004', 'QEDA004', 'MDGA002', 'MEMA005', 'HFMC001', 'MJCA002', 'NCCA010', 'NCPA015', 'MDFA002', 'MDCB005', 'NJPA025', 'QEMA009', 'DEKA001', 'JQGA004', 'NJFA002', 'LLMC004', 'NHPA002', 'QZMA009', 'DELF007', 'NBCB004', 'QAJA005', 'QBJB001', 'HPMA001', 'LHCA010', 'MACA001', 'NBEP001', 'NFPC002', 'NDPA003', 'JJPC003', 'NDCA002', 'HMQA001', 'LMSA002', 'MCCA010', 'MJEA010', 'GAFA002', 'EECA009', 'HGFA004', 'QAJA013', 'AELB002', 'HPFA003', 'NDCA004', 'QEMA005', 'QZJA004', 'QZFA029', 'DDMA018', 'HHCA001', 'MEEA004', 'NJFA005', 'NBMA002', 'DDMA011', 'NFEC002', 'NZHA001', 'PZMA005', 'FCFA012', 'JDFE001', 'NGEP001', 'HJFA011', 'QEMA002', 'HHFE006', 'CAFA002', 'GAMA018', 'NCPA001', 'HGFA003', 'NZMA001', 'EJFA007', 'FCFA017', 'FFFA001', 'FCFA022', 'JGFA005', 'ZZHH008', 'NJMB001', 'DDMA005', 'EGFA002', 'MJFA008', 'MJFA012', 'NEEP002', 'NGPA002', 'PCPA003', 'GAFA005', 'HJFA017', 'BAFA006', 'MEMC002', 'MJCA006', 'QZJP001', 'JKDC001', 'LFDA009', 'NBFA005', 'MCCA008', 'HFCA003', 'MJMA010', 'MJPA005', 'LDCA013', 'FCFC003', 'GFFC005', 'GGNC001', 'NFJA001', 'NJEA003', 'QEFA007', 'NBCA001', 'HMFC001', 'ZBQC001', 'QCJA004', 'JCLE001', 'JDFA025', 'NDCA003', 'NFCA002', 'FCFC001', 'HFCC001', 'HJFA006', 'JKFA006', 'MDCA007', 'NJPA007', 'MDCA004', 'MJPA010', 'GAMA012', 'HHFA010', 'PACC001', 'GDFA005', 'MJFA014', 'NJMA003', 'QEMA003', 'LMFA001', 'MJEA004', 'NCEP002', 'ZZGP001', 'DCJB001', 'GFFC002', 'JLDC015', 'MBCA011', 'NFJA002', 'QZFA006', 'MCCA001', 'NCPA014', 'NGPC001', 'NHDA001', 'NCPA002', 'NFPA002', 'QAJA001', 'JDFE002', 'QZFA019', 'ZZHH006', 'AHPA001', 'HJDC001', 'HFFA005', 'GFFA017', 'HKPA008', 'NDPA009', 'HMFC002', 'MEKA008', 'QZFA030', 'HCFA008', 'LHGA007', 'DCJA001', 'MHCA002', 'QEFA016', 'FCFA027', 'QZEA021', 'HLHB001', 'HHMA002', 'MHPA002', 'MJJA002', 'QAJA007', 'QZEA037', 'LDFA008', 'MCCA004', 'MGCA001', 'KCFA008', 'MEFC002', 'HHCC007', 'LMMA011', 'QAGA001', 'BAMA004', 'PAGB003', 'QCJA003', 'HAFA017', 'MJCA010', 'MEJC001', 'NCCA005', 'NCCA013', 'HCFA009', 'MBCA006', 'MEFC001', 'NBCA005’

CCAM: Classification Commune des Actes Médicaux

Table S5. Echo Doppler CCAM codes

'EJQM004', 'EDQM001'

CCAM: Classification Commune des Actes Médicaux

3. Development and validation of a code-based algorithm using in-hospital medical records to identify patients with pulmonary arterial hypertension in the French Healthcare Database

ELECTRONIC SUPPLEMENTARY MATERIAL

Article Title: Development and Validation of Algorithms to Identify Pulmonary Arterial Hypertension in the French Healthcare Database

Running Title: Pulmonary Arterial Hypertension Identification in French Healthcare Database

Journal: *ERJ Open Research*

Clément Jambon-Barbara [1,2], Alex Hlavaty [1,2], Claire Bernardeau [1], Hélène Bouvaist [3], Marie-Camille Chaumais [4,5,6], Marc Humbert [4,7,8], David Montani [4,7,8], Jean-Luc Cracowski [1,2], Charles Khouri [1,2,9].

[1] Grenoble Alpes University Hospital, Pharmacovigilance Unit, F-38000 Grenoble, France.
[2] Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, F-38000 Grenoble, France.
[3] Grenoble Alpes University Hospital, Cardiology Unit, F-38000 Grenoble, France.
[4] INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France.
[5] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Pharmacy, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.
[6] Université Paris-Saclay, Faculty of Pharmacy, Saclay, France.
[7] Université Paris-Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France.
[8] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Centre, Hôpital Bicêtre, DMU 5 Thorinno, Le Kremlin-Bicêtre, France.
[9] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000 Grenoble, France.

Corresponding author: Charles Khouri, Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
Tel: +33 4 76 76 51 45
Fax: +33 4 76 76 56 55

E-mail: ckhouri@chu-grenoble.fr

Table S1. List of PAH-treatment codes

Selexipag	**ATC code:** B01AC27 **UCD codes:** 9416073, 9416096, 9416104, 9416110, 9416127, 9416133, 9416156, 9416162, 9416179
Iloprost	**ATC code:** B01AC11 **UCD codes:** 9405709, 9405709, 9256965, 9256965, 9297467 9297467
Sildenafil	**ATC code:** C02KX **UCD codes:** 9420399, 9385013, 9279972, 9424167, 9436319, 9437307, 9437951, 9438637
Riociguat	**ATC code:** C02KX05 **UCD codes:** 9400540, 9400557, 9400563, 9400586, 9400592
Ambrisentan	**ATC code:** C02KX02 **UCD codes:** 9000423, 9000424, 9455624, 9455630, 9455759, 9455765, 9456730, 9456747, 9452985, 9452991, 9454783, 9454808, 9316035, 9316041, 9001991
Treprostinil	**ATC code:** B01AC21 **UCD codes:** 9000505, 9000506, 9000507, 9000508, 9442165, 9442171, 9442188, 9442194, 9271539, 9271545, 9271551, 9271568
Epoprostenol	**ATC code:** B01AC09 **UCD codes:** 9354225, 9354231, 9356201, 9356218, 9399877, 9399883, 9184881, 9202886, 9421766, 9421884
Bosentan	**ATC code:** C02KX01 **UCD codes:** 9240013, 9240036, 9342759, 9429785, 9429791, 9425190, 9425209, 9426539, 9426545, 9437276, 9437282, 9426717, 9426723, 9421536, 9421542, 9433634, 9421909, 9421915, 9422211, 9422228, 9433640
Sitaxentan	**ATC code:** C02KX03 **UCD code:** 9298461
Tadalafil	**ATC code:** C02KX **UCD codes:** 9348615, 9425480, 9438643

PAH: Pulmonary Arterial Hypertension, ATC: Anatomical Therapeutic Chemical, UCD: Unité Commune de Dispensation.

Macitentan is not part of the identified PAH specific treatment as it is not a reimbursed treatment in France and is therefore not used.

Table S2. RHC and CTEPH specific procedure CCAM codes

CCAM Codes: Right Heart Catheterization
'EQQF001', 'EQQF002', 'EQQF003', 'EQQF004', 'EQQF006', 'EQQH001', 'EQQH002', 'EQQH004', 'EQQH005', 'EQQH006'
CCAM Codes: Chronic Thromboembolic Pulmonary Hypertension specific procedure
'DAAF001', 'DFAA002', 'DFAA003', 'DFAA004', 'DFAA005', 'DFAF001', 'DFAF002', 'DFAF003', 'DFAF004', 'DFFA003'

RHC: Right Heart Catheterization, CTEPH: Chronic Thromboembolic Pulmonary Hypertension, CCAM: Classification Commune des Actes Médicaux (Medical Procedure Classification)

Table S3. Characteristics identification in the SNDS

PAH associated conditions	
Systemic scleroderma	ICD-10 in-hospital diagnosis code: M34 ICD-10 LTD code: M34
Portal hypertension	ICD-10 diagnosis code: K76.6
HIV positive	ICD-10 diagnosis code: B20 to B24, F02.4, Z21 ICD-10 LTD code: B20 to B24, F02.4, Z21 Drug reimbursement ATC codes: J05AF01, J05AF02, J05AF03, J05AF04, J05AF06, J05AF13, J05AG01, J05AG03, J05AG04, J05AG05, J05AR01, J05AR04, J05AE01, J05AE02, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AE03, J05AR06, J05AR08, J05AR09, J05AR13, J05AR18, J05AR19, J05AR20, J05AR21, J05AX07, J05AX08, J05AX09, J05AX12
Congenital heart disease	ICD-10 diagnosis code: Q211, Q210, Q250, Q251, Q234, Q230, Q221, Q213, Q212, Q203, Q201, Q262, Q252, Q226, Q232, Q230, Q220, Q225, Q224, Q204, Q205, Q202, Q201, Q200
Comorbidities	
COPD	> 3 drug reimbursement from ATC codes: - LABA: R03CC12, R03AC13, R03AC18, R03AC19, R03AC12 - LAMA: R03BB06, R03BB04, R03BB07 - LABA/LAMA association: R03AL04, R03AL06, R03AL03 - LABA/ICS association: R03AK08, R03AK07, R03AK10, R03AK06 - LABA/LAMA/ICS association: R03AL09, R03AL11, R03AL08. AND Exclusion of previous hospitalization for asthma: J45, J46 AND Exclusion of previous use of asthma medications ATC codes: R03BA01, R03BA02, R03BA08, R03BA05, R03BA07, R03DC03, R03DX05, R03DX09, R03DX10, R03DX11, R03AC02, R03CC03, R01AC07, R06AX17, R01AC01
Heart failure	ICD-10 in-hospital diagnosis codes: I11.0, I13.0, I13.2, I13.9, I50, J81 ICD-10 LTD codes: I11, I13, I50
Diabetes	ICD-10 in-hospital diagnosis codes: E10 to E14 ICD-10 in-hospital diagnosis codes for complications: G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3

	ICD-10 LTD codes: E10 to E14 Drug reimbursement ATC code: A10 (excluding A10BX06)
High blood pressure	ICD-10 in-hospital diagnosis codes: I10, I15 ICD-10 LTD codes (before 27/06/2011*): I10, I15 > 3 drug reimbursement from ATC codes: C02 (excluding C02CA02), C03AA01, C03AA03, C03BA04, C03BA05, C03BA06, C03BA07, C03BA08, C03BA09, C03BA10, C03BA11, C03BX03, C03C, C03D, C03EA01, C03EA02, C03EA03, C03EA04, C03EB01, C07, C08, C09A, C09B, C09C, C09D, C09X, C10BX03, C10BX07
VTE	ICD-10 in-hospital diagnosis codes: I26, I80, I82 ICD-10 LTD codes: I26, I80, I82
Chronic dialysis	GHM in-hospital codes: 28Z01Z, 28Z02Z, 28Z03Z, 28Z04Z, 28Z05Z, 28Z06Z CCAM codes: JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008 Service codes: 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2131, 2132, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2142, 2143, 2144, 2145, 2146, 2334
Sickle cell disease	ICD-10 diagnosis code: D57 ICD-10 in-hospital diagnosis codes for complications: H36.8, N08.2, M14.0 ICD-10 LDT code: D57

If one of the parameters was satisfied, the co-morbidity was considered to be present, unless otherwise specified.

* 27/06/2011: application of the decree withdrawing high blood pressure from LTD list

SNDS: Système National des Données de santé, i.e. French healthcare database.

PAH: Pulmonary Arterial Hypertension.

ICD-10: International Classification of Diseases, 10th revision.

LTD: Long-term disease.

HIV: Human Immunodeficiency Virus.

ATC: Anatomical Therapeutic Chemical.

COPD: Chronic Obstructive Pulmonary Disease.

LABA: Long-acting β-agonist.

LAMA: Long-acting muscarinic antagonist.

ICS: Inhaled corticosteroid.

VTE: Venous Thromboembolic Events (i.e. Pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

GHM: Groupe Homogène de Malades, i.e. hospital billing codes.

CCAM: Classification Commune des Actes Médicaux, i.e. common classification of medical procedures.

Table S4. PH Characterization of patients identified by the first algorithm

PAH	PH type II	PH type III	PH type IV	PH type V	No PH
177 (46.9)	10 (2.65)	56 (14.9)	122 (32.4)	10 (2.65)	2 (0.53)

All data are given as n (%)

PAH: Pulmonary Arterial Hypertension, PH: Pulmonary Hypertension, CTEPH: Chronic Thromboembolic Pulmonary Hypertension

Table S5. 2x2 Contingency table for the second algorithm

Variable	PAH [a]	Not-PAH [a]	Total
Positive test [b]	TP: 171	FP: 81	252
Negative test [c]	FN: 17	TN: 235	252
Total	188	316	504

PAH: Pulmonary Arterial Hypertension, 10th revision. TP: true positive. FP: false positive. FN: false negative. TN: true negative.

[a] As determined by the gold standard chart review of primary clinical data.

[b] Patients selected by the algorithm.

[c] Patients selected from the non-case pool.

4. Ticagrelor after acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors

ELECTRONIC SUPPLEMENTARY MATERIAL

Article Title: Ticagrelor following acute coronary syndrome and incident risk of sleep apnoea compared with other P2Y12 receptor inhibitors: A population-based cohort study

Running Title: Sleep Apnoea risk with Ticagrelor

Clément Jambon-Barbara[1,2,*], Sarah Margot Barras[1,*], Jean-Louis Pépin[2,3], Jean-Luc Cracowski[1,2], Marie Joyeux-Faure[2], Charles Khouri[1,2,4,†], Bruno Revol[1,2,†]

[1] Grenoble Alpes University Hospital, Pharmacovigilance Department, F-38000 Grenoble, France.
[2] Univ. Grenoble Alpes, HP2 Laboratory, INSERM U1300, F-38000, Grenoble, France.
[3] Grenoble Alpes University Hospital, EFCR Laboratory, F-38000, Grenoble, France.
[4] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000, Grenoble, France.
* co-first authors
† co-last authors

Corresponding author: Clément Jambon-Barbara, Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
Tel: +33 4 76 76 51 45
Fax: +33 4 76 76 56 55
E-mail: CJambonbarbara@chu-grenoble.fr

Table of Content

Table A. Protocol deviations 4

Table B. Sleep apnoea identification codes 5

Figure A. Outcome definition schematic representation. 6

Table C. MACE identification codes 7

Figure B. Directed acyclic graph of P2Y12 receptor inhibitors and sleep apnoea associated covariates. 8

Table D. Covariates identification codes 9

Table E. Characteristics of Patients, by Exposure Status, before weighting: Ticagrelor versus Clopidogrel 12

Table F. Characteristics of Patients, by Exposure Status, before weighting: Ticagrelor versus Prasugrel 14

Figure C. Ticagrelor and clopidogrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: clopidogrel, exposure 1: ticagrelor. 16

Figure D. Ticagrelor and prasugrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: prasugrel, exposure 1: ticagrelor. 17

Table G. Characteristics of Patients, by Exposure Status, before weighting: Prasugrel versus Clopidogrel 18

Table H. Characteristics of Patients, by Exposure Status, after weighting: Prasugrel versus Clopidogrel 20

Figure E. Prasugrel and clopidogrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: clopidogrel, exposure 1: prasugrel. 22

Table I. Characteristics of Patients, by Exposure Status, after matching: Prasugrel versus Clopidogrel 23

Table J. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: primary analysis for prasugrel versus clopidogrel 25

Table K. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: sensitivity analyses for prasugrel versus clopidogrel 26

Figure F. Cumulative incidence curves of sleep apnoea for prasugrel versus clopidogrel 27

Figure G. Kaplan-Meier survival curves of major adverse cardiovascular events (MACE) for prasugrel use versus clopidogrel use. 28

Figure H. Forest-plot for subgroup analyses displaying hazard ratios for association between prasugrel use and clopidogrel use, and risk of sleep apnoea, and major adverse cardiovascular events (MACE). 29

Table L. Characteristics of Patients, by Exposure Status, after matching: Ticagrelor versus Clopidogrel 30

Table M. Characteristics of Patients, by Exposure Status, before and after matching: Ticagrelor versus Prasugrel 32

Table N. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: sensitivity analyses after matching 34

Table A. Protocol deviations

Covariate adjustment technique	We had specified in the protocol that we would use inverse probability of treatment weighting (IPTW) to manage known confounders but we finally used fine stratification to estimate the average treatment effect of the treated (ATT) with ticagrelor (i.e. the one for which we had a safety signal) and not the whole average treatment effect (ATE). As IPTW could only estimate ATE, we decided to use fine stratification to better answer our research question.

Table B. Sleep apnoea identification codes

Polysomnography and Respiratory polygraph	CCAM codes: GLQP007, AMQP009, AMQP010, AMQP011, AMQP012, AMQP013, AMQP014, AMQP015
Sleep apnoea diagnosis	ICD-10 in-hospital diagnosis codes: G47.3 ICD-10 LTD code: G47.3
Positive airway pressure therapy	LPP codes: 1188684, 1130897, 1189991, 1162093, 1166688, 1188767, 1124460, 1118904, 1103156, 1126660, 1118614, 1132608, 1187880, 1115455, 1192987, 1103446, 1162006, 1124112, 1106663, 1142417, 1152686, 1179248, 1129888, 1116911, 1154806, 1151250, 1102470
Mandibular advancement splint	LPP codes: 2451474, 2412971, 2455325, 2497884, 2407378, 2462680

CCAM: Classification Commune des Actes Médicaux, i.e. common classification of medical procedures.
ICD-10: International Classification of Diseases, 10th revision.
LTD: Long-term disease.
LPP: Liste des Produits et des prestations, i.e. French healthcare codes for products and services.

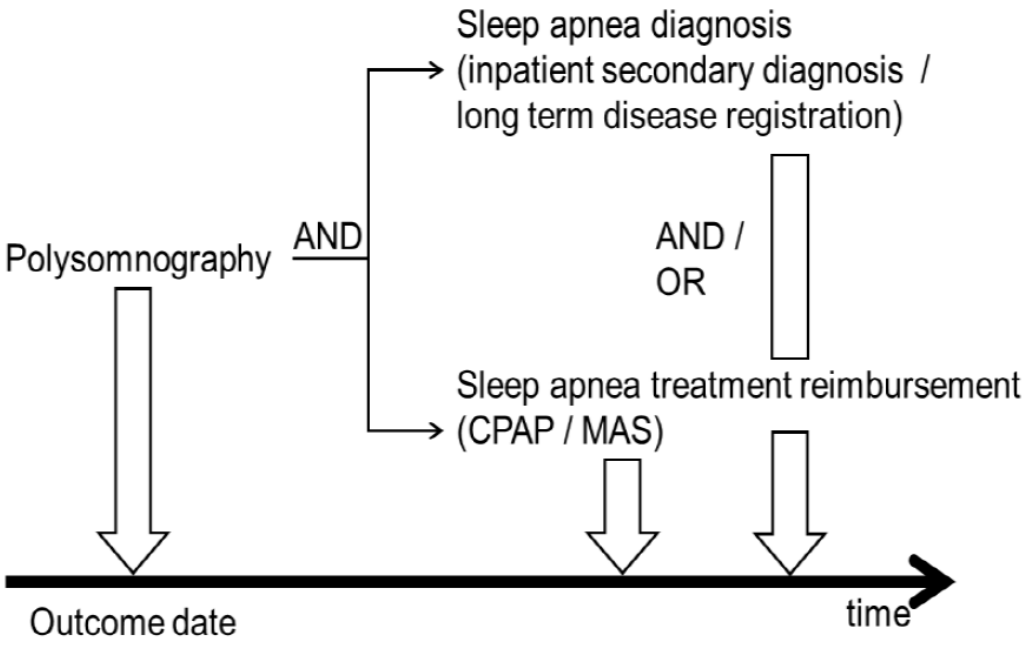


Figure A. Outcome definition schematic representation.

Table C. MACE identification codes

Coronary heart disease	ICD-10 in-hospital diagnosis codes: I20, I21, I22, I23, I24, I25 ICD-10 LTD diagnosis codes: I20, I21, I22, I23, I24, I25
Heart failure	ICD-10 in-hospital diagnosis codes: I50, I110, I130, I132, I139, J81 ICD-10 LTD diagnosis codes: I50, I110, I130, I132, I139, J81
Myocardial infarction	ICD-10 in-hospital diagnosis codes: I21, I22, I23 ICD-10 LTD diagnosis codes: I21, I22, I23
Stroke	ICD-10 in-hospital diagnosis codes: I60, I61, I62, I63, I64, I67, I68, I69 ICD-10 LTD diagnosis codes: I60, I61, I62, I63, I64, I67, I68, I69

MACE: Major adverse cardiovascular events
ICD-10: 10th revision of the International Classification of Diseases
LTD: Long-term disease

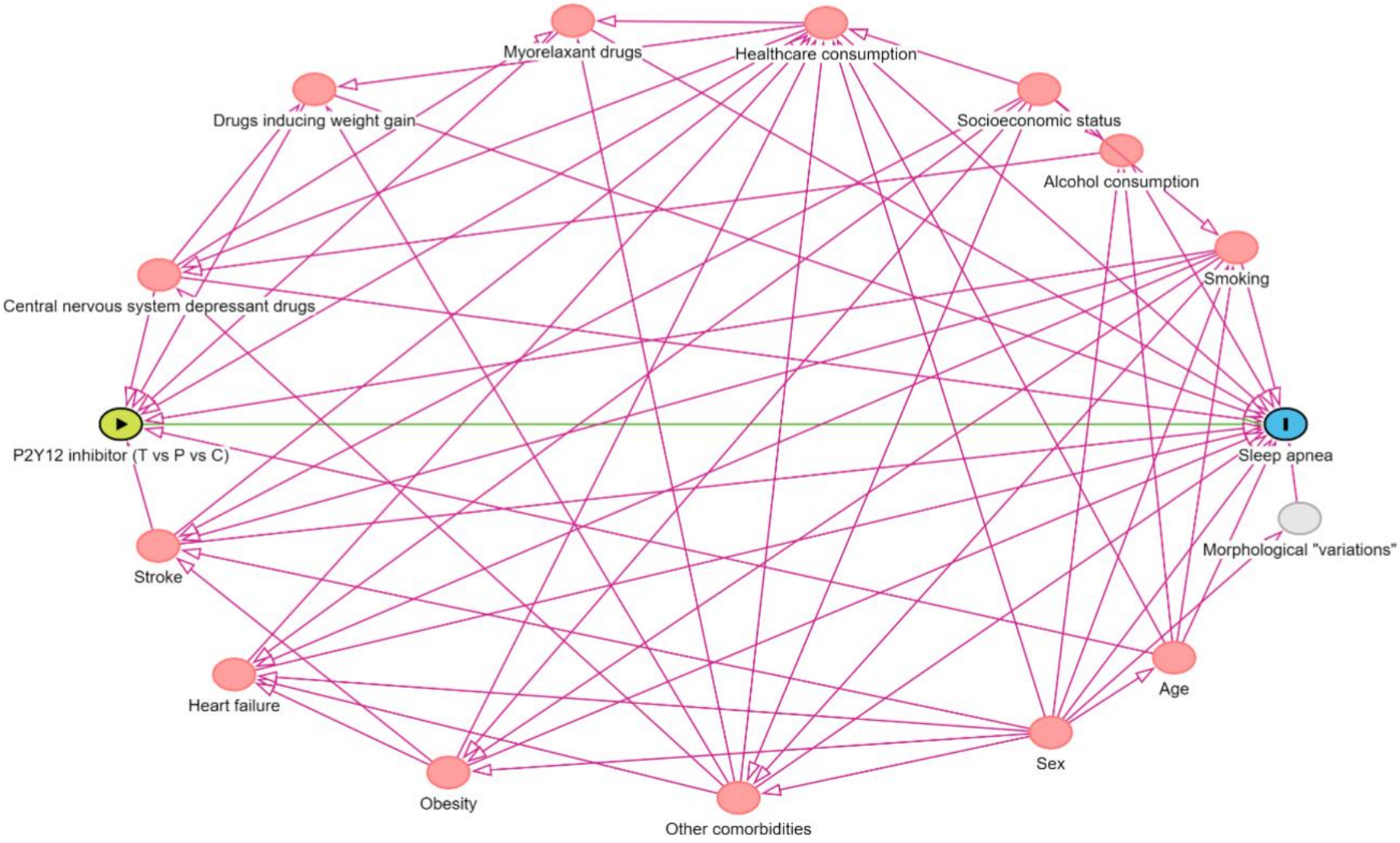


Figure B. Directed acyclic graph of P2Y12 receptor inhibitors and sleep apnoea associated covariates.

Table D. Covariates identification codes

High blood pressure	ICD-10 in-hospital diagnosis codes: I10, I15 ICD-10 LTD codes (before 27/06/2011*): I10, I15 > 3 drug reimbursement from ATC codes: C02 (excluding C02CA02), C03AA01, C03AA03, C03BA04, C03BA05, C03BA06, C03BA07, C03BA08, C03BA09, C03BA10, C03BA11, C03BX03, C03C, C03D, C03EA01, C03EA02, C03EA03, C03EA04, C03EB01, C07, C08, C09A, C09B, C09C, C09D, C09X, C10BX03, C10BX07
COPD	> 3 drug reimbursement from ATC codes: - LABA: R03CC12, R03AC13, R03AC18, R03AC19, R03AC12 - LAMA: R03BB06, R03BB04, R03BB07 - LABA/LAMA association: R03AL04, R03AL06, R03AL03 - LABA/ICS association: R03AK08, R03AK07, R03AK10, R03AK06 - LABA/LAMA/ICS association: R03AL09, R03AL11, R03AL08. AND Exclusion of previous hospitalization for asthma: J45, J46 AND Exclusion of previous use of asthma medications ATC codes: R03BA01, R03BA02, R03BA08, R03BA05, R03BA07, R03DC03, R03DX05, R03DX09, R03DX10, R03DX11, R03AC02, R03CC03, R01AC07, R06AX17, R01AC01
Chronic dialysis	GHM in-hospital codes: 28Z01Z, 28Z02Z, 28Z03Z, 28Z04Z, 28Z05Z, 28Z06Z CCAM codes: JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008 Service codes: 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2131, 2132, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2142, 2143, 2144, 2145, 2146, 2334
Diabetes	ICD-10 in-hospital diagnosis codes: E10 to E14 ICD-10 in-hospital diagnosis codes for complications: G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3 ICD-10 LTD codes: E10 to E14 Drug reimbursement ATC code: A10 (excluding A10BX06)
Heart failure	ICD-10 in-hospital diagnosis codes: I11.0, I13.0, I13.2, I13.9, I50, J81 ICD-10 LTD codes: I11, I13, I50
VTE	ICD-10 in-hospital diagnosis codes: I26, I80, I82 ICD-10 LTD codes: I26, I80, I82
Hyperlipidaemia	ICD-10 in-hospital diagnosis code: E78

	ICD-10 LTD code: E78 Drug reimbursement ATC code: C10
NAFLD	ICD-10 in-hospital diagnosis codes: K75.8, K76.0 ICD-10 LTD codes: K75.8, K76.0
Pulmonary hypertension	ICD-10 in-hospital diagnosis codes: I27.0, I27.2
Cancers	ICD-10 in-hospital diagnosis codes: C0, C1, C2, C3, C4, C5, C6, C7, C8, C9, D0 ICD-10 LTD codes: C0, C1, C2, C3, C4, C5, C6, C7, C8, C9, D0 Drug reimbursement ATC code: G03HA01, L01CD04, L01XX11, L02AA01, L02AA04, L02AE01, L02AE02, L02AE03, L02AE04, L02AE05, L02BB01, L02BB02, L02BB03, L02BB04, L02BX02, L02BX03, V10BX01, V10XX
Arrythmia	ICD-10 in-hospital diagnosis codes: I44, I45, I47, I48, I49 ICD-10 LTD codes: I44, I45, I47, I48, I49 Drug reimbursement ATC codes: C01A, C01B
TIA	ICD-10 in-hospital diagnosis code: G45 ICD-10 LTD code: G45
Stroke	ICD-10 in-hospital diagnosis codes: I60, I61, I62, I63, I64, I67, I68, I69 ICD-10 LTD codes: I60, I61, I62, I63, I64, I67, I68, I69
Smoking status	ICD-10 in-hospital diagnosis codes: Z71.6, F17, T65.2, Z72.0, I73.1, J41, J42, J43, J44, T65.2 Drug reimbursement ATC codes: N06AX12, N07BA, R03AC18, R03AC19, R03BB04, R03BB05, R03BB06, R03BB07, R03AL04, R03AL05, R03AK04
Alcohol consumption	ICD-10 in-hospital diagnosis codes: E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, R780, T51, X45, X65, Y15, Y90, Y91, Y573, Z502, Z714, Z721 Drug reimbursement ATC codes: N07BB01, N07BB03, N07BB04, N07BB05
Obesity	ICD-10 in-hospital diagnosis code: E66 CCAM codes: HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027
Coronary artery diseases	ICD-10 in-hospital diagnosis codes: I20, I21, I22, I23, I24, I25 ICD-10 LTD codes: I20, I21, I22, I23, I24, I25
Pulmonologist visits	Medical specialty code: 13
Drugs associated with sleep apnoea	
Anticonvulsants	Drug reimbursement ATC code: N03A
Gabapentinoids	Drug reimbursement ATC code: N02BF
Antidepressant	Drug reimbursement ATC codes: N06A, N06CA
Antipsychotics	Drug reimbursement ATC code: N05A

Baclofen	Drug reimbursement ATC code: M03BX01
Benzodiazepine and derivatives	Drug reimbursement ATC codes: N03AE, N05BA, N05CD, N05CF
Corticosteroids	Drug reimbursement ATC codes: H02A, H02B
Diuretics	Drug reimbursement ATC code: C03
Hormonal contraceptives	Drug reimbursement ATC code: G03A
Testosterone	Drug reimbursement ATC code: G03BA03
Montelukast	Drug reimbursement ATC codes: R03DC03, R03DC53
Opioids	Drug reimbursement ATC code: N02A
Opium alkaloids and derivatives	Drug reimbursement ATC code: R05DA

If one of the parameters was satisfied, the co-morbidity was considered to be present, unless otherwise specified.

