UNIVERSITE DE PARIS

École Doctorale MTCI (ED N° 563)

INSERM UMR 1266 - Institut de Psychiatrie et Neurosciences de Paris

Équipe Biomarqueurs en Imagerie

Marqueurs de mauvais pronostic fonctionnel malgré succès de la recanalisation par thrombectomie mécanique dans l'accident vasculaire cérébral ischémique aigu.

Par Wajih Ben Hassen

Thèse de Doctorat en Imageries

Dirigée par le Professeur Olivier Naggara

Présentée et soutenue publiquement le 17 Décembre 2021

Devant un jury composé de :

Catherine Oppenheim (PU-PH), Université de Paris, Présidente du Jury

Aymeric Rouchaud (PU-PH), Université de Limoges, rapporteur

Nicolas Menjot de Champfleur (PU-PH), Université de Montpellier, rapporteur

Laurent Spelle (PU-PH), Université Paris Sud, examinateur

Sonia Alamowitch (PU-PH), Université Paris Sorbonne, examinatrice

Olivier Naggara (PU-PH), Université de Paris, directeur de thèse

RESUME

Environ 50 % des patients victimes d'un accident vasculaire cérébral (AVC) ischémique causé par une occlusion d'un gros vaisseau proximal de la circulation antérieure ne retrouvent pas leur indépendance fonctionnelle, même lorsque la recanalisation est obtenue par thrombectomie mécanique (TM). Des facteurs déjà identifiés, tels qu'un âge plus avancé, un score NIHSS (National Institutes of Health Stroke Scale) ou un score ASPECTS (Alberta Stroke Program Early Computed Tomography Score) initial plus élevés sont associés à un mauvais pronostic clinique malgré une recanalisation réussie. Une meilleure compréhension des déterminants clés d'une détérioration clinique, malgré une reperfusion réussie après TM pourrait aider au développement de traitements adjuvants. A travers ce travail, nous avons donc cherché à quantifier l'importance des facteurs prédictifs déjà connus et essayé d'identifier de nouveaux biomarqueurs prédictifs de mauvais pronostic. Une base de données prospective a été constituée, composée de malades traités par thrombectomie mécanique à la phase aiguë de l'occlusion proximale d'une artère intra-crânienne. Cette base a été alimentée par deux centres : le Centre Hospitalier Sainte Anne et Le centre Hospitalo-Universitaire de Lille. En outre, une collaboration internationale avec le groupe MR-CLEAN a permis d'étudier >3100 patients et de hiérarchiser les facteurs prédictifs de mauvais pronostic malgré une bonne reperfusion. L'identification d'un facteur aggravant tel qu'une pneumopathie infectieuse incite à des traitements de prévention spécifique. D'autres facteurs sont dits «post procéduraux», tels que la croissance du volume de l'infarctus ou l'hémorragie cérébrale symptomatique, tout en pouvant être associés à certains marqueurs « perprocéduraux ». Ainsi, un facteur technique de la procédure, le nombre de tentatives nécessaires au retrait du thrombus occlusif, s'avère, au-delà d'un certain seuil, inopérant pour stopper la croissance du volume de l'infarctus. Un autre marqueur, constaté au cours de la procédure, l'opacification veineuse précoce, s'avère fortement associé à la survenue à 24h d'une hémorragie cérébrale symptomatique, pouvant inciter à une surveillance tensionnelle plus étroite chez ces patients, ainsi qu'à une plus grande prudence dans l'utilisation des traitements antiagrégants / anticoagulants. Ce travail constitue donc une aide à une meilleure compréhension des mécanismes contribuant à une évolution clinique défavorable malgré une recanalisation angiographique satisfaisante. Il souligne la nécessité du développement de stratégies de neuroprotection efficaces post recanalisation.

ABSTRACT

Approximately 50% of patients with acute ischemic stroke caused by a large vessel occlusion (AIS-LVO) of the anterior circulation do not regain functional independence, even when a successful recanalization is achieved by mechanical thrombectomy (MT). Previously identified factors such as older age, higher initial National Institutes of Health Stroke Scale (NIHSS) score, or Alberta Stroke Program Early Computed Tomography Score (ASPECTS) are associated with a poor clinical prognosis despite successful recanalization. A better understanding of the key determinants of clinical deterioration despite successful reperfusion after TM could help in the development of adjuvant treatments. Through this work, we therefore sought to quantify the importance of already known predictive factors and tried to identify new predictive biomarkers of poor prognosis. A prospective database was created, composed of patients treated by mechanical thrombectomy. This database was supplied from two comprehensive stroke centers: Sainte Anne Hospital and Lille University Hospital. In addition, an international collaboration with the MR-CLEAN group allowed us to study more than 3100 patients and to rank the predictive factors of poor prognosis despite good reperfusion. The identification of an aggravating factor such as an infectious pneumopathy prompts specific preventive treatments. Other identified factors labeled as "postprocedural" such as infarct volume growth or symptomatic cerebral hemorrhage could be associated with "perprocedural" markers. Thus, a technical factor of the procedure: the number of attempts necessary to remove arterial clot, is correlated beyond a certain threshold to an increased infarct growth. Another marker observed during the procedure, early venous opacification, was found to be strongly associated with the occurrence of symptomatic cerebral hemorrhage at 24 hours, which may lead to closer blood pressure monitoring in these patients, as well as greater caution in the use of antiaggregant/anticoagulant treatments. This work is therefore an aid to a better understanding of the mechanisms contributing to an unfavorable clinical evolution despite satisfactory angiographic recanalization. It underlines the need for the development of effective post-recanization neuroprotection strategies.

Remerciements

Professeur Olivier Naggara, PU-PH, Université de Paris

Cher Olivier, merci pour m'avoir guidé vers la neuro-radiologie interventionelle, de m'avoir accueilli dans cette belle équipe de Sainte-Anne, de m'avoir appris ce beau métier avec rigueur et beaucoup d'humanité. Merci de m'insuffler tous les jours par tes conseils, ton soutien et ta bienveillance, cette volonté d'aller de l'avant et de progresser dans tous les domaines. Tu m'as appris plus qu'un métier, mais également une vision et une manière intelligente et humaine de voir le milieu hospitalier dans sa complexité, le milieu scientifique et académique. Exercer à tes côtés et au sein de l'équipe à Sainte-Anne est un plaisir et surtout une vraie chance. Merci.

Professeur Aymeric Rouchaud, PU-PH, Université de Limoges

Cher Aymeric, merci d'avoir accepté d'être le rapporteur de cette thèse de sciences. Ton dynamisme, ton excellence et bienveillance sont un modèle d'inspiration. Merci pour la richesse et la qualité des intéractions scientifiques ou en congrès.

Professeur Nicolas Menjot de Champfleur, PU-PH, Université de Montpellier

Cher Professeur Menjot de Champfleur, merci pour votre bienveillance et de m'avoir fait l'honneur de lire et juger ce travail.

Professeure Sonia Alamowitch, PU-PH, Sorbonne Université

Chère Professeure Alamowitch, merci d'avoir accepté de juger ce travail avec votre grande expertise. C'est un honneur de vous compter parmi les membres de ce jury.

Professeur Laurent Spelle, PU-PH, Université Paris- Saclay

Cher Pr Spelle, merci de me faire l'honneur de porter votre regard d'expert scientifique mondialement reconnu en neuroradiologie interventionnelle sur ce travail.

Professeure Catherine Oppenheim, PU-PH, Université de Paris

Chère Catherine, merci de m'avoir initié à la recherche avec ta passion contagieuse, ta rigueur et ta ténacité. Merci d'avoir créé ce cadre idéal pour la recherche et pour ton investissement et ta disponibilité de tous les jours. Je profite de ce travail pour t'exprimer toute ma gratitude et te remercier pour ta confiance au quotidien.

Merci au Pr Jean-François Meder,

Cher Jean-François, merci de m'avoir accueilli dans l'équipe de Sainte-Anne. Tes précieux conseils, ta bienveillance constante, ton amour du partage, de la transmission et ta force de travail m'ont forgé et me montrent la voie à suivre pour le reste de ma carrière. Que ce travail soit le témoin de toute ma gratitude.

Merci à la Dream-Team NRI de Sainte-Anne : Denis, Christine, Olivier, Monsieur Aymard, Grégoire et Basile. Merci pour cette ambiance de travail, cette cohésion d'équipe, vos enseignements, votre soutien dans les moments difficiles et pour tous ces moments de bonheur au travail. Merci également à l'autre Dream-Team Diagnostique : Jean François, Catherine, Eric, Sylvie, Charles, Raphaëlle, Myriam, Djallel, Ghazi, Joseph, Corentin, Alix, Sophie et Laurence pour ce plaisir quotidien de travailler à vos côtés. Je me sens chanceux et fier d'appartenir à cette grande famille de Sainte-Anne.

Merci à l'équipe de Manipulateurs de Sainte-Anne: Jean-Philippe, Sawsen, Manue, Isabelle, les cousins Mehdi et Jeremy, le couple Julien-Around, Chloé, Christopher, Elisa, Morgane, Anna, Charlotte, Romain, Laurence et Méline et à Mme Flavie Garcia. Ce travail n'aurait jamais pu voir le jour sans vos efforts quotidiens. Merci pour votre rigueur, vote force de travail et votre bonne humeur. Que ce travail soit l'expression de toute ma gratitude envers toute l'équipe.

Merci à l'équipe de Secrétaires, notamment à Bénédicte et Céline pour leur soutien et leur efficacité. Merci à Philippe (flèche d'or) pour ton professionnalisme, ton dévouement et ton sens du travail toujours pour le bien des malades.

Merci à Michèle Viemont pour ta précieuse aide pour la gestion des bases et des différents essais thérapeutiques, toujours compréhensive et avec le sourire.

Merci à toutes les équipes médicales et paramédiacales du pôle Neurosciences, des services d'Anesthésie et Réanimation, Neurologie, Neurochirurgie et Rééducation pour leur professionnalisme et leur aide au quotidien.

Merci à l'équipe de NRI et de Neurologie de Lille, en particulier aux Dr Nicolas Bricout, Dr Marco Pasi et Dr Hilde Hénon pour avoir accepté de partager leur large base de données qui a permis la réalisation des différents travaux. J'espère que cette collaboration continuera pour les années à venir.

Merci au PSG de bien vouloir gagner la Champions.

A mes parents, ma sœur et mes frères pour leurs soutien et amour sans limites.

Pour Inès, Léopold et Chloé.

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A. Introduction

L'accident vasculaire cérébral (AVC) est la seconde cause de mortalité dans le monde et une cause majeure de handicap,[1] avec un coût de prise en charge pour l'assurance maladie avoisinant les 5.3 milliard d'euros annuels.[2] Plus de 80% des AVC sont de nature ischémique, due à une occlusion artérielle responsable d'une destruction du parenchyme cérébral et d'une détérioration des fonctions neurologiques. Plus d'un tiers des accidents vasculaires cérébraux ischémiques (AVCi) sont causés par une occlusion d'une artère intra-crânienne dite « de gros calibre », c.à.d. la terminaison de l'artère carotide interne ou ses branches de division proximales (M1 ou M2), les segment distaux des artères vertébrales ou l'artère basilaire.[3]

A- I. Evaluation initiale des AVCi

L'installation brutale d'un déficit neurologique « systématisé » à un territoire artériel cérébral est la présentation typique d'un AVC ischémique. La prise en charge initiale doit être rapide, une glycémie capillaire doit être mesurée systématiquement pour exclure une hypoglycémie puis une imagerie cérébrale en urgence droit être pratiquée afin d'écarter la possibilité d'une hémorragie intracérébrale et de visualiser les vaisseaux intra-crâniens à la recherche d'une occlusion artérielle. Les modalités d'imagerie peuvent varier selon les habitudes des centres et la disponibilité des machines entre scanner et IRM ; l'essentiel étant de réaliser l'évaluation dans les meilleurs délais avec des protocoles adaptés.[4] L'imagerie initiale permet d'identifier les patients candidats à un traitement de recanalisation. Le scanner sans injection ou la séquence de Diffusion en IRM permettent de déterminer le Alberta Stroke Program Early Computed Tomography Score (ASPECTS) pour les occlusions de l'artère cérébrale moyenne. Ce score varie de 0 à 10, 0 indiquant un infarcissement de la totalité du territoire sylvien.[5] L'angioscanner ou l'angiographie par résonance magnétique (ARM TOF) permettent de localiser l'occlusion intra-crânienne, l'occlusion du segment terminal de l'artère carotide interne ou du segment M1 de l'artère cébrale moyenne définissant une occlusion dite proximale. Les séquences de Perfusion en scanner ou IRM permettent de mesurer le territoire en souffrance au-delà du cœur de l'infarctus, territoire appelé pénombre ischémique. Une recanalisation rapide permettrait de sauver le parenchyme cérébral en pénombre, mais pas du cœur de l'infarctus, considéré comme définitivement détruit. La gravité du déficit neurologique initial est mesurée au moyen de l'échelle NIHSS (National Institutes of Health Stroke Scale), dont les scores varient de 0 à 42, les chiffres les plus bas correspondent au déficit le plus léger[6]. Le pronostic fonctionnel est mesuré à 3 mois de l'AVC, à l'aide de l'échelle de Rankin modifiée (modified Rankin Scale ou mRS).

A- II. Options thérapeutiques

A-II-1 THROMBOLYSE INTRA-VEINEUSE

La thrombolyse par voie intraveineuse (TIV) par *alteplase* (à une dose de 0,9 mg par kilogramme de poids corporel pendant 60 minutes [dose totale maximale, 90 mg], avec les premiers 10 % de la dose administrés en bolus en une minute) est recommandée depuis 1995 dans les 4.5 heures suivant l'apparition de l'AVC.[7] La réalisation d'un scanner sans injection ou une IRM avec une séquence T2 écho de gradient est nécessaire avant l'injection de l'*alteplase* afin de s'assurer de l'absence d'une hémorragie cérébrale contre-indiquant son utilisation. Un contrôle de la pression artérielle est nécessaire en phase aigüe, avec un objectif tensionnel inférieur à 185/110 mm Hg avant et pendant la perfusion d'*alteplase* et inférieure à 180/105 mm Hg pendant au moins les 24 heures qui suivent. Une méta-analyse de 9 essais randomisés a montré que 35.3% des patients traités par *alteplase* dans les 4h30 après le début des symptômes obtenaient une indépendance fonctionnelle à 3 mois (mRS≤1) contre 30.1% dans le groupe contrôle (odd-ratio ajusté, 1.26 95% CI [1.05-1.51]).[8] Un nouveau agent thrombolytique, la *tenecteplase*, peut également être utilize.[9,10] Le *tenecteplase* présente une plus grande spécificité pour la fibrine et une demi-vie plus longue que l'*alteplase* et s'administre en un bolus unique. Un traitement par *tenecteplase* pourrait être indiqué en première intention chez les patients présentant une occlusion intra-crânienne proximale et éligibles pour un traitement par thrombectomie.[11] Un traitement par *alteplase* peut être proposé au-delà de 4.5h et jusqu'à 9h du début des symptômes chez des patients sélectionnés par imagerie de perfusion. Les patients se présentant sur cette fenêtre thérapeutique tardive doivent présenter les critères suivants en imagerie de perfusion : ratio pénombre ischémique/cœur infarctus > 1.2 et un volume de cœur ischémique <70ml. L'administration d'*alteplase* en fenêtre tardive chez ces malades sélectionnées par perfusion permet d'obtenir un meilleur pronostic fonctionnel (mRS≤1) à 90 jours (36% groupe *alteplase* versus 29% groupe contrôle; odd ratio ajusté : 1.86; 95%IC [1.15-2.99]).[12] L'utilisation de la TIV est souvent limitée par des contre-indications comme un délai trop tardif, au-delà des 4h30 du début des symptômes, en dehors des critères de perfusion énumérés plus haut, un traitement par anticoagulants ou une chirurgie récente.

A-II-2 THROMBECTOMIE MECANIQUE

La thrombectomie mécanique (TM) seule ou en association avec la TIV s'est imposée comme nouveau standard de traitement pour les AVC par occlusion artérielle intra-crânienne proximale (Terminaison carotidienne, M1) suite aux résultats de plusieurs essais thérapeutiques.[13–18] Le principe de la TM est de réaliser un cathétérisme artériel jusqu'au site

de l'occlusion sous contrôle scopique en salle d'angiographie et de capturer le thrombus par un dispositif d'aspiration ou par piégeage entre les mailles d'un stent (technique dite stentriever) afin de restaurer le flux au sein de l'axe artériel. La thrombectomie mécanique présente plusieurs avantages par rapport à une TIV seule :

- des taux de recanalisations très supérieurs à la thrombolyse seule : 75 à 85% de recanalisation artérielle, définie par un score mTICI (modified Thromolysis in Cerebral infarction) ≥2B. Ces taux supérieurs de recanalisation expliquent les meilleurs résultats fonctionnels à 3 mois des malades traités par thrombectomie contre thrombolyse seule sur les données poolées des essais randomisés (46% de mRS 0-2 dans le groupe TM±IV versus 26.5% dans le groupe IV seule).[19]

- une fenêtre de traitement beaucoup plus large, jusqu'à 24h chez des malades sélectionnés. Deux essais[20,21] ont permis d'élargir la fenêtre de traitement jusqu'à 24h après le début des symptômes chez des patients sélectionnés sur la base d'imagerie de perfusion. Le traitement par TM dans cette population à présentation tardive permet d'obtenir une amélioration significative du pronostic fonctionnel à 90jours, avec 45% des patients obtenant un score mRS 0-2 dans le groupe TM contre seulement 17% dans le groupe contrôle.[21]

- elle peut être proposée chez les patients avec des contre-indications à la TIV.

- elle ne présente pas de sur-risque hémorragique ou de complications graves[19]

La sélection des patients est un critère important pour l'éligibilité à un traitement par thrombectomie mécanique. Les essais thérapeutiques ont basé leurs critères d'inclusion sur la présence d'une occlusion proximale de la terminaison carotidienne ou du segment M1, avec un score ASPECT supérieur à 6, un score NIHSS supérieur à 6 et un score mRS avant l'AVCi inférieur ou égal à 1. Plusieurs essais actuels sont en cours pour évaluer l'intérêt d'une extension de ces critères (patient avec des symptômes mineurs et une occlusion proximale, patients avec des gros volumes d'ischémie, patients avec une occlusion artérielle plus distale). Les gestes de thrombectomie sont effectués dans un environnement de bloc opératoire par une équipe expérimentée. L'accès à la thrombectomie se fait soit de manière directe si le patient est orienté d'emblée vers un centre de recours disposant, outre d'une USI Neurovasculaire, de neuroradiologues interventionnels et d'un plateau technique permettant la réalisation de la TM, soit de manière secondaire, avec un transfert depuis une USI NV de territoire vers un centre de recours.

B. Problématique actuelle

La thrombectomie mécanique associée ou non à la thrombolyse intra-veineuse a donc permis de franchir un cap dans la prise en charge des AVC par occlusion artérielle proximale. Plus de la moitié des patients traités par thrombectomie mécanique ont néanmoins un mauvais pronostic fonctionnel malgré une bonne recanalisation obtenue rapidement.[19] Le terme « recanalisation futile » est utilisé dans la littérature pour définir cette situation. Ce terme est un objet de discussion car aucune recanalisation n'est futile par essence.

Plusieurs facteurs déjà identifiés ont un impact direct sur le pronostic fonctionnel et peuvent être classés en 2 catégories :

- **Facteurs dits « non modifiables »:**

  *** pré-thérapeutiques :** L'âge, le score NIHSS à l'arrivée, la qualité de la collatéralité propre à chaque patient,[22,23] le degré de tolérance du parenchyme cérébral à l'ischémie,[24] le délai depuis début des symptômes, l'étendue de l'ischémie (semi-quantitatif par le score ASPECTS ou volumétrique), la charge de leucopathie vasculaire, une atrophie cérébrale pré-existante[25–27]… Si ces facteurs influencent directement le pronostic fonctionnel, une compréhension plus fine de leurs poids dans le pronostic pourrait aider à une meilleure sélection des candidats pour la thrombectomie mécanique.

  *** post-thérapeutiques :** Un phénomène de « no-reflow » est décrit dans la littérature, notamment en cas d'ischémie myocardique. Dans l'AVCi, il correspondrait à un défaut de reperfusion du parenchyme cérébral malgré l'obtention d'une recanalisation complète, et pourrait être dû à une altération de la fonction microcapillaire. Ce défaut de reperfusion parenchymateuse malgré une recanalisation pourrait expliquer le mauvais pronostic fonctionnel. La transformation hémorragique cérébrale symptomatique est également fortement associée à un mauvais pronostic même si une recanalisation complète est obtenue.

- **Facteurs modifiables :** certains facteurs, comme le délai de transfert du patient vers un centre de recours, peuvent sembler contrôlables mais sont soumis à une grande variabilité du fait d'éléments extérieurs. En revanche, des facteurs liés à la procédure de TM (choix du matériel, durée de procédure, nombre de passage), au contrôle de la pression artérielle, de la glycémie à la phase aiguë sont des facteurs potentiellement modifiables.

Le **tableau B-1** résume les principaux facteurs associés à une évolution clinique défavorable malgré un succès de recanalisation par un traitement endovasculaire, déjà publiés dans la littérature (non exhaustif).

Tableau B-1 : Prédicteurs de mauvais pronostic fonctionnel malgré bonne recanalisation

Etude	Année	Nombre de patients	Proportion de recanalisation « futile »	Prédicteurs principaux
Hussein et al[28]	2010	96	49%	**Age / NIHSS initial**
Singer *et al*[29]	2013	223	45.3%	**Durée Procédure / Glycémie /** Age / NIHSS
Shi[30]	2014	228	49%	**Délai jusqu'à recanalisation / ASPECTS /** NIHSS
Rueda *et al*[31]	2015	150	57%	**Statut Collatérales** / ASPECTS
Linfante et al[23]	2016	234	49.6%	**Site de l'occlusion / Nombre de passages / Diabète**
Gilberti *et al*[32]	2017	68	32.4%	**Leucoaroïse**
Wang et al[33]	2018	332	51.5%	**Ratio Neutrophile/Lymphocyte>12 / pas de thrombolyse IV préalable** / Glucose / Collatérales
Lee *et al*[34]	2019	440	48.6%	**HTA/** NIHSS initial / Age
Pedraza *et al*[35]	2020	295	48.8%	**Atrophie corticale**
Xu et al[36]	2020	403	49.6%	**Anesthésie générale** / HTA / délai jusqu'à recanalisation

Le but de ce travail est de mieux comprendre et hiérarchiser les différents facteurs influençant le pronostic fonctionnel malgré l'obtention d'une bonne recanalisation, et plus particulièrement d'identifier les facteurs « modifiables » propres au geste de thrombectomie mécanique. Plusieurs études constituent ce travail. Elles se sont attachées :

- à classer et hiérarchiser l'ensemble des facteurs identifiés comme associé à un mauvais pronostic fonctionnel : **Publication numéro I** (auteur- ***Journal of NeuroInterventional Surgery*** - rang A - Collaboration internationale MRCLEAN, aide statistique et écriture manuscrit).