* 27/06/2011: application of the decree withdrawing high blood pressure from LTD list

ICD-10: International Classification of Diseases, 10th revision.

LTD: Long-term disease.

ATC: Anatomical Therapeutic Chemical.

COPD: Chronic Obstructive Pulmonary Disease.

LABA: Long-acting β-agonist.

LAMA: Long-acting muscarinic antagonist.

ICS: Inhaled corticosteroid.

GHM: Groupe Homogène de Malades, i.e. hospital billing codes.

CCAM: Classification Commune des Actes Médicaux, i.e. common classification of medical procedures.

VTE: Venous Thromboembolic Events (i.e. Pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

NAFLD: Non-alcoholic fatty liver disease.

TIA: Transient ischaemic attack.

[a] Drugs associated with sleep apnoea as defined by Jullian-Desayes et al. study (1).

Table E. Characteristics of Patients, by Exposure Status, before weighting: Ticagrelor versus Clopidogrel

Characteristic	Ticagrelor users (n = 301,749)	Clopidogrel users (n = 160,886)	SMD (%)
Calendar year			
2012	3,057 (1.0)	14,170 (8.8)	
2013	15,373 (5.1)	19,231 (12.0)	
2014	19,024 (6.3)	16,797 (10.4)	
2015	22,206 (7.4)	15,192 (9.4)	
2016	25,941 (8.6)	13,481 (8.4)	
2017	29,106 (9.6)	13,160 (8.2)	
2018	31,763 (10.5)	12,377 (7.7)	
2019	32,803 (10.9)	12,018 (7.5)	
2020	30,592 (10.1)	10,714 (6.7)	
2021	30,822 (10.2)	11,257 (7.0)	
2022	30,531 (10.1)	11,232 (7.0)	
2023	30,531 (10.1)	11,257 (7.0)	
Female	76,867 (25.5)	56,910 (35.4)	- 21.6
Age, years (mean ± SD)	63.1 ± 12.4	72.6 ± 13.0	- 74.3
Severe obesity	30,407 (10.1)	19,633 (12.2)	- 6.8
Smoking status	51,578 (17.1)	27,021 (16.8)	0.8
Alcohol consumption	12,203 (4.0)	6,326 (3.9)	0.6
Cardiovascular history			
Hypertension	157,567 (52.2)	121,869 (75.7)	- 50.6
Heart failure	4,475 (1.5)	14,078 (8.8)	- 33.4
Arrythmia	12,975 (4.3)	34,285 (21.3)	- 52.6
Transient ischaemic attack	1,873 (0.6)	2,266 (1.4)	- 7.9
Stroke	6,031 (2.0)	9,820 (6.1)	- 20.9
Comorbidities			
COPD	8,558 (2.8)	6,351 (3.9)	- 6.1
Dialysis	821 (0.3)	1,802 (1.1)	- 10.2
Diabetes	51,534 (17.1)	41,590 (25.9)	- 21.5
VTE	3,758 (1.2)	5,752 (3.6)	- 15.2
Dyslipidaemia	117,123 (38.8)	89,110 (55.4)	- 33.7
NAFLD	1,919 (0.6)	1,152 (0.7)	- 1.0
Pulmonary hypertension	416 (0.1)	1,536 (1.0)	- 11.1
Cancers	34,037 (11.3)	29,480 (18.3)	- 19.9
Drugs associated with sleep apnoea [a]			
Anticonvulsants	1,253 (0.4)	1,324 (0.8)	- 5.2
Gabapentinoids	5,928 (2.0)	4,405 (2.7)	- 5.1
Antidepressants	8,998 (3.0)	6,765 (4.2)	- 6.6
Antipsychotics	1,784 (0.6)	1,820 (1.1)	- 5.8
Baclofen	691 (0.2)	346 (0.2)	0.3
Benzodiazepines	15,170 (5.0)	10,199 (6.3)	- 5.7
Corticosteroids	28,270 (9.4)	17,002 (10.6)	- 4.0
Diuretics	8,532 (2.8)	10,373 (6.4)	- 17.3
Contraceptives	1,015 (0.3)	284 (0.2)	3.2
Testosterone	130 (0.0)	82 (0.1)	- 0.4

Montelukast	1,799 (0.6)	1,305 (0.8)	- 2.6
Opioids	25,847 (8.6)	15,314 (9.5)	- 3.3
Opium derivatives	17,954 (5.9)	11,064 (6.9)	- 3.8
Number of hospitalizations [b]			
0	1,203 (0.4)	891 (0.6)	- 2.3
1	240,127 (79.6)	108,206 (67.3)	28.2
2	44,176 (14.6)	32,310 (20.1)	- 14.4
3	10,363 (3.4)	10,953 (6.8)	- 15.3
≥ 4	5,880 (1.9)	8,526 (5.3)	- 18.0
Number of pulmonologist visits [b]			
0	284,660 (94.3)	146,539 (91.1)	12.5
1	7,138 (2.4)	5,482 (3.4)	- 6.2
2-6	5,396 (1.8)	4,575 (2.8)	- 7.0
7-11	1,396 (0.5)	1,145 (0.7)	- 3.3
≥ 12	3,159 (1.0)	3,145 (2.0)	- 7.5

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

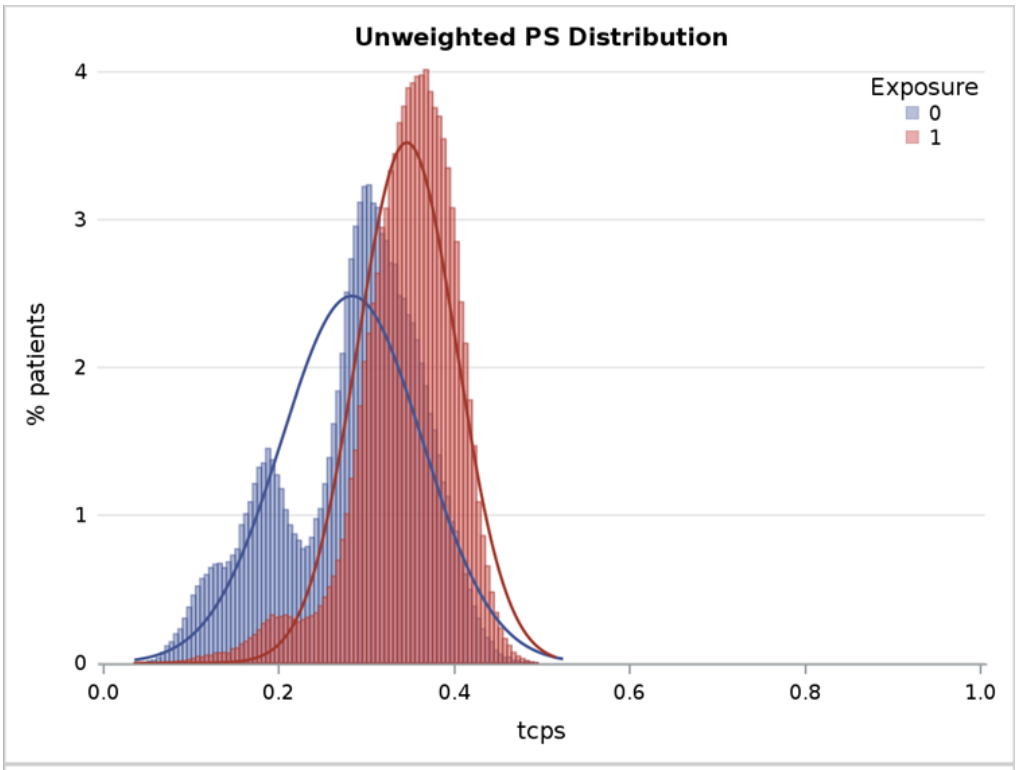
Table F. Characteristics of Patients, by Exposure Status, before weighting: Ticagrelor versus Prasugrel

Characteristic	Ticagrelor users (n = 301,505)	Clopidogrel users (n = 62,387)	SMD (%)
Calendar year			
2012	3,057 (1.0)	7,681 (12.3)	
2013	15,373 (5.1)	9,637 (15.4)	
2014	19,024 (6.3)	8,441 (13.5)	
2015	22,207 (7.4)	7,052 (11.3)	
2016	25,942 (8.6)	6,050 (9.7)	
2017	29,097 (9.7)	4,143 (6.6)	
2018	31,673 (10.5)	2,734 (4.4)	
2019	32,700 (10.8)	2,232 (3.6)	
2020	30,582 (10.1)	3,005 (4.8)	
2021	30,823 (10.2)	4,043 (6.5)	
2022	30,513 (10.1)	3,662 (5.9)	
2023	30,514 (10.1)	3,707 (5.9)	
Female	76,675 (25.4)	9,880 (15.8)	23.9
Age, years (mean ± SD)	63.1 ± 12.4	58.0 ± 10.2	44.7
Severe obesity	30,346 (10.1)	4,848 (7.8)	8.1
Smoking status	51,519 (17.1)	9,068 (14.5)	7.0
Alcohol consumption	12,188 (4.0)	2,317 (3.7)	1.7
Cardiovascular history			
Hypertension	157,322 (52.2)	26,479 (42.4)	19.6
Heart failure	4,374 (1.5)	469 (0.8)	6.7
Arrythmia	12,851 (4.3)	1,515 (2.4)	10.2
Transient ischaemic attack	1,835 (0.6)	165 (0.3)	5.2
Stroke	5,864 (1.9)	459 (0.7)	10.5
Comorbidities			
COPD	8,551 (2.8)	1,738 (2.8)	0.3
Dialysis	800 (0.3)	94 (0.2)	2.5
Diabetes	51,444 (17.1)	9,541 (15.3)	4.8
VTE	3,717 (1.2)	462 (0.7)	5.0
Dyslipidaemia	116,933 (38.8)	20,542 (32.9)	12.2
NAFLD	1,913 (0.6)	332 (0.5)	1.3
Pulmonary hypertension	381 (0.1)	42 (0.1)	1.9
Cancers	33,956 (11.3)	4364 (7)	14.9
Drugs associated with sleep apnoea [a]			
Anticonvulsants	1,251 (0.4)	317 (0.5)	- 1.4
Gabapentinoids	5,907 (2.0)	1,002 (1.6)	2.7
Antidepressants	8,985 (3.0)	1,864 (3.0)	0.0
Antipsychotics	1,783 (0.6)	402 (0.6)	- 0.7
Baclofen	689 (0.2)	187 (0.3)	- 1.4
Benzodiazepines	15,150 (5.0)	3,240 (5.2)	- 0.8
Corticosteroids	28,241 (9.4)	5,909 (9.5)	- 0.4
Diuretics	8,512 (2.8)	1,365 (2.2)	4.1
Contraceptives	1,012 (0.3)	255 (0.4)	- 1.2
Testosterone	125 (0.0)	38 (0.1)	- 0.9

Montelukast	1,798 (0.6)	365 (0.6)	0.1
Opioids	25,822 (8.6)	5,452 (8.7)	- 0.6
Opium derivatives	17,929 (5.9)	3,838 (6.2)	- 0.9
Number of hospitalizations [b]			
0	1,203 (0.4)	351 (0.6)	- 2.4
1	240,050 (79.6)	51,470 (82.5)	- 7.4
2	44,103 (14.6)	8,164 (13.1)	4.5
3	10,323 (3.4)	1,592 (2.6)	5.1
≥ 4	5,826 (1.9)	810 (1.3)	5.0
Number of pulmonologist visits [b]			
0	284,446 (94.3)	59,243 (95.0)	- 2.7
1	7,122 (2.4)	1,319 (2.1)	1.7
2-6	5,388 (1.8)	981 (1.6)	1.7
7-11	1,393 (0.5)	254 (0.4)	0.8
≥ 12	3,156 (1.0)	590 (0.9)	1.0

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

A



B

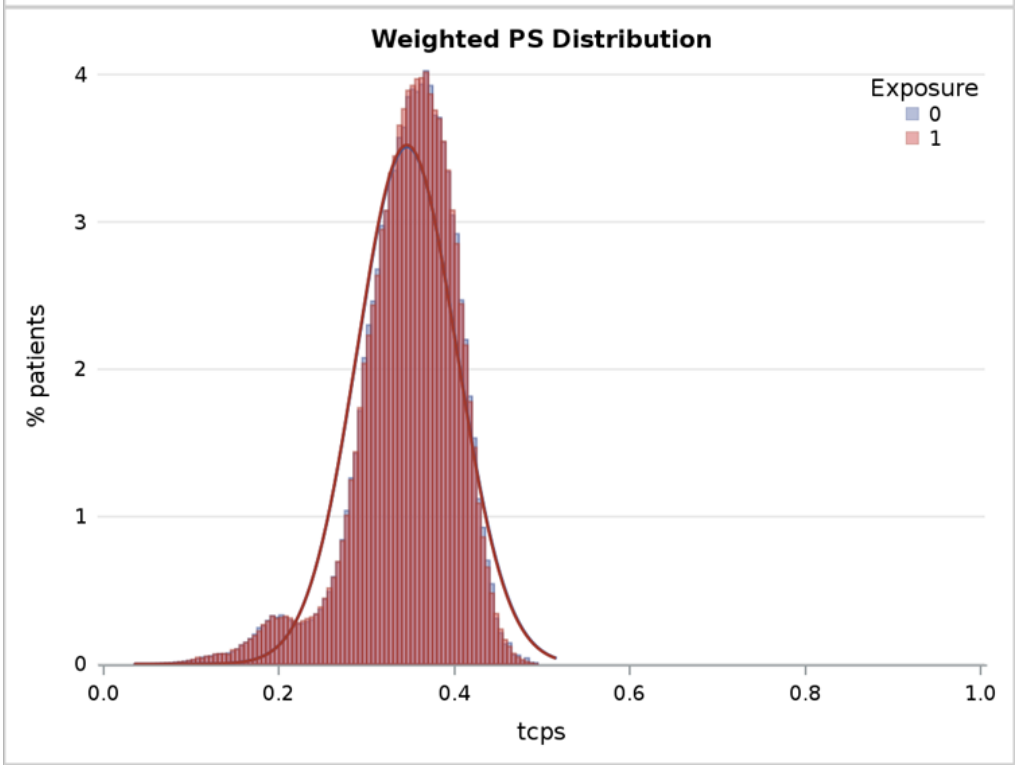
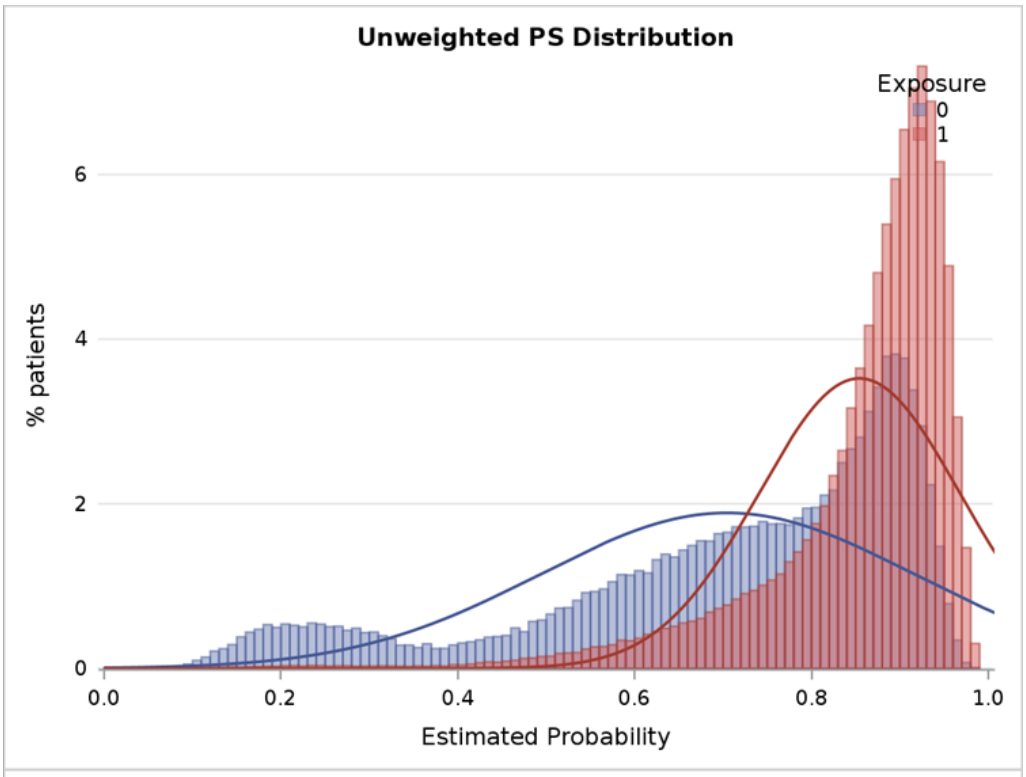


Figure C. Ticagrelor and clopidogrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: clopidogrel, exposure 1: ticagrelor.

A



B

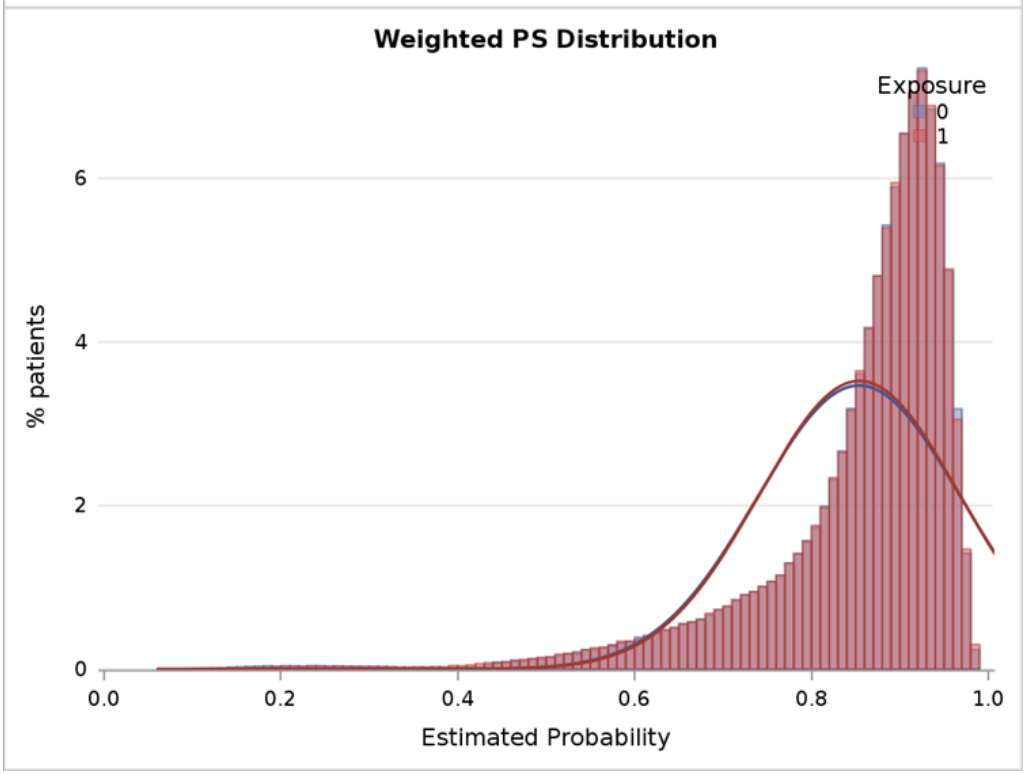


Figure D. Ticagrelor and prasugrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: prasugrel, exposure 1: ticagrelor.

Table G. Characteristics of Patients, by Exposure Status, before weighting: Prasugrel versus Clopidogrel

Characteristic	Prasugrel users (n = 62,385)	Clopidogrel users (n = 160,886)	SMD (%)
Calendar year	7,681 (12.3)	14,170 (8.8)	
2012	9,637 (15.4)	19,231 (12.0)	
2013	8,441 (13.5)	16,797 (10.4)	
2014	7,051 (11.3)	15,192 (9.4)	
2015	6,049 (9.7)	13,481 (8.4)	
2016	4,143 (6.6)	13,160 (8.2)	
2017	2,734 (4.4)	12,377 (7.7)	
2018	2,232 (3.6)	12,018 (7.5)	
2019	3,005 (4.8)	10,714 (6.7)	
2020	4,043 (6.5)	11,257 (7.0)	
2021	3,662 (5.9)	11,232 (7.0)	
2022	3,707 (5.9)	11,257 (7.0)	
2023	7,681 (12.3)	14,170 (8.8)	
Female	9,880 (15.8)	56,910 (35.4)	- 45.9
Age, years (mean ± SD)	58.0 ± 10.2	72.6 ± 13.0	- 124.6
Severe obesity	4,848 (7.8)	19,633 (12.2)	- 14.8
Smoking status	9,068 (14.5)	27,021 (16.8)	- 6.2
Alcohol consumption	2,317 (3.7)	6,326 (3.9)	- 1.1
Cardiovascular history			
Hypertension	26,479 (42.4)	121,869 (75.7)	- 72.0
Heart failure	469 (0.8)	14,078 (8.8)	- 38.3
Arrythmia	1,515 (2.4)	34,285 (21.3)	- 61.0
Transient ischaemic attack	165 (0.3)	2,266 (1.4)	- 12.6
Stroke	459 (0.7)	9,820 (6.1)	- 29.9
Comorbidities			
COPD	1,738 (2.8)	6,351 (3.9)	- 6.4
Dialysis	94 (0.2)	1,802 (1.1)	- 12.2
Diabetes	9,541 (15.3)	41,590 (25.9)	- 26.3
VTE	462 (0.7)	5,752 (3.6)	- 19.6
Dyslipidaemia	20,542 (32.9)	89,110 (55.4)	- 46.4
NAFLD	332 (0.5)	1,152 (0.7)	- 2.3
Pulmonary hypertension	42 (0.1)	1,536 (1.0)	- 12.5
Cancers	4,364 (7.0)	29,480 (18.3)	- 34.6
Drugs associated with sleep apnoea [a]			
Anticonvulsants	317 (0.5)	1,324 (0.8)	- 3.9
Gabapentinoids	1,002 (1.6)	4,405 (2.7)	- 7.8
Antidepressants	1,864 (3.0)	6,765 (4.2)	- 6.5
Antipsychotics	402 (0.6)	1,820 (1.1)	- 5.2
Baclofen	187 (0.3)	346 (0.2)	1.7
Benzodiazepines	3,239 (5.2)	10,199 (6.3)	- 4.9
Corticosteroids	5,909 (9.5)	17,002 (10.6)	- 3.7
Diuretics	1,365 (2.2)	10,373 (6.4)	- 21.1
Contraceptives	255 (0.4)	284 (0.2)	4.3
Testosterone	38 (0.1)	82 (0.1)	0.4

Montelukast	365 (0.6)	1,305 (0.8)	- 2.7
Opioids	5,451 (8.7)	15,314 (9.5)	- 2.7
Opium derivatives	3,838 (6.2)	11,064 (6.9)	- 2.9
Number of hospitalizations [b]			
0	351 (0.6)	891 (0.6)	0.1
1	51,468 (82.5)	108,206 (67.3)	35.7
2	8,164 (13.1)	32,310 (20.1)	- 18.9
3	1,592 (2.6)	10,953 (6.8)	- 20.3
≥ 4	810 (1.3)	8,526 (5.3)	- 22.5
Number of pulmonologist visits [b]			
0	59,241 (95)	146,539 (91.1)	15.3
1	1,319 (2.1)	5,482 (3.4)	- 7.9
2-6	981 (1.6)	4,575 (2.8)	- 8.7
7-11	254 (0.4)	1,145 (0.7)	- 4.1
≥ 12	590 (0.9)	3,145 (2.0)	- 8.4

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

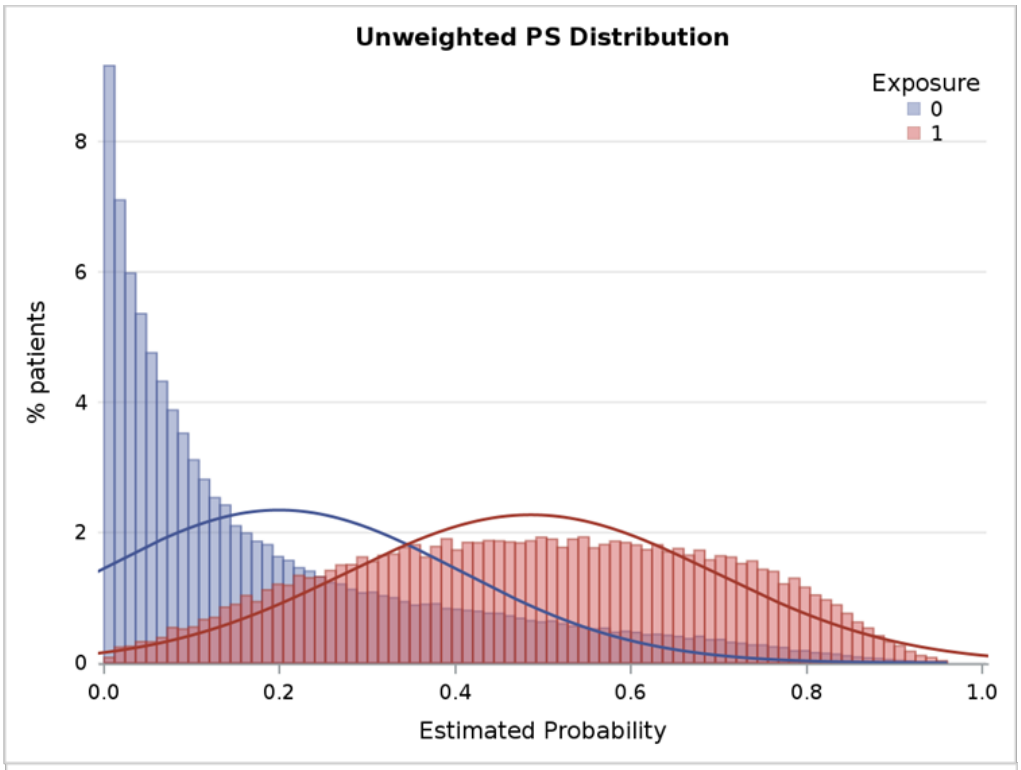
Table H. Characteristics of Patients, by Exposure Status, after weighting: Prasugrel versus Clopidogrel