- à tenter de mettre en évidence un facteur non modifiable post-thérapeutiques, le phénomène de no-reflow : **Publication numéro II** *(3ème auteur – **Journal of Cerebral Flow and Metabolism** – rang B).*

- à identifier les facteurs reliés au geste de thrombectomie afin de mieux les contrôler :

  - Nombre de passages et pronostic :

    *** Publication III** *(1er auteur- **European Journal of Neurology** – rang B).*

    *** Publication IV** *(1er auteur – **Neurology** – Rang A).*

  - Expérience de l'opérateur et pronostic : **Publication V** *(2ème auteur – **Stroke** – Rang A).*

- Modalité anesthésique : *(3ème auteur- **Journal of Neurology, Neurosurgery and Psychiatry** – Rang A).*

- à prédire l'hémorragie symptomatique après recanalisation réussie par l'opacification veineuse précoce :

*** Publication VII** *(1er auteur – En soumisssion).*

*** Publication VIII** *(Dernier auteur – En soumission).*

C. Identification des prédicteurs de mauvais pronostic malgré une bonne recanalisation après thrombectomie mécanique

Dans ce travail de thèse, nous avons souhaité, en première étude, évaluer l'importance des facteurs associés à une évolution clinique défavorable malgré recanalisation, au sein d'une population très large. Pour ce faire, une collaboration a été réalisée avec l'équipe de Rotterdam, sur la base de données multicentrique du registre MR CLEAN. Les patients ont été traités entre 2014 et 2017 dans les centres qui ont participé au premier essai randomisé démontrant le bénéfice de la TM en cas d'occlusion artérielle proximale aigue.

Predictors of poor outcome despite successful endovascular treatment for ischemic stroke: results from the MR CLEAN Registry

Rob A van de Graaf,[1,2] Noor Samuels,[1,2,3] Vicky Chalos,[1,2,3] Geert J Lycklama a Nijeholt,[4] Heleen van Beusekom,[5] Albert J Yoo,[6] Wim H van Zwam ,[7] Charles B L M Majoie,[8] Yvo B W E M Roos,[9] Pieter Jan van Doormaal,[1] Wagih Ben Hassen,[10] Aad van der Lugt,[1] Diederik W J Dippel ,[2] Hester F Lingsma,[3] Adriaan C G M van Es,[11] Bob Roozenbeek,[1,2] MR CLEAN Registry investigators

J NeuroIntervent Surg 2021;**0**:1–6. doi:10.1136/neurintsurg-2021-017726

C-I Résumé Étude N°1

Les patients du registre MR CLEAN avec succès de recanalisation ont été inclus entre mars 2014 et novembre 2017. Dans un premier temps, les prédicteurs ont été sélectionnés sur la base d'avis d'experts et ont été regroupés en fonction de leurs acquisitions au cours du temps (c'est-à-dire les facteurs de base du patient, facteurs d'imagerie, facteurs liés au traitement et facteurs post-procédure). Deuxièmement, plusieurs modèles ont été construits pour prédire le pronostic fonctionnel (mRS). L'importance relative des prédicteurs individuels dans le modèle le plus étendu a été exprimée par la proportion de χ2 unique ajouté au modèle par ce prédicteur individuel. Ceci nous a permis de constater sur 3180 patients, un taux de succès de recanalisation chez 1913 (60 %) patients. Sur ces 1913 patients, 1046 (55%) étaient fonctionnellement toujours dépendants à 90 jours (mRS >2). Les prédicteurs les plus importants du mRS étaient les facteurs de base du patient (c'est-à-dire, mRS avant l'AVC : χ2 0,16 ; NIHSS initial : χ2 0,12 ; âge : χ2 0,10), et les facteurs post-procéduraux (c.-à-d. hémorragie intracrânienne symptomatique (HCIs) : χ2 0,12 ; pneumonie : χ2 0,09). Les facteurs de base du patient et les événements indésirables post procéduraux sont donc d'importants prédicteurs de mauvais pronostic. Cela implique que la prévention des événements indésirables postprocéduraux a le plus grand potentiel pour améliorer encore les résultats chez ces patients.

Ce travail

- Comporte la plus grande population sur le sujet de l'évolution clinque défavorable malgré une bonnne recanalisation (1913 patients, 55% de mRS>2)

- Les facteurs "non modifiables" tel que l'âge, le score NIHSS initial pèsent lourd sur le pronostic même en cas de bonne recanalisation

- Des facteurs post thérapeutiques, tel que l'hémorragie symptomatique et la pneumonie doivent être prévenues

- Des facteurs liés à la procédure, tel que la durée du geste ou l'anesthésie générale ont un effet néfaste sur le pronostic et doivent être mieux contrôlés.

C-II Background

Approximately 50% of the patients with ischemic stroke caused by a proximal large vessel occlusion in the anterior circulation do not recover to functional independence, even when successful reperfusion is achieved by endovascular treatment.[19] Factors such as older age, higher NIHSS at baseline, and higher ASPECTS are associated with worse outcome after successful reperfusion.[23,28,34,37] Better understanding of the key determinants of worse recovery, despite successful reperfusion after EVT, could guide researchers and physicians in the development of new treatments to further improve outcomes. Additionally, such an evaluation could provide insight in whether identification of new factors is warranted. Therefore, we aimed to quantify the importance of predictors for worse functional outcome despite successful reperfusion.

C-III Methods

Study design

We used data from the MR CLEAN Registry, which is an ongoing, national, prospective, open, multicenter, observational monitoring study for stroke intervention centers that perform EVT in the Netherlands. The complete methods and description of variables of the MR CLEAN Registry have been described elsewhere.[38] For the present study, we selected patients who were registered between March 2014 and November 2017 and adhered to the following criteria: age of 18 years or older; presence of a proximal intracranial occlusion in the anterior circulation confirmed on CT angiography (intracranial carotid artery [ICA/ICA-T], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]); groin puncture within 6.5 hours after symptom onset; treatment in a center that participated in the MR CLEAN trial; successful post interventional macrovascular reperfusion status (extended thrombolysis in cerebral infarction [eTICI] ≥2B). The current observational study was guided by the STROBE statement.[39]

Measures and outcomes

We constructed multivariable ordinal regression models to predict functional outcome measured with the modified Rankin Scale at 90 days. We selected candidate predictors based on prior knowledge and expert opinion. [23,28,34,37,40] In the selection, priority was given to causal and modifiable factors. The predictors were clustered in four groups according to the time of acquisition: baseline *patient factors*, *imaging factors*, *treatment factors*, and *postprocedural factors* (i.e. adverse events). To resemble the gain in information on outcome prediction over time, we successively added each group of predictors to a basic model only including patient factors. This resulted in four multivariable ordinal regression models of increasing extensiveness. The most extensive model was used to quantify the relative importance of the

individual predictors. Finally, we evaluated the overall explained variance of the most extensive model.

Subsequently, we repeated these analyses [1] for the subgroup with excellent reperfusion (TICI ≥2C) and [2] using a modified NIHSS score at 24-48 hours as the outcome. A modification of the NIHSS was necessary to also include patients who died within 48 hours, by assigning them the maximum NIHSS score of 42. This early modified NIHSS scale may be a better representation of direct stroke-related factors associated with outcome after EVT as opposed to the mRS and less inflicted by patients who died early.[41]

Statistical methods

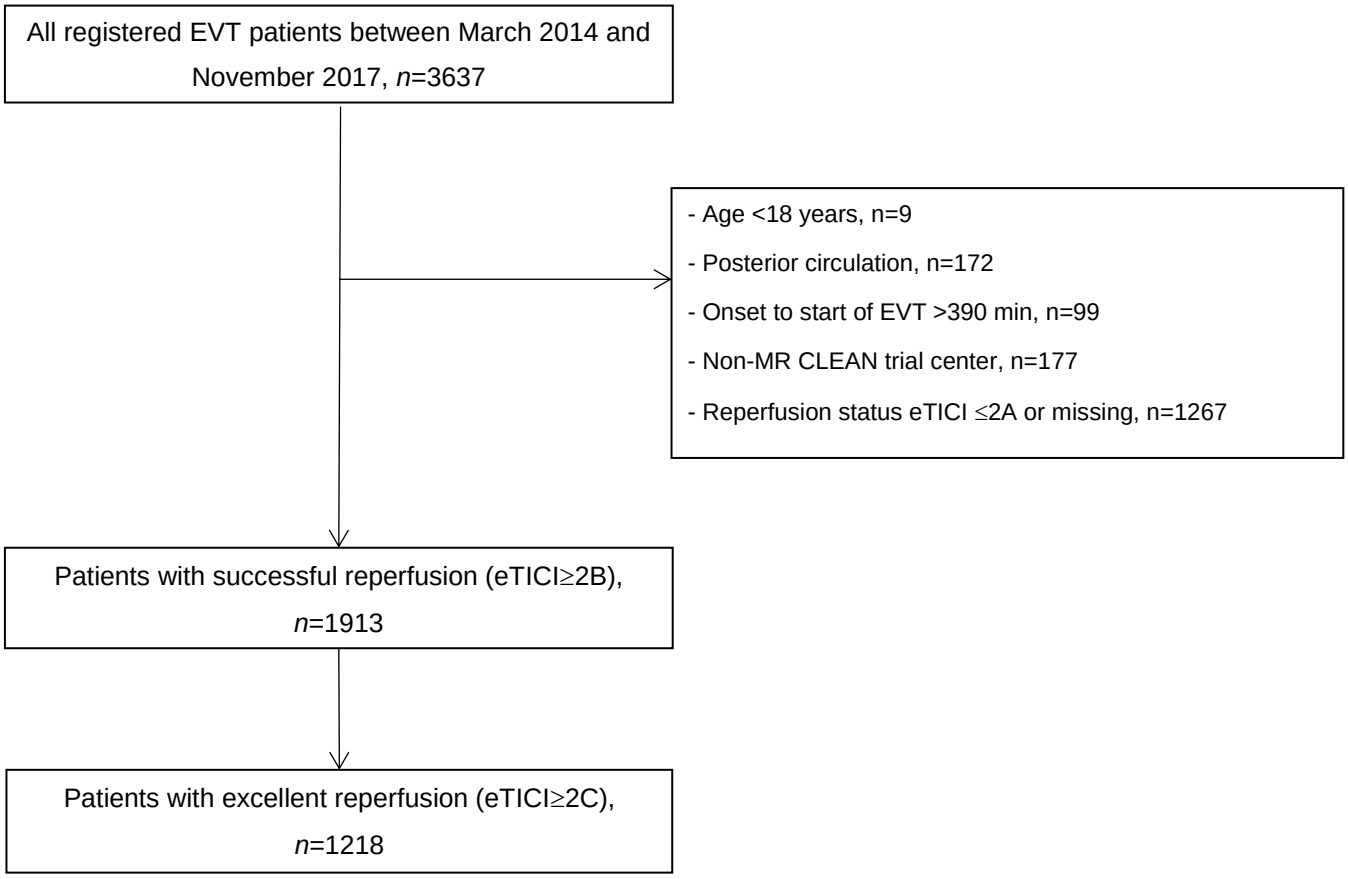
Any mRS score assessed within 30 days of symptom onset was considered invalid and treated as missing. For the purpose of unbiased estimation of associations of outcome with baseline characteristics, we replaced missing outcome and predictor values by values derived from multiple imputation by chained equations with five imputations.[42,43] After constructing ordinal or linear logistic regression models as appropriate, quantification measures were derived. Nagelkerke's pseudo-R^2 for the mRS (ordinal outcome) and R^2 for the modified NIHSS at 24-48 hours (continuous outcome) were applied to quantify the explained variance in outcome by the model. This derived (pseudo-)R^2 reflects the explained variance in outcome of the model by the included predictors, ideally aiming to achieve 100% of variance explanation. Subsequently, the strength of relationship between an individual predictor in the model and the outcome was quantified by the proportion of unique added value in that particular model using the Wald Chi^2 test, taking penalization for degrees of freedom into account. In this evaluation, the sum of all individual Chi^2 proportions can be below or above 1 and quantification measures should be interpreted in context of the model. For example, if all independent variables are perfectly identical (collinear), the model can have good performance, but proportion Chi^2 for all independent variables will be zero, because any single predictor has zero additional explanatory value. On the other hand, if all independent variables together explain the dependent variable perfectly, proportion Chi2 for each predictor will be 1, because whatever is unexplained by all other predictors can perfectly be explained by the remaining variable. The variables age and systolic blood pressure were handled using restricted cubic splines with 3 knots.[40,44] This decision was based on both visual evaluation of quantile-quantile plots and prior knowledge of associations of these variables with outcome. All statistical analyses were performed with R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria).

C-IV Results

Study population

A total of 3180 patients were analyzed. Successful reperfusion was observed in 1913/3180 (60%) and excellent reperfusion in 1218/3180 (38%) patients **(Figure C-1).**

Figure C-1: Flowchart



Characteristics of patients with successful and excellent reperfusion, along with clustering of predictors according to the four predefined groups, are presented in **Table C-1**.

Table C-1: Cohort characteristics				
	eTICI≥2B, n=1913	Missing	eTICI≥2C, n=1218	Missing
Patient factors				
Age	69 (14)	0	70 (14)	0
Male sex	1010 (53)	0	651 (53)	0
NIHSS on admission	16 [11, 19]	1.5	16 [11, 20]	1.6
Ischemia in left hemisphere	1019 (54)	0.6	637 (53)	0.5
Systolic blood pressure on admission	148.7 (24)	3.2	149 (24)	2.9
INR on admission	1.2 (0.4)	19	1.2 (0.4)	18
Glucose level on admission	7.4 (2.6)	11	7.4 (2.5)	11
Previous stroke	309 (16)	0.8	197 (16)	0.7
Atrial fibrillation	427 (23)	1.3	286 (24)	1.3
Hypertension	967 (52)	2.2	626 (52)	1.7
Diabetes mellitus	310 (16)	0.7	209 (17)	0.5
Pre-stroke mRS (%)		2.3		2.1
0 - No symptoms	1280 (69)		823 (69)	
1 - Minor symptoms, no limitations	247 (13)		161 (14)	
2 - Slight disability, no help needed	135 (7.2)		90 (7.5)	
>2	207 (11)		119 (10)	
Prior antiplatelet therapy	601 (32)	1.4	397 (33)	1.0
Time from symptom onset to admission ER (intervention center)	133 [65, 185]	4.9	133 [65, 183]	4.3
Imaging factors				
Occluded segment		3.8		3.4
Intracranial ICA	81 (4.4)		51 (4.3)	
ICA-T	366 (20)		239 (20)	
M1	1118 (61)		730 (62)	
M2	262 (14)		149 (13)	
Other (e.g., M3, ACA)	14 (0.8)		8 (0.7)	
ASPECTS	9 [8, 10]	2.9	9 [8, 10]	2.2
Collaterals		6.1		5.9
Grade 0 - Absent collaterals	101 (5.6)		63 (5.5)	
Grade 1 - Occluded area filling <50%	649 (36)		408 (36)	
Grade 2 - Occluded area 50<filling<100	708 (39)		452 (39)	

Grade 3 - Occluded area filling 100%	338 (19)		223 (20)	
Treatment factors				
Treatment with intravenous alteplase	1472 (77)	0.4	925 (76)	0.4
Time from admission ER (intervention center) to groin puncture	58 [35, 87]	8.9	58 [35, 84]	8.2
Duration procedure	50 [35, 73]	7.4	50 [35, 70]	5.5
General anesthetic management	528 (29)	5.1	363 (31)	4.0
Periprocedural heparin use	548 (29)	0	373 (31)	0
Reperfusion grade after intervention or spontaneous		0		0
eTICI 2B	695 (36)		NA	NA
eTICI 2C	332 (17)		332 (27)	0
eTICI 3	886 (46)		886 (73)	0
Postprocedural factors*				
New ischemic stroke	30 (1.6)	0	17 (1.4)	0
Symptomatic intracranial hemorrhage	88 (4.6)	0	54 (4.4)	0
Pneumonia	177 (9.3)	0	108 (8.9)	0

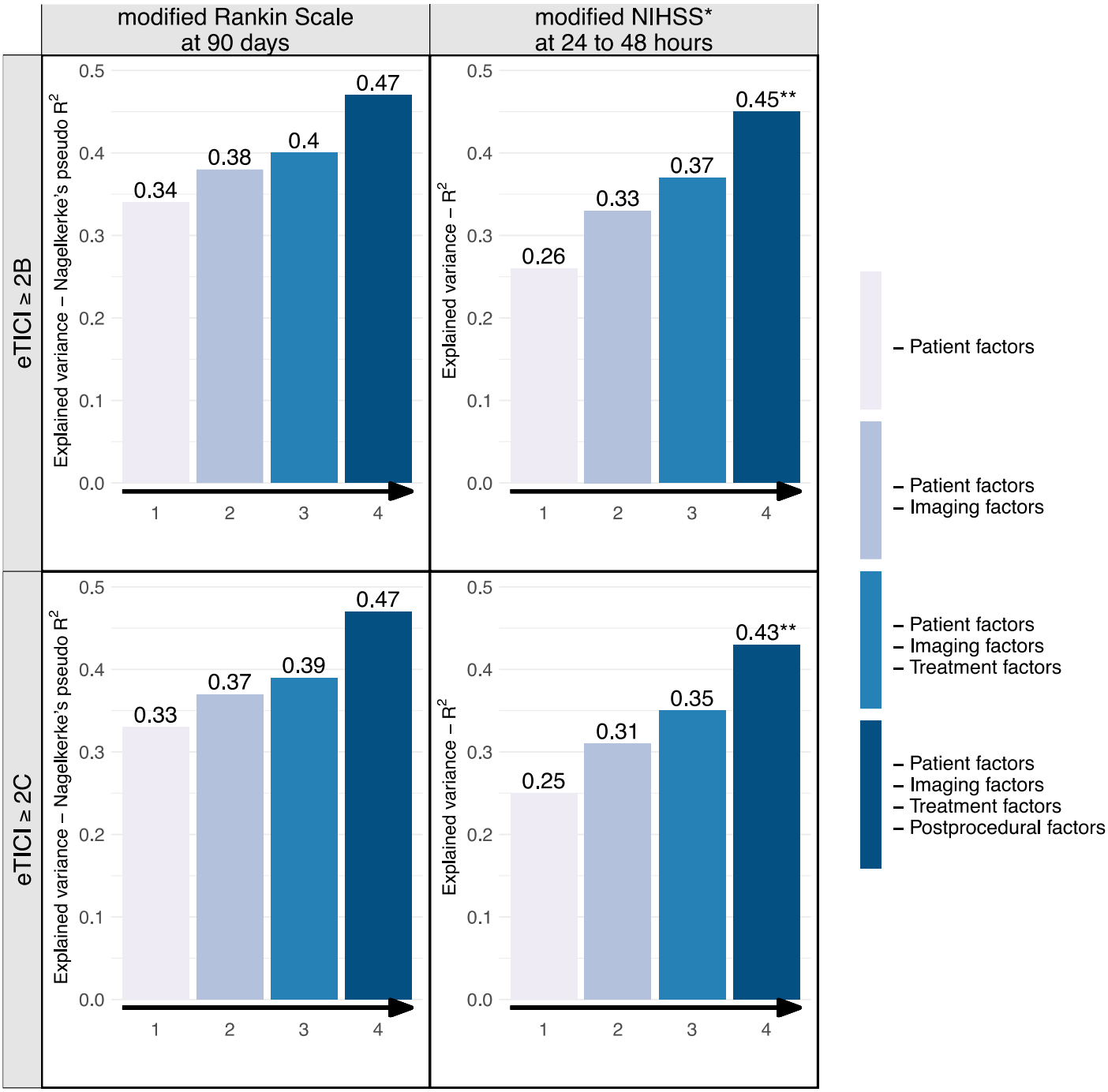
*Legend: Cohort characteristics of patients with successful (eTICI2B) and with excellent reperfusion (eTICI2C). Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as numbers (%). Abbreviations: ACA, anterior cerebral artery; APT, antiplatelet therapy; ASPECTS, Alberta stroke program early computed tomography score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended thrombolysis in cerebral infarction including a 2C grade; ICA (T), internal carotid artery (terminus); M(segment), middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. *For the model with the modified NIHSS at 24-48 hour as outcome, postprocedural factors in the model were restricted to occurrence within 24 hours, which was only recorded for sICH (so new ischemic stroke and pneumonia were excluded).*

Within 90 days following EVT, 900/1913 (51%) patients remained functionally dependent or died (mRS>2) given successful reperfusion was achieved. This was similar for patients with excellent reperfusion with 554/1218 (49%) being dependent or death at 90 days (Figure 2). Given successful reperfusion, 78/1913 (4%) of the patients died within 48 hours and once excellent reperfusion was achieved 46/1218 (4%) patients died within 48 hours. These patients received the maximum score of 42 of the modified NIHSS score at 24-48 hours. Median modified NIHSS score at 24-48 hours was 8 [IQR 3, 15] for successful reperfusion and 7 [IQR 3, 14] for excellent reperfusion.

Variable importance

The variable group including *patient factors* was the most important contributor to the explained variance **(Figure C-2).**

Figure C-2: Performance of models with increasing extensiveness
Performance in patients with successful reperfusion defined as an eTICI≥2B (A, B) and excellent reperfusion defined as an eTICI≥2C (C, D), predicting mRS at 90 days (A, C) and modified NIHSS at 24-48 hours (B, D)



Abbreviations: eTICI, extended thrombolysis in cerebral infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. Captions: * Death within 48 hours was assigned the maximum score of 42; ** For the model with the modified NIHSS at 24-48 hour as outcome, postprocedural factors in the model were restricted to occurrence within 24 hours, which was only recorded for sICH (resulting in exclusion of new ischemic stroke and pneumonia for these analyses).

Successive addition of the other grouped factors (i.e. *imaging factors, treatment factors,* and *postprocedural factors*) increased the explained variance by the models, but these were relatively less important than the contribution of *patient factors*. The four most extensive models, including all independent variables, covered between 43% and 47% of the explanation on outcome prediction given reperfusion after endovascular thrombectomy. In patients with successful reperfusion (TICI ≥2B) the 5 most important individual predictors of functional outcome at 90 days were pre-stroke mRS (added Chi^2: 0.16), NIHSS at baseline (added Chi^2: 0.12), age (added Chi^2: 0.11), sICH (added Chi^2: 0.10), and pneumonia (added Chi^2: 0.09; **Figure C-3A**). The five individual predictors with the highest added Chi^2 were similar in patients with excellent reperfusion (eTICI ≥2C), although the order of importance and the quantity of added Chi^2 differed: pre-stroke mRS (added Chi^2: 0.18), pneumonia (added Chi^2: 0.13), age (added Chi^2: 0.10), sICH (added Chi^2: 0.09), and NIHSS at baseline (added Chi^2: 0.09; **Figure C-3C**). The most important predictors of the modified NIHSS at 24-48 hours as outcome were NIHSS at baseline (added Chi^2: 0.17), sICH that occurred within 24 hours (added Chi^2: 0.16), collaterals (added Chi^2: 0.07), duration of the procedure (added Chi^2: 0.04) and pre-stroke mRS (added Chi^2: 0.02; **Figure C-3B**). In patients with excellent reperfusion, the 5 most important predictors were similar to those with successful reperfusion, only the order and quantity of added Chi^2 differed: sICH that occurred within 24 hours (added Chi^2: 0.17), NIHSS at baseline (added Chi^2: 0.16), collaterals (added Chi^2: 0.07), duration of the procedure (added Chi^2: 0.04) and pre-stroke mRS (added Chi^2: 0.02; **Figure C-3D**).

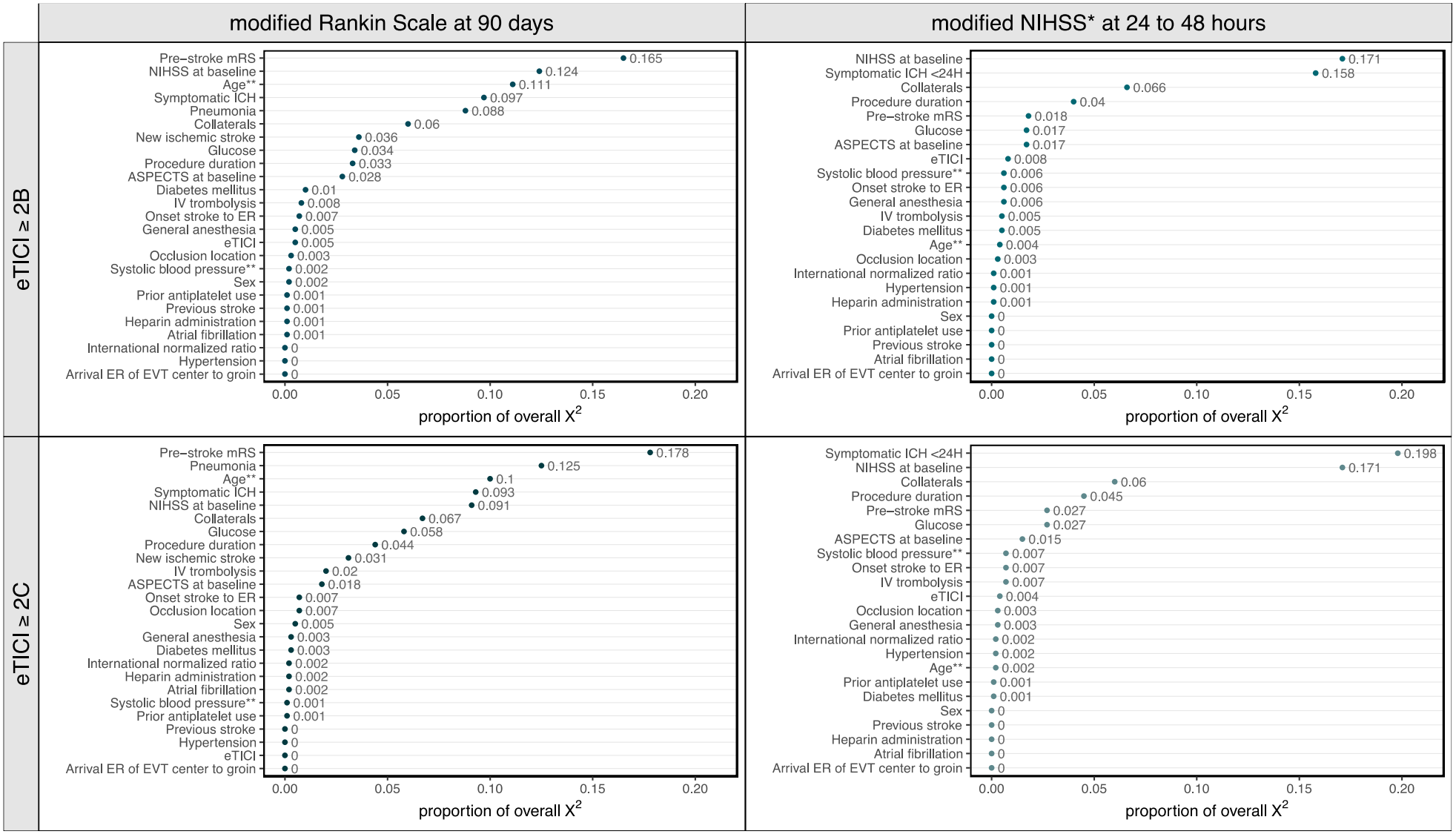


Figure C-3: Individual penalized variable importance within the most extensive models
Importance in patients with successful reperfusion defined as an eTICI≥2B (*A, B*) and excellent reperfusion defined as an eTICI≥2C (*C, D*), predicting mRS at 90 days (*A, C*) and modified NIHSS at 24-48 hours (*B, D*)

Abbreviations: eTICI, extended thrombolysis in cerebral infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale

C-V Discussion

We found that baseline patient factors and postprocedural adverse events are the most important predictors of worse functional outcome in ischemic stroke patients with successful reperfusion after endovascular thrombectomy. It is conceivable that prevention of postprocedural adverse events (i.e. sICH, pneumonia) has the greatest potential to further improve outcomes.

Strategies currently investigated that could be of benefit in prevention of postprocedural adverse events are (I) direct EVT without preceding intravenous alteplase to reduce sICH (MR CLEAN-NO IV [ISRCTN80619088], DIRECT MT [NCT03469206], SKIP [UMIN000021488], SWIFT-DIRECT [NCT03192332], DIRECT-SAFE [NCT03494920], DEVT [ChiCTR-IOR-17013568]), (II) strict blood pressure control to reduce the risk of intracranial hemorrhage (BP TARGET [NCT03160677]) and (III) pharmacological strategies reducing complications like pneumonia (PRECIOUS [ISRCTN82217627]).

The evaluation of predictor importance was presented according to functional outcome (mRS) and the modified NIHSS at 24-48 hours. Since we observed that patient factors (i.e. age and pre-stroke mRS) contributed less to the explained variance in modified NIHSS compared to mRS we expect early modified NIHSS is a good measure of stroke-related disabilities, as opposed to the mRS which includes all types of disabilities. As we expected that reperfusion status (either eTICI ≥2B or eTICI ≥2C) could be of influence on individual variable importance in the most extensive model, we presented our analyses for both reperfusion categories separately. We found that postprocedural reperfusion status only resulted in minor differences regarding the importance of predictors on outcome, assuming that predictor importance seems relatively constant with regard to the level of reperfusion. We observed that the time from stroke onset to admission at the emergency room of the intervention hospital and time from admission at the emergency room of the intervention hospital to groin puncture, were relatively less important compared to duration of the procedure. Possibly, the importance of pre-interventional time intervals was negated by the achievement of successful reperfusion as our analyses were inherent to this selection criterion. The relative importance of duration of the procedure could reflect the difficulty of the procedure, for example caused by agitation of the patient, tortuosity of the vessels, or performance of multiple attempts, which is associated with poor functional outcomes.[45]

Six earlier studies also found that the non-modifiable patient factor baseline NIHSS was a very important predictor of worse functional outcome despite reperfusion. In five of these studies, age was found to be an important predictor for poor functional outcome.[22,23,30,33,34,37] Two studies found, that EVT without prior IV alteplase administration was associated with worse outcome.[23,33] Lower (diffusion weighted imaging [DWI]) ASPECTS on admission was found to

be related to poor functional outcome in two studies.[22,37] Factors such as collateral status, blood glucose, occlusion location, diabetes mellitus, neutrophil-to-lymfocyte ratio, delayed endovascular treatment, mTICI 2B, procedural complications, and higher number of passes (≥3) were found to be associated with poor functional outcome in only one study.[23,30,33,37] Our results confirm the suggestion of an opinion review that unfavorable non-modifiable patient factors (reflecting limited 'brain reserve') are the most notable factors explaining why patients do not recover despite reperfusion.[24] Remarkably, none of these studies evaluated the influence of postprocedural factors such as sICH, pneumonia, and new ischemic stroke (ie, imaging of new brain infarction with corresponding clinical neurologic deficit within 90 days) which, based on our results, are very important in explaining why some patients with successful reperfusion recover well and others do not. It should be kept in mind that the identified factor is not necessarily causal in explaining the detrimental outcomes. For example, it is possible that the occurrence of pneumonia is associated with other conditions like heart failure and sepsis followed by hemodynamic instability and hypoperfusion requiring ICU admission, which actually explains why these patients do worse.

The variance in outcome explained by the models varied between 42% and 47% so a substantial part of the variability in outcome after successful reperfusion is still unexplained. Therefore, we advocate incentivizing the identification of new predictors as well as optimizing the determination of current predictors. Considering the identification of new predictors, additional information on quantification of perfusion at the microvascular level— preferably at an early stage—could be a useful new approach to improve outcome prediction. Current visual scoring techniques are unable to evaluate vessels <90 μm in diameter,[46] yet it is believed that microvascular dysfunction (vasculature <90 μm in diameter) following reperfusion could contribute to poor functional outcomes despite macrovascular reperfusion.[47]

Regarding optimization of predictor determination, our current models could be optimized even more by improving both preinterventional and postinterventional quantification of brain tissue status with more advanced neuroimaging techniques such as MR or CT perfusion instead of CT.

As no baseline MRI-DWI or CT perfusion data (eg, information on preinterventional perfusion status such as cerebral blood flow and core volume) were available in this observational registry, our analyses were limited to ASPECTS evaluation, which is probably a less accurate measure of the infarct core. Also, in-depth information on, for example, the periprocedural device technique used (eg, use of balloon protection, assisted aspiration), periprocedural blood pressure course, and malignant brain edema could be of additional value to further improve outcome explanation. Furthermore, addition of the follow-up infarct volume might have improved the model's performance further.[48–50] However, this assessment was not available in

our dataset. Besides, as we only documented the occurrence of pneumonia, not the occurrence of other infections, this could have limited our study. Nevertheless, pneumonia accounts for at least half of all stroke-related infections and is by far the strongest prognostic factor among the stroke-associated infections.[51,52] Another limitation is the possibility of information bias as factors were selected for the model based on prior knowledge. Furthermore, it should be considered that the chosen outcome of the modified NIHSS (including death) should be interpreted with caution as it is not known whether assigning the maximum NIHSS score of 42 to patients who died before 24–48 hours NIHSS assessment is the most optimal strategy for the evaluation of early stroke-related outcome after EVT. However, this outcome is a strong mediator of the mRS at 90 days and might be seen as a more essential evaluation of neurological deficit and directly stroke-related outcome measure, which is less inflicted by early death.[41] Finally, although we did not detect a large influence of the included modifiable factors—that is, use of antithrombotic medication (eg, antiplatelets, heparin) or anesthesia type—on poor functional outcome despite reperfusion, it should be kept in mind that these treatments were not assigned systematically and confounding by indication may have occurred. To improve outcomes further, we suggest evaluating the effect of modifiable factors in randomized studies as well as incentivizing the identification of additional modifiable predictors. As these treatments are modifiable, this warrants a further randomized study.

C-VI Conclusion

Both patient and postprocedural factors were important factors for predicting outcome in successfully reperfused patients, implying that prevention of postprocedural adverse events has the greatest potential to further improve patient outcomes. Moreover, to better understand the mechanisms behind worse outcomes in succesfully reperfused patients identification of additional contributing factors is warranted.

Dans ce travail, nous avons donc pu stratifier les différents prédicteurs selon leur influence sur le pronostic à 3 mois chez les patients avec succès de recanalisation, montrant que les 5 plus importants sont l'âge, un mRs avant l'AVC>0, un score du NIHSS élevé, une pneumopathie et une hémorragie cérébrale symptomatique.

D. Facteurs « contrôlables » influençant le pronostic fonctionnel après recanalisation réussie

Nous avons tenté de comprendre l'influence pronostique de facteurs liés à la technique de recanalisation par thrombectomie mécanique, donc potentiellement modifiables. Une meilleure compréhension de ces facteurs permettrait d'optimiser le geste de thrombectomie mécanique afin de préserver le meilleur pronostic fonctionnel du malade.

Dans ce travail, nous avons pu analyser les facteurs suivants :

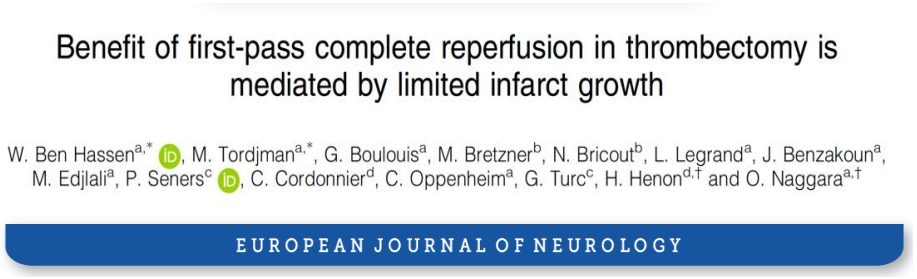
- Le nombre de tentatives (ou passages) lors de la thrombectomie mécanique : Le nombre de passage a été rapporté par plusieurs études[53–57] comme directement corrélé au pronostic fonctionnel. Les patients bénéficiant d'une recanalisation complète (TICI3) à la première tentative ont le meilleur pronostic clinique comparé aux autres patients. Ce phénomène est décrit comme un « effet premier passage » (first Pass effect) dans la littérature. Nous avons cherché à comprendre la relation entre le nombre de passages et le pronostic en étudiant la croissance précoce d'infarctus à 24heures.

- L'expérience de l'opérateur : Une étude multicentrique a été réalisée afin de préciser un éventuel effet d'apprentissage sur les résultats et les complications lors d'un geste de thrombectomie.

- L'anesthésie générale : Une méta-analyse de la littérature a été réalisée pour mieux préciser l'effet des différents modes de gestion anesthésique pendant la thrombectomie sur le pronostic

D- I. Explication de l'effet premier passage et pronostic fonctionnel

Dans ce premier travail concernant spécifiquement le lien entre pronostic clinique et déroulement de la procédure de thrombectomie mécanique, nous avons étudiés les patients inclus prospectivement dans le registre du CH Sainte-Anne et du CHU de Lille, entre janvier 2016 et janvier 2019, pour lequels une recanalisation TICI = 3 a pu être obtenue.


Benefit of first-pass complete reperfusion in thrombectomy is mediated by limited infarct growth

W. Ben Hassen[a,*], M. Tordjman[a,*], G. Boulouis[a], M. Bretzner[b], N. Bricout[b], L. Legrand[a], J. Benzakoun[a], M. Edjlali[a], P. Seners[c], C. Cordonnier[d], C. Oppenheim[a], G. Turc[c], H. Henon[d,†] and O. Naggara[a,†]

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D-I-1 Résumé Étude N°2

Le nombre de tentatives nécessaires pour récupérer un caillot lors d'un AVC ischémique par occlusion d'un vaiseau de gros calibre a un impact sur le pronostic fonctionnel. La recanalisation complète (eTICI= 3) au premier passage, est associée aux taux les plus élevés de pronostic favorable. L'objectif de la présente étude est d'examiner la relation entre la reperfusion complète au premier passage et la croissance de l'infarctus (IG).Nous avons donc inclus des patients avec occlusion antérieure proximale, disposants d'une imagerie par résonance magnétique, issus de deux registres prospectifs (Sainte Anne et CHU de Lille).La croissance de l'infarctus a été mesurée par segmentation à base de voxels des lésions initiales et de celles de l'IRM de diffusion à 24 heures. La croissance de l'infarctus et le score mRS ont été comparés après ajustement entre les patients chez lesquels une reperfusion complète (eTICI 3) a été obtenue en un seul passage (groupe FP) et ceux pour lesquels de plusieurs passages ont été nécessaires, pour obtenir une recanalisation complète. Une analyse de médiation a été réalisée pour examiner l'association entre le premier passage et le score mRS à 3 mois, avec la croissance de l'infarctus comme variable médiatrice. 200 patients ont été inclus, dont 118 (28,9%) ont eu une recanalisation complète au premier passage. Dans l'analyse cas-témoins, le groupe premier passage présentait une croissance d'infarctus moins élevée que le groupe ayant obtenu une recanalisation complète en plisuers passages [8,7 (5,4-12,9) ml vs. 15,2 (11-22,6) ml, respectivement ;P = 0.03). Le pronostic favorable était plus élevé dans la population premier passage par rapport à une population (70,9 % contre 53,2 %, respectivement ; P = 0,04). Le premier passage était associé de manière indépendante à une évolution favorable favorable dans l'analyse de régression multivariable [odds ratio 1,86, intervalle de confiance à 95%(IC) 1,01-4,39 ; P = 0,04]. L'effet de la reperfusion complète en un passage sur le résultat fonctionnel passe par une croissance d'infarctus limitée dans l'analyse de médiation [effet indirect : -0,32 (IC 95 % : -0,47 à -0,09)]. La reperfusion complète au premier passage est donc indépendamment associée à une diminution significative de la croissance d'infarctus expliquant le meilleur pronostic fonctionnel.

Dans ce travail numéro 3, nous avons donc :

- **Confirmé le bénéfice clinique, à la fois à 24h et à 3 mois, d'une recanalisation à la première tentative, par comparaison à une recanalisation ayant nécessité plus de une tentative**

- **Montré que ce bénéfice est médié par une moindre croissance des lésions ischémiques, mesurées en IRM de diffusion**

D-I-2 Introduction

Endovascular Therapy (EVT) has drastically improved the functional outcome of patients with acute ischemic stroke (AIS) due to large cerebral vessel occlusion (LVO).[58–60] The number of clot retrieval attempts or passes before obtaining a complete reperfusion has been recently identified as a prognostic marker of functional outcome,[53–57] and led authors to coin the term "First Pass Effect" (FPE), to describe the critical influence of first pass complete reperfusion (defined by a expanded treatment in cerebral ischemia [eTICI] score = 3) on improving the rates of early neurological improvement (ENI) and functional outcome. The relationship between number of passes and functional outcome is not straightforward. Outcome results are expected to be similar if complete reperfusion is achieved in a similar time window, regardless of number of passes. The effect of endovascular treatment can be measured by quantifying early infarct Growth (IG), indicating whether viable brain tissue was preserved by the restoration of adequate tissular perfusion, predicting long term functional outcome[61]. Early growth of infarct core measured at 24h can be easily assessed using Diffusion weighted imaging (DWI). The mechanism of clinical benefit improvement when comparing complete reperfusion at a single versus multiple passes is unknown. In this study, we aimed to measure the effect of single versus multiple passes complete reperfusion on IG.

D-I-3 Methods

Patients

Clinical and radiological data were retrospectively extracted between January 2016 and January 2019 from prospective registries including consecutive patients treated by MT for LVO in two comprehensive stroke centers (Center 1: Centre Hospitalo-Universitaire de Lille, France Center 2: Centre Hospitalier Sainte-Anne, Paris, France). Patients meeting the following criteria were included: age ≥ 18 years, proximal anterior circulation LVO with known symptoms onset, initial and 24h follow-up MRI imaging with DWI sequence of adequate quality for volume quantification, treatment with mechanical thrombectomy achieving complete reperfusion defined by an expanded Treatment In Cerebral Ischemia [eTICI] score = 3 . Patients with MRI contraindications or posterior circulation occlusions were excluded. Clinical data, vascular risk factors, admission and 24hours National Institutes of Health Stroke Scale (NIHSS) score, occlusion site, initial intravenous thrombolysis, time from onset -to MRI, -to needle, -to groin puncture, -to follow up MRI, procedure time and number of passes were prospectively recorded and retrospectively extracted. Subgroups were defined according to the final recanalization status and number of passes: First Pass (FP): Population achieving full (eTICI=3) reperfusion at first attempt; multiple passes (MP): eTICI3 reperfusion achieved by more than one attempt. Prospective registries were hold in accordance with national ethic recommendation (CNIL004).

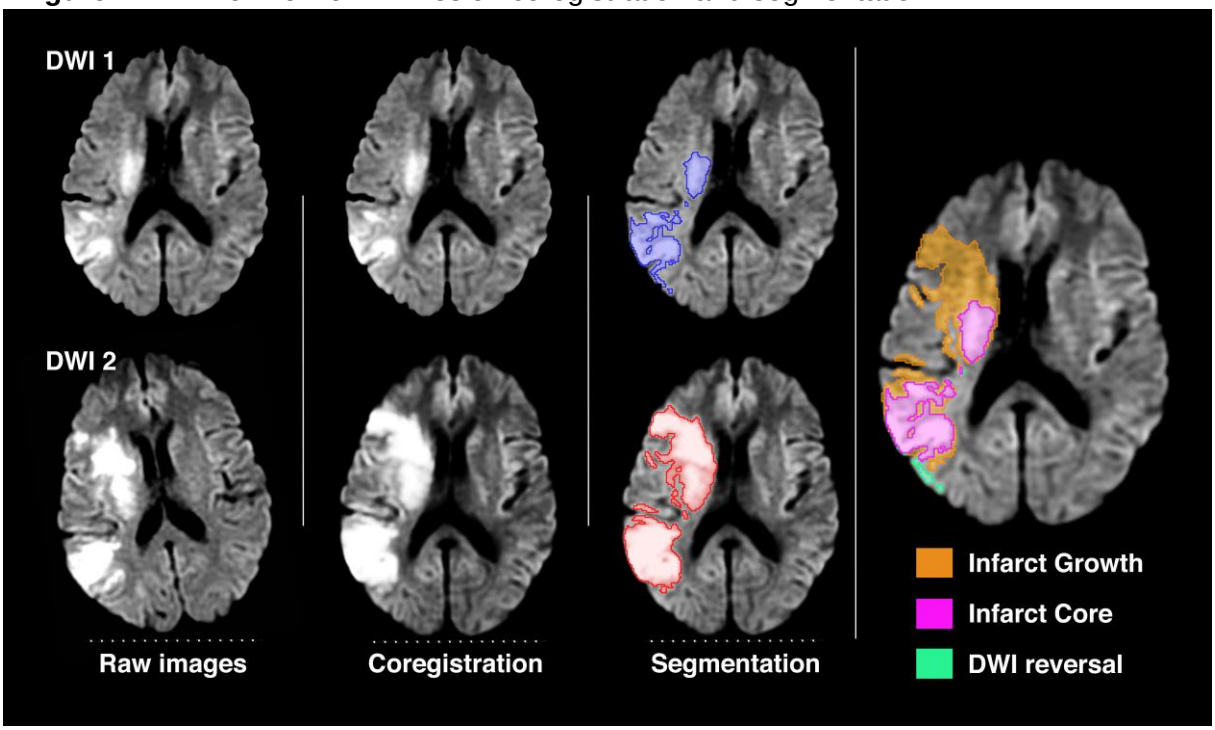
Mechanical thrombectomy procedures

Procedures were performed under conscious sedation, local or general anesthesia using thrombo-aspiration devices, stent-retriever systems or a combined technique (Association of Aspiration and Stentriever devices). The choice of the initial recanalization method and number of passes was at the discretion of the operator.

Clinical, imaging and angiographic data analysis

All MR exams were performed with a standardized protocol at each institution, where MR imaging is used as the first line imaging technique for acute stroke. All exams included at least a fast DWI sequence (Center 1: 1.5T Philips Achieva; Center 2: 1.5T Signa EchoSpeed, GE Healthcare). IG was obtained by a voxel-based segmentation of initial and follow up MRI with a standardized protocol.[62] Two readers, blinded to clinical and radiological data processed DWI segmentation. 24-hours follow-up DWI (DWI2) images were coregistered to initial DWI images (DWI1) with an automated three-dimensional rigid registration (FMRIB's Linear Image Registration Tool; FLIRT, V5.5).[63] Readers manually outlined DWI lesions based on DWI signal intensity and Apparent Diffusion Coefficient (ADC) map using a value-based filter set at 0.6 to exclude any areas of T2 shine-through effect and include areas of decreased ADC with subtle DWI signal changes (MANGO software, V3.1.1, Research imaging Institute, UTHSCSA). Segmented DWI2 volume was back-projected on DWI1 and checked to ensure a complete incorporation in brain tissue **(Figure D-I-1)**. To avoid any underestimation of Infarct Growth (IG), hemorrhagic transformation was included on DWI2 volume. (IG) was defined as voxels with signal changes on DWI2 that were normal on DWI1 (IG = DWI2 \ DWI 1= {x | x∉DWI1 and x∈DWI2}).[62]

Figure D-I-1: Workflow of DWI lesion coregistration and segmentation.