Characteristic	Prasugrel users (n = 62,385)	Clopidogrel users (n = 160,886)	SMD (%)
Calendar year	7,681 (12.3)	14,170 (8.8)	
2012	9,637 (15.4)	19,231 (12.0)	
2013	8,441 (13.5)	16,797 (10.4)	
2014	7,051 (11.3)	15,192 (9.4)	
2015	6,049 (9.7)	13,481 (8.4)	
2016	4,143 (6.6)	13,160 (8.2)	
2017	2,734 (4.4)	12,377 (7.7)	
2018	2,232 (3.6)	12,018 (7.5)	
2019	3,005 (4.8)	10,714 (6.7)	
2020	4,043 (6.5)	11,257 (7.0)	
2021	3,662 (5.9)	11,232 (7.0)	
2022	3,707 (5.9)	11,257 (7.0)	
2023	7,681 (12.3)	14,170 (8.8)	
Female	9,880 (15.8)	26,669 (16.6)	- 2.0
Age, years (mean ± SD)	58.0 ± 10.2	58.0 ± 11.4	0.1
Severe obesity	4,848 (7.8)	14,235 (8.8)	- 3.9
Smoking status	9,068 (14.5)	26,234 (16.3)	- 4.9
Alcohol consumption	2,317 (3.7)	6,853 (4.3)	- 2.8
Cardiovascular history			
Hypertension	26,479 (42.4)	71,000 (44.1)	- 3.4
Heart failure	469 (0.8)	1,004 (0.6)	1.5
Arrythmia	1,515 (2.4)	2,991 (1.9)	3.9
Transient ischaemic attack	165 (0.3)	462 (0.3)	- 0.4
Stroke	459 (0.7)	1,186 (0.7)	0.0
Comorbidities			
COPD	1,738 (2.8)	4,526 (2.8)	- 0.2
Dialysis	94 (0.2)	251 (0.2)	- 0.1
Diabetes	9,541 (15.3)	25,449 (15.8)	- 1.4
VTE	462 (0.7)	1,357 (0.8)	- 1.2
Dyslipidaemia	20,542 (32.9)	55,121 (34.3)	- 2.8
NAFLD	332 (0.5)	977 (0.6)	- 1.0
Pulmonary hypertension	42 (0.1)	101 (0.1)	0.2
Cancers	4,364 (7.0)	11,597 (7.2)	- 0.8
Drugs associated with sleep apnoea [a]			
Anticonvulsants	317 (0.5)	766 (0.5)	0.5
Gabapentinoids	1,002 (1.6)	2,698 (1.7)	- 0.6
Antidepressants	1,864 (3.0)	4,802 (3.0)	0.0
Antipsychotics	402 (0.6)	1,045 (0.6)	- 0.1
Baclofen	187 (0.3)	452 (0.3)	0.3
Benzodiazepines	3,239 (5.2)	8,492 (5.3)	- 0.4
Corticosteroids	5,909 (9.5)	15,174 (9.4)	0.1
Diuretics	1,365 (2.2)	3,538 (2.2)	- 0.1
Contraceptives	255 (0.4)	698 (0.4)	- 0.4
Testosterone	38 (0.1)	89 (0.1)	0.2

Montelukast	365 (0.6)	962 (0.6)	- 0.2
Opioids	5,451 (8.7)	14,008 (8.7)	0.1
Opium derivatives	3,838 (6.2)	9,808 (6.1)	0.2
Number of hospitalizations [b]			
0	351 (0.6)	1,137 (0.7)	- 1.8
1	51,468 (82.5)	131,523 (81.7)	2.0
2	8,164 (13.1)	21,828 (13.6)	- 1.4
3	1,592 (2.6)	4,289 (2.7)	- 0.7
≥ 4	810 (1.3)	2,109 (1.3)	- 0.1
Number of pulmonologist visits [b]			
0	59,241 (95.0)	152,056 (94.5)	2.0
1	1,319 (2.1)	3,732 (2.3)	- 1.4
2-6	981 (1.6)	2,798 (1.7)	- 1.3
7-11	254 (0.4)	715 (0.4)	- 0.6
≥ 12	590 (0.9)	1,585 (1.0)	- 0.4

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

A



B

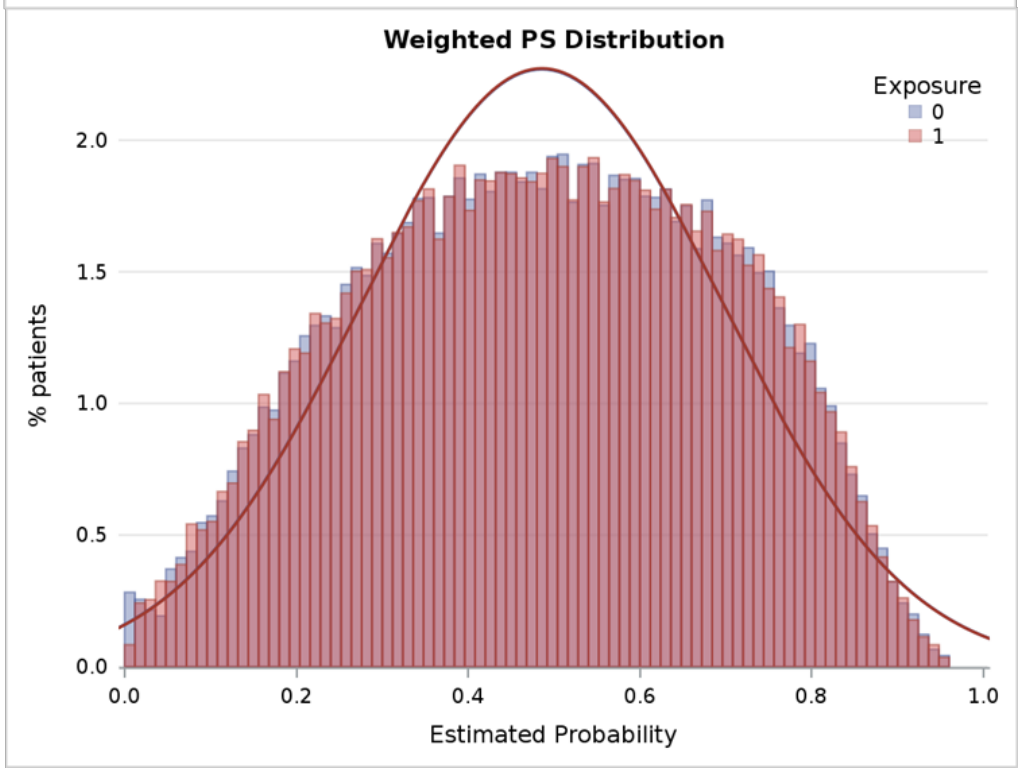


Figure E. Prasugrel and clopidogrel propensity score distribution pre- (A) and post- (B) weighting. Exposure 0: clopidogrel, exposure 1: prasugrel.

Table I. Characteristics of Patients, by Exposure Status, after matching: Prasugrel versus Clopidogrel

Characteristic	Prasugrel users (n = 50,148)	Clopidogrel users (n = 50,148)	SMD (%)
Calendar year			
2012	6,169 (12.3)	6,169 (12.3)	
2013	7,356 (14.7)	7,356 (14.7)	
2014	6,323 (12.6)	6,323 (12.6)	
2015	5,347 (10.7)	5,347 (10.7)	
2016	4,605 (9.2)	4,605 (9.2)	
2017	3,501 (7.0)	3,501 (7.0)	
2018	2,586 (5.2)	2,586 (5.2)	
2019	2,161 (4.3)	2,161 (4.3)	
2020	2,689 (5.4)	2,689 (5.4)	
2021	3,273 (6.5)	3,273 (6.5)	
2022	3,082 (6.1)	3,082 (6.1)	
2023	3,056 (6.1)	3,056 (6.1)	
Female	9,189 (18.3)	9,029 (18.0)	0.8
Age, years (mean ± SD)	60.2 ± 9.5	60.3 ± 10.8	- 0.6
Severe obesity	4,200 (8.4)	4,378 (8.7)	- 1.3
Smoking status	7,561 (15.1)	7,881 (15.7)	- 1.8
Alcohol consumption	1,951 (3.9)	2,145 (4.3)	- 2.0
Cardiovascular history			
Hypertension	24,204 (48.3)	24,997 (49.8)	- 3.2
Heart failure	461 (0.9)	387 (0.8)	1.6
Arrythmia	1,504 (3.0)	1,129 (2.3)	4.7
Transient ischaemic attack	160 (0.3)	160 (0.3)	0.0
Stroke	458 (0.9)	404 (0.8)	1.2
Comorbidities			
COPD	1,520 (3.0)	1,603 (3.2)	- 1.0
Dialysis	93 (0.2)	79 (0.2)	0.7
Diabetes	8,583 (17.1)	8,913 (17.8)	- 1.7
VTE	441 (0.9)	453 (0.9)	- 0.3
Dyslipidaemia	18,494 (36.9)	19,182 (38.3)	- 2.8
NAFLD	275 (0.5)	297 (0.6)	- 0.6
Pulmonary hypertension	41 (0.1)	30 (0.1)	0.8
Cancers	4,161 (8.3)	4,127 (8.2)	0.2
Drugs associated with sleep apnoea [a]			
Anticonvulsants	266 (0.5)	275 (0.5)	- 0.2
Gabapentinoids	885 (1.8)	880 (1.8)	0.1
Antidepressants	1,554 (3.1)	1,552 (3.1)	0.0
Antipsychotics	343 (0.7)	338 (0.7)	0.1
Baclofen	137 (0.3)	139 (0.3)	- 0.1
Benzodiazepines	2,705 (5.4)	2,748 (5.5)	- 0.4
Corticosteroids	4,832 (9.6)	4,883 (9.7)	- 0.3
Diuretics	1,299 (2.6)	1,299 (2.6)	0.0
Contraceptives	199 (0.4)	218 (0.4)	- 0.6
Testosterone	30 (0.1)	34 (0.1)	- 0.3

Montelukast	316 (0.6)	319 (0.6)	- 0.1
Opioids	4,421 (8.8)	4,457 (8.9)	- 0.3
Opium derivatives	3,163 (6.3)	3,298 (6.6)	- 1.1
Number of hospitalizations [b]			
0	322 (0.6)	359 (0.7)	- 0.9
1	40,445 (80.7)	40,238 (80.2)	1.0
2	7,129 (14.2)	7,262 (14.5)	- 0.8
3	1,469 (2.9)	1503 (3)	- 0.4
≥ 4	783 (1.6)	786 (1.6)	0.0
Number of pulmonologist visits [b]			
0	47,321 (94.4)	47,125 (94.0)	1.7
1	1,153 (2.3)	1,251 (2.5)	- 1.3
2-6	902 (1.8)	922 (1.8)	- 0.3
7-11	232 (0.5)	256 (0.5)	- 0.7
≥ 12	540 (1.1)	594 (1.2)	- 1.0

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

Table J. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: primary analysis for prasugrel versus clopidogrel

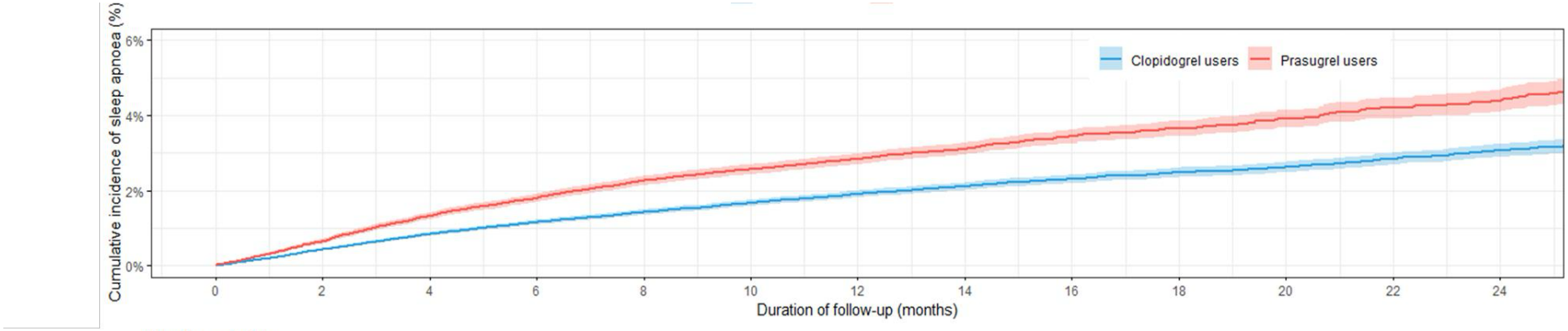
Exposure	No of patients	Events	Person-years	Incidence rate (95%CI)[a]	Hazard Ratio (95%CI)	p-value	NNH
Sleep apnoea main analysis (As-treated)							
Clopidogrel	160,886	3,237	130,090	24.9 (24.0 to 25.8)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	1,771	66,729	26.5 (25.3 to 27.8)	1.04 (0.98 to 1.11)	0.167	604
MACE main analysis (As-treated)							
Clopidogrel	160,886	38,985	105,046	371.1 (367.4 to 374.8)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	14,560	54,201	268.6 (264.3 to 273.0)	0.82 (0.81 to 0.84)	< 0.001	/

[a] Per 1000 person-years. MACE: major adverse cardiovascular events; CI: confidence interval; NNH: number of patients exposed for one year needed to harm.

Table K. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: sensitivity analyses for prasugrel versus clopidogrel

Exposure	No of patients	Events	Person-years	Incidence rate (95%CI)[a]	Hazard Ratio (95%CI)	p-value	NNH
Sleep apnoea: sensitivity analyses							
Modified intention to treat with a follow-up of one year							
Clopidogrel	160,886	3,998	141,946	28.2 (27.3 to 29.1)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	1,655	55,361	29.9 (28.5 to 31.4)	1.06 (1.00 to 1.12)	0.048	578
Modified intention to treat with a follow-up of two years							
Clopidogrel	160,886	5,883	264,952	22.2 (21.6 to 22.8)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	2,269	99,275	22.9 (21.9 to 23.8)	1.01 (0.97 to 1.07)	0.564	1,537
As-treated, post-matching on propensity score							
Clopidogrel	50,148	974	41,290	23.6 (22.1 to 25.1)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	1,420	53,057	26.8 (25.4 to 28.2)	1.09 (1.01 to 1.19)	0.033	315
As-treated, sensitive outcome definition							
Clopidogrel	160,886	6,722	118,123	56.9 (55.6 to 58.3)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	3,648	61,048	59.8 (57.8 to 61.7)	1.03 (0.99 to 1.07)	0.205	351
MACE: sensitivity analyses							
Modified intention to treat with a follow-up of one year							
Clopidogrel	160,886	42,941	115,556	371.6 (368.1 to 375.1)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	14,371	46,555	308.7 (303.7 to 313.8)	0.84 (0.83 to 0.86)	< 0.001	/
Modified intention to treat with a follow-up of two years							
Clopidogrel	160,886	49,117	208,647	235.4 (233.3 to 237.5)	1.00 (reference)	Reference	Reference
Prasugrel	62,385	15,892	81,437	195.1 (192.1 to 198.2)	0.82 (0.81 to 0.83)	< 0.001	/
As-treated, post-matching on propensity score							
Clopidogrel	50,148	12,380	33,266	372.2 (365.6 to 378.8)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	11,959	42,921	278.6 (273.7 to 283.7)	0.83 (0.81 to 0.86)	< 0.001	/

[a] Per 1000 person-years. MACE: major adverse cardiovascular events; CI: confidence interval; NNH: number of patients exposed for one year needed to harm.



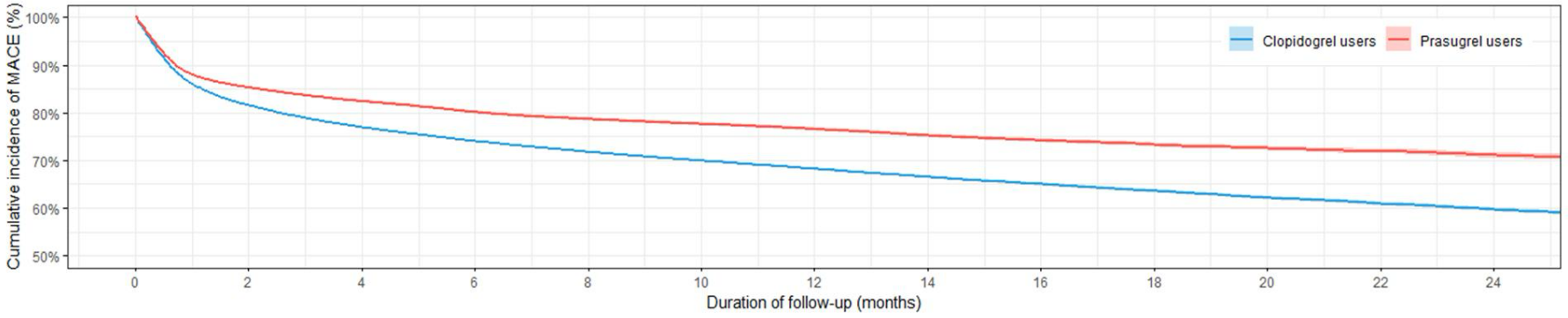
Number at risk

Clopidogrel users	160886	121401	93048	77776	64397	55887	47110	32167	24633	20184	17070	14714	12859
Prasugrel users	62385	58637	53684	49864	45969	42666	36899	18720	11727	8378	6336	5024	4107

Cumulative number of events

Clopidogrel users	13	639	1072	1343	1534	1683	1810	1890	1947	1986	2013	2050	2081
Prasugrel users	9	392	774	1029	1257	1392	1510	1586	1636	1658	1677	1694	1703

Figure F. Cumulative incidence curves of sleep apnoea for prasugrel versus clopidogrel



Number at risk

Clopidogrel users	160886	102268	76703	63151	51445	44352	36827	24251	18381	14952	12550	10788	9413
Prasugrel users	62385	50610	45366	41370	37715	34762	29601	13842	8290	5768	4328	3427	2780

Cumulative number of events

Clopidogrel users	38	28980	34122	36833	38596	39846	40863	41609	42091	42461	42771	43007	43209
Prasugrel users	7	9120	10789	11999	12727	13212	13669	14027	14173	14258	14308	14341	14378

Figure G. Kaplan-Meier survival curves of major adverse cardiovascular events (MACE) for prasugrel use versus clopidogrel use.

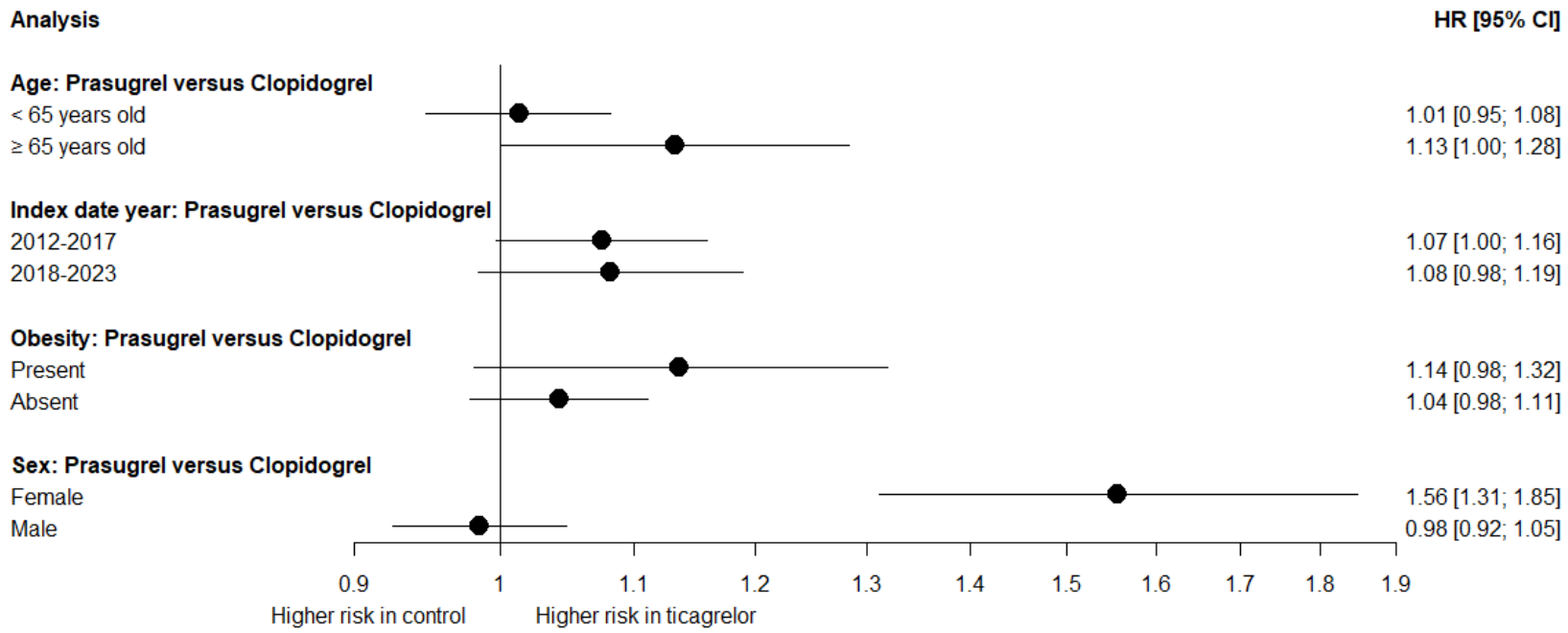


Figure H. Forest-plot for subgroup analyses displaying hazard ratios for association between prasugrel use and clopidogrel use, and risk of sleep apnoea, and major adverse cardiovascular events (MACE).

Table L. Characteristics of Patients, by Exposure Status, after matching: Ticagrelor versus Clopidogrel

Characteristic	Ticagrelor users (n = 114,729)	Clopidogrel users (n = 114,729)	SMD (%)
Calendar year			
2012	3,057 (2.7)	3,057 (2.7)	
2013	11,776 (10.3)	11,776 (10.3)	
2014	11,432 (10.0)	11,432 (10.0)	
2015	11,055 (9.6)	11,055 (9.6)	
2016	10,402 (9.1)	10,402 (9.1)	
2017	10,636 (9.3)	10,636 (9.3)	
2018	10,126 (8.8)	10,126 (8.8)	
2019	9,829 (8.6)	9,829 (8.6)	
2020	8,823 (7.7)	8,823 (7.7)	
2021	9,198 (8.0)	9,198 (8.0)	
2022	9,233 (8.0)	9,233 (8.0)	
2023	9,162 (8.0)	9,162 (8.0)	
Female	36,836 (32.1)	36,942 (32.2)	- 0.2
Age, years (mean ± SD)	69.4 ± 12.1	69.8 ± 12.9	- 2.9
Severe obesity	13,226 (11.5)	13,233 (11.5)	0.0
Smoking status	18,821 (16.4)	18,830 (16.4)	0.0
Alcohol consumption	4,591 (4.0)	4,577 (4.0)	0.1
Cardiovascular history			
Hypertension	79,172 (69.0)	79,839 (69.6)	- 1.3
Heart failure	3,975 (3.5)	4,047 (3.5)	- 0.3
Arrythmia	12,043 (10.5)	11,684 (10.2)	1.0
Transient ischaemic attack	1,164 (1.0)	1,111 (1.0)	0.5
Stroke	4,527 (3.9)	4,452 (3.9)	0.3
Comorbidities			
COPD	4,001 (3.5)	4,113 (3.6)	- 0.5
Dialysis	630 (0.5)	700 (0.6)	- 0.8
Diabetes	26,691 (23.3)	26,837 (23.4)	- 0.3
VTE	2,759 (2.4)	2,718 (2.4)	0.2
Dyslipidaemia	58,489 (51.0)	58,884 (51.3)	- 0.7
NAFLD	828 (0.7)	818 (0.7)	0.1
Pulmonary hypertension	373 (0.3)	415 (0.4)	- 0.6
Cancers	18,870 (16.4)	18,912 (16.5)	- 0.1
Drugs associated with sleep apnoea [a]			
Anticonvulsants	679 (0.6)	656 (0.6)	0.3
Gabapentinoids	2,842 (2.5)	2,777 (2.4)	0.4
Antidepressants	4,121 (3.6)	4,085 (3.6)	0.2
Antipsychotics	904 (0.8)	880 (0.8)	0.2
Baclofen	267 (0.2)	256 (0.2)	0.2
Benzodiazepines	6,483 (5.7)	6,439 (5.6)	0.2
Corticosteroids	11,293 (9.8)	11,274 (9.8)	0.1
Diuretics	5,526 (4.8)	5,443 (4.7)	0.3
Contraceptives	265 (0.2)	253 (0.2)	0.2
Testosterone	53 (0)	59 (0.1)	- 0.2

Montelukast	873 (0.8)	835 (0.7)	0.4
Opioids	10,117 (8.8)	10,219 (8.9)	- 0.3
Opium derivatives	7,358 (6.4)	7,430 (6.5)	- 0.3
Number of hospitalizations [b]			
0	645 (0.6)	662 (0.6)	- 0.2
1	83,150 (72.5)	83,168 (72.5)	0.0
2	20,882 (18.2)	20,847 (18.2)	0.1
3	6,094 (5.3)	6,046 (5.3)	0.2
≥ 4	3,958 (3.4)	4,006 (3.5)	- 0.2
Number of pulmonologist visits [b]			
0	105,927 (92.3)	105,857 (92.3)	0.2
1	3,435 (3.0)	3,429 (3.0)	0.0
2-6	2,827 (2.5)	2,888 (2.5)	- 0.3
7-11	689 (0.6)	715 (0.6)	- 0.3
≥ 12	1,851 (1.6)	1,840 (1.6)	0.1

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

Table M. Characteristics of Patients, by Exposure Status, before and after matching: Ticagrelor versus Prasugrel

Characteristic	Ticagrelor users (n = 57,439)	Prasugrel users (n =57,439)	SMD (%)
Calendar year			
2012	2,744 (4.8)	2,744 (4.8)	
2013	9,636 (16.8)	9,636 (16.8)	
2014	8,441 (14.7)	8,441 (14.7)	
2015	7,049 (12.3)	7,049 (12.3)	
2016	6,050 (10.5)	6,050 (10.5)	
2017	4,143 (7.2)	4,143 (7.2)	
2018	2,734 (4.8)	2,734 (4.8)	
2019	2,232 (3.9)	2,232 (3.9)	
2020	3,002 (5.2)	3,002 (5.2)	
2021	4,042 (7.0)	4,042 (7.0)	
2022	3,662 (6.4)	3,662 (6.4)	
2023	3,704 (6.4)	3,704 (6.4)	
Female	8,826 (15.4)	9,330 (16.2)	- 2.4
Age, years (mean ± SD)	58.6 ± 11.2	58.2 ± 10.2	2.9
Severe obesity	4,649 (8.1)	4,647 (8.1)	0.0
Smoking status	8,653 (15.1)	8,616 (15.0)	0.2
Alcohol consumption	2,221 (3.9)	2,215 (3.9)	0.1
Cardiovascular history			
Hypertension	24,775 (43.1)	24,497 (42.6)	1.0
Heart failure	361 (0.6)	430 (0.7)	- 1.5
Arrythmia	1,294 (2.3)	1,460 (2.5)	- 1.9
Transient ischaemic attack	137 (0.2)	164 (0.3)	- 0.9
Stroke	372 (0.6)	445 (0.8)	- 1.5
Comorbidities			
COPD	1,586 (2.8)	1,573 (2.7)	0.1
Dialysis	83 (0.1)	88 (0.2)	- 0.2
Diabetes	8,764 (15.3)	8,743 (15.2)	0.1
VTE	413 (0.7)	444 (0.8)	- 0.6
Dyslipidaemia	19,194 (33.4)	18,961 (33)	0.9
NAFLD	308 (0.5)	315 (0.5)	- 0.2
Pulmonary hypertension	32 (0.1)	39 (0.1)	- 0.5
Cancers	4,081 (7.1)	4,204 (7.3)	- 0.8
Drugs associated with sleep apnoea [a]			
Anticonvulsants	246 (0.4)	252 (0.4)	- 0.2
Gabapentinoids	943 (1.6)	914 (1.6)	0.4
Antidepressants	1,666 (2.9)	1,694 (2.9)	- 0.3
Antipsychotics	372 (0.6)	362 (0.6)	0.2
Baclofen	173 (0.3)	168 (0.3)	0.2
Benzodiazepines	3,018 (5.3)	2,931 (5.1)	0.7
Corticosteroids	5,337 (9.3)	5,345 (9.3)	0.0
Diuretics	1,253 (2.2)	1,269 (2.2)	- 0.2
Contraceptives	226 (0.4)	230 (0.4)	- 0.1
Testosterone	27 (0.0)	31 (0.1)	- 0.3

Montelukast	332 (0.6)	338 (0.6)	- 0.1
Opioids	4,965 (8.6)	4,988 (8.7)	- 0.1
Opium derivatives	3,478 (6.1)	3,450 (6.0)	0.2
Number of hospitalizations [b]			
0	292 (0.5)	329 (0.6)	- 0.9
1	47,245 (82.3)	47,307 (82.4)	- 0.3
2	7,684 (13.4)	7,554 (13.2)	0.7
3	1,482 (2.6)	1,502 (2.6)	- 0.2
≥ 4	736 (1.3)	747 (1.3)	- 0.2
Number of pulmonologist visits [b]			
0	54,574 (95.0)	54,555 (95.0)	0.2
1	1,202 (2.1)	1,207 (2.1)	- 0.1
2-6	913 (1.6)	912 (1.6)	0.0
7-11	226 (0.4)	232 (0.4)	- 0.2
≥ 12	524 (0.9)	533 (0.9)	- 0.2

Characteristics are measured any time before index date unless otherwise specified.
Data are given as n (%) unless otherwise specified.
SMD: Standardized Mean Differences.
[a] Drugs associated with sleep apnoea as defined by the review of Jullian-Desayes *et al.*(1).
[b] Measured in the year before index date.
COPD: Chronic Obstructive Pulmonary Disease.
VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).
NAFLD: Non-alcoholic fatty liver diseases.

Table N. Incidence rates, hazard ratios and number needed to harm for sleep apnoea and MACE: sensitivity analyses after matching

Exposure	No of patients	Events	Person-years	Incidence rate (95%CI)[a]	Hazard Ratio (95%CI)	p-value	NNH
Sleep apnoea: sensitivity analyses							
Modified intention to treat with a follow-up of one year							
Clopidogrel	114,729	2,237	101,300	22.1 (21.2 to 23.0)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	2,698	96,259	28.0 (27.0 to 29.1)	1.26 (1.19 to 1.33)	< 0.001	168
Prasugrel	57,439	1,553	50,905	30.5 (29.0) to 32.1)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	1,601	50,004	32.0 (30.5 to 33.6)	1.05 (0.98 to 1.12)	0.193	662
Clopidogrel	50,148	1,184	44,498	26.6 (25.1 to 28.2)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	1,332	44,309	30.1 (28.5 to 31.7)	1.13 (1.04 to 1.22)	0.003	290
Modified intention to treat with a follow-up of two years							
Clopidogrel	114,729	3,353	187,012	17.9 (17.3 to 18.5)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	3,596	170,943	21.0 (20.4 to 21.7)	1.15 (1.10 to 1.21)	< 0.001	322
Prasugrel	57,439	2,126	91,260	23.3 (22.3 to 24.3)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	2,163	90,258	24.0 (23.0 to 25.0)	1.03 (0.97 to 1.09)	0.334	1,496
Clopidogrel	50,148	1,765	83,364	21.2 (20.2 to 22.2)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	1,812	79,283	22.9 (21.8 to 23.9)	1.06 (0.99 to 1.13)	0.077	594
As-treated, sensitive outcome definition							
Clopidogrel	114,729	3,628	85,313	42.5 (41.2 to 43.9)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	4,876	94,433	51.6 (50.2 to 53.1)	1.13 (1.08 to 1.18)	< 0.001	110
Prasugrel	57,439	3,394	55,487	61.2 (59.1 to 63.3)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	3,238	52,089	62.2 (60.0 to 64.3)	1.00 (0.95 to 1.05)	0.975	1,005
Clopidogrel	50,148	1,996	37,832	52.8 (50.5 to 55.1)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	2,884	48,284	59.7 (57.6 to 62.0)	1.09 (1.03 to 1.15	0.004	143
MACE: sensitivity analyses							
Modified intention to treat with a follow-up of one year							
Clopidogrel	114,729	33,894	81,828	414.2 (409.8 to 418.6)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	28,635	80,116	357.4 (353.3 to 361.6)	0.85 (0.84 to 0.86)	< 0.001	/
Prasugrel	57,439	13,209	42,811	308.5 (303.3 to 313.9)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	13,195	42,092	313.5 (308.2 to 318.9)	1.01 (0.98 to 1.03)	0.593	203
Clopidogrel	50,148	13,658	36,111	378.2 (371.9 to 384.6)	1.00 (reference)	Reference	Reference

Prasugrel	50,148	11,809	37,098	318.3 (312.6 to 324.1)	0.85 (0.83 to 0.81)	< 0.001	/
Modified intention to treat with a follow-up of two years							
Clopidogrel	114,729	40,334	145,242	277.7 (275.0 to 280.4)	1.00 (reference)	Reference	Reference
Ticagrelor	114,729	32,680	138,224	236.4 (233.9 to 239.0)	0.82 (0.81 to 0.84)	< 0.001	/
Prasugrel	57,439	14,599	74,896	194.9 (191.8 to 198.1)	1.00 (reference)	Reference	Reference
Ticagrelor	57,439	14,788	74,082	199.6 (196.4 to 202.9)	1.02 (1.00 to 1.04)	0.086	213
Clopidogrel	50,148	15,716	65,317	240.6 (236.9 to 244.4)	1.00 (reference)	Reference	Reference
Prasugrel	50,148	13,095	64,682	202.5 (199.0 to 205.9)	0.83 (0.81 to 0.85)	< 0.001	/

[a] Per 1000 person-years. MACE: major adverse cardiovascular events; CI: confidence interval; NNH: number of patients exposed for one year needed to harm.

5. Use of Bisphosphonates and the Risk of Skin Ulcer: A National Cohort Study Using Data from the French Health Care Claims Database

ELECTRONIC SUPPLEMENTARY MATERIAL

Article Title: Use of Bisphosphonates and the Risk of skin Ulcer: a National Cohort Study using data from the French healthcare claims database

Running Title: Association between skin ulcer and bisphosphonates in the French population

Journal: Drug Safety

Authors:

Clément Jambon-Barbara [1], Claire Bernardeau [1], Julien Bezin [2,3], Matthieu Roustit [4,5], Sophie Blaise [4,6], Jean-Luc Cracowski [1,4], Charles Khouri [1,4,5].

[1] Pharmacovigilance Department, Grenoble Alpes University Hospital, F-38043 Grenoble, France.

[2] Univ. Bordeaux, INSERM, BPH, team AHeaD, U1219, F-33000 Bordeaux, France

[3] CHU de Bordeaux, Clinical Pharmacology Unit, F-33000 Bordeaux, France

[4] Univ. Grenoble Alpes, Inserm U1300, HP2, F-38000, Grenoble, France.

[5] Univ. Grenoble Alpes, Inserm CIC1406, Grenoble Alpes University Hospital, F-38000, Grenoble, France.

[6] Univ. Grenoble Alpes, Department of Vascular Medicine, Grenoble Alpes University Hospital, F-38000 Grenoble, France.

Corresponding author:

Charles Khouri

Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France

Telephone: +33 4 76 76 51 45

E-mail: ckhouri@chu-grenoble.fr

Table S1. List of variables used for outcome, exposure and matching identification

Variables of interest: matching confounders and exclusion criteria	
Sex	ben_sex_cod in table EB_PRS_F of EGB
Age	ben_ama_cod in table EB_PRS_F of EGB
Peripheral vascular disease	ICD-10 diagnosis codes: I73, I87
Urinary incontinence	ICD-10 diagnosis codes: N39.3, N39.4, R32, F98.0
Faecal incontinence	ICD-10 diagnosis codes: R15, F98.1
Number of hospitalizations	exe_soi_dtd in table T_MCOaaB of PMSI
Diabetes	ICD-10 diagnosis codes: E10, E11, E12, E13, E14 ICD-10 diagnosis codes for complications: H28.0, H36.0, M14.2, G59.0, G63.2, G99.0, I79.2, M14.6 ALD code: 8 Drug reimbursement data: ATC codes A10 (excluding A10BX06)
Thrombosis	ICD-10 diagnosis codes: I74, I82
High blood pressure	ICD-10 diagnosis codes : I10 (primary), I15 (secondary) Drug reimbursement data: ATC codes C02AB, C02AC, C02CA, C02DC, C03, C07, C08, C09
Hyperlipidaemia	ICD-10 diagnosis codes: E78 Drug reimbursement data: ATC codes C10
Smoking status	ICD-10 diagnosis codes: Z71.6, F17, T65.2, Z72.0 Drug reimbursement data: ATC codes N06AX12, N07BA since 2014 ICD-10 diagnosis codes: I73.1, J41, J42, J43, J44, T65.2 and a drug reimbursement for ATC codes: R03AC18, R03AC19, R03BB04, R03BB05, R03BB06, R03BB07, R03AL04, R03AL05, R03AK04 since 2014 Reimbursement of nicotine replacement therapy or smoking cessation consultation since 2006
Obesity	ICD-10 diagnosis codes: E66 (excluding codes E6603, E6613, E6683, E6693) Bariatric surgery CCAM codes: HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027
Corticoid use	Drug reimbursement data: ATC codes H02A, H02B
Cancers	ICD-10 diagnosis codes: C, D0 ALD code: 30

	Drug reimbursement data: ATC codes G03HA01, L01CD04, L01XX11, L02AA01, L02AA04, L02AE01, L02AE02, L02AE03, L02AE04, L02AE05, L02BB01, L02BB02, L02BB03, L02BB04, L02BX02, L02BX03, V10BX01, V10XX
Fracture	ICD-10 diagnosis codes: M84, S02, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M484, M907, M966, P130, P134, T142, T902, T911, T912, T921, T922, T931, T932, Z094, Z470, Z544
Date of death	ben_dcd_dte in table EB_PRS_F of EGB
Exposure	
Bisphosphonates	Drug reimbursement data: ATC codes M05BA, M05BB Exclusion of non-oral bisphosphonates: "SOLUTION POUR PERFUSION", "SOLUTION A DILUER POUR PERFUSION", "SOLUTION INJECTABLE" from variable pha_frc_lib in table IR_PHA_R of references
Outcome	
Wound dressing	LPP codes: Supplementary table S2.
Use of anti-bedsore mattress, cushion	LPP codes: Supplementary table S3.
Use of compression bandage	LPP codes: Supplementary table S4.
Hospitalization for orthopaedic surgery	CCAM codes: Supplementary table S5.
Echo Doppler	CCAM codes: EJQM004, EDQM001

Table S2. Wound dressing LPP codes (n = 329)

LPP Codes: hydrocolloid dressing
1322792, 1387113, 1321321, 1343788, 1396632, 1342926, 1335004, 1399518, 1323805, 1362188, 1386042, 1314261, 1344859, 1311446, 1390530, 1339090, 1385321, 1399895, 1303688, 1331383
LPP Codes: foam dressing
1351374, 1316136, 1328085, 1388590, 1344428, 1398163, 1315102, 1350653, 1304736, 1319063, 1366980, 1308094, 1314723, 1370220, 1310783, 1387188, 1301347, 1371106, 1353870, 1381642, 1347875, 1342240, 1375050, 1327370, 1353864, 1354355, 1347823, 1302996, 1375564, 1316320, 1338936, 1322065, 1327186, 1315384, 1365270, 1326502, 1311943, 1357106, 1301070, 1307692, 1326666, 1308898, 1397732, 1365755, 1370704, 1351747, 1348633, 1348679, 1374381, 1365117, 1308668, 1312760, 1319643, 1333399, 1380074, 1326560, 1303470, 1393616, 1372672, 1337026, 1370236, 1320913, 1333198, 1389112, 1392717, 1335866, 1336558, 1359097, 1364342, 1358152, 1328493, 1376990, 1314829, 1306497, 1368185, 1351262, 1396690, 1336015, 1303748, 1318030, 1315852, 1316107, 1360717, 1381576, 1306400, 1321982, 1398708, 1358399, 1349710, 1327536, 1346829, 1350509, 1392114, 1348946, 1375618, 1379378, 1322326, 1358347, 1356331, 1384238, 1378485, 1375587, 1338942, 1388319, 1378048, 1394975, 1314278, 1301525, 1307700, 1380097, 1356348, 1310620, 1383397, 1382759, 1388153, 1374932, 1319904, 1300744, 1392574, 1367501, 1379444, 1307769, 1370897, 1357336, 1376747, 1324868, 1355136, 1328748, 1363325, 1365904, 1330082, 1399263, 1356207, 1310033, 1302298, 1345942, 1370800, 1349319, 1323113, 1332968, 1340330, 1354600, 1381056, 1364974, 1368363, 1373565, 1330805, 1314284, 1342872, 1348484, 1337820, 1374694, 1356319
LPP Codes: alginates dressing
1306155, 1319040, 1319896, 1310300, 1366128, 1351871, 1316633, 1393160, 1310464, 1334737, 1395259, 1304972, 1342174, 1346597, 1372420, 1384988, 1306304, 1345830, 1330840, 1365465, 1345037, 1394521, 1316120, 1371253
LPP Codes: hydrogel dressing
1334690, 1311624, 1396939, 1305718, 1351109, 1340399, 1354154, 1355350, 1340399, 1339404, 1396891, 1328895, 1328501
LPP Codes: fibre dressing
1357833, 1347830, 1325299, 1304498, 1333695, 1305026, 1344842, 1365488, 1371388, 1393295, 1379088, 1305598, 1310346, 1327039, 1390055, 1338132, 1304742, 1355165, 1358063, 1333732, 1361800, 1331667
LPP Codes: active carbon
1346628, 1327772, 1339321, 1311469, 1309202, 1345557, 1333436
LPP codes: Dressings containing hyaluronic acid
1300299, 1369227, 1395420, 1348550, 1380950, 1360350, 1335062, 1366921, 1397790, 1335040, 1351463, 1353485

LPP Codes: dressing with interfaces
1318767, 1398281, 1310910, 1387633, 1355604, 1346002, 1372301, 1329682, 1379527, 1382825, 1344434, 1324101, 1318572, 1347102, 1316142, 1386473, 1324673, 1350564, 1331526, 1358324, 1325508, 1334252, 1368877, 1359045, 1338379, 1330254, 1342613, 1341252, 1346315, 1348410, 1343311, 1349934
LPP Codes: dressing with petroleum jelly
1366074, 1348998, 1369322, 1369078, 1314367, 1317851, 1356408
LPP Codes: adhesive dressing
1300810, 1374004, 1368015, 1347310, 1316290, 1365264, 1334619, 1375140, 1395868, 1305960, 1397749, 1330478, 1307893, 1368222, 1394751, 1332282, 1392367, 1305457, 1301130, 1337150, 1335872, 1383641, 1389320, 1300709, 1391089, 1390010, 1333962, 1387314, 1334743, 1370064, 1346769, 1362797, 1307195, 1375475, 1314166, 1329452, 1306847, 1393326, 1325550

Table S3. Anti-bedsore mattress, cushions or overlays LPP codes (n = 247)

1221855, 1253051, 1265410, 1289942, 1277465, 1212000, 1223624, 1235478, 1286978, 1274395, 1264178, 1233002, 1206956, 1201717, 1269320, 1238778, 1299870, 1230423, 1209972, 1297002, 1244260, 1233427, 1211851, 1267969, 1262110, 1263977, 1274076, 1247518, 1249374, 1283900, 1202250, 1236911, 1256730, 1283359, 1204012, 1209908, 1264764, 1258657, 1293180, 1201433, 1231960, 1241941, 1286955, 1217003, 1247665, 1249411, 1240485, 1217658, 1296876, 1244678, 1286381, 1298734, 1287340, 1265090, 1290129, 1273438, 1277749, 1255096, 1291904, 1276951, 1213028, 1246424, 1228395, 1273875, 1245459, 1200072, 1230972, 1280562, 1201700, 1238650, 1200014, 1270180, 1226315, 1253878, 1289422, 1228857, 1204035, 1226410, 1218020, 1222429, 1270687, 1272545, 1247754, 1259177, 1223920, 1251773, 1280036, 1256546, 1223297, 1204242, 1243680, 1233143, 1259214, 1257155, 1206904, 1251460, 1229160, 1258864, 1260677, 1229785, 1231233, 1272344, 1262713, 1239022, 1294653, 1231865, 1285690, 1261725, 1224084, 1262699, 1271379, 1258730, 1245844, 1245034, 1253766, 1215808, 1204288, 1202705, 1296793, 1292789, 1217664, 1255274, 1243510, 1223452, 1289652, 1296103, 1267343, 1236710, 1278329, 1231285, 1283260, 1294570, 1204302, 1240150, 1211265, 1219462, 1294794, 1237804, 1241668, 1280065, 1283589, 1214134, 1212276, 1238554, 1224138, 1297841, 1234600, 1265166, 1295960, 1256813, 1263753, 1252689, 1220028, 1285111, 1256428, 1205425, 1225273, 1253677, 1232468, 1273065, 1236696, 1297427, 1224233, 1203290, 1293932, 1214269, 1228350, 1230624, 1225729, 1223423, 1214890, 1294506, 1213092, 1269342, 1236839, 1260602, 1222808, 1203640, 1266421, 1221536, 1251840, 1216937, 1216682, 1228917, 1259220, 1202272, 1234728, 1233433, 1249517, 1284057, 1298119, 6269097, 6274052, 6245665, 6270500, 6255592, 6276298, 6240515, 6229710, 1203633, 6255617, 6276654, 6276269, 6229778, 1279317, 1206548, 1238896, 1255506, 1263351, 1290342, 1282006, 1257296, 1283537, 1280680, 1203113, 1295374, 1254984, 1297628, 1215205, 1252815, 1218280, 1278045, 1294802, 1220034, 1224411, 1200250, 1267449, 1284927, 1250259, 1249138, 1204220, 1244900, 1237218, 1224078, 1251342, 1237017, 1227770, 1205477, 6278647, 6255563, 6276306, 6229962, 6231634, 1203679, 1233367, 1248713, 1293872

Table S4. Compression bandage LPP codes (n = 238)

6316098, 6316112, 6316106, 6372932, 6313792, 6362715, 6313846, 6361101, 6324100, 6366311, 6332430, 6311497, 6372926, 6313817, 6363525, 6318594, 6361093, 6324092, 6376516, 6366328, 6332571, 6311505, 6372910, 6313786, 6362589, 6312485, 6361118, 6324117, 6376491, 6366305, 6330247, 6311480, 6316649, 6313770, 6313763, 6312060, 1349727, 1384853, 1349756, 1395526, 1368370, 6313800, 6363175, 6316750, 6361087, 6324086, 6376485, 6366334, 6332507, 6311511, 1316981, 1330892, 1364030, 1317489, 1328665, 1307002, 1375386, 1318052, 1397620, 1306110, 1371282, 1385025, 1324957, 6380558, 6380104, 6311468, 6312002, 6356979, 6362649, 6312657, 6324330, 6364306, 6325111, 6371677, 6381888, 6381285, 1325891, 1322208, 1330231, 1355857, 6325128, 1345971, 1395839, 6382793, 6379880, 6380564, 6311474, 6312048, 6356991, 6363554, 6318810, 6346171, 6324324, 6363927, 6371660, 6381291, 1303889, 1327826, 1329268, 1380298, 1332307, 1320103, 1352712, 1395437, 1387426, 6382801, 6330721, 1370934, 1340301, 1332508, 1389307, 1313528, 1393987, 6313591, 1311966, 1365146, 1389052, 1322384, 1334482, 1340873, 6313600, 1399180, 1317555, 1317472, 1349414, 1346143, 1395147, 1344629, 1331934, 6324235, 6332453, 1398499, 6324198, 6332588, 1377540, 1317354, 1315177, 1301117, 6339283, 6310747, 6324229, 6330129, 1331733, 6313852, 6324206, 1358330, 6344918, 6316490, 6324181, 6332499, 1321835, 6339290, 6312545, 6324175, 6330276, 1366105, 1319130, 1315220, 1344061, 1322355, 1388242, 6332559, 1349147, 6315153, 6324318, 6320585, 6332482, 1394202, 6318536, 6324293, 6320579, 6332565, 6315124, 1345362, 6324270, 6320562, 6332476, 1327217, 6320556, 6332418, 1397896, 1368587, 6332513, 1378858, 6317092, 6313272, 6324301, 6320540, 6332536, 1372689, 6317040, 6324287, 6320533, 6332520, 1325460, 6312663, 6324264, 6320527, 6332401, 1381100, 6317123, 6324258, 6320510, 6332542, 1322237, 1307309, 6312108, 6324212, 1361480, 1384451, 1374872, 1302967, 1330277, 1351173, 1340152, 1349058, 1335323, 1390977, 1378410, 1367961, 1387202, 1324791, 1324213, 1381286, 1306310, 1367412, 1338557, 1346574, 1314746, 1359714, 1312598, 1352741, 1328518, 1387030, 1326689, 1313238, 1314769, 6332447

Table S5. Orthopedic surgery in the 30-day period before dressing supply CCAM codes (n = 482)

‘QBFA007', 'QZJA011', 'EJGA002', 'QZMA001', 'QEMA013', 'PDFA001', 'EPLF002', 'HMFC004', 'EBLA003', 'QCJA001', 'AHPA009', 'QZMA004', 'NFFC004', 'PAGA011', 'NEKA020', 'EJFA002', 'QEFA008', 'ENLF001', 'QBPA001', 'NFMC003', 'QZFA011', 'ZZQP119', 'QZFA004', 'MEMC005', 'LMMA009', 'HFFC018', 'NDPA011', 'QAMA002', 'BFGA004', 'AHPC001', 'LMMA012', 'LMMA004', 'QZFA036', 'HKPA006', 'MJEC002', 'QZJA001', 'EJFA006', 'QEFA017', 'MJFA010', 'NFFC003', 'MEMC003', 'HKPA007', 'QEFA020', 'HKPA004', 'QEMA012', 'MJCA012', 'LMMC002', 'LMMA010', 'QEFA004', 'AHPA022', 'QZJA012', 'MJDC001', 'LMMA006', 'HHFA009', 'HMFA007', 'QZFA014', 'QZEA020', 'HFCC003', 'MJFA006', 'NFKA007', 'ZCJA002', 'HHFA002', 'NCCA017', 'EBGA001', 'QBFA012', 'HHFA016', 'QEJA001', 'MJMA002', 'QBFA005', 'MJFA018', 'QZJA009', 'QZFA007', 'MCCB004', 'PDFA002', 'AHPA028', 'HKPA005', 'QZJA022', 'GGJB001', 'MJFA015', 'QBFA001', 'NFKA008', 'MDCA011', 'HJFA004', 'EJGA001', 'NDPA013', 'QEFA019', 'QELH001', 'LFFA002', 'MCCA005', 'QEMA006', 'HHCA002', 'MJFA003', 'QEMA008', 'ZCQA001', 'HHFA006', 'MDCB003', 'MJEC001', 'QBFA008', 'HGFA007', 'HFCB001', 'QEKA001', 'QEMA010', 'HHFA008', 'QZEA045', 'HFMC007', 'QZFA002', 'NFFC002', 'EJGA003', 'QZJA017', 'JQGA003', 'HGSA001', 'QZFA039', 'MJCA001', 'HJFA002', 'HPFA004', 'NCCB006', 'HHFA025', 'GAFA007', 'QZJA013', 'NCCA012', 'YYYY062', 'PZMA004', 'HGFA005', 'ZCJA004', 'HHMA003', 'NEKA011', 'QEFA001', 'LMMC020', 'MDCA014', 'HGPA004', 'EZMA001', 'QZFA035', 'NJPA018', 'QEGA004', 'GGJB002', 'HGCA008', 'LFFA001', 'FCFA006', 'PAGA009', 'QZFA020', 'FCFA029', 'NBCA010', 'JQQP001', 'MJJA001', 'JKFA028', 'NHDA004', 'NEKA014', 'EJSA001', 'FCFA008', 'DELF005', 'LMMC001', 'MJJA003', 'FCFA018', 'JGFA006', 'QZJA010', 'MJPA011', 'NGCA001', 'MJPA013', 'NCCA016', 'QEMA004', 'QZJA002', 'MZFA013', 'QBFA004', 'JJFC003', 'HHFA014', 'AHCA023', 'HHSA001', 'MJJA004', 'LFAA002', 'LMMA001', 'NFJC001', 'QBFA003', 'JJFC010', 'NHMA002', 'JQGA002', 'NBCA006', 'PDFA003', 'LMMA017', 'PCCA002', 'PAGA010', 'HPPA002', 'NZFA005', 'NDPA008', 'FCFA013', 'MJPA002', 'NDPA002', 'HHFA001', 'EPLF005', 'QAGA004', 'HGCA004', 'NHFA001', 'FCFA011', 'MZEA010', 'NFKA006', 'JGFA015', 'HGCA002', 'HHFA018', 'KCFA005', 'JGFC001', 'HJFA007', 'JHFA009', 'NDPA014', 'QBFA002', 'QZFA009', 'AHLB001', 'MJPA009', 'QZJA015', 'CAFA005', 'NCCA004', 'FCFA019', 'HPPC003', 'MHDB001', 'LHFA016', 'QZJA005', 'QZJB002', 'QEKA002', 'AFLB008', 'MJFA005', 'QZJA021', 'QZEA027', 'MCCB002', 'MJEA006', 'MJFA004', 'PCPA004', 'QZMP001', 'QZFA001', 'HHFA011', 'MBCA005', 'PAFA010', 'HLFA019', 'MHFA001', 'GGPA002', 'NJCA001', 'QZFA027', 'MHFA002', 'PCCA001', 'MHDA005', 'LMGA001', 'MEMA006', 'GFFA013', 'NGFA002', 'CAMA022', 'HFCA002', 'JJFA004', 'MJPA012', 'NBGA007', 'NEKA012', 'DBKA006', 'QZEA008', 'NDGA003', 'HHFA024', 'YYYY026', 'FCFA016', 'QZMA007', 'MBCB002', 'MHJA001', 'QZJA016', 'NCCA002', 'MHPA004', 'QAJA006', 'AHPA011', 'NDPA004', 'JHJA001', 'QEFA002', 'QZJA007', 'JKFA027', 'MJFC001',

'QZMA006', 'HNFA007', 'HGLA001', 'MGFA004', 'QEGA002', 'QZJB003', 'NCCA018', 'ZZJH003', 'HDQE001', 'QAJA012', 'HJFA019', 'QEDA002', 'AHPA021', 'LMMC015', 'MCCA011', 'MGFA007', 'JCPC002', 'JHFA013', 'MJDA001', 'HHFA026', 'AHCA015', 'HHFA017', 'QZFA024', 'FCFA010', 'JKFA015', 'JDLF001', 'NEFA004', 'NJFA008', 'QZGA003', 'HHFA020', 'MHMA005', 'MJCA003', 'NFFA004', 'QEDA004', 'MDGA002', 'MEMA005', 'HFMC001', 'MJCA002', 'NCCA010', 'NCPA015', 'MDFA002', 'MDCB005', 'NJPA025', 'QEMA009', 'DEKA001', 'JQGA004', 'NJFA002', 'LLMC004', 'NHPA002', 'QZMA009', 'DELF007', 'NBCB004', 'QAJA005', 'QBJB001', 'HPMA001', 'LHCA010', 'MACA001', 'NBEP001', 'NFPC002', 'NDPA003', 'JJPC003', 'NDCA002', 'HMQA001', 'LMSA002', 'MCCA010', 'MJEA010', 'GAFA002', 'EECA009', 'HGFA004', 'QAJA013', 'AELB002', 'HPFA003', 'NDCA004', 'QEMA005', 'QZJA004', 'QZFA029', 'DDMA018', 'HHCA001', 'MEEA004', 'NJFA005', 'NBMA002', 'DDMA011', 'NFEC002', 'NZHA001', 'PZMA005', 'FCFA012', 'JDFE001', 'NGEP001', 'HJFA011', 'QEMA002', 'HHFE006', 'CAFA002', 'GAMA018', 'NCPA001', 'HGFA003', 'NZMA001', 'EJFA007', 'FCFA017', 'FFFA001', 'FCFA022', 'JGFA005', 'ZZHH008', 'NJMB001', 'DDMA005', 'EGFA002', 'MJFA008', 'MJFA012', 'NEEP002', 'NGPA002', 'PCPA003', 'GAFA005', 'HJFA017', 'BAFA006', 'MEMC002', 'MJCA006', 'QZJP001', 'JKDC001', 'LFDA009', 'NBFA005', 'MCCA008', 'HFCA003', 'MJMA010', 'MJPA005', 'LDCA013', 'FCFC003', 'GFFC005', 'GGNC001', 'NFJA001', 'NJEA003', 'QEFA007', 'NBCA001', 'HMFC001', 'ZBQC001', 'QCJA004', 'JCLE001', 'JDFA025', 'NDCA003', 'NFCA002', 'FCFC001', 'HFCC001', 'HJFA006', 'JKFA006', 'MDCA007', 'NJPA007', 'MDCA004', 'MJPA010', 'GAMA012', 'HHFA010', 'PACC001', 'GDFA005', 'MJFA014', 'NJMA003', 'QEMA003', 'LMFA001', 'MJEA004', 'NCEP002', 'ZZGP001', 'DCJB001', 'GFFC002', 'JLDC015', 'MBCA011', 'NFJA002', 'QZFA006', 'MCCA001', 'NCPA014', 'NGPC001', 'NHDA001', 'NCPA002', 'NFPA002', 'QAJA001', 'JDFE002', 'QZFA019', 'ZZHH006', 'AHPA001', 'HJDC001', 'HFFA005', 'GFFA017', 'HKPA008', 'NDPA009', 'HMFC002', 'MEKA008', 'QZFA030', 'HCFA008', 'LHGA007', 'DCJA001', 'MHCA002', 'QEFA016', 'FCFA027', 'QZEA021', 'HLHB001', 'HHMA002', 'MHPA002', 'MJJA002', 'QAJA007', 'QZEA037', 'LDFA008', 'MCCA004', 'MGCA001', 'KCFA008', 'MEFC002', 'HHCC007', 'LMMA011', 'QAGA001', 'BAMA004', 'PAGB003', 'QCJA003', 'HAFA017', 'MJCA010', 'MEJC001', 'NCCA005', 'NCCA013', 'HCFA009', 'MBCA006', 'MEFC001', 'NBCA005’

Table S6. Skin ulcer ICD-10 codes

ICD-10 Code: Pressure ulcer	L89
ICD-10 Codes: Vascular ulcer	I830, I832
ICD-10 Codes: Diabetic foot ulcer	E105, E115, E125, E135, E145

Table S7. Concordance analysis between identification of skin ulcer type from the algorithm and from ICD-10 hospitalization codes

		Skin ulcers identified from hospitalization		
		Pressure	Vascular	Diabetic
Skin ulcers identified from the algorithm	Pressure	71 (61.2)	32 (27.6)	13 (11.2)
	Vascular	48 (33.6)	76 (52.4)	20 (14.0)
	Diabetic	9 (10.7)	34 (40.5)	41 (48.8)

Data are given as n (%) unless otherwise specified.