Follow-up DWI (DWI2) native image is coregistrated to the initial DWI (DWI1). Voxels with bright signal and Apparent Diffusion Coeffecient ADC<0.6 were segmented on DWI1 (blue) and DWI2 (red). Infarct Growth was determined voxelwise as the area of coregistrated DWI2 that did not lie within the area of DWI1. DWI indicates Diffusion Weighted Imaging. DWI Reversal refers to area of DWI1 that did not lie within coregistrated DWI2 area. All angiographic exams of included cases were reviewed by two experienced interventional neuroradiologists, blinded to clinical data and MRI data. Readers evaluated eTICI score at the end of procedure and identified multiple and First Pass population using previously described criteria: Complete revascularization of occluded arterial territory (Modified treatment in cerebral ischemia (eTICI) score 3), obtained by a single pass of first device, with no use of any other rescue therapy.[55] Number of passes was prospectively recorded by each operator. Collateral Status was scored by consensus by the two readers using the American Society of Intervention and Therapeutic Neuroradiology / Society of interventional Radiology score (ASITN/SIR). ASITN/SIR scores of 0, 1 and 2 were considered as poor collateral status, scores of 3 and 4 as good collateral status. Early neurological improvement (ENI) was defined as an improvement of at least 4points in the NIHSS score at 24 hours compared to baseline.[64] Symptomatic intracerebral haemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study 2 (ECASS II) criteria.[65] Favorable outcome was defined as modified Rankin Scale (mRS) ≤2 at 90-days. This report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[39]

Statistical Analysis

Baseline variables, procedural and functional outcome were compared between the single and multiple passes. Variables were described as absolute number (percentage) for discrete variables and mean (Standard Deviation) or median and interquartile range [IQR] as appropriate. Chi-square, Fisher's exact test, Student's t-test, and Mann-Whitney U tests were used as appropriate for the univariable analyses, with a p-value < 0.05 as the threshold for statistical significance. Multivariable analysis was performed using logistic regression models to identify independent predictor of functional outcome.

Propensity Score matching Analysis

To identify the true effect of FP, outcomes were compared after propensity score matching (PSM) for known confounding factors in outcome and infarct growth comparison[66–68]: initial NIHSS score (continuous), Collateral Status (good versus bad), prior treatment with IV t-PA (Yes/No), clot localization (ICA versus M1) and onset to reperfusion time. PSM without replacement, priority to exact correspondence (SPSS V22, IBM, Armonk, NY).

Mediation Analysis

Mediation analysis was performed to explain the association between a causal variable (FP) and outcome (3-months mRS) with a mediating variable (24-hours Infarct Growth). We analyzed mediation within a path analysis framework by using a logistic regression path analysis modeling macro for SPSS producing asymmetric bootstrap confidence interval with no requirement of normality of sampling distribution[69] (Process macro V3.3, SPSS V22, IBM, Armonk, NY). The primary goal of mediation analysis is to see whether the effect of the causal variable (FP) on the functional outcome (3 months mRS) can be mediated by a change in the mediating variable (IG). The statistical analysis of mediation was performed as follows: Step 1) test of the effect of FP on the mediating variable (IG), represented by regression coefficient *a*; Step 2) test of the relationship between the mediator (IG) and the functional outcome controlling for FP, represented by regression coefficient *b*. The effect of FP on functional outcome through IG is estimated by the product of regression coefficients *a* and *b*. A mediation is present if the indirect effect is statistically significant.[69] Bootstrap (5000 samples) confidence interval for indirect effect was used to support significant mediation. Associations between FP and IG; FP and IG with 3 months mRS were tested with univariable and multivariable analysis, using logistic regression and reported as unadjusted (cOR) and adjusted common odd ratios (acOR). Multivariable modelling included prespecified prognostic variables: age, initial NIHSS score, onset to recanalization and symptomatic intra-cranial Hemorrhage (sICH).

D-I-4 **Results**

Population Characteristics

200 patients with complete reperfusion (eTICI=3) after mechanical thrombectomy were extracted between January 2016-2019. First Pass eTICI3 was obtained in 118 (59%) patients. Single and multiple passes populations did not differ for baseline demographic or clinical data **(Table D-I-1)**.

Table D-I-1: Baseline Characteristics of First Pass (eTICI3 at first attempt) compared to multiple passes complete reperfusion population (unmatched analysis).

	First Pass (n=118)	**Multiple passes** (n=82)	**P value**
Male sex	57 (48.3%)	51 (62.2%)	0.053
Age, mean (SD), years	71 (14)	69 (17)	0.6
>80 years	31 (26.2%)	25 (30.5%)	0.5
Comorbidities and risk factors (missing cases)			
Hypertension (n=21)	67/110 (61%)	54/80 (67.5%)	0.35
Current smoker (n=20)	19/110 (17%)	16/80 (20%)	0.6
Dyslipidemia (n=20)	46/110 (42%)	33/80 (41.2%)	0.99
Diabetes mellitus (n=20)	15/110 (14%)	12/80 (15%)	0.8
Serum glucose (mmol/L), mean (SD)	7.20 (1.83)	7.24 (2.6)	0.5
Baseline NIHSS, median [IQR]	16 (15-18)	16 [16-18]	0.3
Treatment with IV-tPA	86 (72.9%)	57 (69.5%)	0.6
Workflow, median [IQR], min			
Onset-to-MRI	105 [79-142]	114 [103-118]	0.4
Onset-to-groin puncture	229 [170-295]	207 [183-231]	0.06
Onset-to-IV-tPA	130 [109-162]	140 [120-150]	0.6
Control Imaging Interval	24 [23-28]	24 [22-26]	0.9
Imaging			
DWI-ASPECTS, median [IQR]	7 [6-9]	7 [7-8]	0.06
Thrombus location (Angiography)			
ICA termination +/- M1	19 (16.1%)	20 (24.4%)	0.1
M1	92 (78%)	57 (69.5%)	0.2
M2	7 (5.9%)	5 (6.1%)	0.9
Collateral Status (ASITN/SIR)*			
Poor (1-2)	66 (55.9%)	40 (48.9%)	0.33
Good (3-4)	52 (44.1%)	425 (51.2%)	0.32

*NIHSS=National Institutes of Health Stroke Scale; mRS=modified Rankin Scale; MRI= Magnetic Resonance Imaging, Ivt-PA= intravenous tissue plasminogen activator; DWI-ASPECTS=Diffusion-Weighted Imaging Alberta Stroke Program Early CT Score; ICA=Internal Carotid Artery; M1: First segment of Middle Cerebral Artery; T shaped Occlusion: Ocllusion of ICA termination + M1 segment + A1 (first segment of Anterior Cerebral Artery), L shaped Occlusion: Occlusion of ICA termination and M1 segment. * American Society of Intervention and Therapeutic Neuroradiology / Society of interventional Radiology*

In unmatched analysis, FP population had lower median IG volume than MP (8.6ml versus 15.3ml respectively, p=0.04), shorter median procedure time (22min versus 39min respectively, $p<10^{-4}$) **(Table D-I-2)**.

Table D-I-2: Imaging, Procedural, Safety and Functional outcome in First versus Multiple Passes complete reperfusion population (unmatched analysis).

	First Pass (n=118)	**Multiple passes** (n=82)	**P value**
Imaging*			
Baseline DWI Volume (ml)	11.4 [3.4 -33]	14.2 [9-23.4]	0.3
Final (24H) DWI Volume (ml)	22.1 [8.4-52]	28.8 [20.7-32.8]	0.2
Infarct Growth (ml)	8.6 [6.8-12.6]	15.3 [11-18.9]	**0.04**
Procedure			
Procedure time (min)*	22 [16-33]	39 [38-46]	**10^{-4}**
Onset to recanalization(min)*	220 [163-283]	240 [221-296]	0.3
General Anesthesia	1 (0.2%)	1 (1.2%)	
First technique			
Stentriever	32 (27.1%)	19 (23.2%)	0.5
Aspiration	39 (33%)	28 (34.1%)	0.5
Combination (Stent +Aspiration)	47 (39.8%)	35 (42.7%)	0.7
Number of retrieval attempts*	1	2 [2-3]	-
Emboli to new territory	0	1 [1.2%]	0.27
Arterial Perforation	0	0	-
Outcome			
Early Neurological Improvement (ENI)	86 (72.9%)	53 (64.6%)	0.16
sICH	7 (5.9%)	6 (7.3%)	0.7
Favorable Outcome (mRS≤2)	74 (62.7%)	46 (56.1%)	0.3

**median values with [IQR]. DWI=Diffusion-Weighted Imaging; eTICI= Modified Treatment in Cerebral Infarction Scale; sICH= symptomatic Intracranial Hemorrhage; ENI= improvement of at least four points in the National Institutes of Health Stroke Scale score at 24 hours; mRS=modified Rankin Scale.*

Median IG volume increased with number of passes. Results were consistent between single and multiple passes for IG (8.7ml versus 15.2ml respectively, p=0.03) after case-control matching for prespecified confounders (initial NIHSS score, IV t-PA, Collateral Status, clot localization, onset to reperfusion time) **(Table D-I-3).**

Table D-I-3. Propensity Score matching analysis* of clinical and Imaging outcomes in First versus Multiple passes complete reperfusion population.

	First Pass (n=71)	**Multiple passes (n=71)**	**P value**
Infarct Growth (ml), median [IQR]	8.9 [6.84-11.5]	15.7 [11-19.4]	0.03
mRS≤2 (90 days)	49 (69%)	37(52.1%)	0.04
ENI	56 (78.9%)	45 (63.4%)	0.04
sICH	4 (5.6%)	6 (8.5%)	0.5
Mortality	5 (7%)	10 (21%)	0.02

*mRS=modified Rankin Scale; ENI= Early Neurological Improvement: improvement of at least four points in the National Institutes of Health Stroke Scale score at 24 hours; sICH= symptomatic Intracranial Hemorrhage as defined in ECASSII. P values for univariable analysis. *: Propensity score matching on initial NIHSS score, Collateral Status, prior IV-tPA, clot localization and onset to reperfusion.*

First Pass and Outcome

Case-control comparison between single and multiple passes populations showed better 3-months outcome in the FP group (70.9% versus 53.2% respectively, p=0.04) (**Table D-I-3)**. FP achievement was independently associated with favorable outcome (OR=1.86 95%CI [1.01-4.39] P=0.04) in logistic regression multivariable analysis, whereas procedure time was not (OR=1.01; 95%CI [0.99-1.03], P=0.24) (Nagelkerke R^2=0.404) **(Table D-I-4)**.

Table D-I-4. Multivariable logistic regression model for favorable functional outcome (mRS 0-2).

	OR [95%CI]	P value
Age	*0.98 [0.96-1.1]*	*0.16*
Initial NIHSS score	*0.98 [0.92-1.05]*	*0.8*
Blood Glucose level at admission (mmol/l)	*0.88 [0.75-1.03]*	*0.13*
ASPECT score	*1.27 [0.99-1.5]*	*0.06*
M1 versus ICA occlusion	*1.18 [0.85-1.6]*	*0.32*
IV t-PA treatment before MT	*3.21 [1.34-7.68]*	*0.009*
Collateral Status* (good versus poor)	*2.7 [1.5-5.1]*	*0.001*
Infarct Growth (per 1 cm^3)	*0.96 [0.94-0.98]*	*0.003*
eTICI 3 at first pass	*1.86 [1.01-4.39]*	*0.04*
Onset to final recanalization (min)	*0.99 [0.99-1.004]*	*0.58*
Procedure time (min)	*1.01 [0.99-1.03]*	*0.24*

(R^2Nagelkerke = 0.404, Collinearity testing, all variables VIF<3)

*CI: Confidence Interval; NIHSS=National Institutes of Health Stroke Scale; ASPECT= Alberta Stroke Program Early CT score; mRS=modified Rankin Scale;M1: first segment of middle cerebral artery; ICA: internal Carotid Artery; IV t-PA= intravenous tissue plasminogen activator; MT: Mechanical thrombectomy; eTICI= Modified Treatment in Cerebral Infarction Scale. * American Society of Intervention and Therapeutic Neuroradiology / Society of interventional Radiology (ASITN/SIR) score: Poor status: ASITN/SIR score 1 or 2, Good: ASITN/SIR score 3 or 4.*

Mediation by the Infarct Growth of the association between FP and mRS score

FP was independently associated with a better functional outcome in multivariable analysis, *c path:* acOR [95%CI], -0.78 [- 0.43 to -0.4] and with smaller infarct growth (*a* path): acOR [95%CI], -22.43 [-33.5 to -11.39] ($p<10^{-4}$ respectively). Infarct Growth was a predictor of functional outcome (*b* path): acOR [95%CI], 0.014 [0.01-0.17] ($p<10^{-4}$). A mediation of the effect of FP on functional outcome through IG was significant, with an estimated indirect effect (95% bootstrap CI) of -0.32 (-0.47 to -0.09) **(Table D-I-5).**

Table D-I-5: Effect of First Pass on ordinal 3-months mRS mediated by 24-hours Infarct Growth

	Unadjusted		*Adjusted*	
Pathway	*cOR (95% CI)*	*P value*	*acOR (95% CI)*	*P value*
a	*-26.68 (-38.29 to -15.07)*	*$<10^{-4}$*	*-22.43 (-33.5 to -11.39)*	*10^{-4}*
b	*0.02 (0.016-0.22)*	*$<10^{-4}$*	*0.014 (0.01-0.17)*	*$<10^{-4}$*
c	*-0.87 (-1.27 to -0.48)*	*$<10^{-4}$*	*-0.78 (- 0.43 to -0.4)*	*$<10^{-4}$*
c'	*-0.34 (-0.71 to -0.03)*	*0.03*	*-0.46 (-0.78 to -0.13)*	*0.005*
Indirect effect (95% bootstrap CI)	*-0.5 (-0.68 to -0.31)*		*-0.32 (-0.47 to -0.09)*	

a: regression coefficient representing the effect of First Pass on the mediating variable (IG), b: regression coefficient representing the effect of IG on outcome (3 months modified Rankin Score), c: Total effect of First Pass on outcome without controlling for IG, c': Direct effect of First Pass on outcome after controlling for IG, cOR: common Odd Ratio, acOR: adjusted common Odd Ratio

D-I-5 **Discussion**

Fast achievement of complete reperfusion is a key predictor of favorable outcome in AIS-LVO patients.[59] In this multicentric study, we confirmed that the population achieving a complete reperfusion (eTICI=3) at first pass had higher rates of 24h-early neurological improvement and better 3 months functional outcome compared to the population with complete reperfusion obtained by multiple passes.[55,57] Using baseline and final DWI data, we found a significantly lower growth of the early infarct core in case of complete reperfusion (eTICI=3) at a first attempt than in case of complete reperfusion in more than one attempt. This result was consistent between unmatched and matched populations for known confounding factors affecting infarct growth[66–68]: initial NIHSS score, IV-tPA, Collateral Status, clot localization and onset to final reperfusion time. Obtaining a complete reperfusion at first attempt was an independent predictor of good functional outcome. In addition, we demonstrated that the physiopathology of the first-pass effect lies in a limitation of infarct growth mediating the positive effect of single pass on 3 months functional outcome.

The reduction of IG and the higher rates of good functional outcome and ENI in the FP group compared to fully reperfused patients with multiple passes could be explained by several

factors. Procedural time from arterial puncture to reperfusion were significantly shorter in FP group, allowing a reduced onset-to-recanalization delay. However, the observed effect of first pass on IG is not only linked to the time saving to complete reperfusion since FPE group remain with lower growth of the early core than control matched group after adjustment for onset-to-recanalization delay as a confounding factor in multiple regression. FPE is not only associated with shorter recanalization but also with less intra-arterial saline infusion combined to minimal blood loss, associated with procedure-induced anemia.[70] This may have an impact on IG since anemia jeopardize the oxygen-carrying capacity of the blood and is associated, in AIS, with larger IG, unfavorable outcome and increased mortality.[70]

Lower rates of per procedural complications may explain lower IG in the FP population. Hence, new territory emboli or vessel perforation rates were lower in the FP group. Repeated maneuvers at the contact of the clot as increase the number of passes may contribute to endothelial damage and clot fragmentation since every thrombectomy maneuver results in thousands of small clot fragments that may occlude small arterioles and capillaries.[54,71,72] Increased risk of micro-embolism in perforating and small capillaries may also occur more frequently with multiple passes, leading to micro-circulatory dysfunction and the “no-reflow” phenomenon, with higher infarct volume on 24h DWI, contributing to observed differences of IG volumes between first and multiples passes populations. This finding is also supported by a better functional outcome when cervical flow reversal is obtained using balloon guide catheter, minimizing distal embolic fragment from the occlusive clot.[73,74] In addition, increasing procedure time with multiple passes can lead to hemodilution due to per-procedural saline infusion, which is associated with larger IG by induced anemia, impairing oxygen-carrying capacity of the blood and increasing brain injury.[75,76]

Achieving complete reperfusion at first pass appears to be a new independent valid metric to measure procedural and clinical efficacy.[55] The definition of successful procedure in stroke endovascular therapy is continuously shifting toward more complete and faster recanalization[55,77–79] and eTICI 3 at first attempt represents the ultimate goal. The rate of successful recanalization at first pass is present in ~28% of patients treated with mechanical thrombectomy.[55,80] This low rate underlines the need to develop strategy and devices that can successfully retrieve thrombi in fewer passes.

It was previously demonstrated that growth of the early infarct core can be influenced by others factors than the clot retrieval attempts number, such as initial infarct volume, age, dyslipidemia, active smoking,[67] in case of poor brain reserve[81] or early secondary re-occlusion.[82] Elderly population with impaired brain reserve could experience higher volumes of infarct growth even with prompt reperfusion. Consequently, the use of retrieval attempts number as an indicator of IG should be cautious, since many other factors may have influenced infarct progression.

Our study has several strengths including precise measurement of infarct growth by quantification of voxel changes between baseline and 24h MRI. The voxel based analysis quantification of core volume using DWI offer a more precise, quantitative, analysis of evolution over time, than semi-quantitative CT or DWI-ASPECT evaluation, hence identifying both core progression and regression as a result of the recanalization treatment.[62] To note, previous studies confirmed that the use of MRI as standard imaging admission modality did not impact global workflow,[14,20,83,84] as neither time metrics nor functional outcome differed between first CT or first MRI groups**.**

Our study also has several limitations. To obtain a precise quantification of infarct growth, we excluded cases where CT-scan was performed instead of MRI at admission or at 24hours control. However, excluded patients did not differ in terms of initial clinical presentation or outcome from study population (data not shown), minimizing the effects of potential selection biases. Several clinical and procedural factors could have affected the number of passes. Arterial tortuosity, clot composition and burden, use of intravenous tPA, and thrombectomy technique[85] are all assumptive factors affecting the recanalization result although evidence for any of them is scarce. Within a retrospective design and due to a relatively small sample size, it was impossible to control all those confounding factors, but a large number of patients from multiple experienced operators might mitigate some of those factors.

D-I-6 **Conclusion**

AIS-LVO patients achieving complete reperfusion at first attempt seems to have an independent effect on functional outcome, explained by a smaller infarct growth. These results reinforce the concept of First Pass effect as a primary objective of endovascular procedures in ischemic stroke.

Ce travail a permis de démontrer que la relation rapportée dans la littérature entre l'obtention d'une recanalisation complète à la première tentative et le bon pronostic fonctionnel est médiée en partie par une limitation de la croissance aigue de l'infarctus cérébral. Afin de confirmer cette hypothèse, un deuxième travail complémentaire a été réalisée cherchant à démontrer une relation entre croissance d'infarctus et le nombre de passages en thrombectomie.

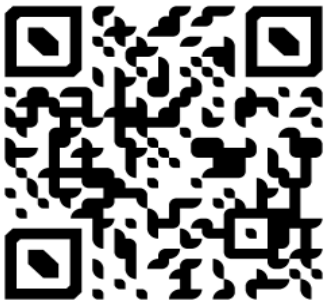
D- II. Relation entre nombre de passage et croissance d'infarctus

Si le bénéfice clinique d'une recanalisation dès la première tentative d'une occlusion artérielle proximale intracrânienne aigue est confirmée par notre précédent travail, l'hypothèse que ce bénéfice soit médié par une moindre croissance de l'ischémie cérébrale à 24h nécessitait, pour la soutenir, la démonstration d'une relation linéaire ou « dose effet » entre le nombre de tentatives et la croissance, en donnée continue, du volume de tissu cérébral infarci.

Impact of Repeated Clot Retrieval Attempts on Infarct Growth and Outcome After Ischemic Stroke

Wagih Ben Hassen, MD,* Caroline Touloupas, MD,* Joseph Benzakoun, MD, Gregoire Boulouis, MD, Martin Bretzner, MD, Nicolas Bricout, MD, Laurence Legrand, MD, Christine Rodriguez, MD, Alice Le Berre, MD, Pierre Seners, MD, PhD, Guillaume Turc, MD, PhD, Charlotte Cordonnier, MD, PhD, Catherine Oppenheim, MD, PhD, Hilde Henon, MD, PhD,† and Olivier Naggara, MD, PhD†

Neurology® 2021;97:e444-e453. doi:10.1212/WNL.0000000000012321



D-II-1 **Résumé Étude N°3**

Pour démontrer un effet-dose entre le nombre de pasage et la croissance d'infarctus, les données de cas avec occlusion proximale dans le territoire antérieur traités par thrombectomie mécanique ont été extraites de deux registres prospectifs multicentriques (CHSA + Lille) entre janvier 2016 et 2019. Les cas ayant une imagerie pondérée par la diffusion (DWI) avant le traitement et 24 heures après la TM ont été inclus. La croissance de l'infarctus a été obtenue par une segmentation semi-automatique basée sur les voxels après co-registration des images DWI. Les associations entre le nombre de tentative de thrombectomie, la croissance de l'infarctus et le résultat fonctionnel à 3 mois ont été analysées dans le groupe de recanalisation réussie définie par un score [eTICI] 2b, 2C ou 3. 419 patients ont été inclus. Les patients avec un seul passage ont présenté le plus faible volume de croissance d'infarctus et le meilleur pronostic fonctionnel. Le nombre de passages était indépendamment associé à l'augmentation du volume de l'infarctus (Odds Ratio (OR) : 7,2 par passage, intervalle de confiance à 95% [CI]=[3,2-11,9], p=0,001) et à une augmentation du taux d'embols dans de nouveaux territoires (β = 2.7 [95% CI 1.21–4.1], p = 0.03). Un résultat fonctionnel défavorable (score de Rankin modifié > 2 à 3 mois) augmentait avec chaque tentative supplémentaire. La croissance d'infarctus était un facteur prédictif indépendant de l'issue défavorable (OR=1,04, 95%CI [1,03-1,05] par 1mL d'augmentation de l'IG (p=0,001). Le volume de croissance de l'infarctus augmente donc avec le nombre de tentative de thrombectomie pour les patients recanalisés avec succès. Chaque tentative supplémentaire de recanalisation est associée à une croissance accrue de l'infarctus et à une dégradation du pronostic fonctionnel.

Cette étude a donc montré, chez 419 patients, le lien entre nombre de tentatives de thrombectomie et:

- **croissance du volume de tissu infarci à 24h**
- **la survenue d'embols dans de nouveaux territoires artériels, initialement non infarcis**

D-II-2 Introduction

Recovery of adequate cerebral perfusion is the primary target of endovascular therapy (EVT) in patients with acute ischemic stroke due to large vessel occlusion (AIS-LVO), decreasing handicap and mortality by limiting infarct growth (IG).[86] However, despite complete recanalization being achieved in >80% (expanded Thrombolysis in Cerebral Infarction Scale [eTICI] scores 2b-2c-3), less than half of AIS-LVO patients achieved a 3-month favorable outcome.[19,87] The number of clot retrieval attempts (CRA) has recently been identified as a marker of clinical outcome, independent of final recanalization success, with a detrimental effect of increasing CRA on 3-month functional outcome.[88–92] Moreover, obtaining a complete recanalization at the first CRA is associated with a favorable outcome and decreased mortality.[80,93–95] The detrimental effect of repeated CRA on functional outcome is not straightforward and has not yet been explained. Additional CRA could result in an increased per procedural clot fragmentation, leading to emboli to new (initially unaffected) territory (ENT),[96,97] associated with IG[98] and potentially explaining the detrimental effect of CRA on functional outcome.[99–101] In this study, we aimed to elucidate the link between the number of CRA and the functional outcome in a successfully recanalized population. We hypothesized that, after adjustment for time metrics, increasing the number of CRA could be associated with higher rates of ENT, leading to an increased IG volume and explaining the 3-month unfavorable outcome.

D-II-3 Methods

Primary research question and evidence level

Is there an impact of repeated CRA on IG and outcome after ischemic stroke? This study provides Class II evidence that, for patients with acute stroke undergoing successful recanalization, an increased number of CRA is associated with poorer functional outcome.

Study population

Data were extracted from two prospective registries including consecutive AIS-LVO patients treated with mechanical thrombectomy (MT) between January 2016 and 2019 in two large comprehensive stroke centers (Center 1: Centre Hospitalo-Universitaire de Lille, France; Center 2: Centre Hospitalier Sainte-Anne, Paris, France). Inclusion criteria were: 1) AIS-LVO with known symptoms onset treated with EVT; 2) available initial diffusion-weighted Imaging (DWI_1) and 24 hours post-treatment DWI (DWI_2) for IG measurement. Patients with tandem occlusions (extra- and intracranial occlusions), posterior circulation occlusions and magnetic resonance imaging (MRI) contraindications were excluded. The following were prospectively recorded: clinical and demographic data; National Institutes of Health Stroke Scale (NIHSS)

score at admission; occlusion site; initial intravenous thrombolysis (IVT); time from onset to MRI, to needle, to groin puncture, to follow-up MRI; procedure time; and number of clot retrieval attempts (CRA). This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[39]

Standard protocol approvals, registrations, and patient consents

Data were extracted from prospective registries held after approval of the National Ethics Committee (CNIL, MRO004). This retrospective analysis was approved by the local ethics committee.

CRA and procedural outcomes assessment

Endovascular procedures were performed under conscious sedation or local or general anesthesia using standardized techniques. The choice of MT device was retrospectively recorded. Two interventional neuroradiologists, blinded to clinical and DWI data, registered the number of CRA, the final eTICI score and per-procedural complications for each case (vasospasm, dissection, vessel perforation, distal or new territory emboli). Registry inclusion required operators to save per-procedural video loops of each retrieval attempt. The number of CRA was retrospectively reviewed by blinded readers who excluded cases with a discrepancy between the number of retrieval attempts and the number of recorded angiographic video loops (number excluded=0). Successful recanalization was defined as final eTICI score = 2B, 2C or 3. Full recanalization was defined as final eTICI score = 3. ENT was defined as the presence on final angiogram of a clot fragment in an initially unaffected artery as seen on initial MR examination (occlusion of anterior [ACA] or posterior [PCA] cerebral artery or a different M2 branch for M2 occlusions). Distal emboli in an initially occluded territory were not considered as ENT. Collateral status was graded by consensus by the two readers using the American Society of Intervention and Therapeutic Neuroradiology/Society of interventional Radiology (ASITN/SIR) scale. ASITN/SIR scores of 0, 1 and 2 were considered as poor collateral status, scores of 3 and 4 as good collateral status.

MT Procedures

Vascular access for mechanical thrombectomy was obtained via using an 8- French vascular sheath introduced into the femoral artery in 398/419 patients (95%), the humeral or radial arteries in 20 (4.7%) patients and direct carotid puncture in 1(0.03%) patient. First line device used for clot retrieval and eventual rescue technique were retrospectively recorded. No balloon guided catheters were used during the study period. For Aspiration technique, a large bore aspiration catheter (5-Max ACE, ACE 64 or ACE 68, Penumbra, Alameda, CA or SOFIA, MicroVention, Tustin, CA) was positioned over a 0.014-inch guidewire immediately adjacent to the proximal end of the arterial clot, and suction was applied using an aspiration pump

system or a manual aspiration using a 60mL syringe. Stentriever technique consisted of placing a microcathter beyond the occlusion site, delivering a stent retriever (Solitaire 6x20mm or 4x20mm; Medtronic, Irvine, CA or TREVO stent 4x20mm or 6x25mm; Stryker, CA, USA). Stent retriever position was considered optimal when covering the entire length of the clot, allowing thrombus entrapment between the stent struts. Stent with incorporated clot was then slowly retrieved. A combined technique consisted of using both aspiration and stentriever devices to achieve flow restoration. In this case, stent retriever is positioned as previously described, and a continuous aspiration was applied when the stent is pulled back into the large bore aspiration catheter.

Imaging analysis

All MR examinations were performed with a standardized protocol at each institution, where MR imaging is used as a routine first line imaging technique for acute stroke. All examinations included a fast DWI sequence (Center 1: 1.5T Philips Achieva; Center 2: 1.5T Signa EchoSpeed, GE Healthcare). IG was obtained by a semi-automatic voxel-based segmentation after co-registration of DWI_1 and DWI_2 images using a previously described method.[62] Bright voxels on DWI_1 and DWI_2 were outlined. Segmented DWI voxels were projected onto apparent diffusion coefficient (ADC) maps to exclude any areas of T2 shine-through effect and include areas of decreased ADC with subtle DWI signal changes. IG was measured after back-projection of segmented DWI_2 on coregistered DWI_1, and defined as signal changes on DWI_2 that were normal on DWI_1. IG measurement reflects infarct progression in the initially affected territory and newly formed infarct in an initially unaffected territory. Hemorrhagic transformations were included in DWI_2 segmentation to avoid underestimation of IG. Symptomatic intracerebral hemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study 2 (ECASS II) criteria.[65] Unfavorable outcome was defined as modified Rankin Scale (mRS) score >2 evaluated at 3 months.

Statistical analysis

Baseline variables and procedural and functional outcome were compared according to the total number of CRA. Variables were described as absolute number (percentage) for discrete variables and mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Chi-square, Fisher's exact test, Student's t-test, and Mann-Whitney U tests were used, as appropriate, for the univariable analyses, with a p-value < 0.05 as the threshold for statistical significance. Test for linear trend was performed between number of CRA and IG and number of CRA and unfavorable outcome with simple linear regression. Correlation between number of CRA and ENT or infarct in new territory was measured by Spearman's rank correlation coefficient. Multivariable analysis was performed using linear or logistic

regression models after collinearity testing (variance inflation factor: VIF) including number of CRA, entered as a categorical variable in the full model, with adjustment for age, initial NIHSS score, prior IV thrombolysis, onset-to-recanalization time, procedure time and final recanalization status (eTICI score 3 versus score 2B or C), to identify independent predictors of infarct growth or functional outcome.

Data Availability Statement:

All data can be made available upon reasonable request to the corresponding author and after approval by the local ethics committee.

D-II-4 **Results**

Population

Amongst 902 anterior circulation stroke patients with known onset time treated with MT between January 2016-2019, 502 subjects (56.1% female sex; mean age 68 ± 15 years) were eligible (exclusion for pre-treatment CT scan [n=105], clot access failure or recanalization before mechanical treatment [n=109], 24 hours post treatment CT scan [n=186]). A total of 419 patients achieving successful recanalization were included. The excluded population was similar to the study population in terms of initial stroke severity, workflow or procedural or functional outcome but was significantly older and had a higher contraindication rate for IVT **(table D-II-1).**

Table D-II-1 Characteristics of excluded population (N=400) compared to study population

	Study Population (n=419)	**Initial CT (n=105)**	P value	**24H CT (n=186)**	P value
Characteristics					
Male sex	184 (43.9%)	60 (57.1%)	**0.01**	94 (50.5%)	0.1
Age, mean (SD), years	68 (16)	73 (15)	**0.02**	74 (14)	**10^{-4}**
Comorbidities and risk factors*					
Hypertension	235/389 (60.4%)	69 (65.6%)	0.34	103 (55.6%)	0.22
Current smoker	84/388 (21.6%)	12 (11.5%)	**0.01**	28 (14.8%)	**0.03**
Dyslipidemia	133/392 (33.9%)	28 (27.1%)	0.1	50 (27%)	**0.04**
Diabetes mellitus	55/390 (14.1%)	17 (16.1%)	0.65	40 (21.7%)	**0.02**
Baseline NIHSS score, median [IQR]	18 [17-19]	18 [17-20]	0.6	18 [17-19]	0.7
Treatment with IV-tPA	294 (70.2%)	47 (44.3%)	**10^{-4}**	119 (64%)	0.18
Workflow, median [IQR], min					
Onset-to-imaging	115 [109-121]	111 [105-120]	0.26	115 [102-130]	0.22
Onset-to-groin puncture	232 [214-245]	213 [192-253]	0.34	240 [225-260]	0.42
Onset-to-IV-tPA	140 [135-153]	135 [122-160]	0.52	150 [137-178]	0.07
Onset to final TICI score	259 [248-274]	284 [260-320]	0.49	305 [285-325]	0.05
Imaging					
ASPECTS, median [IQR]	7 [7-8]	7 [7-8]	0.3	7 [7-8]	0.06
Thrombus location (angiography)					
ICA +/- M1	97 (23.1%)	25 (23.9%)	0.9	52 (28%)	0.26
M1	283 (67.6%)	76 (72.4%)	0.24	111 (59.6%)	0.09
M2	39 (9.3%)	4 (3.8%)	0.06	23 (12.4%)	0.3
Procedure					
Procedure time (min), median [IQR]	30 [28-34]	39 [23-60]	0.19	37 [22-63]	0.34
General anesthesia	7 (1.7%)	8.4 (8%)	**0.005**	13 (7.1%)	**0.004**
Emboli to new territory	23 (5.5%)	2 (2.1%)	0.43	8 (4.3%)	0.67
Arterial perforation	2 (0.5%)	2 (1.9%)	0.9	2 (1.3%)	0.54
eTICI score≥2B	100%	82 (77.7%)	-	144 (77.6%)	-
Outcome					
sICH	29 (6.9%)	4 (3.8%)	0.08	9 (4.8%)	0.07
Favorable outcome* (mRS score≤2)	209/367 (57%)	75 (42.6%)	0.27	92 (49.4%)	0.83

*Abbreviations: NIHSS = National Institutes of Health Stroke Scale; IVt-PA = intravenous tissue plasminogen activator; mRS = modified Rankin Scale; eTICI = Expanded Treatment in Cerebral Infarction Scale; ASPECTS = Alberta Stroke Program Early CT Score; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; M2 = second segment of middle cerebral artery; sICH = symptomatic intracranial hemorrhage. * missing data*

Baseline characteristics of the study population and its stratification by number of retrieval attempts are detailed in **table D-II-2.** Successful recanalization was obtained after one CRA in 224/419 patients (53.5%), two CRA in 107 patients (25.5%), three CRA in 49 (11.7%) patients and four or more CRA in 39 patients (9.3%).

Table D-II-2 General characteristics of overall population and according to number of clot retrieval attempts

	Study population (n=419)	**1 Attempt (n=224)**	**2 Attempts (n=107)**	**3 Attempts (n=49)**	**≥4 Attempts (n=39)**
Characteristics					
Male sex	184 (43.9%)	104 (46.4%)	44 (41.1%)	20 (40.8%)	16 (41%)
Age, mean (SD), years	68 (16)	69 (15)	69(19)	68 (18)	66 (19)
Risk factors (missing cases)					
Hypertension (n=30)	235/389 (60.4%)	124/209 (59%)	63/98 (64.3%)	27/45 (60%)	21/37 (57%)
Current smoker (n=31)	84/388 (21.6%)	44/209 (21%)	20/100 (20%)	12/44 (27.2%)	12/35 (34.3%)
Dyslipidemia (n=27)	133/392 (33.9%)	69/212 (32.5%)	38/97 (40.2%)	13/46 (28.3%)	13/37 (35.1%)
Diabetes mellitus (n=29)	55/390 (14.1%)	28/210 (13.3%)	17/96 (17.7%)	5/45 (11.1%)	5/39 (12.8%)
Baseline NIHSS score	18 [17-19]	16 [15-17]	17 [17-19]	18 [17-19]	18 [17-19]
Treatment with IV-tPA	294 (70.2%)	159 (70.9%)	73 (68.2%)	34 (69.4%)	28 (71.7%)
Workflow, median [IQR], min					
Onset-to-imaging	115 [109-121]	106 [97-112]	112 [105-125]	110 [98-123]	110 [105-128]
Onset-to-IV-tPA	140 [135-153]	133 [120 -140]	140 [127-150]	140 [120-160]	139 [129-160]
Onset-to-groin puncture	232 [214-245]	224 [208-241]	218 [201–234]	225 [205-241]	224 [212-270]
Imaging-to-groin puncture	97 [84-111]	107 [86-120]	83 [71-95]	116 [90-137]	85 [61-142]
Imaging					
DWI-ASPECTS, median [IQR]	7 [7-8]	8 [8-9]	7 [7-8]	6 [6-8]	7 [7-8]
Thrombus location*					
ICA +/- M1	97 (23.1%)	48 (21.4%)	28 (26.2%)	11 (22.4%)	10 (25.6%)
M1	283 (67.6%)	156 (69.6%)	69 (64.5%)	34 (63.4%)	24 (61.6%)
M2	39 (9.3%)	20 (9%)	10 (9.3%)	4 (8.2%)	5 (12.8%)

values are median [IQR] if not otherwise specified, NIHSS = National Institutes of Health Stroke Scale; IV tPA = intravenous tissue plasminogen activator; DWI-ASPECTS = Diffusion-Weighted Imaging Alberta Stroke Program Early CT Score; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; M2 = second segment of middle cerebral artery. Thrombus location as defined on catheter angiography.*

Emboli to new territory, infarct growth and clot retrieval attempts

Occurrence of ENT was highly correlated to increasing number of CRA (ρ=0.73, p=10^{-4}), with 23 (5.5%) cases in the whole study population, 2 (1%) in the one CRA group, 3 (2.8%) in two CRA group, 7 (14.3%) in three CRA group and 11 (28.2%) in four or more CRA **(table D-II-3).**

Table D-II-3: Imaging, procedural, safety and clinical outcome according to number of clot retrieval attempts

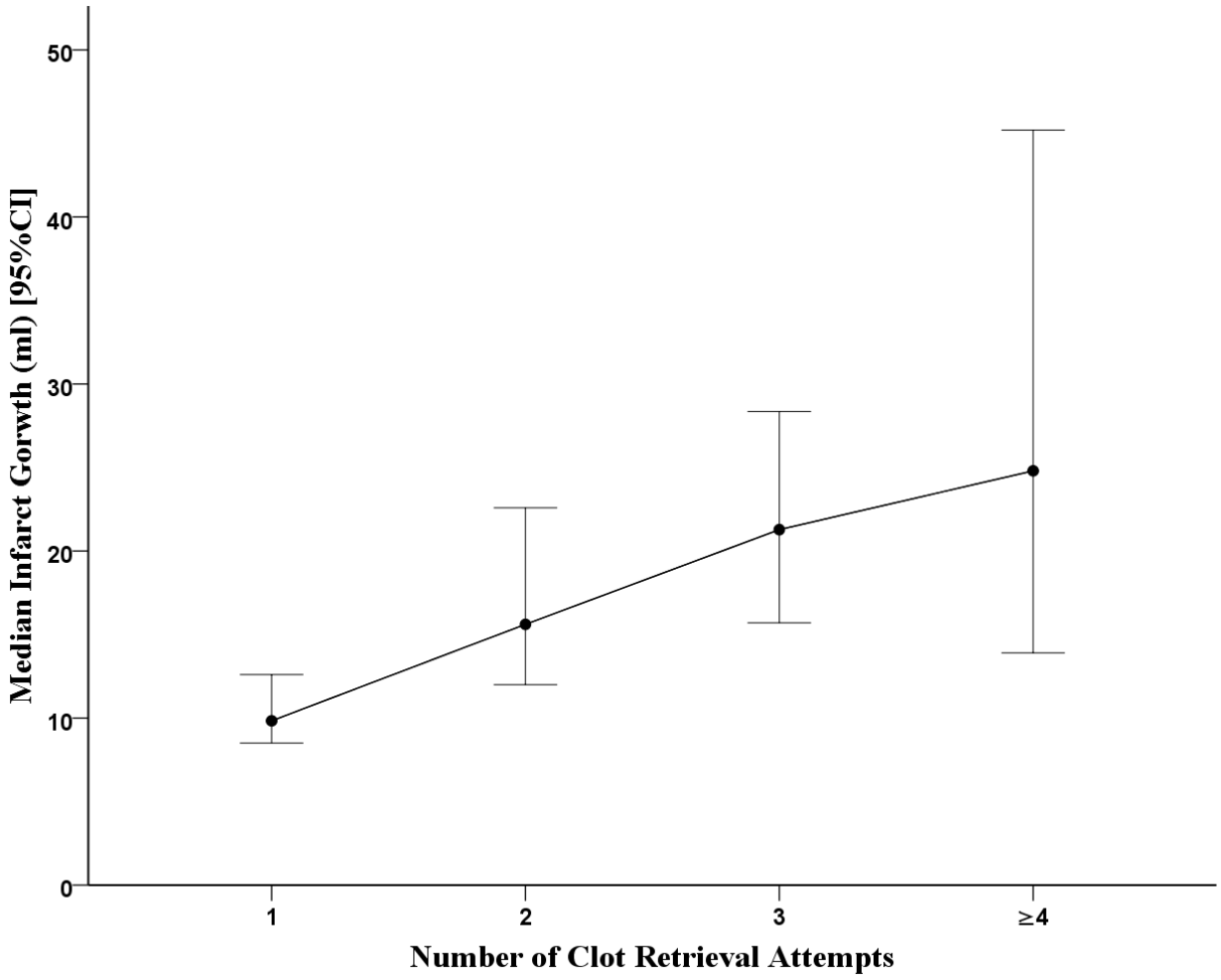
	Study population (n=419)	1 Attempt (n=224)	2 Attempts (n=107)	3 Attempts (n=49)	≥4 Attempts (n=39)
Procedure					
First technique					
Stentriever	80 (19.1%)	43 (19.2%)	20 (18.7%)	10 (20.5%)	7 (18%)
Aspiration	211 (50.3%)	123 (54.9%)	47 (43.9%)	21 (42.8%)	20 (51.3%)
Combination*	128 (30.5%)	58 (25.9%)	40 (37.4%)	18 (36.7%)	12 (30.8%)
Rescue technique	34 (8.1%)	0 (0%)	5 (4.8%)	6 (12.2%)	23 (59%)
Stentriever	5 (14.7%)	0 (0%)	0 (0%)	0 (0%)	5 (21.7%)
Aspiration	2 (5.9%)	0 (0%)	0 (0%)	0 (0%)	2 (8.7%)
Combination	27 (79.4%)	0 (0%)	5 (100%)	6 (100%)	16 (69.6%)
Final eTICI score					
2B	163 (38.9%)	75 (33.5%)	50 (46.7%)	18 (36.7%)	16 (41%)
2C	122 (29.1%)	74 (33%)	24 (22.4%)	16 (32.6%)	10 (25.6%)
3	134 (32%)	75 (33.5%)	33 (30.8%)	15 (30.6%)	13 (33.4%)
Collateral Status (ASITN/SIR)†					
Poor (0-1-2)	94/232 (40.5%)	52/133 (39.1%)	25/52 (48%)	8/24 (33%)	9/23 (39.1%)
Good (3-4)	138/232 (59.5%)	81/133 (60.9%)	27/52 (52%)	16/24 (66%)	14/23 (60.9%)
Onset to final eTICI score (min)	259 [248-274]	255 [233-273]	253 [240-275]	274 [233-297]	284 [238-372]
Procedure time (min), median [IQR]	30 [28-34]	22 [21-24]	37 [33-40]	46 [42-55]	63 [33-71]
General anesthesia	7 (1.7%)	1 (0.4%)	2 (1.9%)	0 (0%)	4 (10%)
Emboli in new territory	23 (5.5%)	2 (1%)	3 (2.8%)	7 (14.3%)	11 (28.2%)
Arterial perforation	2 (0.5%)	0 (0%)	0(0%)	0 (0%)	2 (5%)
Imaging, median [IQR]					
Control imaging (hours)	24 [24-26]	24 [24-26]	24 [23-28]	22 [20-26]	23 [20-25]
Pre-treatment DWI volume (ml)	14 [12-26]	12 [9-26]	15 [12-21]	15 [9-27]	13 [9-27]
24-h control DWI volume (ml)	27 [25-31]	22 [19-26]	30 [26-42]	35 [27-68]	36 [20-77]
Infarct in new territory	32 (7.6%)	4 (1.8%)	7 (6.5%)	11 (22.4%)	10 (25.6%)
Infarct growth (ml)	14 [12-16]	9.8 [9-12.5]	15.6 [12-23]	21 [16-28]	25 [11-67]
Hemorrhagic transformation					
HI1	71 (16.9%)	35 (15.6%)	20 (18.7%)	9 (18.4%)	7 (17.9%)
HI2	63 (15%)	35 (15.6%)	16 (15%)	6 (12.2%)	6 (15.4%)
PH1	29 (6.9%)	12 (5.5%)	9 (8.4%)	4 (8.7%)	4 (10.2%)
PH2	13 (3.1%)	4 (1.8%)	3 (2.8%)	3 (6.1%)	3 (7.7%)
Outcome					
sICH	29 (6.9%)	13 (5.8%)	9 (8.4%)	3 (6.1%)	4 (10%)
Favorable outcome‡ (mRS score≤2)	209/367 (57%)	124/200 (62%)	51/92 (55%)	19/39 (49%)	15/36 (41.7%)

eTICI = extended Treatment in Cerebral Infarction Scale; ASITN/SIR = American Society of Intervention and Therapeutic Neuroradiology / Society of interventional Radiology; DWI = diffusion-weighted imaging; HI = hemorrhagic infarct type 1 or 2; PH = parenchymal hemorrhage type 1 or 2; sICH = symptomatic intracranial hemorrhage; mRS = modified Rankin Scale.

** Combination of stentriever and aspiration techniques. †: Non-assessable collateral status on angiography (n = 214). ‡ Missing data (n = 52).*

IG volume was higher in the ENT group (ENT+: 26.9 ml [10.7–49] versus ENT-: 12.6 ml [4.5–32.1]; p=0.01). One CRA group had the lowest IG volume (p=0.001) and the lowest rates of ENT (p=0.01). IG increased linearly with the number of CRA ($p<10^{-4}$) **(Figure D-II-1).**

Figure D-II-1: Linear increase of median Infarct Growth volume (ml) according to number of clot retrieval attempts in successfully recanalized (eTICI 2B, 2C, 3) population.