Table S8. PERR cohort and post exclusion of prior skin ulcers characteristics on the Cox cohort

	PERR cohort (n = 37,007)		Cox cohort (n = 35,034)		
Characteristic	**Users of bisphosphonates (n = 7,402)**	**Nonusers of bisphosphonates (n = 29,605) [a]**	**Users of bisphosphonates (n = 6,922)**	**Nonusers of bisphosphonates (n = 28,112) [a]**	**SMD %**
Male	1,200 (16.2)	4,209 (14.2)	1,098 (15.9)	3,955 (14.1)	- 9.16
Age, years (mean ± SD)	67.3 ± 12.1	68.2 ± 14.0	67.2 ± 11.9	67.9 ± 14.0	- 6.59
PVD	120 (1.62)	504 (1.70)	109 (1.57)	406 (1.44)	0.42
Urinary incontinence	98 (1.32)	446 (1.51)	84 (1.21)	386 (1.37)	- 0.84
Faecal incontinence	5 (0.07)	100 (0.34)	2 (0.03)	82 (0.29)	- 1.24
Diabetes	845 (11.4)	3,316 (11.2)	753 (10.9)	2,984 (10.6)	0.65
Thrombosis	60 (0.81)	308 (1.04)	45 (0.65)	221 (0.79)	- 1.05
Hypertension	2,348 (31.7)	9,362 (31.6)	2,128 (30.7)	8,538 (30.4)	0.20
Hyperlipidaemia	1,866 (25.2)	7,447 (25.2)	1,709 (24.7)	6,887 (24.5)	0.12
Tobacco use	575 (7.77)	2,041 (6.89)	507 (7.32)	1,796 (6.39)	3.34
Obesity	368 (4.97)	1,432 (4.84)	320 (4.62)	1,253 (4.46)	0.60
Hospitalizations [b]	0.74 ± 2.53	0.55 ± 5.13	0.69 ± 2.47	0.45 ± 3.93	4.50
Corticoids [c]	2,895 (39.1)	10,664 (36.0)	2,662 (38.5)	9,982 (35.5)	6.37
≤ 30 days use	173 (2.34)	734 (2.48)	158 (2.28)	709 (2.52)	- 0.65
31 to 90 days use	1,506 (20.4)	5,984 (20.2)	1,386 (20.0)	5,676 (20.2)	0.33
> 90 days use	1,216 (16.4)	3,946 (13.3)	1,118 (16.2)	3,597 (12.8)	8.37

Data are given as n (%) unless otherwise specified. PVD, Periphery Vascular Disease.

[a] Characteristics at index date. [b] Number of hospitalizations in year preceding index date (mean ± SD). [c] Cumulative corticoids use assessed by DDD in the 2 years preceding index date.

Table S9. Future exposed cohort characteristics

Characteristic	PERR cohort (n = 39,622)			Cox cohort (n = 37,470)		
	Users of bisphosphonates (n = 7,998)	Future users of bisphosphonates (n = 31,624) [a]	SMD %	Users of bisphosphonates (n = 7,443)	Future users of bisphosphonates (n = 30,027) [a]	SMD %
Male	1,066 (13.3)	3,864 (12.2)	- 5.09	971 (13.1)	3,620 (12.1)	- 4.54
Age, years (mean ± SD)	67.9 ± 12.2	67.8 ± 11.2	0.40	67.7 ± 12.1	67.8 ± 11.2	- 0.42
PVD	113 (1.41)	415 (1.31)	0.46	97 (1.30)	336 (1.12)	0.85
Urinary incontinence	95 (1.19)	361 (1.14)	0.21	84 (1.13)	313 (1.04)	0.40
Faecal incontinence	2 (0.03)	4 (0.01)	0.06	2 (0.03)	3 (0.01)	0.08
Diabetes	832 (10.4)	3,000 (9.49)	3.06	725 (9.74)	2,752 (9.17)	1.97
Thrombosis	49 (0.61)	172 (0.54)	0.32	37 (0.50)	144 (0.48)	0.08
Hypertension	2,356 (29.5)	9,044 (28.6)	1.89	2,093 (28.1)	8,309 (27.7)	1.00
Hyperlipidaemia	1,894 (23.7)	7,299 (23.1)	1.42	1,698 (22.8)	6,786 (22.6)	0.51
Tobacco use	502 (6.28)	1,832 (5.79)	2.03	432 (5.80)	1,606 (5.35)	1.99
Obesity	350 (4.38)	1,252 (3.96)	1.91	283 (3.80)	1,080 (3.60)	0.94
Hospitalizations [b]	0.57 ± 1.51	0.44 ± 1.83	7.86	0.53 ± 1.46	0.40 ± 1.72	8.33
Corticoids [c]	2,944 (36.8)	11,540 (36.5)	0.66	2,687 (36.1)	10,763 (35.8)	0.53
≤ 30 days use	199 (2.49)	726 (2.30)	0.88	181 (2.43)	655 (2.18)	1.15
31 to 90 days use	1,551 (19.4)	6,276 (19.9)	- 1.14	1,421 (19.1)	5,899 (19.7)	- 1.40
> 90 days use	1,194 (14.9)	4,538 (14.4)	1.64	1,085 (14.6)	4,209 (14.0)	1.60

Data are given as n (%) unless otherwise specified. PVD, Periphery Vascular Disease.

[a] Characteristics at index date. [b] Number of hospitalizations in year preceding index date (mean ± SD). [c] Cumulative corticoids use assessed by DDD in the 2 years preceding index date.

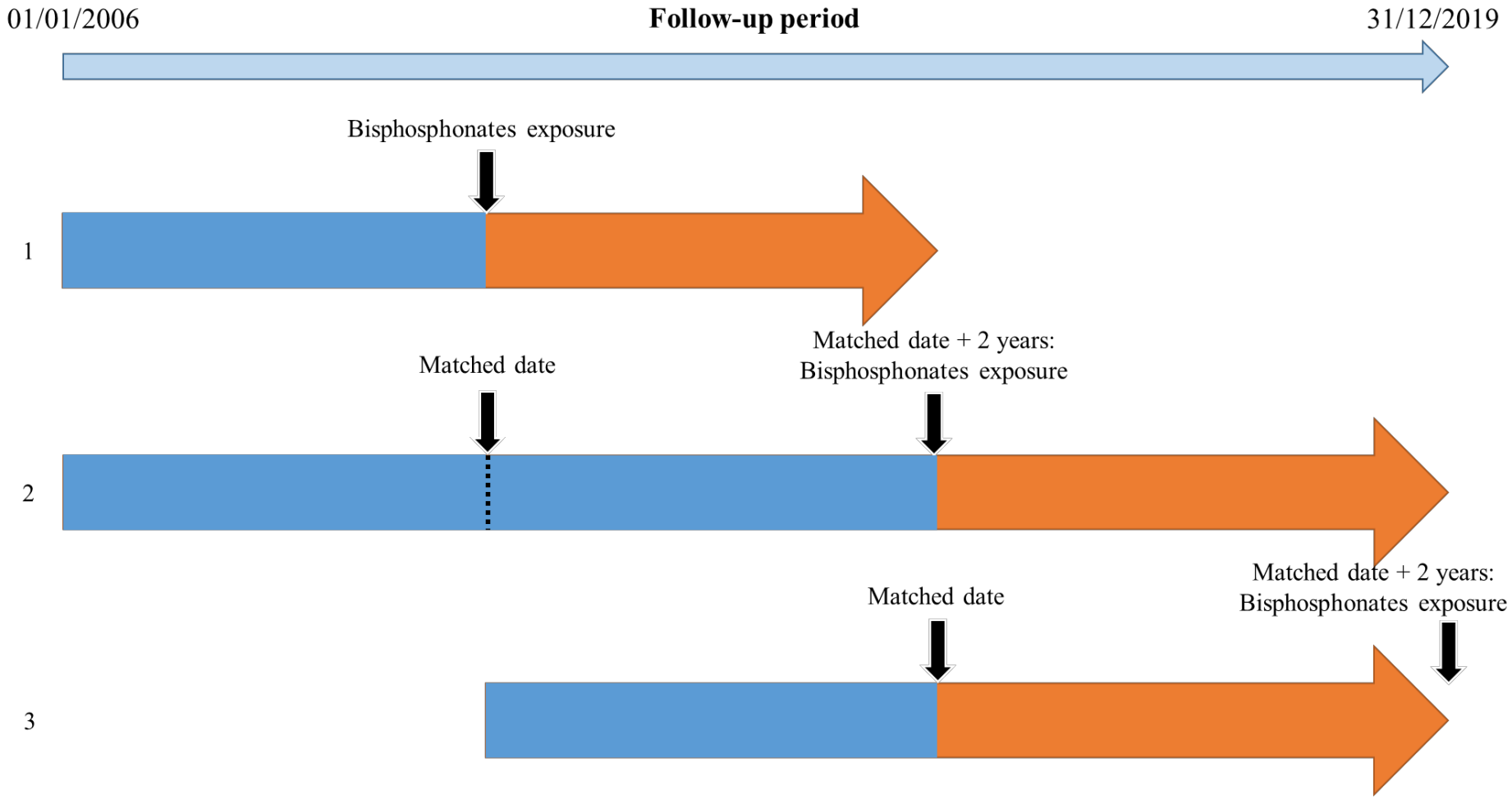


Figure S1: Second control group selection

Patient 2 is the control matched to patient 1 at the exposure date of patient 1.

Patient 3 is the control matched to patient 2 at the exposure date of patient 2.

Table S10. Standardized mean differences between PERR cohort and Cox cohort

Characteristics	PERR cohort (n = 37,007)	Cox cohort (n = 35,034)	Standardized mean difference (%)
Male	5,409 (14.6)	5,053 (14.4)	-0.89
Age, years (mean ± SD)	68.0 ± 13.7	67.8 ± 13.6	1.33
PVD	624 (1.69)	515 (1.47)	0.99
Urinary incontinence	544 (1.47)	470 (1.34)	0.59
Faecal incontinence	105 (0.28)	84 (0.24)	0.20
Diabetes	4,161 (11.2)	3,737 (10.7)	1.85
Thrombosis	368 (0.99)	266 (0.76)	1.08
Hypertension	11,710 (31.6)	10,666 (30.4)	2.59
Hyperlipidaemia	9,513 (25.2)	8,596 (24.5)	1.46
Tobacco use	2,616 (7.07)	2,303 (6.57)	1.96
Obesity	1,800 (4.86)	1,573 (4.49)	1.72
Hospitalizations [a]	0.59 ± 4.73	0.50 ± 3.69	2.19
Corticoids [b]	13,559 (36.6)	12,644 (36.1)	1.14
≤ 30 days use	907 (2.45)	867 (2.47)	-0.11
31 to 90 days use	7,490 (20.2)	7,062 (20.2)	0.20
> 90 days use	5,162 (14.0)	4,715 (13.5)	1.43

Data are given as n (%) unless otherwise specified. PVD, Periphery Vascular Disease.
[a] Number of hospitalizations in year preceding index date (mean ± SD). [b] Cumulative corticoids use assessed by DDD in the 2 years preceding index date.

6. Second- and Third-generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study

ELECTRONIC SUPPLEMENTARY MATERIAL

Article Title: Second- and Third- generation BCR-ABL Tyrosine-Kinase Inhibitors and the Risk of Pulmonary Arterial Hypertension: A Prevalent new-user Population-based Cohort Study

Running Title: PAH Risk with BCR-ABL TKI: Cohort study

Clément Jambon-Barbara [1,2], Samy Suissa [3,4], Sophie Dell'Aniello [3], Alex Hlavaty [1,2], Jean-Luc Cracowski [1,2], Marie-Camille Chaumais [5,6,7], Marc Humbert [5,8,9], David Montani [5,8,9], Charles Khouri [1,2,10]

[1] Grenoble Alpes University Hospital, Pharmacovigilance Unit, F-38000 Grenoble, France.
[2] Univ. Grenoble Alpes, HP2 Laboratory, Inserm U1300, F-38000 Grenoble, France.
[3] Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada.
[4] Department of Epidemiology, Biostatistics and Occupational Health and Department of Medicine, McGill University, Montreal, Quebec, Canada.
[5] INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France.
[6] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Pharmacy, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.
[7] Université Paris-Saclay, Faculty of Pharmacy, Saclay, France.
[8] Université Paris-Saclay, Faculty of Medicine, Le Kremlin-Bicêtre, France.
[9] Assistance Publique-Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Centre, Hôpital Bicêtre, DMU 5 Thorinno, Le Kremlin-Bicêtre, France.
[10] Grenoble Alpes University Hospital, Clinical Pharmacology Department INSERM CIC1406, F-38000 Grenoble, France.

Corresponding author: Charles Khouri and Clément Jambon-Barbara, Pharmacovigilance department, Grenoble Alpes University Hospital, Grenoble, France.
Postal address: Centre Regional de Pharmacovigilance, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
Tel: +33 4 76 76 51 45
Fax: +33 4 76 76 56 55
E-mail: ckhouri@chu-grenoble.fr & cjambonbarbara@chu-grenoble.fr

Table of Content

Supplementary methods: vibration of effect framework 5

Table S1. List of PAH-treatment codes 6

Table S2. RHC and CTEPH specific procedure CCAM codes 7

Table S3. Characteristics identification in the SNDS 8

Figure S1. Sunburst diagram presenting trajectories of BCR-ABL tyrosine kinase inhibitor use in the French Healthcare database. 11

Figure S2. Dasatinib time-conditional propensity score distribution pre- (A) and post- (B) matching. 12

Table S4. Number of matched control patients per exposed ones 13

Table S5. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for nilotinib versus imatinib cohort 14

Table S6. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for bosutinib versus imatinib cohort 16

Table S7. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for ponatinib versus imatinib cohort 18

Figure S3. Nilotinib time-conditional propensity score distribution pre- (A) and post- (B) matching 20

Figure S4. Bosutinib time-conditional propensity score distribution pre- (A) and post- (B) matching 21

Figure S5. Ponatinib time-conditional propensity score distribution pre- (A) and post- (B) matching 22

Table S8. Characteristics of Patients, by Outcome Status, for dasatinib patients: Specific algorithm 23

Table S9. Characteristics of Patients, by Outcome Status, for dasatinib patients: Sensitive algorithm 25

Table S10. Incidence rates, hazard ratios and number needed to harm for PAH: specific outcome sensitivity analyses 27

Figure S6. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for dasatinib-associated PAH. 29

Figure S7. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for nilotinib-associated PAH. 30

Figure S8. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for bosutinib-associated PAH. 31

Figure S9. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for ponatinib-associated PAH. 32

Table S11. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Dasatinib incident new-users 33

Table S12. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Dasatinib prevalent new-users 35

Table S13. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Nilotinib incident new-users 37

Table S14. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Nilotinib prevalent new-users 39

Table S15. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Bosutinib incident new-users 41

Table S16. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Bosutinib prevalent new-users 43

Table S17. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Ponatinib incident new-users 45

Table S18. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Ponatinib prevalent new-users 47

Figure S10. Time-dependant hazard ratio of pulmonary arterial hypertension (PAH) in the dasatinib versus imatinib cohort. 49

REFERENCES 50

Supplementary methods: vibration of effect framework

To assess the impact of outcome misclassification we used the vibration of effect framework to vary outcome classification according to estimated sensitivity and specificity (1). We estimated the variation in HR when replacing outcomes by random values from a binomial distribution with a probability of success equal to the specificity (0.75), and replacing non-events identified by ICD codes I27.0 by random values from a binomial distribution with a probability of success equal to 1-sensitivity (0.10). We ran the analysis a thousand times and presented the results in a sensitivity analysis and in Supplementary Material Figure S6.

Table S1. List of PAH-treatment codes

Selexipag	**ATC code:** B01AC27 **UCD codes:** 9416073, 9416096, 9416104, 9416110, 9416127, 9416133, 9416156, 9416162, 9416179
Iloprost	**ATC code:** B01AC11 **UCD codes:** 9405709, 9405709, 9256965, 9256965, 9297467 9297467
Sildenafil	**ATC code:** C02KX **UCD codes:** 9420399, 9385013, 9279972, 9424167, 9436319, 9437307, 9437951, 9438637
Riociguat	**ATC code:** C02KX05 **UCD codes:** 9400540, 9400557, 9400563, 9400586, 9400592
Ambrisentan	**ATC code:** C02KX02 **UCD codes:** 9000423, 9000424, 9455624, 9455630, 9455759, 9455765, 9456730, 9456747, 9452985, 9452991, 9454783, 9454808, 9316035, 9316041, 9001991
Treprostinil	**ATC code:** B01AC21 **UCD codes:** 9000505, 9000506, 9000507, 9000508, 9442165, 9442171, 9442188, 9442194, 9271539, 9271545, 9271551, 9271568
Epoprostenol	**ATC code:** B01AC09 **UCD codes:** 9354225, 9354231, 9356201, 9356218, 9399877, 9399883, 9184881, 9202886, 9421766, 9421884
Bosentan	**ATC code:** C02KX01 **UCD codes:** 9240013, 9240036, 9342759, 9429785, 9429791, 9425190, 9425209, 9426539, 9426545, 9437276, 9437282, 9426717, 9426723, 9421536, 9421542, 9433634, 9421909, 9421915, 9422211, 9422228, 9433640
Sitaxentan	**ATC code:** C02KX03 **UCD code:** 9298461
Tadalafil	**ATC code:** C02KX **UCD codes:** 9348615, 9425480, 9438643

PAH: Pulmonary Arterial Hypertension, ATC: Anatomical Therapeutic Chemical, UCD: Unité Commune de Dispensation.

Macitentan is not part of the identified PAH specific treatment as it is not a reimbursed treatment in France and is therefore not used.

Table S2. RHC and CTEPH specific procedure CCAM codes

CCAM Codes: Right Heart Catheterization
'EQQF001', 'EQQF002', 'EQQF003', 'EQQF004', 'EQQF006', 'EQQH001', 'EQQH002', 'EQQH004', 'EQQH005', 'EQQH006'
CCAM Codes: Chronic Thromboembolic Pulmonary Hypertension specific procedure
'DAAF001', 'DFAA002', 'DFAA003', 'DFAA004', 'DFAA005', 'DFAF001', 'DFAF002', 'DFAF003', 'DFAF004', 'DFFA003'

RHC: Right Heart Catheterization, CTEPH: Chronic Thromboembolic Pulmonary Hypertension, CCAM: Classification Commune des Actes Médicaux (Medical Procedure Classification)

Table S3. Characteristics identification in the SNDS

PAH associated conditions	
Systemic scleroderma	ICD-10 in-hospital diagnosis code: M34 ICD-10 LTD code: M34
Portal hypertension	ICD-10 diagnosis code: K76.6
HIV positive	ICD-10 diagnosis code: B20 to B24, F02.4, Z21 ICD-10 LTD code: B20 to B24, F02.4, Z21 Drug reimbursement ATC codes: J05AF01, J05AF02, J05AF03, J05AF04, J05AF06, J05AF13, J05AG01, J05AG03, J05AG04, J05AG05, J05AR01, J05AR04, J05AE01, J05AE02, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AE03, J05AR06, J05AR08, J05AR09, J05AR13, J05AR18, J05AR19, J05AR20, J05AR21, J05AX07, J05AX08, J05AX09, J05AX12
Sickle cell disease	ICD-10 diagnosis code: D57 ICD-10 in-hospital diagnosis codes for complications: H36.8, N08.2, M14.0 ICD-10 LDT code: D57
Congenital heart disease	ICD-10 diagnosis code: Q211, Q210, Q250, Q251, Q234, Q230, Q221, Q213, Q212, Q203, Q201, Q262, Q252, Q226, Q232, Q230, Q220, Q225, Q224, Q204, Q205, Q202, Q201, Q200
Comorbidities	
COPD	> 3 drug reimbursement from ATC codes: - LABA: R03CC12, R03AC13, R03AC18, R03AC19, R03AC12 - LAMA: R03BB06, R03BB04, R03BB07 - LABA/LAMA association: R03AL04, R03AL06, R03AL03 - LABA/ICS association: R03AK08, R03AK07, R03AK10, R03AK06 - LABA/LAMA/ICS association: R03AL09, R03AL11, R03AL08. AND Exclusion of previous hospitalization for asthma: J45, J46 AND Exclusion of previous use of asthma medications ATC codes: R03BA01, R03BA02, R03BA08, R03BA05, R03BA07, R03DC03, R03DX05, R03DX09, R03DX10, R03DX11, R03AC02, R03CC03, R01AC07, R06AX17, R01AC01
High blood pressure	ICD-10 in-hospital diagnosis codes: I10, I15 ICD-10 LTD codes (before 27/06/2011*): I10, I15

	> 3 drug reimbursement from ATC codes: C02 (excluding C02CA02), C03AA01, C03AA03, C03BA04, C03BA05, C03BA06, C03BA07, C03BA08, C03BA09, C03BA10, C03BA11, C03BX03, C03C, C03D, C03EA01, C03EA02, C03EA03, C03EA04, C03EB01, C07, C08, C09A, C09B, C09C, C09D, C09X, C10BX03, C10BX07
Heart failure	ICD-10 in-hospital diagnosis codes: I11.0, I13.0, I13.2, I13.9, I50, J81 ICD-10 LTD codes: I11, I13, I50
Diabetes	ICD-10 in-hospital diagnosis codes: E10 to E14 ICD-10 in-hospital diagnosis codes for complications: G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3 ICD-10 LTD codes: E10 to E14 Drug reimbursement ATC code: A10 (excluding A10BX06)
VTE	ICD-10 in-hospital diagnosis codes: I26, I80, I82 ICD-10 LTD codes: I26, I80, I82
Chronic dialysis	GHM in-hospital codes: 28Z01Z, 28Z02Z, 28Z03Z, 28Z04Z, 28Z05Z, 28Z06Z CCAM codes: JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008 Service codes: 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2131, 2132, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2142, 2143, 2144, 2145, 2146, 2334
Interstitial lung diseases	ICD-10 in-hospital diagnosis codes: J70.2, J70.3, J70.4, J84, B22.1 ICD-10 LTD codes: J70.2, J70.3, J70.4, J84
Lung transplant	CCAM codes: GFEA001, GFEA002, GFEA003, GFEA004, GFEA005, GFEA006, GFEA007
Lung cancer	ICD-10 in-hospital diagnosis codes: C33, C34, D021, D022 ICD-10 LTD codes: C33, C34, D021, D022
Drugs associated with PAH (possible and definite association) [a]	
Benfluorex	Drug reimbursement ATC code: A10BX06
Cyclophosphamide	Drug reimbursement ATC code: L01AA01
Mitomycin C	Drug reimbursement ATC code: L01DC03
Sofosbuvir	Drug reimbursement ATC code: J05AP08, J05AP51, J05AP55, J05AP56
Leflunomide	Drug reimbursement ATC code: L04AK01
Not available and/or identifiable in France	Dexfenfluramine (A08AA04), Fenfluramine (A08AA02, N03AX26), Diazoxide (C02DA01, V03AH01), Interferons alpha and beta (L03AB with exclusion od L03AB03), Phenylpropanolamine (R01BA01, R01BA51), Carfilzomib (L01XG02), Trichloroethylene (N01AB05)

If one of the parameters was satisfied, the co-morbidity was considered to be present, unless otherwise specified.

* 27/06/2011: application of the decree withdrawing high blood pressure from LTD list

[a] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

SNDS: Système National des Données de santé, i.e. French healthcare database.

PAH: Pulmonary Arterial Hypertension.

ICD-10: International Classification of Diseases, 10th revision.

LTD: Long-term disease.

HIV: Human Immunodeficiency Virus.

ATC: Anatomical Therapeutic Chemical.

COPD: Chronic Obstructive Pulmonary Disease.

LABA: Long-acting β-agonist.

LAMA: Long-acting muscarinic antagonist.

ICS: Inhaled corticosteroid.

VTE: Venous Thromboembolic Events (i.e. Pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

GHM: Groupe Homogène de Malades, i.e. hospital billing codes.

CCAM: Classification Commune des Actes Médicaux, i.e. common classification of medical procedures.