In multivariable linear regression, number of CRA and ENT were associated with IG, among poor collateral status, blood glucose level and initial NIHSS score independently from time metrics (procedure time or onset-to-recanalization time) **(table D-II-4).**

Table D-II-4 Multivariable linear regression full model for infarct growth (ml)

	Infarct growth (ml)	
Variable	β coefficient (95% CI)	*p* value
Age	0.158 (-0.32–0.64)	0.051
NIHSS score (per 1 point increase)	1.25 (0.52–2.58)	0.01
Blood glucose (mmol/l)	4.13 (0.97–7.66)	0.012
TICI score 2B or 2C versus TICI score 3	3.8 (-17.6–9)	0.6
IV tPA before MT	-4.04 (-12.5–20)	0.63
Poor collateral status	7.99 (2.4–29.3)	0.001
Onset to final recanalization (min)	0.05 (-.048–0.15)	0.3
Procedure duration (min)	0.03 (-0.41–0.47)	0.89
Initial DWI volume (per 1-ml increase)	0.38 (0.15-0.61)	0.001
Number of clot retrieval attempts	1.6 (0.97–9.74)	0.037
Emboli to new territory	2.7 (1.21–4.1)	0.04

R^2 Nagelkerke = 0.47. No collinearity between tested variables (VIF = 1.28)

NIHSS = National Institutes of Health Stroke Scale; eTICI = expanded Treatment in Cerebral Infarction Scale; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; IV tPA = intravenous tissue plasminogen activator; MT = mechanical thrombectomy; DWI = diffusion-weighted imaging.

Functional outcome

Symptomatic Intra-cranial hemorrhage (sICH) rates increased with CRA number, with the group of one retrieval attempt experiencing the lowest rate of sICH (5.8%) versus 8.4% in the group of two CRA, 6.1% for three CRA and 10% in the group of four or more CRA. Favorable functional outcome decreased with each additional CRA in the successfully recanalized population **(table D-II-3).** The 1 CRA group had the highest rate of favorable outcome (124/200, 62% versus 85/167, 50.9%, p=0.03). IG was an independent negative predictor of favorable outcome in binary logistic regression analysis: adjusted OR=1.05 (1.02-1.07) per 1-ml increase in IG (p=0.0001) **(table D-II-5).**

Table D-II-5 Multivariable binary logistic regression full model for 90-day bad functional outcome (mRS score >2)

	90-day mRS score >2	
Variable	aOR (95% CI)	*p* value
Age	1.03 (1.003–1.07)	0.03
NIHSS score	1.19 (1.09–1.31)	0.002
Blood glucose (mmol/l)	1.42 (1.05–1.94)	0.02
TICI score 2B or 2C versus TICI score 3	1.02 (0.55–3.01)	0.35
No IV tPA before MT	4.8 (0.66–14.1)	0.31
Initial DWI volume (per 1-ml increase)	1.002 (0.91–1.02)	0.06
Bad collateral status*	1.15 (1.01–3.17)	0.04
Onset to final recanalization (per min)	1.008 (1.002–1.015)	0.016
Procedure duration (min)	1.01 (0.99–1.04)	0.78
Infarct growth (per 1-ml increase)	1.05 (1.02-1.08)	0.0001

*R^2 Nagelkerke = 0.55. aOR = adjusted odds ratio; NIHSS = National Institutes of Health Stroke Scale; eTICI = expanded Treatment in Cerebral Infarction Scale; IV-tPA = intravenous tissue plasminogen activator; MT = mechanical thrombectomy; DWI = diffusion-weighted imaging. * Collateral status 0, 1 or 2 according to ASITN/SIR classification.*

D-II-5 **Discussion**

Recent studies have reported a link between the number of CRA and functional outcome.[88–91,102] To explore the possible mechanisms of this association, we analyzed the impact of the number of CRA on the occurrence of ENT and 24-hour IG volume in a successfully recanalized population. Using pre-treatment and 24-hour DWI data of >400 AIS-LVO successfully recanalized patients, we found that increased number of CRA was associated with increased IG volume and was strongly associated with unfavorable outcome. Increased number of CRA was also highly correlated to the occurrence of ENT, explaining the higher IG volumes. These findings could help to explain the reported link between number of CRA and functional outcome.[88–91,102]

Recent studies linked the detrimental effect of repeated CRA on functional outcome to the drastic decrease of successful recanalization rates after each additional attempt.[88,89,102] In this study, we included patients with similar a baseline infarct volume who achieved successful

recanalization, to better identify an independent effect of repeated thrombectomy attempts. Repeated thrombectomy maneuvers led to an increased rate of ENT, correlated to substantial infarct growth. Clot fragmentation by repeated retrieval attempts[103,104] results in embolism to initially unaffected vascular territory or to the distal territory of the occluded territory. Emboli to perforating and small capillaries favors micro-circulatory dysfunction and potential “no-reflow” phenomenon,[105] potentially explaining the observed difference in IG values even when successful recanalization is achieved. Increasing the number of CRA can also lead to an increased risk of endothelial damage, vessel perforation[106] or hemorrhagic transformation.[107] Another potential indicator highlighting the detrimental effect of clot manipulation and fragmentation is the reported modification of successful recanalization effect on outcome depending on how recanalization was achieved: sudden successful recanalization defined by whole clot retrieval (direct shift from mTICI 0 to 2B-3) is associated with better clinical outcomes than progressive successful recanalization (patients achieving an intermediate mTICI 2A before final recanalization).[108]

Time from symptoms onset to successful recanalization and procedure duration[109] are also prominent factors for IG evaluation, both increased with the number of CRA. However, the link between the number of CRA, IG volume and outcome persisted even after adjusting for these durations, underlining a potential independent effect of the number of CRA. Other confounding effects adjusted for in our analysis were initial infarct volume[110] and final recanalization status, since eTICI 3 patients are expected to have the lowest infarct growth volumes. No difference in final recanalization results between CRA groups was found in this study.

Achieving successful recanalization with the fewest number of CRA, ideally with a single pass, appears to be a new goal, redefining procedural “success” in stroke endovascular therapy and underlining the need to develop a new generation of devices designed to increase the rate of complete revascularization at the first attempt. However, caution is needed when using retrieval attempt metrics as prognostic predictors.[111,112] Hence, in the present cohort, when eTICI 2b, 2c or 3 recanalization was obtained after a third CRA, 45% of patients still had a favorable outcome. Successful recanalization, even after multiple attempts is still better than no recanalization. Consequently, in our opinion, it is irrelevant to suggest some sort of “three strikes law” for endovascular procedures in AIS-LVO, and one should rather draw attention to the potential impact of multiple CRA and encourage operators to use the best technique available to achieve full recanalization with a minimal number of maneuvers.[113,114] Achieving successful recanalization is important but so is the way used to achieve it: if the thrombectomy device placement is suboptimal, i.e., if a stent retriever does not fully cover the arterial clot or if the aspiration catheter cannot be positioned immediately adjacent to the site of occlusion, it is more important to try to reposition the device or to change the technique rather than carry

on with a suboptimal retrieval attempt. Similarly, if a combined technique (aspiration + stent retriever) appears most likely to produce a successful result, then it should be used as the first technique and not be tried after a single device attempt. Our findings also raise the question of the optimal timing for changing thrombectomy technique when the first attempt is unsuccessful: should the operator switch immediately to another technique (changing from contact aspiration to combined aspiration + stent retriever for example) or continue with the same technique for a second or a third attempt? The limit on the number of attempts before changing strategy is highly variable between centers and operators and no guidelines are currently available. A randomized trial is needed to address this issue and define the best strategy after a first attempt failure.

Our study suffers from several limitations: the retrospective nature of the study exposes it to confounding effects and 52/419 (12%) 90-day mRS scores were missing. Infarct growth is also affected by several other factors, such as the patient's brain reserve[81], use of general anesthesia[115] or early secondary re-occlusion.[82] , IV thrombolysis , Collateral status, glycemia, age, final recanalization status, onset to recanalization and procedure times are known confounding factors affecting infarct growth[101,116–118] and were adjusted for, but the sample size between subgroups could limit this analysis. The choice of thrombectomy device can also lead to technical biases. The multicentric aspect of the study implies different practices and technical approaches for each operator that may have changed over time. All procedures were performed without balloon guided catheters, which are associated with lower risk of ENT when the stent retriever technique is used.[114,119] The use of MRI as a first imaging procedure can also be discussed. MRI is now widely used in large randomized acute stroke trials,[20,83,14] with standardized protocols lasting around 10 minutes,[83,84] a time frame similar to CT-based workflow.[84] Finally, due to the low number of patients, it was impossible to analyze separately patients with more than five CRA or to adjust for general anesthesia in IG or outcome prediction models, since only 7/419 (1.7%) patients were treated under general anesthesia.

D-II-6 **Conclusions**

Among successfully recanalized patients, clot retrieval at the first CRA significantly reduced IG and improved functional outcome. Each additional retrieval attempt was correlated with a higher rate of ENT and a greater increase in IG volume, reducing the odds of favorable functional outcome. These findings highlight the need for a randomized trial to define the appropriate therapeutic strategy when a first clot retrieval attempt is unsuccessful.

Ce deuxième travail, dans la continuité du précédent a permis de confirmer le lien entre le nombre de tentatives de thrombectomie et la croissance du volume de tissu cérébral infarci, en partie liée à un taux plus élevé d'embols dans de nouveaux territoires. Le nombre de tentatives de thrombectomie apparaît donc comme un facteur procédural « contrôlable » dont la maîtrise est importante, puisque corrélé à la croissance d'infarctus et au pronostic fonctionnel. Parrallèlement à ces deux travaux liant procédure, évolution tissulaire et évolution clinique, nous avons souhaité étudier l'impact de l'expérience de l'opérateur sur le déroulement de la procédure.

D- III. Effet de l'expérience de l'opérateur sur le succès de la thrombectomie

Montrer l'impact de l'expérience de l'opérateur sur le succès d'une intervention, travail largement réalisé dans d'autres domaines de la médecine (refs 186-188), n'avait pas été réalisé pour la thrombectomie mécanique. Les résultats d'un tel travail pourraient permettre de participer à la définition de « l'expérience minimale personnelle » mentionnée de manière peu claire dans les différentes recommandantions européennes et Nord-américaine concernant la thrombectomie des AVC. Cette étude nécessitait pour sa réalisation un panel le plus large d'opérateurs, d'expérience variée. Les données procédurales de 5 centres, participants au registre Français ETIS (Endovascular Treatment in Ischemic Stroke), impliquant plus de 4000 patients et 36 opérateurs ont pu être utilisées.

Effect of Operator's Experience on Proficiency in Mechanical Thrombectomy

François Zhu, MD, MSc; Wagih Ben Hassen, MD; Nicolas Bricout, MD; Basile Kerleroux, MD; Kevin Janot, MD; Benjamin Gory, MD, PhD; René Anxionnat, MD, PhD; Sébastien Richard, MD, PhD; Adrien Marchal, MD; Raphael Blanc, MD; Michel Piotin, MD; Arturo Consoli, MD, MSc; Denis Trystram, MD; Christine Rodriguez Regent, MD; Jean-Philippe Desilles, MD; David Weisenburger-Lile, MD; Simon Escalard, MD; Denis Herbreteau, MD, PhD; Heloise Ifergan, MD; Igor Lima Maldonado, MD; Julien Labreuche, BST; Hilde Henon, MD; Olivier Naggara, MD, PhD; Bertrand Lapergue, MD, PhD; Grégoire Boulouis, MD, PhD; on behalf of the ETIS Registry and Study Collaborators*

Stroke. 2021;52:2736–2742. DOI: 10.1161/STROKEAHA.120.031940

D-III-1. Résumé Étude N°4

Les données procédurales individuelles de MT provenant de 5 centres du registre Endovascular Treatment in Ischemic Stroke (ETIS) et de 2 autres centres d'AVC de grand volume ont été regroupées. L'expérience des opérateurs a été définie pour chaque opérateur comme une variable continue, cumulant le nombre de procédures de TM effectuées depuis janvier 2015. Nous avons testé les associations entre l'expérience de l'opérateur et les métriques procédurales. Un total de 4516 procédures ont été incluses, réalisées par 36 opérateurs dans 7 centres distincts, avec une médiane de 97.5 procédures par opérateur (interquartile, 57-170,2) au cours de la période d'étude. Une plus grande expérience de l'opérateur analysée comme une variable continue, a été associée à une durée de procédure significativement plus courte (β=-3,98 [IC 95 %, -5,1 à -2,8] ; P<0,001), ainsi qu'à l'anesthésie locale et à la localisation de l'occlusion M1 dans les modèles multivariables. L'augmentation de l'expérience était associée à de meilleurs résultats de recannalisation (estimation, 1,02 [1-1,04] ;P=0.013). L'augmentation de l'expérience en TM est donc associée à une durée de procédure significativement plus courte et à une meilleure recannalisation avec un effet plafond théorique observé après environ 100 procédures.

Cette étude numéro 4 a permis de montrer :

- **L'absence de surcroit de complication en cas d'expérience moindre**
- **Une durée de procédure raccourcie chez les opérateurs expérimentés**
- **Un taux de recanalisation croissant avec l'expérience mais sans difference sur la recanalisation à la première tentative**
- **Un impact de l'expérience sur la recanalisation et sur la durée de la procédure se prolongeant, respectivement, au-delà de 80 et 100 procédures**

D-III-2. Introduction

The benefit of mechanical thrombectomy for acute ischemic stroke (AIS) due to emergent large vessel occlusion (LVO) is, amongst other factors, dependent on procedural delay until revascularization, successful revascularization, and the number of device attempts before revascularization[120–122]. These procedural efficiency metrics are known to vary with various factors, amongst which site experience[123], as well as center[124] and operator's yearly case volumes.[125]

Technical efficiency has been shown to increase with previous endovascular experience in the cardio-interventionist literature[126] and others neuro-intervention procedures including the endovascular treatment of intracranial aneurysms[127] or carotid stenting[128]. Yet the impact of individual experience on endovascular treatment (EVT) procedural efficiency remains poorly reported.

Recently, international guidelines issued by the Joint commission[129], the American Heart Association/American Stoke Association (AHA/ASA)[130], and the European Stroke Organization (ESO) / European Society of Minimally Invasive Neurological Therapy (ESMINT)[131] have recommended a minimum personal experience in neuro-interventions at high-volume stroke centers before performing EVT in autonomy. This "minimum personal experience" is unclearly defined[132,133], and it is unknown whether technical efficiency increases after training, along with increasing EVT experience.

In this study we aimed to evaluate amongst trained interventional neuroradiologists (INR), whether increasing individual experience was associated with an improvement in EVT procedural performance metrics in ETIS (Endovascular Treatment in Ischemic Stroke), a national large-scale multicenter registry.

D-III-3. Materials and Methods

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients selection

We pooled individual EVT procedural data from 5 centers of the ETIS (Endovascular Treatment in Ischemic Stroke) registry and two additional high-volume stroke centers. In this retrospective analysis, we included all patients treated by mechanical thrombectomy, for which the operator and procedural metrics were prospectively recorded. Ethics Committee of each participating

center approved all aspects of this study. Detailed materials have been previously described[134,135].

Operator experience definition

Operator experience was defined for each operator as a continuous variable, cumulating the number of mechanical thrombectomy procedures performed since January 2015, as EVT became standard of care or, if later than this date, since the operator started performing mechanical thrombectomies in autonomy.

Each procedure was assigned an experience tag, corresponding to the cumulated number of prior MTs performed by the individual operator. To best capture individual initial progression, we excluded operators that realized less than 20 EVT over the study period. We tested the association between operator's experience and procedural metrics defined in study endpoints. We also studied the effect of prior operator's experience, defined as experience in neurointerventions before 2015.

Study endpoints

Study endpoints included (1) duration of procedure defined by the time between groin puncture and final angiogram, (2) final angiographic recanalization according to the modified Thrombolysis In Cerebral Infarction (mTICI) classification,[121] the overall rate of first-pass complete recanalization defined as a mTICI score of 2c or 3 after a single pass of thrombectomy,[122] and the rate of severe procedural complication (defined as arterial perforation or arterial dissection).

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation or median (interquartile range) and categorical variables are expressed as numbers (percentage).

Main baseline characteristics and outcomes were compared between procedures according operator's experience in uniand multivariable models, considering the experience as a continuous variable, and in secondary analyses as an ordinal variable with 4 categories (0 to 20 procedures, 21 to 40 procedures, 41 to 60 procedures and 61 or more procedures) and for every 10 operator's experience increase. In multivariable models, association of operator experience with study endpoints were adjusted for pre-specified confounding factors (age, on vs off hours, off hours defined as procedure performed between 6 p.m. and 8 a.m., occlusion location defined by Middle Cerebral Artery [MCA] or Internal Carotid Artery [ICA] and prior IV thrombolysis) by using mixed binary logistic regression models for binary outcomes, mixed ordinal logistic regression model for mTICI score, and linear mixed model for time from puncture to successful reperfusion, taking into account center as random effect. These

analyses were repeated after stratification by revascularisation strategy (Stent Retriever, contact aspiration or combined strategy). We conducted an incremental analysis of the influence of experience, by sequentially excluding bins of 20 procedures (0-20, 0-40, 0-60, 0-80, etc..) so as to unmask a ceiling effect and evaluate if there remained an effect of experience above procedures. The effect of operator's experience on the rates of first-pass recanalization was finally tested in uni and multivariable analyses.

Statistical testing was done at the two-tailed α level of 0.05. Data were analyzed using the JMP (SAS Institute, Cary, NC) software.

D-III-4. Results

Study population

Among 4516 patients treated with EVT between January 2015 and January 2020, 504 procedures were excluded. Most procedures were excluded for missing operator data (325/504, 64%).

A total of 4012 procedures were included, performed by 36 operators at 7 distinct centers, with a median of 97.5 EVT procedures per operator (IQR: 57 – 170.2) over the study period. The interaction between individual center and operator XP was not significant, using center as a random variable in sensitivity analyses.

Mean age of study subjects was 70.0 ± SD 15.3 years old, A total of 2225 (55.5%) patients received IV-tPA prior to EVT, 401 (10.0%) were treated under general anesthesia, and 2033 (50.7%) were treated off-hours.

Main variables and outcomes

EVT duration

Overall median MT duration was 40.0 minutes [IQR 25.0 - 62.0] and recanalization success (TICI Score 2b or above) achieved in 80% of patients. Factors associated with shorter EVT duration in univariable analyses were higher operator's experience, intravenous thrombolysis prior to EVT, local (vs general) anesthesia and MCA occlusion location (See **Table D-III-1** for details).

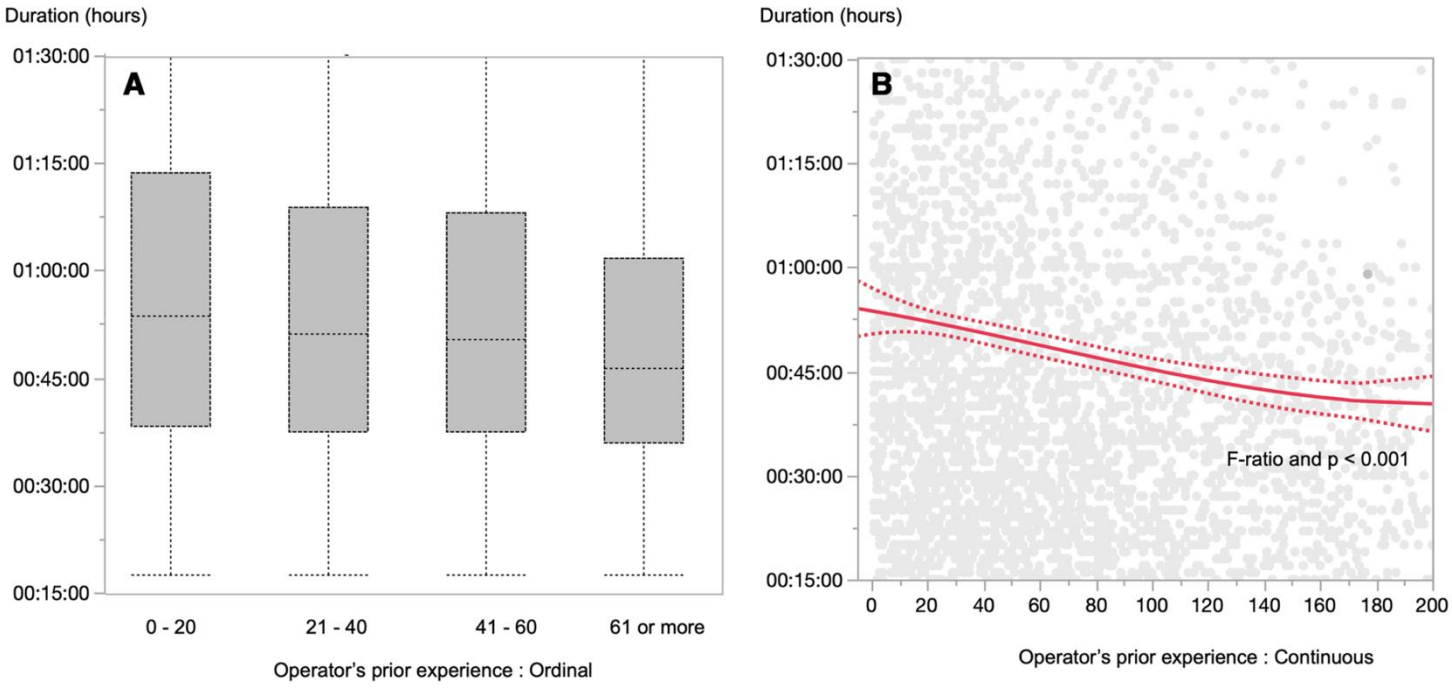
Table D-III-1. Univariable analyses of factors influencing EVT duration

	MT Duration		p value
Age (years)	Correlation 0,003 [-0,03-0,036],		0,865
Use of IV-tPA (Yes vs No)	39 [24-60]	40 [25-60]	0.025
Off vs Working hours	39 [24-60]	38 [23-59]	0.901
First 60MT vs 61 or More MT	42 [26-65]	36 [23-55]	< 0.001
Operators experience	Correlation -0.118 [-0.148--0.087]		<0.001
Occlusion loc. ICA vs MCA	44.4 [30-66]	37 [23-58]	< 0.001
GA vs non-GA	50 [32-79.75]	39 [25-59]	< 0.001

MT:Mechanical Thrombectomy; Occlusion Loc: Occlusion Location; ICA: Internal Carotid Artery; MCA: Middle Cerebral Artery; GA: General Anesthesia.

Similar results were found when considering experience as an ordinal variable, with MT EVT duration decreasing as operator's experience category increased **(Figure D-III-1).**

Figure D-III-1. Operator's experience as an ordinal (A) and continuous (B) variable against endovascular treatment duration.



In multivariable analysis, higher operator's experience as a continuous variable was associated with a significantly shorter procedural duration (β estimate: -3.98 95% CI [-5.1 to -

2.8]; p<0.001), along with anesthesia type and occlusion location (both p < 0.001, See **Table D-III-2**), whereas prior operator's experience was associated with longer procedural duration.