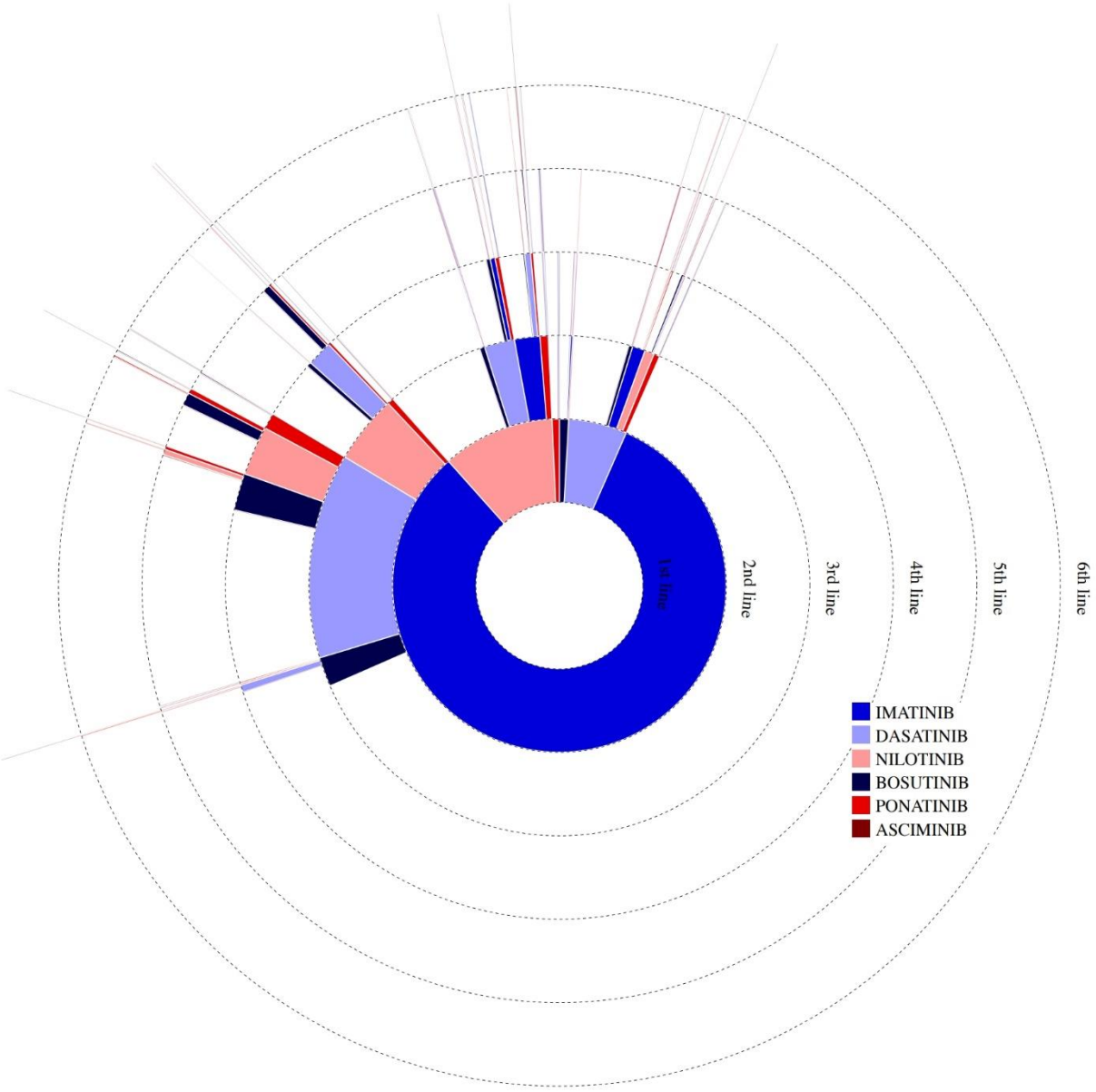


Figure S1. Sunburst diagram presenting trajectories of BCR-ABL tyrosine kinase inhibitor use in the French Healthcare database.

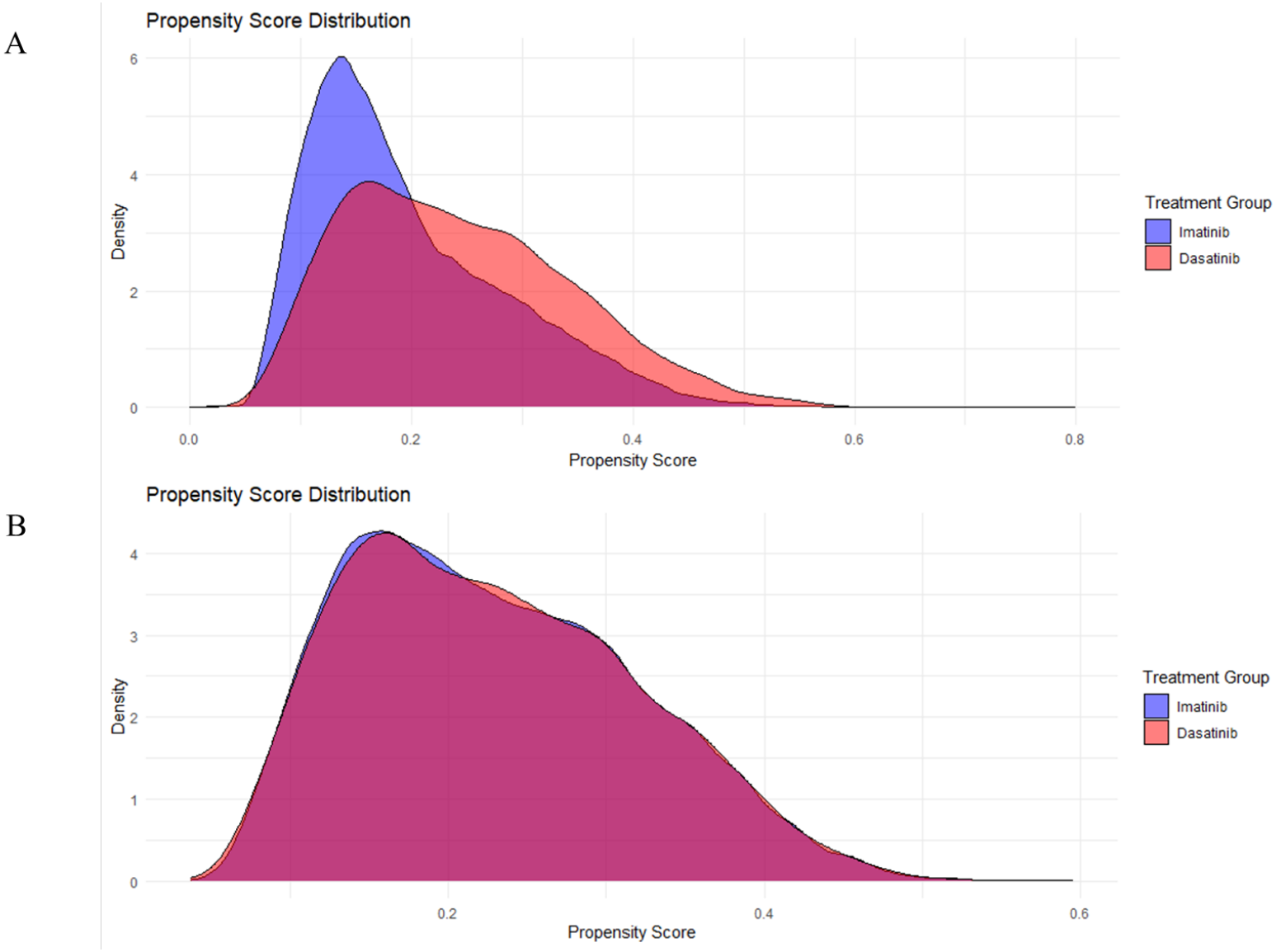


Figure S2. Dasatinib time-conditional propensity score distribution pre- (A) and post- (B) matching.

Table S4. Number of matched control patients per exposed ones

	Dasatinib use (n = 5,644)	**Nilotinib use (n = 4,668)**	**Bosutinib use (n = 1,756)**	**Ponatinib use (n = 1,019)**
1 control	1,094 (19.4)	1,154 (24.7)	196 (11.2)	185 (18.2)
2 controls	1,278 (22.6)	1,134 (24.3)	263 (15.0)	137 (13.4)
3 controls	950 (16.8)	686 (14.7)	286 (16.3)	95 (9.3)
4 controls	739 (13.1)	557 (11.9)	188 (10.7)	70 (6.9)
5 controls	563 (10.0)	331 (7.1)	162 (9.2)	51 (5.0)
6 controls	409 (7.2)	209 (4.5)	150 (8.5)	66 (6.5)
7 controls	226 (4.0)	167 (3.6)	87 (5.0)	53 (5.2)
8 controls	148 (2.6)	116 (2.5)	82 (4.7)	56 (5.5)
9 controls	93 (1.6)	61 (1.3)	62 (3.5)	32 (3.1)
10 controls	43 (0.8)	57 (1.2)	49 (2.8)	39 (3.8)
11 controls	27 (0.5)	31 (0.7)	38 (2.2)	28 (2.7)
12 controls	20 (0.4)	36 (0.8)	34 (1.9)	22 (2.2)
13 controls	14 (0.2)	42 (0.9)	29 (1.7)	23 (2.3)
14 controls	12 (0.2)	19 (0.4)	17 (1.0)	21 (2.1)
15 controls	28 (0.5)	68 (1.5)	113 (6.4)	141 (13.8)

Data are given as n (%) unless otherwise specified.

Table S5. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for nilotinib versus imatinib cohort

Characteristic	Nilotinib users	Imatinib users	SMD (%)
Number of patients	4,668	16,438	/
Weighted number of patients	4,668	4,668	/
Female	2,045 (43.8)	2,019 (43.3)	1.1
Age, years (mean ± SD)	55.9 ± 15.0	55.9 ± 8.0	0.0
Imatinib exposure [a]	0 (0 – 270)	0 (0 – 270)	Matching variable
Prevalent user status	2,185 (46.8)	2,185 (46.8)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	2 (0.0)	2 (0.0)	Matching variable
2012	801 (17.2)	801 (17.2)	Matching variable
2013	490 (10.5)	490 (10.5)	Matching variable
2014	363 (7.8)	363 (7.8)	Matching variable
2015	403 (8.6)	403 (8.6)	Matching variable
2016	354 (7.6)	354 (7.6)	Matching variable
2017	396 (8.5)	396 (8.5)	Matching variable
2018	432 (9.3)	432 (9.3)	Matching variable
2019	377 (8.1)	377 (8.1)	Matching variable
2020	333 (7.1)	333 (7.1)	Matching variable
2021	347 (7.4)	347 (7.4)	Matching variable
2022	370 (7.9)	370 (7.9)	Matching variable
Comorbidities			
COPD	159 (3.4)	179 (3.8)	- 2.3
Hypertension	2,068 (44.3)	2,155 (46.2)	- 3.7
Heart Failure	192 (4.1)	211 (4.5)	- 2.0
Diabetes	578 (12.4)	631 (13.5)	- 3.4
VTE	219 (4.7)	257 (5.5)	- 3.7
Dialysis	12 (0.3)	16 (0.3)	- 1.5
Interstitial lung diseases	32 (0.7)	26 (0.6)	1.7
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	33 (0.7)	42 (0.9)	- 2.1
PAH associated conditions			
Systemic Scleroderma	4 (0.1)	5 (0.1)	- 0.7
Portal Hypertension	3 (0.1)	3 (0.1)	0.2
HIV positive	5 (0.1)	8 (0.2)	- 1.9

Sickle cell disease	8 (0.2)	6 (0.1)	0.8
Congenital heart disease	6 (0.1)	8 (0.2)	- 1.2
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	3 (0.1)	1 (0.0)	1.6
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	2 (0.0)	1 (0.0)	1.2
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	1,907 (40.9)	1,771 (37.9)	6.0
1	1,505 (32.2)	1,495 (32.0)	0.4
2	607 (13.0)	651 (13.9)	- 2.8
3	256 (5.5)	290 (6.2)	- 3.1
≥ 4	393 (8.4)	461 (9.9)	- 5.1
Number of pulmonologist visits [c]			
0	4,309 (92.3)	4,289 (91.9)	1.6
1	110 (2.4)	93 (2)	2.4
2-6	123 (2.6)	140 (3)	- 2.2
7-11	33 (0.7)	37 (0.8)	- 1.1
≥ 12	93 (2)	108 (2.3)	- 2.2

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a nilotinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S6. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for bosutinib versus imatinib cohort

Characteristic	Bosutinib users	Imatinib users	SMD (%)
Number of patients	1,756	9,491	/
Weighted number of patients	1,756	1,756	/
Female	725 (41.3)	718 (40.9)	0.9
Age, years (mean ± SD)	64.5 ± 13.6	64.5 ± 5.8	- 0.3
Imatinib exposure [a]	210 (30–548)	210 (30–548)	Matching variable
Prevalent user status	1,338 (76.2)	1,338 (76.2)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	2 (0.1)	2 (0.1)	Matching variable
2014	28 (1.6)	28 (1.6)	Matching variable
2015	134 (7.6)	134 (7.6)	Matching variable
2016	109 (6.2)	109 (6.2)	Matching variable
2017	158 (9.0)	158 (9.0)	Matching variable
2018	178 (10.1)	178 (10.1)	Matching variable
2019	207 (11.8)	207 (11.8)	Matching variable
2020	297 (16.9)	297 (16.9)	Matching variable
2021	305 (17.4)	305 (17.4)	Matching variable
2022	338 (19.2)	338 (19.2)	Matching variable
Comorbidities			
COPD	113 (6.4)	105 (6.0)	1.9
Hypertension	1,308 (74.5)	1,298 (73.9)	1.4
Heart Failure	224 (12.8)	198 (11.3)	4.5
Diabetes	410 (23.3)	425 (24.2)	- 2.0
VTE	105 (6.0)	115 (6.5)	- 2.3
Dialysis	8 (0.5)	7 (0.4)	1.1
Interstitial lung diseases	27 (1.5)	17 (0.9)	5.4
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	25 (1.4)	37 (2.1)	- 5.0
PAH associated conditions			
Systemic Scleroderma	3 (0.2)	3 (0.2)	0.5
Portal Hypertension	3 (0.2)	4 (0.2)	- 1.5
HIV positive	2 (0.1)	2 (0.1)	- 0.2

Sickle cell disease	3 (0.2)	1 (0.0)	4.4
Congenital heart disease	3 (0.2)	2 (0.1)	1.2
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	0 (0.0)	0 (0.0)	0.0
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	1 (0.1)	1 (0.0)	0.9
Number of hospitalizations [c]			
0	697 (39.7)	704 (40.1)	- 0.8
1	480 (27.3)	471 (26.8)	1.1
2	253 (14.4)	250 (14.2)	0.6
3	137 (7.8)	125 (7.1)	2.6
≥ 4	189 (10.8)	207 (11.8)	- 3.2
Number of pulmonologist visits [c]			
0	1,508 (85.9)	1,491 (84.9)	2.7
1	65 (3.7)	81 (4.6)	- 4.5
2-6	79 (4.5)	73 (4.2)	1.5
7-11	26 (1.5)	25 (1.4)	0.6
≥ 12	78 (4.4)	86 (4.9)	- 2.1

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a bosutinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S7. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls for ponatinib versus imatinib cohort

Characteristic	Ponatinib users	Imatinib users	SMD (%)
Number of patients	1,019	6,452	/
Weighted number of patients	1,019	1,019	/
Female	453 (44.5)	429 (42.1)	4.7
Age, years (mean ± SD)	56.6 ± 15.2	56.5 ± 6.0	0.1
Imatinib exposure [a]	60 (0 – 300)	60 (0 – 300)	Matching variable
Prevalent user status	567 (55.6)	567 (55.6)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	0 (0.0)	0 (0.0)	Matching variable
2014	0 (0.0)	0 (0.0)	Matching variable
2015	0 (0.0)	0 (0.0)	Matching variable
2016	152 (14.9)	152 (14.9)	Matching variable
2017	114 (11.2)	114 (11.2)	Matching variable
2018	120 (11.8)	120 (11.8)	Matching variable
2019	149 (14.6)	149 (14.6)	Matching variable
2020	139 (13.6)	139 (13.6)	Matching variable
2021	169 (16.6)	169 (16.6)	Matching variable
2022	176 (17.3)	176 (17.3)	Matching variable
Comorbidities			
COPD	37 (3.6)	35 (3.4)	1.1
Hypertension	562 (55.2)	573 (56.3)	- 2.2
Heart Failure	66 (6.5)	67 (6.6)	- 0.3
Diabetes	166 (16.3)	181 (17.8)	- 3.9
VTE	79 (7.8)	90 (8.8)	- 3.8
Dialysis	4 (0.4)	5 (0.5)	- 1.0
Interstitial lung diseases	11 (1.1)	11 (1.0)	0.4
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	10 (1.0)	17 (1.7)	- 6.1
PAH associated conditions			
Systemic Scleroderma	1 (0.1)	1 (0.1)	1.5
Portal Hypertension	2 (0.2)	1 (0.1)	1.7
HIV positive	3 (0.3)	3 (0.3)	- 0.3

Sickle cell disease	3 (0.3)	2 (0.2)	1.2
Congenital heart disease	2 (0.2)	3 (0.3)	- 1.5
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	1 (0.1)	0 (0.0)	4.4
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	309 (30.3)	316 (31)	- 1.5
1	208 (20.4)	209 (20.5)	- 0.3
2	139 (13.6)	146 (14.3)	- 1.9
3	77 (7.6)	81 (8.0)	- 1.5
≥ 4	286 (28.1)	267 (26.2)	4.2
Number of pulmonologist visits [c]			
0	929 (91.2)	905 (88.8)	8.0
1	26 (2.6)	32 (3.1)	- 3.5
2-6	33 (3.2)	36 (3.6)	- 1.8
7-11	10 (1.0)	13 (1.2)	- 2.4
≥ 12	21 (2.1)	34 (3.3)	- 7.7

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a ponatinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

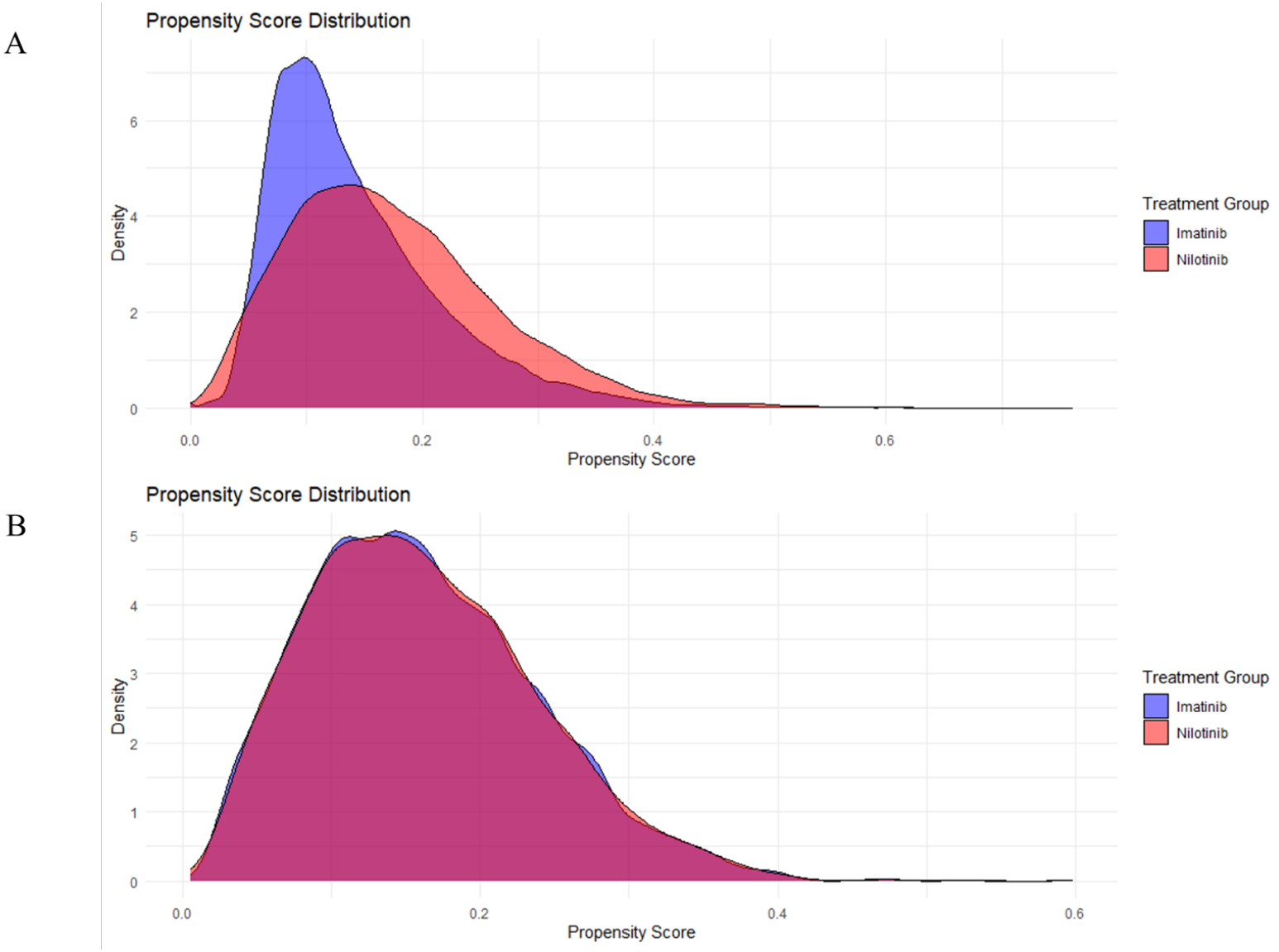


Figure S3. Nilotinib time-conditional propensity score distribution pre- (A) and post- (B) matching

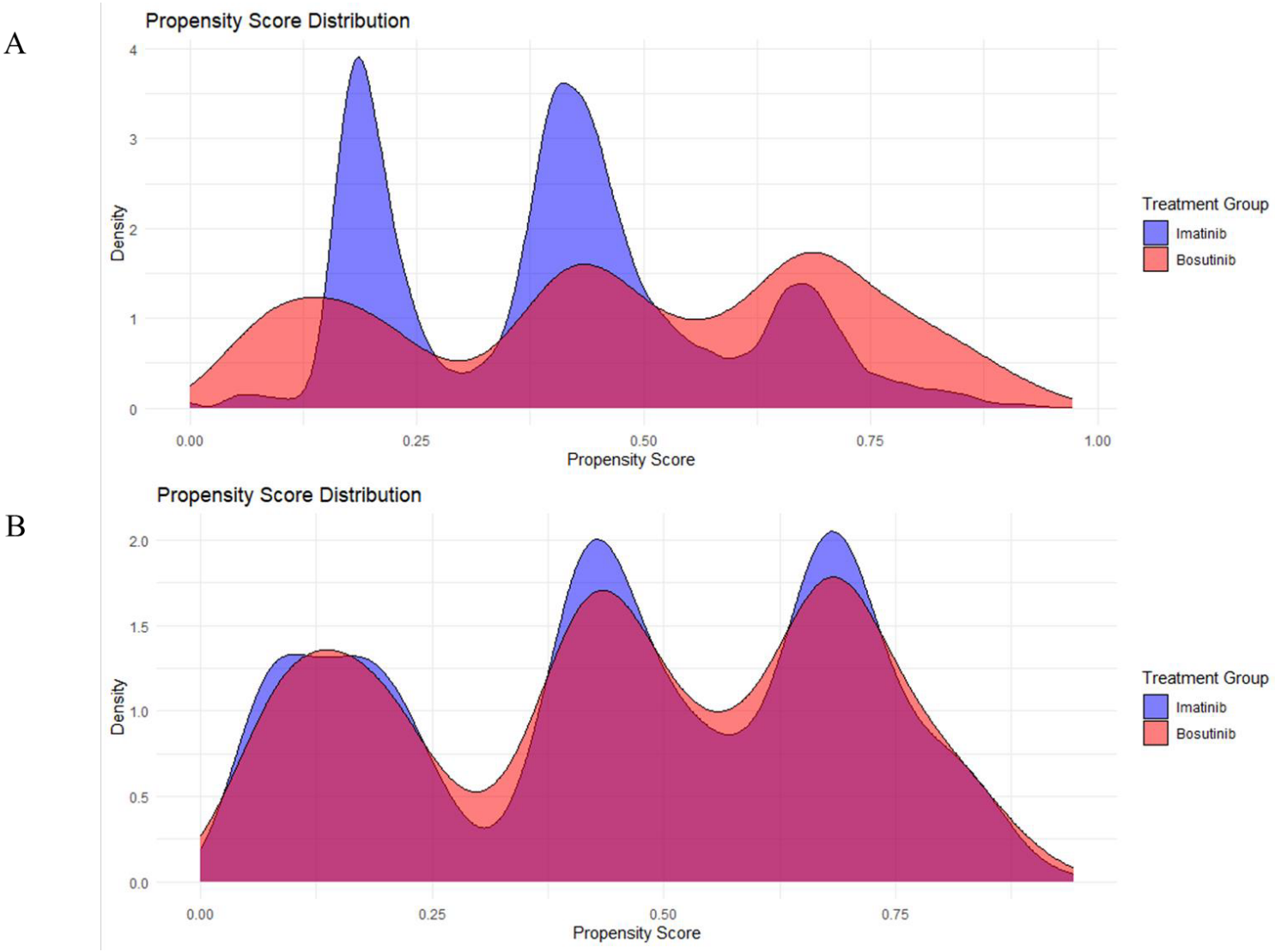


Figure S4. Bosutinib time-conditional propensity score distribution pre- (A) and post- (B) matching

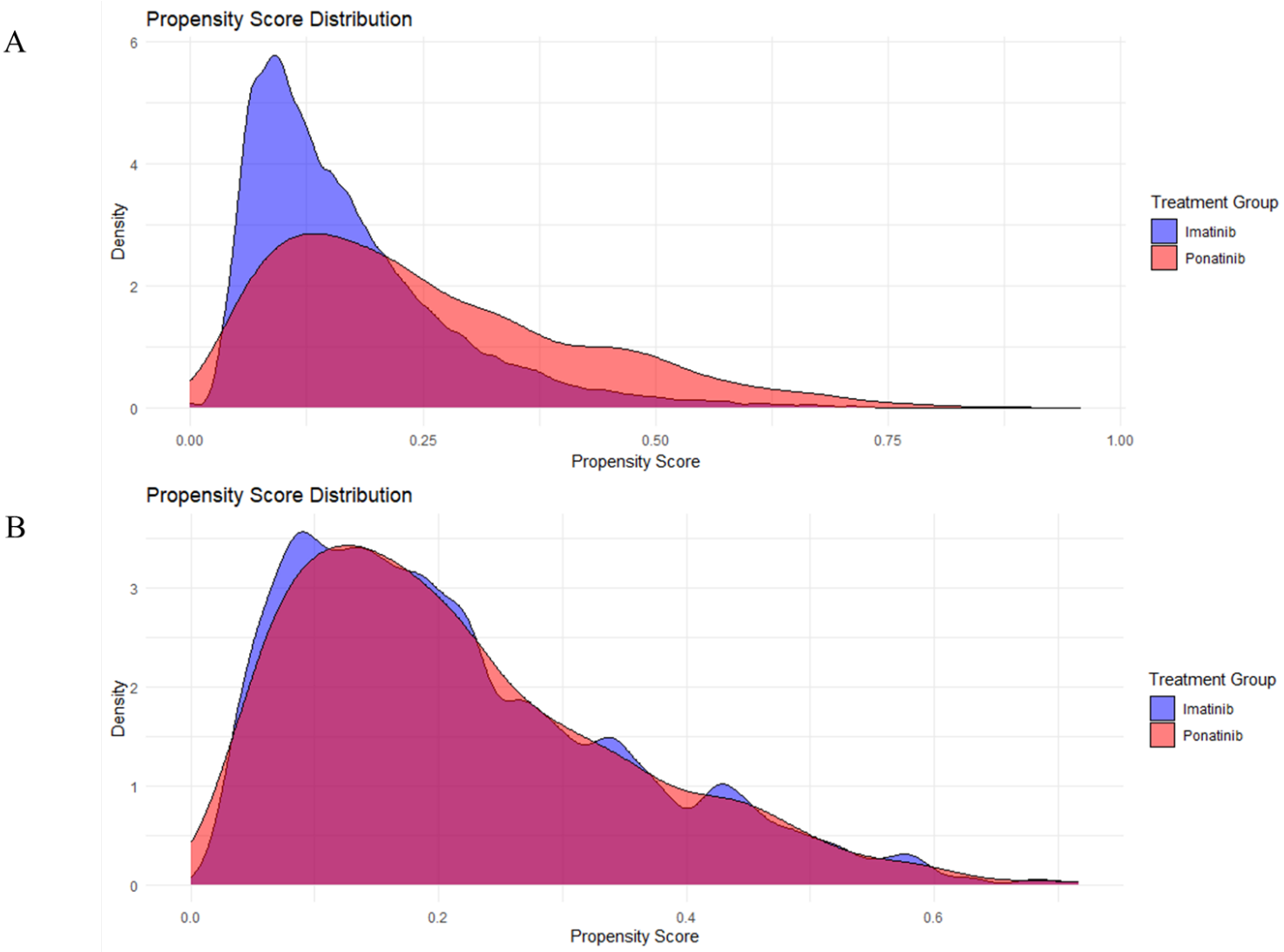


Figure S5. Ponatinib time-conditional propensity score distribution pre- (A) and post- (B) matching

Table S8. Characteristics of Patients, by Outcome Status, for dasatinib patients: Specific algorithm

Characteristic	PAH onset (n = 7)	No PAH onset (n = 5,637)
Female	3 (42.9)	2,483 (44.1)
Age, years (mean ± SD)	56.9 ± 11.0	59.6 ± 15.2
Imatinib exposure [a]	90 (0 – 300)	150 (0 – 450)
Prevalent user status	4 (57.1)	3,863 (68.5)
Calendar year		
2008	1 (14.3)	113 (2.00)
2009	0 (0.00)	239 (4.24)
2010	2 (28.6)	264 (4.68)
2011	2 (28.6)	326 (5.78)
2012	0 (0.00)	323 (5.73)
2013	0 (0.00)	373 (6.62)
2014	1 (14.3)	401 (7.11)
2015	0 (0.00)	390 (6.92)
2016	0 (0.00)	474 (8.41)
2017	0 (0.00)	488 (8.66)
2018	0 (0.00)	451 (8.00)
2019	0 (0.00)	458 (8.12)
2020	1 (14.3)	405 (7.18)
2021	0 (0.00)	465 (8.25)
2022	0 (0.00)	467 (8.28)
Comorbidities		
COPD	0 (0.00)	216 (3.83)
Hypertension	3 (42.9)	3,029 (53.7)
Heart Failure	0 (0.00)	309 (5.48)
Diabetes	0 (0.00)	1,001 (17.8)
VTE	0 (0.00)	317 (5.62)
Dialysis	0 (0.00)	23 (0.41)
Interstitial lung diseases	0 (0.00)	40 (0.71)
Lung transplant	0 (0.00)	0 (0.00)
Lung cancer	0 (0.00)	45 (0.80)
PAH associated conditions		
Systemic Scleroderma	0 (0.00)	8 (0.14)
Portal Hypertension	0 (0.00)	10 (0.18)
HIV positive	0 (0.00)	17 (0.30)
Sickle cell disease	0 (0.00)	7 (0.12)
Congenital heart disease	0 (0.00)	7 (0.12)

Drugs associated with PAH (possible and definite association) [b]		
Benfluorex	0 (0.00)	1 (0.02)
Cyclophosphamide	0 (0.00)	3 (0.05)
Mitomycin C	0 (0.00)	0 (0.00)
Sofosbuvir	0 (0.00)	1 (0.02)
Leflunomide	0 (0.00)	0 (0.00)
Number of hospitalizations [c]		
0	0 (0.00)	2,126 (37.7)
1	3 (42.9)	1,456 (25.8)
2	1 (14.3)	840 (14.9)
3	1 (14.3)	402 (7.13)
≥ 4	2 (28.6)	813 (14.4)
Number of pulmonologist visits [c]		
0	6 (85.7)	5,184 (92.0)
1	0 (0.00)	136 (2.41)
2-6	1 (14.3)	141 (2.50)
7-11	0 (0.00)	45 (0.80)
≥ 12	0 (0.00)	131 (2.32)

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation).

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S9. Characteristics of Patients, by Outcome Status, for dasatinib patients: Sensitive algorithm

Characteristic	PAH onset (n = 20)	No PAH onset (n = 5,624)
Female	10 (50.0)	2,476 (44.0)
Age, years (mean ± SD)	56.3 ± 12.1	59.6 ± 15.2
Imatinib exposure [a]	120 (15 – 390)	150 (0 – 450)
Prevalent user status	15 (75.0)	3,852 (68.5)
Calendar year		
2008	1 (14.3)	113 (2.00)
2009	0 (0.00)	239 (4.24)
2010	2 (28.6)	264 (4.68)
2011	2 (28.6)	326 (5.78)
2012	0 (0.00)	323 (5.73)
2013	0 (0.00)	373 (6.62)
2014	1 (14.3)	401 (7.11)
2015	0 (0.00)	390 (6.92)
2016	0 (0.00)	474 (8.41)
2017	0 (0.00)	488 (8.66)
2018	0 (0.00)	451 (8.00)
2019	0 (0.00)	458 (8.12)
2020	1 (14.3)	405 (7.18)
2021	0 (0.00)	465 (8.25)
2022	0 (0.00)	467 (8.28)
Comorbidities		
COPD	0 (0.00)	216 (3.84)
Hypertension	13 (65.0)	3,019 (53.7)
Heart Failure	2 (10.0)	307 (5.46)
Diabetes	5 (25.0)	996 (17.7)
VTE	1 (5.00)	316 (5.62)
Dialysis	0 (0.00)	23 (0.41)
Interstitial lung diseases	0 (0.00)	40 (0.71)
Lung transplant	0 (0.00)	0 (0.00)
Lung cancer	0 (0.00)	45 (0.80)
PAH associated conditions		
Systemic Scleroderma	0 (0.00)	8 (0.14)
Portal Hypertension	0 (0.00)	10 (0.18)
HIV positive	0 (0.00)	17 (0.30)
Sickle cell disease	0 (0.00)	7 (0.12)
Congenital heart disease	0 (0.00)	7 (0.12)

Drugs associated with PAH (possible and definite association) [b]		
Benfluorex	0 (0.00)	1 (0.02)
Cyclophosphamide	0 (0.00)	3 (0.05)
Mitomycin C	0 (0.00)	0 (0.00)
Sofosbuvir	0 (0.00)	1 (0.02)
Leflunomide	0 (0.00)	0 (0.00)
Number of hospitalizations [c]		
0	5 (25.0)	2,121 (37.7)
1	7 (35.0)	1,452 (25.8)
2	5 (25.0)	836 (14.9)
3	0 (0.00)	403 (7.17)
≥ 4	3 (15.0)	812 (14.4)
Number of pulmonologist visits [c]		
0	17 (85.0)	5,173 (92.0)
1	0 (0.00)	136 (2.42)
2-6	2 (10.0)	140 (2.50)
7-11	0 (0.00)	45 (0.80)
≥ 12	1 (5.00)	130 (2.31)

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation).

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S10. Incidence rates, hazard ratios and number needed to harm for PAH: specific outcome sensitivity analyses

Exposure	No of patients	No of events	Person-years	Incidence rate (95%CI)[a]	Hazard Ratio (95%CI)	NNH
As-treated:						
Imatinib	20,065	2	54,647	9.8 (0.0 to 86.7)	1.00 (reference)	Reference
Dasatinib	5,644	5	15,221	328.5 (106.7 to 766.6)	**9.05 (1.76 to 46.70)**	3,137
Imatinib	16,438	0	44,647	0.0 (0.0 to 82.6)	/	/
Nilotinib	4,668	0	14,122	0.0 (0.0 to 261.2)	/	/
Imatinib	9,491	0	18,056	0.0 (0.0 to 204.3)	/	Reference
Bosutinib	1,756	2	3,218	621.5 (75.3 to 2,245.1)	/	1,609
Imatinib	6,452	0	12,801	0.0 (0.0 to 288.2)	/	/
Ponatinib	1,019	0	1,543	0.0 (0.0 to 2,391.0)	/	/
Only incident users (i.e. no prior exposure to imatinib):						
Imatinib	8,398	0	35,026	0.0 (0.0 to 105.3)	/	Reference
Dasatinib	1,777	3	7,564	396.6 (81.8 to 1,159.0)	/	2,521
Imatinib	9,014	0	30,664	0.0 (0.0 to 120.3)	/	/
Nilotinib	2,483	0	10,380	0.0 (0.0 to 355.4)	/	/
Imatinib	3,729	0	7,667	0.0 (0.0 to 481.2)	/	/
Bosutinib	418	0	915	0.0 (0.0 to 4,031.7)	/	/
Imatinib	3,345	0	7,629	0.0 (0.0 to 483.5)	/	/
Ponatinib	452	0	942	0.0 (0.0 to 3,916.2)	/	/
Only prevalent users (i.e. prior exposure to imatinib):						
Imatinib	11,667	3	50,311	14.6 (0.1 to 101.4)	1.00 (reference)	Reference
Dasatinib	3,867	4	13,600	294.1 (80.1 to 753.0)	**5.65 (1.25 to 25.55)**	3,577
Imatinib	7,424	1	33,287	7.5 (0.0 to 126.1)	/	/
Nilotinib	2,185	0	7,729	0.0 (0.0 to 477.3)	/	/
Imatinib	5,762	0	15,547	0.0 (0.0 to 237.3)	/	Reference
Bosutinib	1,338	2	3,164	632.2 (76.6 to 2,283.7)	/	1,582
Imatinib	3,107	0	8,582	0.0 (0.0 to 429.9)	/	/
Ponatinib	567	0	1,318	0.0 (0.0 to 2,799.5)	/	/
Including riociguat treated patients:						
Imatinib	20,065	3	85,336	8.6 (0.1 to 59.8)	1.00 (reference)	Reference

Dasatinib	5,644	7	21,164	330.7 (133.0 to 681.5)	**10.16 (2.61 to 39.55)**	3,104
Imatinib	16,438	1	63,951	3.9 (0.0 to 65.6)	/	/
Nilotinib	4,668	0	18,109	0.0 (0.0 to 203.7)	/	/
Imatinib	9,491	0	23,214	0.0 (0.0 to 158.9)	/	Reference
Bosutinib	1,756	2	4,079	490.4 (59.4 to 1,771.4)	/	2,039
Imatinib	6,452	0	16,211	0.0 (0.0 to 227.6)	/	/
Ponatinib	1,019	0	2,260	0.0 (0.0 to 1,632.5)	/	/
1:1 Matching						
Imatinib	5,644	1	24,344	41.1 (1.0 to 228.9)	1.00 (reference)	Reference
Dasatinib	5,644	7	21,160	330.8 (133.0 to 681.6)	**8.28 (1.02 to 67.30)**	3,451
Imatinib	4,668	0	19,629	0.0 (0.0 to 187.9)	/	/
Nilotinib	4,668	0	18,109	0.0 (0.0 to 203.7)	/	/
Imatinib	1,756	0	4,222	0.0 (0.0 to 873.7)	/	Reference
Bosutinib	1,756	2	4,077	490.5 (59.4 to 1,771.9)	/	2,039
Imatinib	1,019	0	2527	0.0 (0.0 to 1,459.8)	/	/
Ponatinib	1,019	0	2260	0.0 (0.0 to 1,632.1)	/	/

[a] Per million person-years. PAH: pulmonary arterial hypertension; No: Number; CI: confidence interval; NNH: number of patients exposed for one year needed to harm; RHC: right heart catheterization.

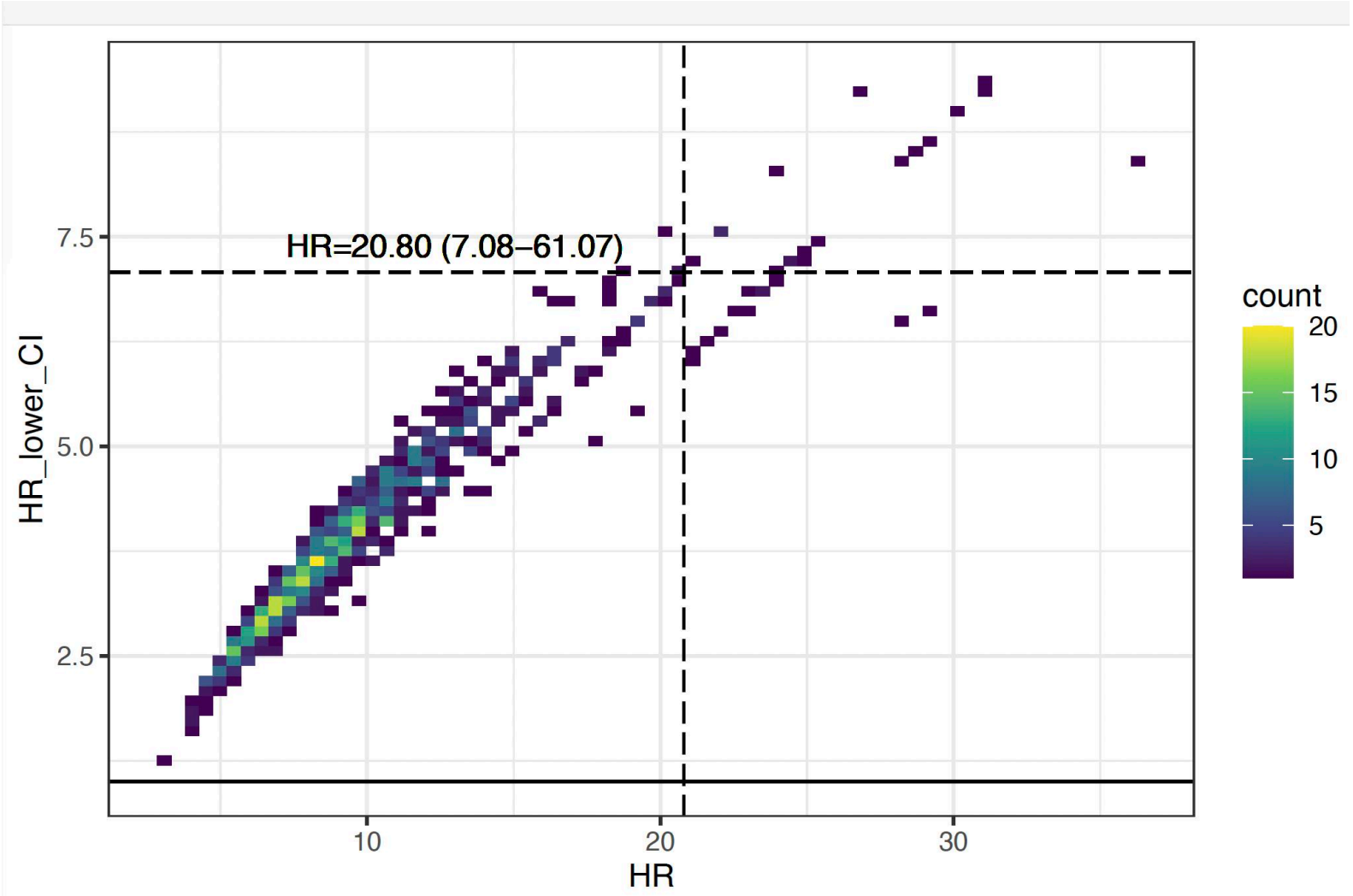


Figure S6. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for dasatinib-associated PAH. Dotted lines represent result of the main analysis (HR=20.80, 95%CI (7.08-61.07)). Solid line represents the value 1 for the lower bound of the HR 95% confidence interval, i.e. limit of significance.

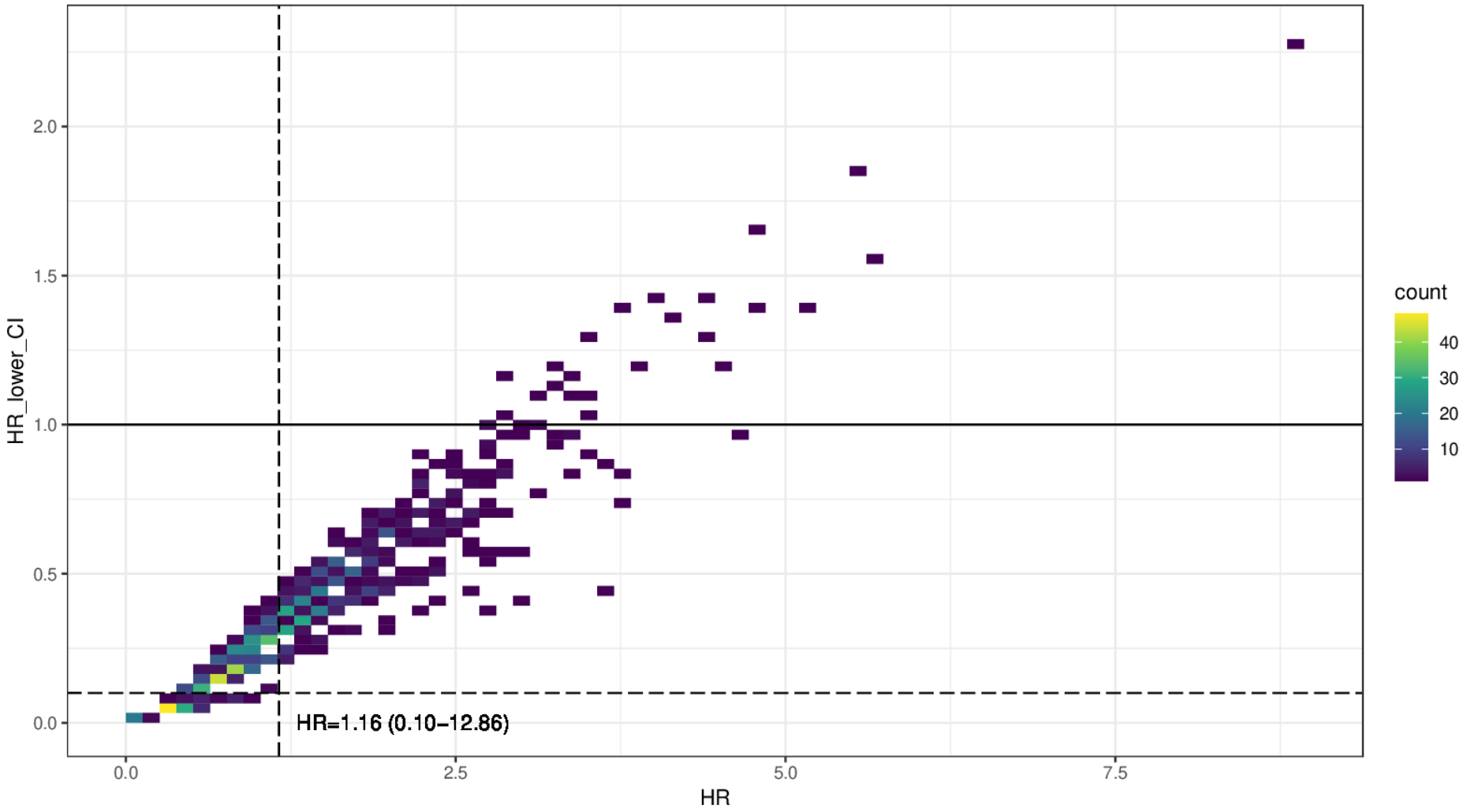


Figure S7. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for nilotinib-associated PAH. Dotted lines represent result of the main analysis (HR=1.16, 95%CI (0.10-12.86)). Solid line represents the value 1 for the lower bound of the HR 95% confidence interval, i.e. limit of significance.

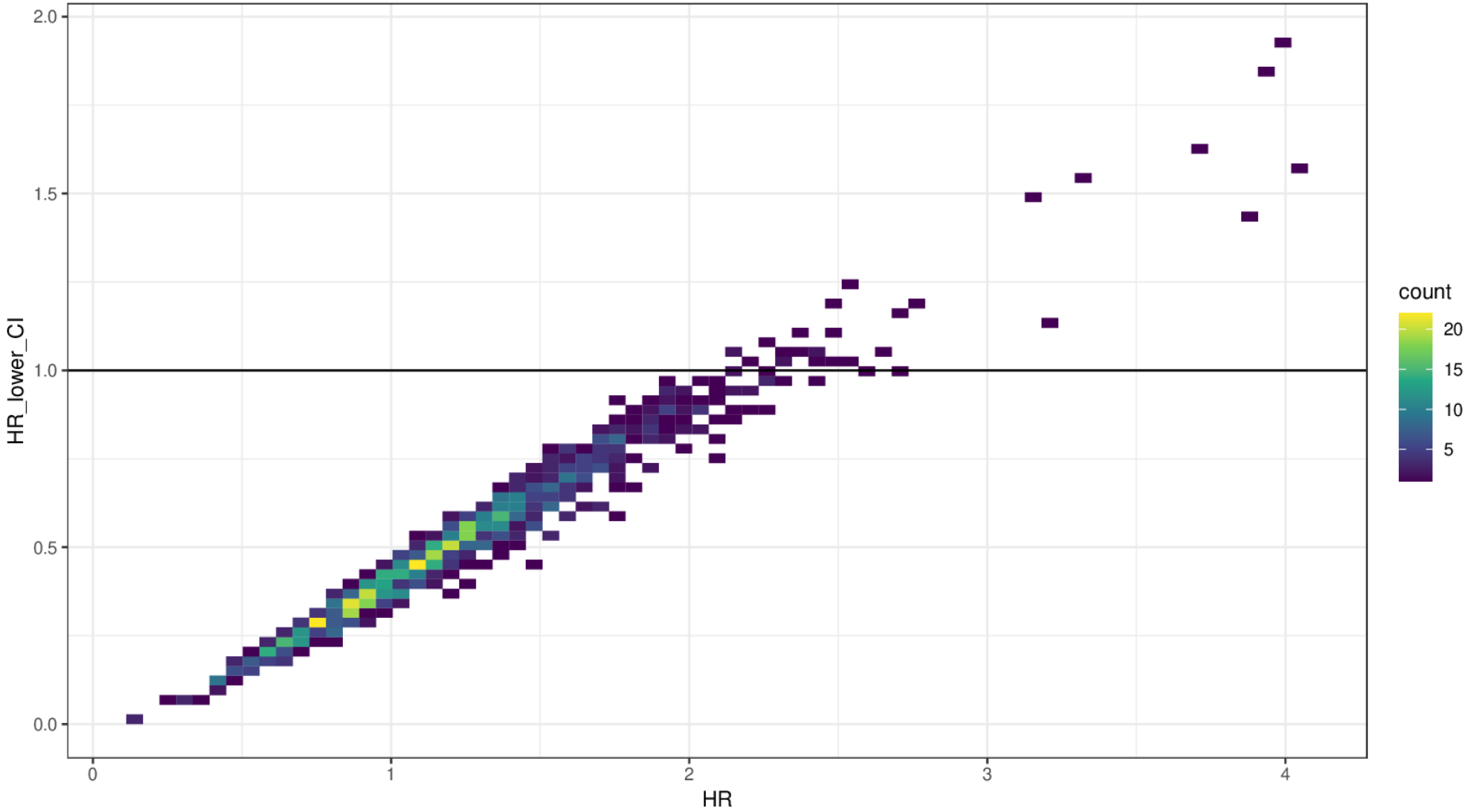


Figure S8. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for bosutinib-associated PAH. Solid line represents the value 1 for the lower bound of the HR 95% confidence interval, i.e. limit of significance.

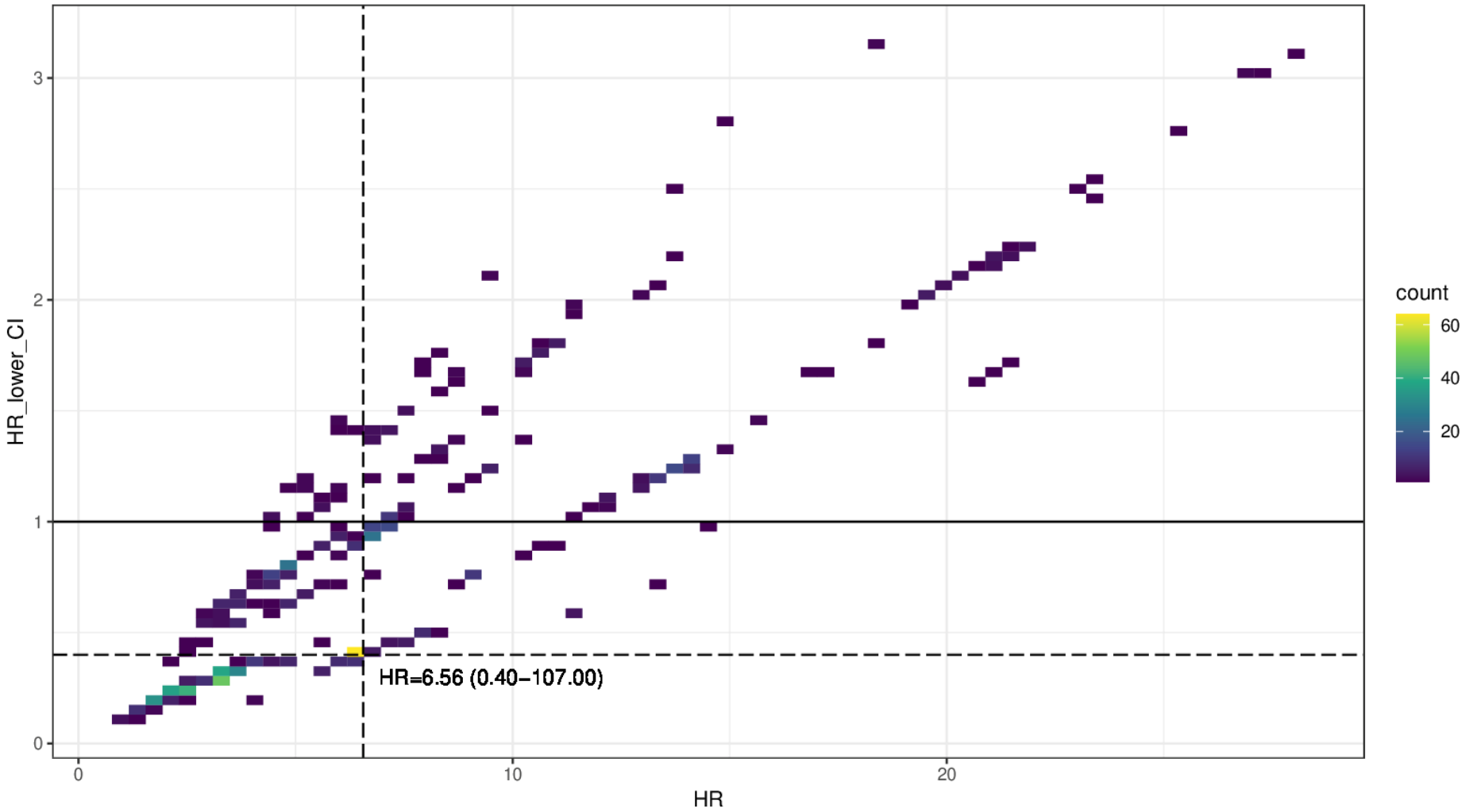


Figure S9. Volcano plot presenting the vibration of effect of HR estimates according to lower bound of HR confidence intervals for ponatinib-associated PAH. Dotted lines represent result of the main analysis (HR=6.56, 95%CI (0.40-107.00)). Solid line represents the value 1 for the lower bound of the HR 95% confidence interval, i.e. limit of significance.