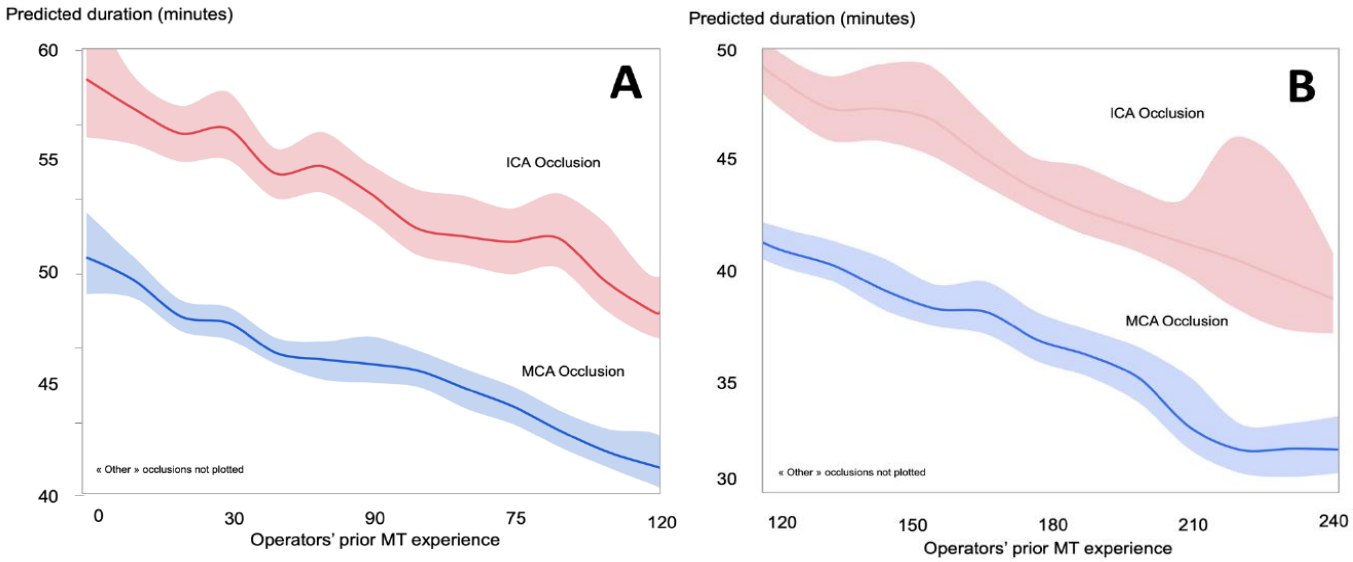
Table D-III-2. Multivariable analysis of factors associated with EVT duration

	Estimate [95% Confidence Interval]	p value
Operator's experience	-3.98 [-5.15—-2.8]	<0.001
Operator's prior experience	259.43 [110.47—408.4]	0.0006
tPA use	-90.48 [-290.22-109.26]	0.374
Occlusion Loc. ICA	220.78 [108.85-332.7]	0.0001
Occlusion Loc. MCA	-193.39 [-293.18—93.6]	0.0001
General anesthesia	449.4 [323.5-575.29]	<0.001

Standard least squares with emphasis on effect leverage. Abbreviations: Occlusion Loc, Occlusion Location; ICA, Internal Carotid Artery: MCA, Middle Cerebral Artery

Figure D-III-1 is a graphical illustration of EVT duration probability formula derived from the fully adjusted multivariable model presented in **Table D-III-2** plotted against increasing operator's experience. The direction and amplitude of effects were not affected when "On vs Off hours" was forced into the model, and there was no significant interaction between "On vs Off hours" and procedure duration according to experience.

Figure D-III-1: EVT predicted duration from 0 to 120 procedures (A) and for 120 to 240 procedures (B)



In sensitivity analysis, when considering only operators who started performing EVT after 2015 (n=16), the results were of similar magnitude and direction with increasing experience being

significantly associated with decreased procedural duration. To assess for a potential ceiling effect in operator's XP influence on MT duration, we sequentially excluded previous procedures by steps of 20 units. Using this method, we observed that prior XP lost its significant association with MT duration between 100 procedures (p=0.02) and 120 procedures (p=0.06).

Recanalization status

Increasing operator's experience was significantly associated with recanalization success rates as dichotomous variable, both in univariable analysis, and in the multivariable model (**Table D-III-3**).

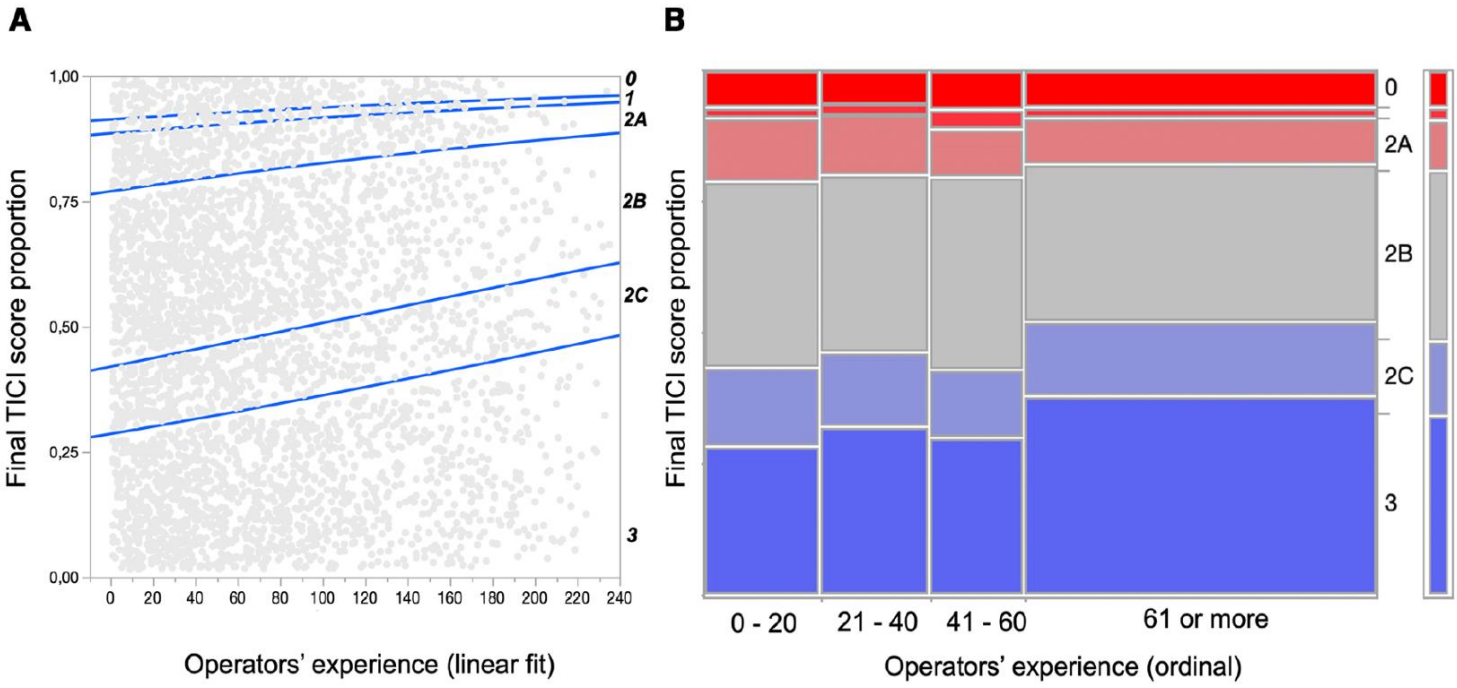
Table D-III-3: Mutlivariable regression of recanalization success predictors defined as dichotomous variable

	Estimate[95% CI]	p value
Operator's experience / 10	1.02 [1-1.04]	0.013
Age	0.99 [0.99-1]	0.017
ICA occlusion	1.73 [-0.337--0.112]	0.002
MCA occlusion	0.07 [-0.581-0.17]	0.152
tPA use	0.13 [-0.085-0.34]	<0.005
General anesthesia	-0.215 [-0.366--0.006]	<0.007

Abbreviations: Operator's experience / 10: Operator's experience every 10 procedures, ICA, Internal Carotid Artery: MCA, Middle Cerebral Artery.

When considering final TICI score as an ordinal variable, there was also an association between increasing experience and increasing TICI score, that remained independent after adjustment for occlusion location, prior IV-tPA and anesthesia type **(Figure D-III-2).**

Figure D-III-2: Univariable fit of Thrombolysis in Cerebral Infarction (TICI) score per increasing operators' experience.
Experience is presented as a continuous (A) and ordinal (B) variable.



We assessed for a ceiling effect in the association between experience and successful recanalization by sequentially excluding prior procedures, by incremental steps of 20 procedures, and the loss of significance of the association happened between 80 (p=0.03) and 100 procedures (p=0.08) **(Table D-III-4).**

Table D-III-4: Incremental analysis of the influence of experience on successful recanalization, by sequentially excluding prior procedures by steps of 20 units

Procedures included	Estimate[95% CI]	P value
XP tag > 20	0,24 [0,03;0,44]	0.0244
XP tag > 40	0,34 [0,09;0,6]	0.009
XP tag > 60	0,4 [0,07;0,73]	0.02
XP tag > 80	0,5 [0,07;0,94]	0.03
XP tag >100	0,21 [-0,28;1,49]	0.08

There was no effect of prior Operators experience when forced into the model (p=0.56), nor did “On vs Off hours” influence the rates of successful recanalization

First-Pass Recanalization

After adjustment for general anesthesia, occlusion location, age and tPA use, there was no effect of operator’s experience on overall first pass complete recanalization rates (p=0.57). In subgroup analyses according to the first line strategy (Stent Retriever, contact aspiration or combined strategy), there was a significant positive effect of increasing operator’s experience on the rate of first-pass complete recanalization rate using CA technique. In this subgroup of 1312 procedures, after adjustment for occlusion location, patient’s age and tPa, the odds ratio for first past recanalization was 1.06 [1.02 – 1.10] for every 10 operator’s experience unit increase (p=0.03). No difference was observed in stent retriever or combined approach.

Complications

A total of 82/2713 (3.0%) intracranial arterial perforations were reported, only determined by occlusion location type (5.8% in ICA, vs 1.9% in other locations, p<0.001). There was no association between operator’s experience and perforation in either direction (positive or negative). Similarly, there was no association between operator’s experience and the rate of reported arterial dissections.

D-III-5. Discussion

In this large multicenter retrospective study, we showed that EVT procedure duration was contingent to interventionalist’s individual prior EVT experience with measurable shorter procedural duration with increasing operator’s experience. We also showed that higher operator’s experience was associated with better revascularization statuses using the mTICI scale. No association was found between experience and the rates of arterial dissection or perforation.

Effect of operator’s experience has been already studied for other neurointerventions as intracranial aneurysm EVT[127] and carotid stenting[136] with a positive effect of increasing experience, but no such data has been reported in the current thrombectomy era.

Our study adds to the evidence provided by a previous analysis on the ETIS registry demonstrating that higher annual operator volume was associated with better reperfusion rates[125]. Although this study highlighted an operator’s effect, it did not analyze the individual performances metrics for each procedure, and prior experience was dichotomized to account for the fact that the first mechanical thrombectomy had been performed in 2010, a time were EVT was not as technically advanced and standardized as it is since 2015, and when EVT were performed much less often. Further, the overall annual volume assessed in the previous

work was independent of experience, which is conversely the principal aspect of the present analysis that wad focused on assessing the learning curve for efficiency in EVT.

Previous preliminary data are available from the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular treatment of Acute ischemic stroke in Netherland) pre-trial registry. In this work, the authors did not find a significant effect of interventionists' experience on the duration of the procedure, complication rate, or clinical outcome when strictly using the MR CLEAN trial inclusion criteria. A subgroup analysis with a larger patients sample showed a negative association between interventionists' experience and the duration of the procedure in the entire MR CLEAN cohort[137] (adjusted beta coefficient -0.67, 95% CI: [- 1.24 to -0.11]). However, this analysis was performed from 2002 to 2010, before the advent of MT and standardization of technical aspects for EVT, with patients treated with intra-arterial thrombolysis.

First-Pass recanalization is a known strong prognostic factor[122,138] and in turn is the desired goal for every EVT procedure. In our sample, we did not find a difference in overall First-pass recanalization rates according to operator experience. Nevertheless, our subgroups analysis showed a significant increased rate of First-Pass recanalization using CA contact aspiration as operator's experience increased. No differences were observed on combined strategy or stent retriever alone. Regarding the latter strategy, no differences were observed on rates of reperfusion, adverse events and clinical outcomes in patients treated in the initial roll-in and subsequent randomized phases of the SWIFT (Solitaire™ With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) study suggesting a rapid learning curve for the SR[139]. Moreover, a time flow improvement was observed every 25 procedure in a monocentric analysis of patients treated exclusively by Solitaire™ (Medtronic Inc.) stentriever[140]. Our results in that sense reinforce the assertion that EVT learning curve is steep, provided that thrombectomy devices are used by trained neuro-interventionalists.

From a more general point of view, the notion of "experience" is unclear, and the minimal number of performed procedures before reaching autonomy is an ongoing debate[141], considering the limited data on the effect of individual experience in EVT in the current era[132].

Our study in that sense highlights that, even in trained neuro-interventionists, operating in autonomy, increasing experience in EVT is associated with better procedural metrics. The optimal balance between procedural efficiency and safety, and the growing need for thrombectomy-trained interventionalists[142,143] is still to be found. Our study contributes to the evidence that mechanical thrombectomy is a high-level technical procedure, with enhanced procedural metrics as operator's experience increases, and prompts caution with regards to degraded trainings. Indeed while most training guidelines[129,144] recommend a minimum of

around 50 EVT performed as first operator before autonomization, we found in this analysis that operators' experience influenced procedural metrics long after 50 EVT, with a remaining statistically significant effect after over 80 procedures for successful revascularization, and after 100 for procedural duration. This persisting effect is, further, likely to be minimized due to loss of statistical power inherent to the method used to test for a ceiling effect. In this context, metric-based simulation appears to be a reliable alternative to improve the training process[144], so as to better tailor individual training to learning curves, background and learning paces.

Limitations of this study are mainly related to its retrospective design, resulting in memorization bias and data loss. We chose to consider 2015 as the appearance of modern EVT in clinical practice, since the publication of the first positive randomized trials[145]; this choice could be objectionable as EVT was performed in most of stroke centers before. In addition, experience could be influenced by training and volume for other endovascular procedure and patient selection may also influence procedural times and likely evolves with operator experience, notwithstanding the modifications in thrombectomy related guidelines over the study period. These possible and hardly measurable confounders for clinical outcome after EVT explain our pragmatic decision not to include functional outcome as a data point in this study. Moreover, reasons of EVT failure and complexity are diverse[146], such as tandem occlusions, potentially leading to additional acute stenting, calcified occlusions or extracranial vascular tortuosity but such granularity was not recorded in this study and could be considered as a confounding factor, independent of operator's experience.

D-III-6. Conclusion

In trained interventional neuroradiologists, increasing experience in mechanical thrombectomy is associated with significantly shorter procedural duration and better reperfusion rates. These results may inform future training and practice guidelines to set minimal experience standards before autonomization, and to set-up operators' recertification processes tailored to individual case volume and prior experience.

Ce travail a donc montré que l'expérience de l'opérateur est un élément clé associé à des durées de procédures plus courtes et de meilleurs résultats en termes de succès de recanalisation. Le temps de procédure et le nombre de passage sont durablement impactés par l'expérience de l'opérateur, au-delà de 100 et 80 procédures. Outre ces métriques, les conditions de réalisation anesthésique de la thrombectomie peuvent influencer le pronostic fonctionnel malgré une bonne recanalisation, du fait de son impact sur la durée de la procédure, de la rapidité de recanalisation mais aussi du risque de survenue d'une pneumopathie précoce, identifiée dans notre travail numéro 1 comme une complication fortement associée à une mauvaise évolution clinique. Nous avons donc souhaité évaluer l'impact du type d'anesthésie générale ou non, sur le devenir clinique.

D- IV. **Modalité anesthésique durant la thrombectomie mécanique**

Dans ce travail, nous avons souhaité comparer les résultats de la thrombectomie mécanique réalisée sous anesthésie générale par comparaison à ceux de celle réalisée sans anesthésie générale et discuter les impacts, au plan physiopathologique, des deux modalités. Pour ce faire, du fait de l'existence des résultats de trois essais randomisés contradictoires et de plusieurs études de registre prospectif, nous avons réalisé une revue systématique suivie d'une méta analyse de ces données.

Anaesthetic management during intracranial mechanical thrombectomy: systematic review and meta-analysis of current data

Guillaume Gravel,[1] Grégoire Boulouis,[1] Wagih Benhassen,[1] Christine Rodriguez-Regent,[1] Denis Trystram,[1] Myriam Edjlali-Goujon,[1] Jean-François Meder,[1] Catherine Oppenheim,[1] Serge Bracard,[2] Waleed Brinjikji,[3] Olivier N Naggara[1]

Gravel G, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**90**:68–74. doi:10.1136/jnnp-2018-318549

D-IV-1 **Résumé Etude N°5:**

Une recherche de la littérature existante a été effectuée dans les bases de données PubMed, Embase et Cochrane pour identifier les études portant sur la modalité anesthésique et la TM. En utilisant un modèle avec effet pondéré fixe ou aléatoire selon les variables, nous avons évalué les résultats suivants : mortalité à 3 mois, score de Rankin modifié (mRs) 0-2, succès de la recanalisation (mTICI≥2b) et transformation hémorragique intracérébrale symptomatique (HICs). Nous avons identifié sept cohortes (dont trois essais contrôlés randomisés dédiés), totalisant 1929 patients (932 avec AG). Sur l'ensemble de l'échantillon les taux de mortalité, de mRs 0-2, de TICI≥2b et de sICH étaient respectivement de : 17,5% (IC 99% 9,7% à 29,6% ;Q-value : 60,1 ; I^2 : 93 %, 1 717 patients), 42,1 % (IC99 % : 33,3 % à 51,7 % ;Q-value : 60,1; I^2: 93 %,1 717 patients), 82.9% (IC-99% : 74,0 % à 89,1 % ; Q-value : 20,7 ; I^2 : 80,6 %, 1 006 patients) et 5,5 % (IC-99 % : 2,8 % à 10,8 % ; Q-value :18.6 ; I^2: 78.5%). La TM réalisée chez les patients sans AG était associée à un meilleur résultat fonctionnel à 3 moi (OR, 1,35 ; IC à 99% 1,04 à 1,76 ; Q-value : 24,0 ;I^2 : 9,2%, 1 845 patients) et à un taux de mortalité à 3 mois plus faible (OR, 0,70 ; 99%-CI : 0,49 à 0,98 ; Q-value :1,4 ; I^2: 0%, 1 717 patients ; modèle à effet pondéré fixe) par rapport à l'AG. Le non recours à l'anesthésie générale pendant la thrombectomie mécanique semble associé à un meilleur résultat fonctionnel à 3 mois et à un taux de mortalité plus faible. Ces estimations non ajustées sont évidemment sujettes à des biais et doivent être interprétées avec précautions.

Les résultats de cette revue systématique et méta-analyse sont :

- **Une mortalité plus élevée et une évolution clinique plus souvent défavorable en cas de thrombectomie réalisée sous anesthésie générale**
- **L'absence de différence en terme de recanalisation**

D-IV-2 Introduction

Recent randomized controlled trials (RCTs) and an individual patient-level meta-analysis have provided compelling level 1A evidence on the efficacy of mechanical thrombectomy (MT) using stentretriever or direct contact aspiration in patients with acute ischemic stroke (AIS) due to anterior circulation large vessel occlusion (LVO),[19] resulting in the modification of practice guidelines and profound changes in worldwide stroke care organisation.[147] Yet, in patients with AIS-LVO undergoing MT, the question of optimal anaesthetic management is still unclear, in the absence of definite non-conflicting data, and often depends on operator or institutional preferences.

In this setting, general anaesthesia (GA) and non-GA (local anaesthesia with or without conscious sedation) are most commonly used to ensure patient and operator comfort as well as procedural safety, the latter being used in over 90% of cases in some recent positive RCTs.[19,16] GA may improve procedural safety, while non-GA allows monitoring of patients' clinical status during the procedure while minimizing delays in treatment initiation. Most recent systematic reviews comparing anaesthesia techniques in MT[148–150] failed to demonstrate higher odds of favorable neurological outcome for patients receiving GA compared with non-GA. Yet the majority of patients included in these pooled analyses were treated before 2012, with earlier generation devices, abandoned in recent positive RCTs, and at a time when MT was neither standard nor routinely performed in most centres. Hence, these reviews may have represented earlier experience with endovascular stroke treatment. In addition, patients with posterior circulation AIS were also included, although practice guidelines, initial severity and clinical outcomes significantly differ from patients with anterior LVO.

With the evolution of indications as well as advancement of technological performances of devices for MT,[151] the literature was enriched, among others, by pooled post-hoc analysis from large RCTs[152] or dedicated RCTs comparing non-GA and GA, yet with conflicting results.[153–155] Our aim was to assess the association between GA or non-GA and the effect of MT on 3-month functional outcome through a systematic review and meta-analysis of the literature focusing on data published in the current era of stent retriever/contact aspiration devices.

D-IV-3 Methods

Before conducting this review, we developed a detailed protocol including objectives and plans for collecting and analysing data. The manuscript was prepared in accordance with the guidelines of the Meta-analysis Of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[156,157] This study

was designed, conducted and analysed, and the manuscript was written independent of industry or any financial support.

Search strategy and selection criteria

The medical literature on MT for AIS was reviewed from March 2014 to 1st November 2017 using PubMed, Embase and Cochrane databases. Candidate studies were screened by combining the following keywords/medical subject headings terms using Boolean logic operators: "stroke," "ischemic," "conscious," "sedation," "general," and "anesthesia." The detailed search strategy is provided in online supplementary appendix I. Prespecified inclusion criteria for study selection were (1) 3-month mortality and modified Rankin score (mRs), in non-GA and GA subgroups; (2) peer-reviewed publication;

(3) original study; (4) at least 50 patients; (5) treated using stent retriever and/or contact aspiration; and (6) methodological quality score ≥16, as defined below.

Data extraction

Data were independently extracted by two authors (GG/ON) using a standardised critical appraisal and data extraction form and disagreements resolved by consensus. The data extraction form was subdivided into three sections: (1) study characteristics, (2) baseline characteristics and (3) clinical and imaging outcome measures.

Study characteristics

The following data were extracted: single institution/multicentre, prospective/retrospective data collection, consecutive/ sporadic cases, midyear of study (defined as median calendar year of treatment dates) and country.

Patients' characteristics

Patients' baseline extracted data included sex, number, mean age of eligible patients, initial clinical presentation according to the National Institute of Health Stroke Scale (NIHSS), and comorbidities including vascular risk factors as reported.

Data extraction of procedural and imaging data

Data included site of occlusion, indication and type of anaesthesia (non-GA or GA), devices used for intra-arterial treatment (stent retriever and/or aspiration), procedure duration, time from symptom onset to groin puncture, time from symptom onset to revascularisation, and successful recanalisation.

Quality of reporting in included studies

We assessed reporting quality (but not validity) of all included studies based on the Strengthening the Reporting of Observational Studies in Epidemiology statements checklist,[39] used to build a quality score of 0–28.

Risk of bias assessment

After selection of studies, quality and risk of bias when pooling in meta-analysis were critically appraised based on the scheme suggested by the Cochrane Collaboration tool,[158] by the two authors who reviewed the literature.