Table S11. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Dasatinib incident new-users

Characteristic	Dasatinib users	Imatinib users	SMD (%)
Number of patients	1,777	8,398	/
Weighted number of patients	1,777	1,777	/
Female	775 (43.6)	783 (44.1)	- 0.9
Age, years (mean ± SD)	55.1 ± 15.3	55.1 ± 7.1	0.1
Imatinib exposure [a]	0 (0 – 0)	0 (0 – 0)	Matching variable
Prevalent user status	0 (0.0)	0 (0.0)	Matching variable
Calendar year			
2008	99 (5.6)	99 (5.6)	Matching variable
2009	119 (6.7)	119 (6.7)	Matching variable
2010	71 (4.0)	71 (4.0)	Matching variable
2011	95 (5.3)	95 (5.3)	Matching variable
2012	93 (5.2)	93 (5.2)	Matching variable
2013	105 (5.9)	105 (5.9)	Matching variable
2014	105 (5.9)	105 (5.9)	Matching variable
2015	112 (6.3)	112 (6.3)	Matching variable
2016	144 (8.1)	144 (8.1)	Matching variable
2017	135 (7.6)	135 (7.6)	Matching variable
2018	133 (7.5)	133 (7.5)	Matching variable
2019	139 (7.8)	139 (7.8)	Matching variable
2020	110 (6.2)	110 (6.2)	Matching variable
2021	153 (8.6)	153 (8.6)	Matching variable
2022	164 (9.2)	164 (9.2)	Matching variable
Comorbidities			
COPD	55 (3.1)	62 (3.5)	- 2.3
Hypertension	704 (39.6)	705 (39.6)	- 0.1
Heart Failure	76 (4.3)	89 (5.0)	- 3.5
Diabetes	244 (13.7)	258 (14.5)	- 2.3
VTE	96 (5.4)	110 (6.2)	- 3.3
Dialysis	5 (0.3)	6 (0.4)	- 1.4
Interstitial lung diseases	9 (0.5)	12 (0.7)	- 2.3
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	15 (0.8)	17 (1.0)	- 1.4
PAH associated conditions			
Systemic Scleroderma	1 (0.1)	0 (0.0)	3.4
Portal Hypertension	3 (0.2)	5 (0.3)	- 2.2
HIV positive	7 (0.4)	10 (0.6)	- 2.3

Sickle cell disease	3 (0.2)	3 (0.2)	- 0.6
Congenital heart disease	1 (0.1)	0 (0.0)	1.5
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	1 (0.1)	1 (0.1)	0.1
Cyclophosphamide	1 (0.1)	3 (0.2)	- 3.5
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	1 (0.1)	0 (0.0)	3.4
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	688 (38.7)	661 (37.2)	3.1
1	441 (24.8)	449 (25.3)	- 1.1
2	264 (14.9)	276 (15.5)	- 1.9
3	119 (6.7)	112 (6.3)	1.5
≥ 4	265 (14.9)	279 (15.7)	- 2.1
Number of pulmonologist visits [c]			
0	1,669 (93.9)	1,657 (93.3)	2.6
1	43 (2.4)	45 (2.5)	- 0.8
2-6	30 (1.7)	38 (2.1)	- 3.3
7-11	7 (0.4)	8 (0.4)	- 0.7
≥ 12	28 (1.6)	29 (1.6)	- 0.3

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a dasatinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S12. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Dasatinib prevalent new-users

Characteristic	Dasatinib users	Imatinib users	SMD (%)
Number of patients	3,867	11,667	/
Weighted number of patients	3,867	3,867	/
Female	1,711 (44.2)	1,669 (43.2)	2.2
Age, years (mean ± SD)	61.7 ± 14.6	61.7 ± 8.4	- 0.1
Imatinib exposure [a]	315 (120–645)	315 (120–645)	Matching variable
Prevalent user status	3,867 (100)	3,867 (100)	Matching variable
Calendar year			
2008	15 (0.4)	15 (0.4)	Matching variable
2009	120 (3.1)	120 (3.1)	Matching variable
2010	195 (5.0)	195 (5.0)	Matching variable
2011	233 (6.0)	233 (6.0)	Matching variable
2012	230 (5.9)	230 (5.9)	Matching variable
2013	268 (6.9)	268 (6.9)	Matching variable
2014	297 (7.7)	297 (7.7)	Matching variable
2015	278 (7.2)	278 (7.2)	Matching variable
2016	331 (8.6)	331 (8.6)	Matching variable
2017	352 (9.1)	352 (9.1)	Matching variable
2018	318 (8.2)	318 (8.2)	Matching variable
2019	319 (8.2)	319 (8.2)	Matching variable
2020	296 (7.7)	296 (7.7)	Matching variable
2021	312 (8.1)	312 (8.1)	Matching variable
2022	303 (7.8)	303 (7.8)	Matching variable
Comorbidities			
COPD	161 (4.2)	176 (4.5)	- 1.9
Hypertension	2,328 (60.2)	2,384 (61.6)	- 2.9
Heart Failure	233 (6)	232 (6)	0.1
Diabetes	757 (19.6)	768 (19.9)	- 0.7
VTE	221 (5.7)	227 (5.9)	- 0.7
Dialysis	18 (0.5)	15 (0.4)	1.2
Interstitial lung diseases	31 (0.8)	31 (0.8)	0.1
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	30 (0.8)	37 (1.0)	- 2.0
PAH associated conditions			
Systemic Scleroderma	7 (0.2)	5 (0.1)	1.0
Portal Hypertension	7 (0.2)	5 (0.1)	1.3
HIV positive	10 (0.3)	13 (0.3)	- 1.3

Sickle cell disease	4 (0.1)	4 (0.1)	- 0.2
Congenital heart disease	6 (0.2)	5 (0.1)	0.8
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	2 (0.1)	3 (0.1)	- 1.2
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	0 (0.0)	0 (0.0)	- 1.3
Number of hospitalizations [c]			
0	1,438 (37.2)	1,394 (36.1)	2.3
1	1,018 (26.3)	1,026 (26.5)	- 0.4
2	577 (14.9)	620 (16)	- 3.1
3	284 (7.3)	289 (7.5)	- 0.5
≥ 4	550 (14.2)	538 (13.9)	0.9
Number of pulmonologist visits [c]			
0	3,522 (91.1)	3,487 (90.2)	3.1
1	92 (2.4)	98 (2.5)	- 1.0
2-6	112 (2.9)	129 (3.3)	- 2.6
7-11	38 (1.0)	49 (1.3)	- 2.8
≥ 12	103 (2.7)	104 (2.7)	- 0.1

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a dasatinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S13. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Nilotinib incident new-users

Characteristic	Nilotinib users	Imatinib users	SMD (%)
Number of patients	2,483	9,014	/
Weighted number of patients	2,483	2,483	/
Female	1,102 (44.4)	1,090 (43.9)	1.0
Age, years (mean ± SD)	52.2 ± 14.3	52.2 ± 7.5	0.0
Imatinib exposure [a]	0 (0 – 0)	0 (0 – 0)	Matching variable
Prevalent user status	0 (0.0)	0 (0.0)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	358 (14.4)	358 (14.4)	Matching variable
2013	246 (9.9)	246 (9.9)	Matching variable
2014	170 (6.8)	170 (6.8)	Matching variable
2015	220 (8.9)	220 (8.9)	Matching variable
2016	200 (8.1)	200 (8.1)	Matching variable
2017	208 (8.4)	208 (8.4)	Matching variable
2018	224 (9.0)	224 (9.0)	Matching variable
2019	221 (8.9)	221 (8.9)	Matching variable
2020	199 (8.0)	199 (8.0)	Matching variable
2021	194 (7.8)	194 (7.8)	Matching variable
2022	243 (9.8)	243 (9.8)	Matching variable
Comorbidities			
COPD	66 (2.7)	78 (3.1)	- 2.9
Hypertension	799 (32.2)	779 (31.4)	1.7
Heart Failure	71 (2.9)	79 (3.2)	- 1.9
Diabetes	236 (9.5)	251 (10.1)	- 2.1
VTE	103 (4.1)	127 (5.1)	- 4.6
Dialysis	6 (0.2)	9 (0.3)	- 1.9
Interstitial lung diseases	6 (0.2)	7 (0.3)	- 0.8
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	7 (0.3)	13 (0.5)	- 3.9
PAH associated conditions			
Systemic Scleroderma	1 (0.0)	1 (0.0)	- 0.1
Portal Hypertension	1 (0.0)	1 (0.0)	0.2
HIV positive	5 (0.2)	8 (0.3)	- 2.6

Sickle cell disease	6 (0.2)	4 (0.2)	1.7
Congenital heart disease	3 (0.1)	4 (0.2)	- 1.1
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	1 (0.0)	1 (0.0)	- 0.3
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	1 (0.0)	1 (0.0)	1.2
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	1,114 (44.9)	1,098 (44.2)	1.3
1	901 (36.3)	903 (36.4)	- 0.2
2	261 (10.5)	245 (9.9)	2.2
3	83 (3.3)	86 (3.5)	- 0.6
≥ 4	124 (5.0)	152 (6.1)	- 4.8
Number of pulmonologist visits [c]			
0	2,348 (94.6)	2,335 (94.0)	2.3
1	45 (1.8)	45 (1.8)	0.0
2-6	43 (1.7)	54 (2.2)	- 3.3
7-11	11 (0.4)	13 (0.5)	- 1.0
≥ 12	36 (1.4)	36 (1.5)	0.0

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a nilotinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S14. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Nilotinib prevalent new-users

Characteristic	Nilotinib users	Imatinib users	SMD (%)
Number of patients	2,185	7,424	/
Weighted number of patients	2,185	2,185	/
Female	943 (43.2)	929 (42.5)	1.3
Age, years (mean ± SD)	60.2 ± 14.5	60.2 ± 7.9	0.0
Imatinib exposure [a]	300 (120–690)	300 (120–690)	Matching variable
Prevalent user status	2,185 (100)	2,185 (100)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	2 (0.1)	2 (0.1)	Matching variable
2012	443 (20.3)	443 (20.3)	Matching variable
2013	244 (11.2)	244 (11.2)	Matching variable
2014	193 (8.8)	193 (8.8)	Matching variable
2015	183 (8.4)	183 (8.4)	Matching variable
2016	154 (7.0)	154 (7.0)	Matching variable
2017	188 (8.6)	188 (8.6)	Matching variable
2018	208 (9.5)	208 (9.5)	Matching variable
2019	156 (7.1)	156 (7.1)	Matching variable
2020	134 (6.1)	134 (6.1)	Matching variable
2021	153 (7.0)	153 (7.0)	Matching variable
2022	127 (5.8)	127 (5.8)	Matching variable
Comorbidities			
COPD	93 (4.3)	101 (4.6)	- 1.8
Hypertension	1,269 (58.1)	1,376 (63.0)	- 10.0
Heart Failure	121 (5.5)	132 (6.0)	- 2.1
Diabetes	342 (15.7)	379 (17.4)	- 4.6
VTE	116 (5.3)	130 (6.0)	- 2.9
Dialysis	6 (0.3)	7 (0.3)	- 1.1
Interstitial lung diseases	26 (1.2)	19 (0.9)	3.2
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	26 (1.2)	28 (1.3)	- 1.0
PAH associated conditions			
Systemic Scleroderma	3 (0.1)	4 (0.2)	- 1.1
Portal Hypertension	2 (0.1)	2 (0.1)	0.2
HIV positive	0 (0.0)	0 (0.0)	0.0

Sickle cell disease	2 (0.1)	2 (0.1)	- 0.6
Congenital heart disease	3 (0.1)	4 (0.2)	- 1.3
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	2 (0.1)	0 (0.0)	3.5
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	1 (0.0)	1 (0.0)	1.2
Number of hospitalizations [c]			
0	793 (36.3)	673 (30.8)	11.7
1	604 (27.6)	592 (27.1)	1.2
2	346 (15.8)	406 (18.6)	- 7.3
3	173 (7.9)	204 (9.3)	- 5.1
≥ 4	269 (12.3)	310 (14.2)	- 5.5
Number of pulmonologist visits [c]			
0	1,961 (89.7)	1,954 (89.4)	1.1
1	65 (3.0)	48 (2.2)	4.8
2-6	80 (3.7)	86 (3.9)	- 1.4
7-11	22 (1.0)	25 (1.1)	- 1.2
≥ 12	57 (2.6)	72 (3.3)	- 4.1

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a nilotinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S15. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Bosutinib incident new-users

Characteristic	Bosutinib users	Imatinib users	SMD (%)
Number of patients	418	3,729	/
Weighted number of patients	418	418	/
Female	155 (37.1)	156 (37.2)	- 0.3
Age, years (mean ± SD)	58.2 ± 14.7	58.3 ± 4.9	- 0.2
Imatinib exposure [a]	0 (0 – 0)	0 (0 – 0)	Matching variable
Prevalent user status	0 (0.0)	0 (0.0)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	0 (0.0)	0 (0.0)	Matching variable
2014	9 (2.2)	9 (2.2)	Matching variable
2015	32 (7.7)	32 (7.7)	Matching variable
2016	23 (5.5)	23 (5.5)	Matching variable
2017	18 (4.3)	18 (4.3)	Matching variable
2018	32 (7.7)	32 (7.7)	Matching variable
2019	33 (7.9)	33 (7.9)	Matching variable
2020	65 (15.6)	65 (15.6)	Matching variable
2021	97 (23.2)	97 (23.2)	Matching variable
2022	109 (26.1)	109 (26.1)	Matching variable
Comorbidities			
COPD	15 (3.6)	14 (3.4)	1.1
Hypertension	238 (56.9)	222 (53.2)	7.6
Heart Failure	33 (7.9)	27 (6.5)	5.2
Diabetes	69 (16.5)	77 (18.4)	- 4.9
VTE	19 (4.5)	25 (6.0)	- 6.3
Dialysis	1 (0.2)	2 (0.4)	- 2.8
Interstitial lung diseases	3 (0.7)	3 (0.7)	- 0.3
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	3 (0.7)	5 (1.1)	- 4.1
PAH associated conditions			
Systemic Scleroderma	0 (0.0)	0 (0.0)	0.0
Portal Hypertension	1 (0.2)	1 (0.1)	2.2
HIV positive	0 (0.0)	0 (0.0)	- 1.9

Sickle cell disease	0 (0.0)	0 (0.0)	0.0
Congenital heart disease	1 (0.2)	1 (0.2)	0.8
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	0 (0.0)	0 (0.0)	0.0
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	197 (47.1)	192 (45.8)	2.6
1	117 (28.0)	111 (26.4)	3.5
2	51 (12.2)	54 (13.0)	- 2.4
3	23 (5.5)	25 (5.9)	- 1.8
≥ 4	30 (7.2)	37 (8.8)	- 6.1
Number of pulmonologist visits [c]			
0	378 (90.4)	374 (89.5)	3.2
1	12 (2.9)	13 (3.0)	- 0.8
2-6	14 (3.3)	14 (3.3)	0.3
7-11	3 (0.7)	4 (1.1)	- 3.7
≥ 12	11 (2.6)	13 (3.2)	- 3.3

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a bosutinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S16. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Bosutinib prevalent new-users

Characteristic	Bosutinib users	Imatinib users	SMD (%)
Number of patients	1,338	5,762	/
Weighted number of patients	1,338	1,338	/
Female	570 (42.6)	562 (42.0)	1.2
Age, years (mean ± SD)	66.4 ± 12.6	66.4 ± 6.1	- 0.3
Imatinib exposure [a]	360 (150–735)	360 (150–735)	Matching variable
Prevalent user status	1,338 (100)	1,338 (100)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	2 (0.1)	2 (0.1)	Matching variable
2014	19 (1.4)	19 (1.4)	Matching variable
2015	102 (7.6)	102 (7.6)	Matching variable
2016	86 (6.4)	86 (6.4)	Matching variable
2017	140 (10.5)	140 (10.5)	Matching variable
2018	146 (10.9)	146 (10.9)	Matching variable
2019	174 (13.0)	174 (13.0)	Matching variable
2020	232 (17.3)	232 (17.3)	Matching variable
2021	208 (15.5)	208 (15.5)	Matching variable
2022	229 (17.1)	229 (17.1)	Matching variable
Comorbidities			
COPD	98 (7.3)	91 (6.8)	2.1
Hypertension	1,070 (80.0)	1,075 (80.4)	- 1.0
Heart Failure	191 (14.3)	171 (12.8)	4.4
Diabetes	341 (25.5)	348 (26.0)	- 1.2
VTE	86 (6.4)	90 (6.7)	- 1.2
Dialysis	7 (0.5)	5 (0.4)	2.2
Interstitial lung diseases	24 (1.8)	13 (1.0)	6.7
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	22 (1.6)	32 (2.4)	- 5.3
PAH associated conditions			
Systemic Scleroderma	3 (0.2)	3 (0.2)	0.6
Portal Hypertension	2 (0.1)	4 (0.3)	- 2.6
HIV positive	2 (0.1)	2 (0.2)	- 0.1

Sickle cell disease	3 (0.2)	1 (0.0)	5.1
Congenital heart disease	2 (0.1)	1 (0.1)	1.4
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	0 (0.0)	0 (0.0)	0.0
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	1 (0.1)	1 (0.0)	1.1
Number of hospitalizations [c]			
0	500 (37.4)	512 (38.3)	- 1.9
1	363 (27.1)	361 (27.0)	0.4
2	202 (15.1)	195 (14.6)	1.4
3	114 (8.5)	100 (7.5)	3.8
≥ 4	159 (11.9)	170 (12.7)	- 2.4
Number of pulmonologist visits [c]			
0	1,130 (84.5)	1,117 (83.5)	2.6
1	53 (4.0)	68 (5.1)	- 5.5
2-6	65 (4.9)	60 (4.5)	1.9
7-11	23 (1.7)	20 (1.5)	1.5
≥ 12	67 (5.0)	72 (5.4)	- 1.8

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a bosutinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S17. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Ponatinib incident new-users

Characteristic	Ponatinib users	Imatinib users	SMD (%)
Number of patients	452	3,345	/
Weighted number of patients	452	452	/
Female	201 (44.5)	196 (43.4)	2.2
Age, years (mean ± SD)	52.5 ± 15.6	52.5 ± 5.7	0.2
Imatinib exposure [a]	0 (0 – 0)	0 (0 – 0)	Matching variable
Prevalent user status	0 (0.0)	0 (0.0)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	0 (0.0)	0 (0.0)	Matching variable
2014	0 (0.0)	0 (0.0)	Matching variable
2015	0 (0.0)	0 (0.0)	Matching variable
2016	62 (13.7)	62 (13.7)	Matching variable
2017	42 (9.3)	42 (9.3)	Matching variable
2018	48 (10.6)	48 (10.6)	Matching variable
2019	64 (14.2)	64 (14.2)	Matching variable
2020	59 (13.1)	59 (13.1)	Matching variable
2021	74 (16.4)	74 (16.4)	Matching variable
2022	103 (22.8)	103 (22.8)	Matching variable
Comorbidities			
COPD	12 (2.7)	12 (2.7)	- 0.1
Hypertension	207 (45.8)	208 (46.0)	- 0.4
Heart Failure	27 (6.0)	27 (6.0)	- 0.1
Diabetes	53 (11.7)	61 (13.4)	- 5.1
VTE	35 (7.7)	38 (8.4)	- 2.4
Dialysis	1 (0.2)	1 (0.3)	- 0.6
Interstitial lung diseases	5 (1.1)	2 (0.5)	6.9
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	3 (0.7)	3 (0.7)	- 0.9
PAH associated conditions			
Systemic Scleroderma	0 (0.0)	0 (0.0)	- 1.7
Portal Hypertension	1 (0.2)	1 (0.2)	1.3
HIV positive	1 (0.2)	1 (0.2)	- 0.2

Sickle cell disease	2 (0.4)	0 (0.0)	8.0
Congenital heart disease	1 (0.2)	1 (0.3)	- 1.0
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	0 (0.0)	0 (0.0)	0.0
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	129 (28.5)	140 (31.0)	- 5.5
1	100 (22.1)	98 (21.6)	1.3
2	56 (12.4)	53 (11.7)	2.0
3	28 (6.2)	28 (6.2)	0.1
≥ 4	139 (30.8)	133 (29.5)	2.8
Number of pulmonologist visits [c]			
0	423 (93.6)	416 (91.9)	6.4
1	10 (2.2)	8 (1.7)	3.7
2-6	11 (2.4)	14 (3.2)	- 4.7
7-11	2 (0.4)	3 (0.7)	- 3.4
≥ 12	6 (1.3)	11 (2.5)	- 8.3

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a ponatinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

Table S18. Characteristics of Patients, by Exposure Status, Matched on TCPS and weighted by the number of controls: Ponatinib prevalent new-users

Characteristic	Ponatinib users	Imatinib users	SMD (%)
Number of patients	567	3,107	/
Weighted number of patients	567	567	/
Female	252 (44.4)	233 (41.1)	6.7
Age, years (mean ± SD)	59.8 ± 14.0	59.8 ± 6.0	0.0
Imatinib exposure [a]	270 (120–480)	270 (120–480)	Matching variable
Prevalent user status	567 (100)	567 (100)	Matching variable
Calendar year			
2008	0 (0.0)	0 (0.0)	Matching variable
2009	0 (0.0)	0 (0.0)	Matching variable
2010	0 (0.0)	0 (0.0)	Matching variable
2011	0 (0.0)	0 (0.0)	Matching variable
2012	0 (0.0)	0 (0.0)	Matching variable
2013	0 (0.0)	0 (0.0)	Matching variable
2014	0 (0.0)	0 (0.0)	Matching variable
2015	0 (0.0)	0 (0.0)	Matching variable
2016	90 (15.9)	90 (15.9)	Matching variable
2017	72 (12.7)	72 (12.7)	Matching variable
2018	72 (12.7)	72 (12.7)	Matching variable
2019	85 (15.0)	85 (15.0)	Matching variable
2020	80 (14.1)	80 (14.1)	Matching variable
2021	95 (16.8)	95 (16.8)	Matching variable
2022	73 (12.9)	73 (12.9)	Matching variable
Comorbidities			
COPD	25 (4.4)	23 (4.0)	1.9
Hypertension	355 (62.6)	365 (64.4)	- 3.8
Heart Failure	39 (6.9)	40 (7.0)	- 0.5
Diabetes	113 (19.9)	120 (21.2)	- 3.2
VTE	44 (7.8)	52 (9.1)	- 4.9
Dialysis	3 (0.5)	4 (0.6)	- 1.2
Interstitial lung diseases	6 (1.1)	8 (1.5)	- 3.7
Lung transplant	0 (0.0)	0 (0.0)	0.0
Lung cancer	7 (1.2)	14 (2.4)	- 9.0
PAH associated conditions			
Systemic Scleroderma	1 (0.2)	1 (0.1)	2.4
Portal Hypertension	1 (0.2)	1 (0.1)	2.1
HIV positive	2 (0.4)	2 (0.4)	- 0.3

Sickle cell disease	1 (0.2)	2 (0.4)	- 3.9
Congenital heart disease	1 (0.2)	2 (0.3)	- 1.9
Drugs associated with PAH (possible and definite association) [b]			
Benfluorex	0 (0.0)	0 (0.0)	0.0
Cyclophosphamide	1 (0.2)	0 (0.0)	5.9
Mitomycin C	0 (0.0)	0 (0.0)	0.0
Sofosbuvir	0 (0.0)	0 (0.0)	0.0
Leflunomide	0 (0.0)	0 (0.0)	0.0
Number of hospitalizations [c]			
0	180 (31.7)	176 (31.0)	1.6
1	108 (19.0)	111 (19.7)	- 1.5
2	83 (14.6)	93 (16.4)	- 4.8
3	49 (8.6)	53 (9.4)	- 2.6
≥ 4	147 (25.9)	134 (23.6)	5.4
Number of pulmonologist visits [c]			
0	506 (89.2)	489 (86.2)	9.2
1	16 (2.8)	24 (4.3)	- 7.9
2-6	22 (3.9)	22 (3.9)	0.1
7-11	8 (1.4)	9 (1.7)	- 2.0
≥ 12	15 (2.6)	23 (4.0)	- 7.4

Characteristics post-matching on calendar year (exact), imatinib exposure since base cohort entry (exact), prevalent status (exact), age (± 1 year) and TCPS (± 0.2*standard deviation). Imatinib users were weighted in accordance to the number of controls that were matched to the exposed patient to whom they were matched. For example, an imatinib user matched to a ponatinib user with 10 controls, will have a weight of 0.1.

Characteristics are measured any time before index date unless otherwise specified.

Data are given as n (%) unless otherwise specified.

TCPS: Time Conditional Propensity Score.

SMD: Standardized Mean Differences.

[a] Duration of imatinib exposure since base cohort entry, days, median (IQR).

[b] Drugs associated with pulmonary arterial hypertension as defined by the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2).

[c] Measured in the year before index date.

COPD: Chronic Obstructive Pulmonary Disease.

VTE: Venous Thromboembolic Events (i.e. pulmonary embolism, phlebitis and thrombophlebitis, other venous embolism and thrombosis).

PAH: Pulmonary Arterial Hypertension.

HIV: Human Immunodeficiency Virus.

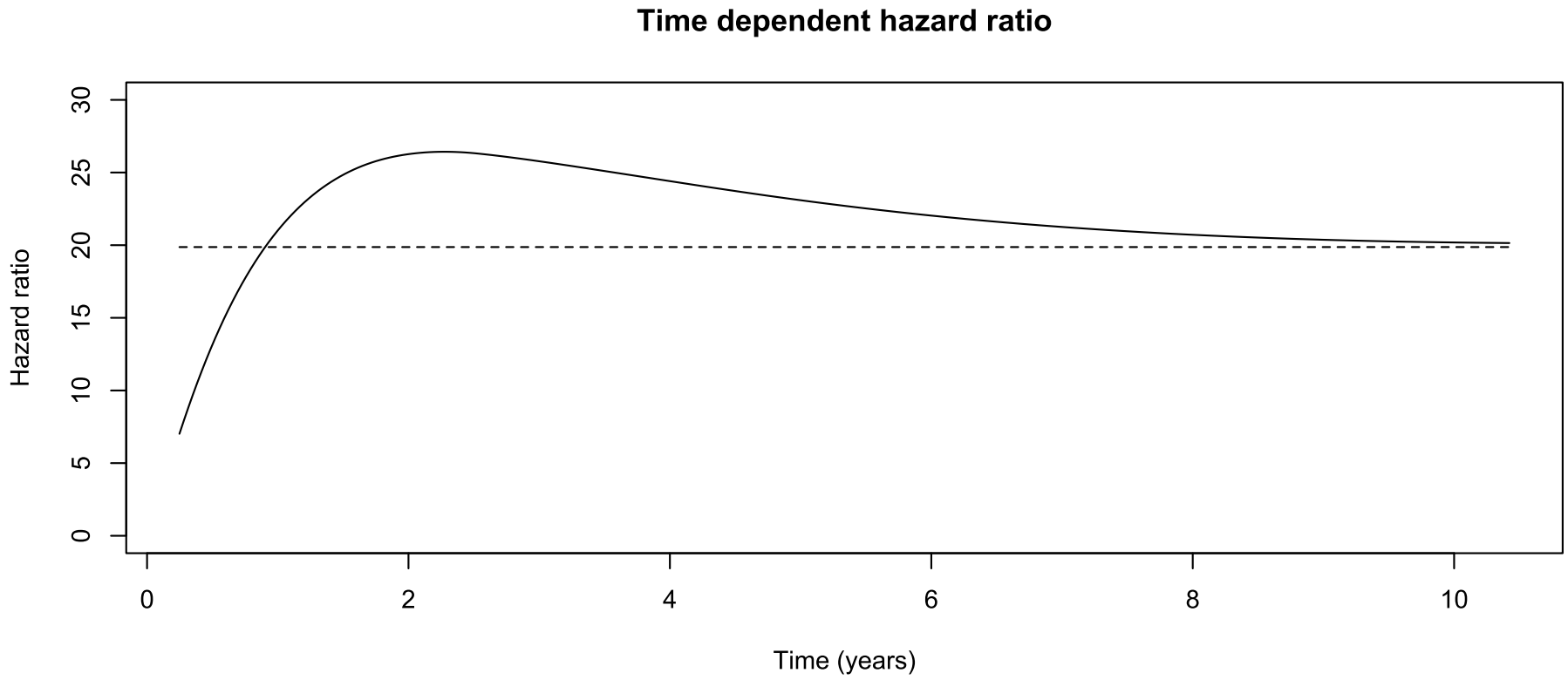


Figure S10. Time-dependant hazard ratio of pulmonary arterial hypertension (PAH) in the dasatinib versus imatinib cohort.

REFERENCES

1. Klau S, Hoffmann S, Patel CJ, Ioannidis JP, Boulesteix AL. Examining the robustness of observational associations to model, measurement and sampling uncertainty with the vibration of effects framework. Int J Epidemiol. 3 mars 2021;50(1):266-78.

2. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 11 oct 2022;43(38):3618-731.