Outcome measures

A clinical favourable outcome was defined as a 3-month mRs score ≤2. Successful recanalisation outcome was defined as a thrombolysis in cerebral infarction (TICI) 2b–3 scale.[159] Conversion rate from non-GA to GA, symptomatic intracerebral haemorrhage (sICH), intracranial vascular, respiratory complications and procedural delays were also registered.

Statistical analysis

We calculated mRs≤2, mortality, TICI≥2b and sICH rate using fixed-effect meta-analysis according to the Mantel-Haenszel method or using the DerSimonian-Laird random-effects meta-analysis, as appropriate. In all analyses, inconsistency of findings across studies was assessed using Cochran's Q statistics and the I^2 statistics. [158] We used a fixed-effects weighted model to calculate the pooled estimates except where p(heterogeneity)

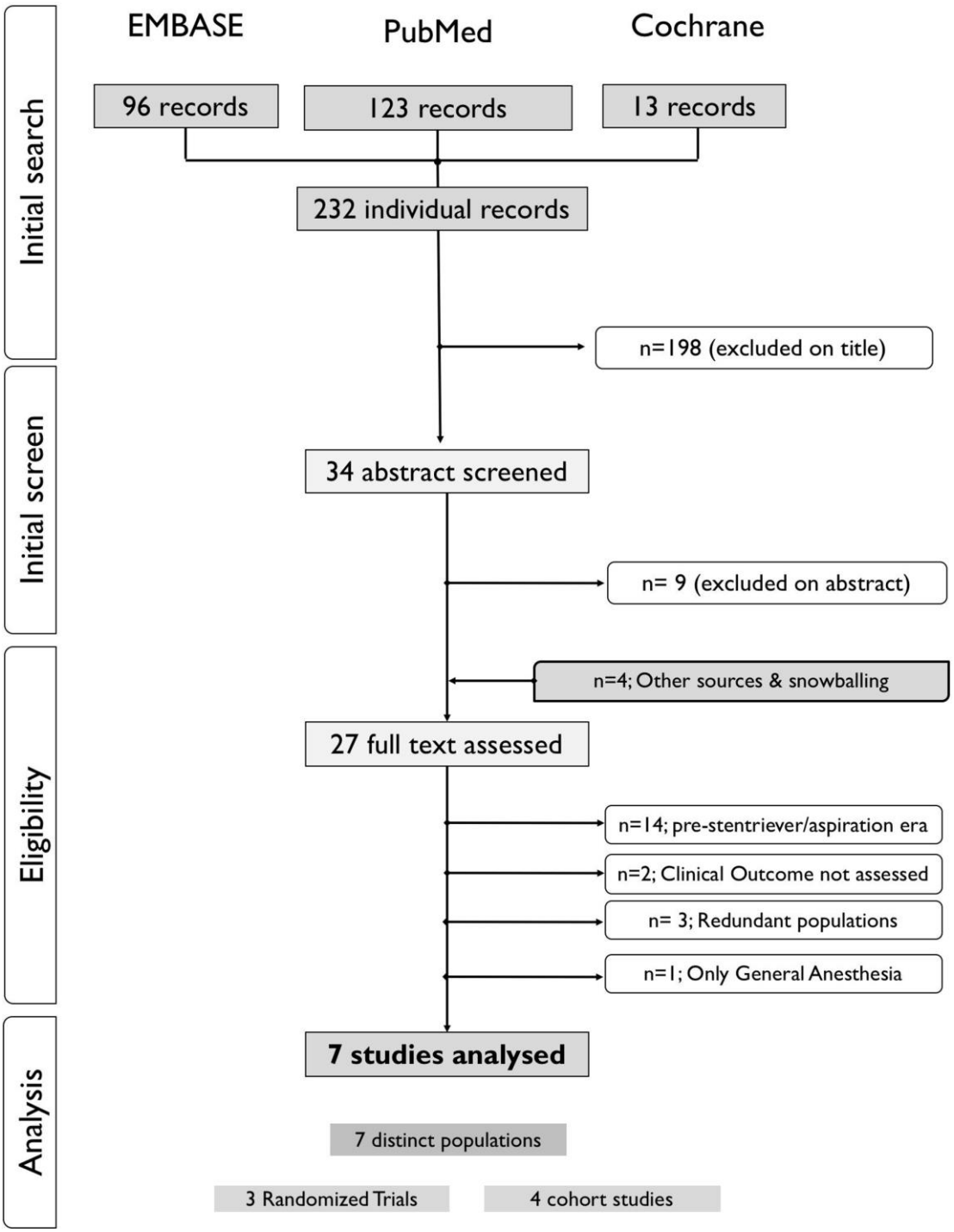
<0.10 or I^2>30%, in which case a random-effects weighted model was used. We assessed publication bias using visual inspection of scatter plots according to study size or precision, that is, 'funnel plot'.[160]

We assessed the relationship between anaesthesia groups (non-GA or GA) and sex, age, vascular risk factors, baseline median NIHSS score, occlusion location (internal carotid artery, middle cerebral artery (MCA), M1/M2 segments of the MCA and tandem occlusion) and time intervals (onset-to-groin puncture, onset-to-recanalisation and groin puncture-to-recanalisation). We compared mRs≤2, mortality, TICI≥2b and sICH rate, considering studies providing crude data for individual patients and at least one patient in each condition. Due to marked heterogeneity, uncontrolled nature of the data and multiplicity of testing, a two-sided p value of <0.01 was prespecified to indicate a convincing statistical difference. All p values were two-tailed. Analyses were performed using Comprehensive Meta-Analysis V.2.0 for Windows (Biostat, Englewood, New Jersey, USA).

D-IV-4 Results

The initial search yielded 232 records, and 7 studies[152–155,161–163]were finally included in the analysis (detailed flow chart of study selection is presented in **Figure D-IV-1**), with a total of 1929 patients.

Figure D-IV-1: Flow chart of the selection of studies.



Study characteristics

The mean value of the methodological quality scores was 23.5 out of 28 (±SD 2.9). No study scored positively on all items. In most studies (5/7, 71.5), the median year of publication was 2017 and the median year of treatment was 2014 (range, 2012–2016). The case series were from Germany (n=2), Australia, Canada, Denmark, France, the Netherlands, South Korea, Spain, Sweden, Switzerland, UK and USA (n=1).

Patients' baseline characteristics

Among the 1929 included patients, 932 were treated with MT under GA and 997 under non-GA. Three studies randomised patients to GA or non-GA. The largest study had 797 patients (236 with non-GA), and the smallest study had 84 patients (31 with non-GA). Baseline data are presented in **Table D-IV-1.**

Table D-IV-1: Population characteristics in pooled studies

	n, available (studies)	rate (%) or mean value ±sd (n)	99% CI	P(het) values	²/ Q-value	non-general anaesthesia	General anaesthesia	P values
Patients	1929 (7)	–	–	–	–	–	–	-
Non-general anaesthesia	997 (7)	54.0	34.8 to 72.2	<0.001	97/213	–	–	-
General anaesthesia	932 (7)	–	–	–	–	–	–	-
Sex (female)	1801 (6)	47.8 (859)	44.7 to 50.8	0.24	25.5/6.7	465 (49.8)	394 (45.4)	0.017
Age, years, mean±SD	1801 (6)	68.1±3.3	–	–	–	68.1±4.7 (934)	68.0±4.9 (869)	1
Hypertension	1801 (6)	66.5 (1176)	55.6 to 75.8	<0.001	90/50.6	546 (58.5)	630 (72.7)	0.29
Diabetes mellitus	1801 (6)	20.3 (368)	14.0 to 28.5	0.03	59.4/12.3	189 (20.3)	179 (20.6)	0.46
Smoking	1728 (6)	26.8 (570)	18.3 to 37.4	<0.001	90.2/51.3	289 (33.0)	281 (33.0)	0.70
Dyslipidaemia	1786 (6)	33.1 (666)	23.5 to 44.4	<0.001	90.9/54.9	347 (37.7)	319 (36.9)	0.06
Atrial fibrillation	1006 (5)	41.0 (385)	31.6 to 51.1	<0.001	80.8/20.8	144 (38.6)	241 (38.1)	0.81
Coronary disease	491 (2)	20.5 (491)	16.2 to 25.6	0.21	35.8/1.6	26 (14.4)	74 (23.8)	0.02
Baseline NIHSS score	1801 (6)	17.0±1.1	–	–	–	16.3 (934)	17.8 (867)	<0.001

Values are expressed as absolute number of patients (studies) or percentage, unless otherwise specified. NIHSS, National Institute of Health Stroke Scale; P(het), p(heterogeneity).

Patients with GA were more likely to present higher initial NIHSS score (p<0001) and had higher rates of coronary artery disease. Regarding time intervals (details presented

Table D-IV-2), patients with GA had longer onset-to-groin puncture and onset-to-recanalisation delay, whereas groin puncture-to-recanalisation delays were significantly shorter (all p<0001).

Table D-IV-2: Occlusion location and time intervals

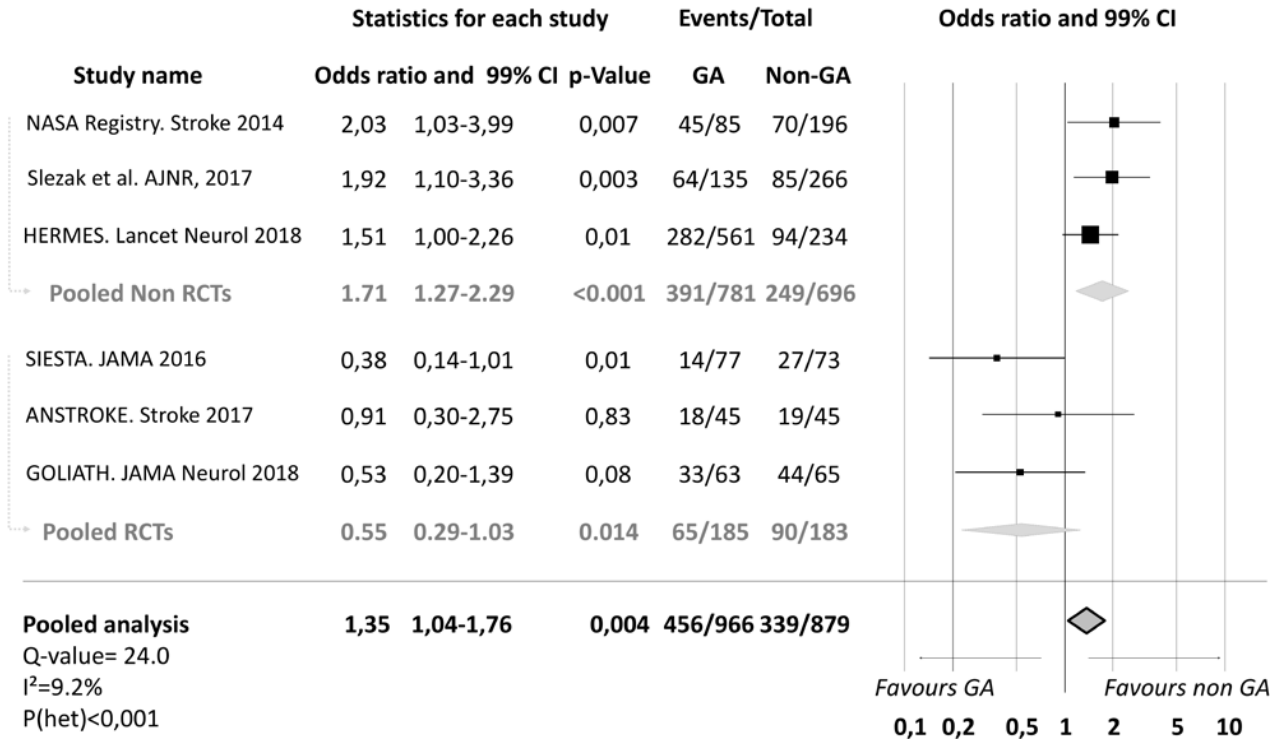
	n, available (studies)	non-general anaesthesia	General anaesthesia	P values	Time reduction (99% CI)
Anterior circulation	1648 (6)	912	736	–	–
MCA occlusion	1033	611	422	0.03	–
M1 segment occlusion	952	552	400	0.01	–
M2 segment occlusion	81	59	22	–	–
ICA occlusion*	440	210	230	<0.001	–
ACA occlusion	1	1	0	–	–
Tandem occlusion	3	1	2	–	–
Time intervals, min					
Onset to groin puncture	772 (3)	298.5 (265)	303.5 (507)	0.001	5.0 (2.0 to 8.0)
Groin puncture to recanalisation	605 (4)	91.0 (238)	75.8 (367)	<0.001	−15.2 (−11.9 to −18.5)
Onset to recanalisation	885 (2)	285.2 (606)	294.3 (279)	<0.001	9.1 (6.3 to 12.0)

*Values are expressed as absolute number (studies) and percentage (or number of available patients for corresponding subanalysis), unless otherwise specified. *ICA, occlusion includes internal carotid artery terminus occlusion, T and L occlusion. ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.*

Outcomes

Detailed pooled outcomes are reported in **Figure D-IV-2** and **Table D-IV-3.**

Figure D-IV-2: Forest plot for favourable clinical outcome (mRs 0–2 at 90 days).



ANSTROKE, anesthesia during stroke; GA, general anaesthesia; GOLIATH, General or Local anesthesia in Intra arterial Therapy; mRs, modified Rankin score; p(het), p(heterogeneity); RCT, randomised controlled trial; SIESTA, sedation vs Intubation for endovascular stroke Treatment

Table D-IV-3 : Pooled outcome measures

	n, available (studies)	*Rate, % (n)*	*99% CI*	*P(het) values*	*I²/Q-values*	*Non-general anaesthesia*	*General Anesthesia*	*OR (99% CI)*	*P(het) values*	*I²/Q-values*	*P(sig) values*
mRS 0-2 (90days)	1845 (6)	42.1 (795)	33.3 to 51.7	<0.001	87.9/41.3	456 (47.2)	339 (38.6)	1.35 (1.04 to 1.76)	0.25	9.2/24.0	0.004
Death											
In-hospital	240 (2)	10.0 (23)	5.9 to 16.3	0.13	56.0/2.3	12 (9.8)	11 (9.3)	1.07 (0.34 to 3.34)	0.88	0/0	0.88
3 months	1717 (5)	17.5 (331)	9.7 to 29.6	<0.001	93.3/60.1	135 (15.0)	196 (24.1)	0.70 (0.49 to 0.98)	0.84	0/1.4	0.008
Recanalization											
TICI 2b–3	1006 (5)	82.9 (823)	74.0 to 89.1	<0.001	80.6/20.7	305 (81.8)	528 (83.4)	0.82 (0.52 to 1.30)	0.83	0/1.5	0.27
Complications											
Symptomatic ICH	1652 (5)	5.5 (92)	2.8 to 10.8	<0.001	78.5/18.6	39 (4.7)	52 (7.0)	0.84 (0.45 to 1.57)	0.47	0/2.6	0.47
Subarachnoïd Hemorrhage	175 (5)	2.5 (5)	0.2 to 22.2	0.17	46.5/1.9	1 (1.3)	3 (3.1)	0.31 (0.02 to 6.6)	1	0/0	0.33
Distal emboli	491 (2)	10.5 (51)	7.4 to 14.7	0.21	37.5/1.6	13 (7.2)	38 (12.2)	0.61 (0.26 to 1.46)	0.26	22.6/1.3	0.14
Respiratory complications	1035 (3)	9.7 (100)	7.6 to 12.4	0.27	22.9/2.6	57 (8.3)	43 12.2)	0.68 (0.38 to 1.20)	0.23	32.7/3.0	0.08

Values are expressed in absolute number of patients (studies) or percentage, unless otherwise specified.

ICA, occlusion include internal carotid artery terminus occlusion, T and L occlusion.

mRs, modified Rankin Score; TICI, thrombolysis in cerebral infarction; ICH, intracerebral haemorrhage; P(het), p(heterogeneity); TICI, thrombolysisin cerebral infarction

Mortality, 3-month mRs 0–2, TICI≥2b and sICH rates were, respectively 17.5% (99% CI 9.7% to 29.6%; Q-value: 60.1; I^2: 93%, 1717 patients), 42.1% (99% CI 33.3% to 51.7%; Q-value: 41.3; I^2: 87.9%), 82.9% (99% CI 74.0% to 89.1%; Q-value: 20.7; I^2: 80.6%, 1006 patients) and 5.5% (99% CI 2.8% to 10.8%; Q-value: 18.6; I^2: 78.5%). Non-GA patients had significantly better 3-month functional outcome (pooled OR, 1.35; 99% CI 1.04 to 1.76; p(sig)=0.004; Q-value: 24.0; I^2: 9.2%, 1845 patients; fixed weighted effect model) and lower 3-month mortality rate (pooled OR, 0.70; 99% CI 0.49 to 0.98; p(sig)=0.008; Q-value: 1.4; I^2: 0%, 1717 patients; fixed weighted effect model) compared with GA patients. Similar TICI≥2b recanalisation rate (pooled OR, 0.82; 99% CI 0.52 to 1.30; p(sig)=0.27; Q-value: 1.5; I^2: 0%, 1006 patients; fixed weighted effect model) and symptomatic ICH (pooled OR, 0.84; 99% CI 0.45 to 1.57; p(sig)=0.47; Q-value: 2.6; I^2: 0%, 1652 patients; fixed weighted effect model) were shown. Respiratory complications were non-significantly less likely in the non-GA population (pooled OR, 0.68; 99% CI 0.38 to 1.20; p(sig)=0.08; Q-value: 3.0; I^2: 32.7%, 1652 patients; fixed weighted effect model) than in the GA population. Conversion rate from non-GA to GA was 11.1% (99% CI 6.9% to 17.2%; Q-value: 5.6; I^2: 46.5%, 289 patients).

D-IV-5 Discussion

In this systematic review and meta-analysis of current data, we showed that patients treated with stent retriever and/or aspiration MT for anterior circulation AIS-LVO were more likely to have 3-month favourable functional outcome and had lower rates of mortality when treated under conscious sedation or local anaesthesia versus GA. In contrast, no differences in recanalisation rates, vascular and respiratory complications were found. Procedural times were shorter in the GA group, while onset-to-recanalisation delays were longer.

During MT, patients' immobility is critical to procedural safety and recanalisation success; for this purpose, two anaesthetic techniques can be used: GA with tracheal intubation and mechanical ventilation (which offers airway control, optimal oxygenation and perfect immobility) and non-GA (which allows to monitor patient status and to maintain haemodynamic autoregulation). To date, in the context of modern reperfusion technologies, no study has demonstrated a significant association between either anaesthetic technique and functional outcomes after MT. Recently, Brinjikji and colleagues[150] demonstrated that patients with AIS undergoing MT had worse clinical outcomes when treated with GA as compared with non-GA.However, many of the included studies and patients in this systematic review (14/22 and 2918/4716, respectively) were managed with intra-arterial tissue-type plasminogen activator, Merci device (a first-generation mechanical device, abandoned in modern practice) or with unspecified modality of endovascular approach,[150] leading to poor generalisability in the modern stentriever/aspiration era. In our analysis, focusing on the most recent recanalisation techniques, that is, stent retriever and/or contact aspiration, in patients treated under new

practice guidelines (with deemed more homogeneous indications), we provide contemporary pooled estimates contributing to the evidence that non-GA patients may, indeed, more likely to experience favourable outcome than those under GA during MT. Different factors may explain the difference in outcomes between anaesthetic management techniques. First, delay in treatment initiation (owing to the time needed for GA induction, emergent tracheal intubation and need for a readily available anaesthesiologist) has been hypothesised to be a plausible explanation as to why GA may be associated with poorer neurological outcomes after MT for patients with AIS. For instance, in the GA versus non-GA subgroup analysis of the HERMES collaboration, Campbell *et al* [152]reported that randomisation-to-reperfusion times were ≈20 min longer in the GA group, a substantial delay when the overall median time was 92 min.In the present study, aggregate door-to-puncture times were significantly longer in the GA group despite reduced puncture to reperfusion times, as has been reported in a subgroup analysis of the SIESTA (Sedation vs Intubation for Endovascular Stroke Treatment) trial.[164] It is reasonable to hypothesise that this delay may confer a disadvantage to patients treated under GA. Another factor likely to contribute to worse clinical outcome rates seen in GA patients is intraprocedural arterial pressure drop. Some intravenous and inhalational anaesthetic agents used for GA are known to be associated with hypotension and rapid blood pressure modifications, and in most studies reporting this variable in the context of MT, blood pressure has been shown to be significantly lower with GA.[165] Moreover, a fall in the mean arterial pressure has been demonstrated to be an independent predictor for poor neurological outcome at the acute phase of AIS and during endovascular procedure of MT.[165,166] Consistent with this hypothesis, in the AnStroke (Anesthesia During Stroke) trial, in which intraprocedural blood pressure did not differ between GA (n=45) and non-GA (n=45) patients, the outcomes were similar between groups.[154] A likely mechanism is concomitant reduction in cerebral blood flow to the ischaemic penumbra potentiating the extent of injury.[167] In addition, hypocapnic conditions during GA have the potential risk of inducing cerebral vasoconstriction, which may further impair the effectiveness of collateral perfusion to penumbral brain tissue,[168] hence contributing to worse clinical outcomes.

Conversely, the main argument favouring GA over non-GA is reduced procedural time, higher recanalisation rates and increased patient safety. Here, we confirmed a significantly shorter groin-to-recanalisation time in the GA group, mitigated by the longer onset-to-groin puncture delay. It is considered that patient agitation may hamper catheterisation and degrade intracranial arterial navigation, leading to delay in recanalisation, and higher risk of distal wire perforation injury resulting in intracerebral or subarachnoid haemorrhage. However, we did not find a higher incidence of arterial complication and similarly failed to demonstrate a higher TICI 2b–3 recanalisation rate in the GA group. Conversely, there was a trend towards a higher incidence of respiratory complications in GA patients. This aggregate-level analysis, using the

most currently available data, provides evidence that non-GA may not be associated with an increase in intraprocedural complications and therefore should offset concerns of a potential disadvantage of non-GA during MT in this regard. Furthermore, the conversion rate from non-GA to GA of 11.1% shown in this study may support a sequential approach, with non-GA being the preferred first line and GA being an escalating option in case of a patient's agitation or compromised airway. In the SIESTA trial (150 patients), for instance,[153] the conversion rate was 14% and patients who were converted to GA on an emergency basis did not develop more complications or have longer stay in the intensive care unit. Prospective studies are needed to examine the suggested benefit of such a sequential approach.

Of key importance, the findings of the present meta-analysis come in contrast to data from three RCTs[153–155] with direct comparison of GA with non-GA included in the present study. The SIESTA[153] and GOLIATH (General or Local Anesthesia in Intra Arterial Therapy, 128 patients) trials[155] indeed showed that the proportion of patients having mRs≤2 at 3 months was significantly higher in the GA group. Of note, since the difference in mRs 0–2 was not paralleled by a consistent shift over all mRs categories, these results need to be interpreted with caution. The third RCT, AnStroke (90 patients),[154] showed no difference in 3-months neurological outcome. In all studies, age, baseline NIHSS score and occlusion location did not differ between groups. A separate pooled analysis of these studies, performed in this study, showed a trend towards better outcome in the GA groups, a result that contradicted the general finding of the meta-analysis (see **Figure D-IV-II**). However, these three single-centre RCTs shared similar limitations, including small relative sample size (368 from 1929 included patients), underpowered and not designed to primarily investigate 3-month functional outcomes.[154] Patients were managed under the guidance of a highly specialised anaesthesia care team with, for instance in the AnStroke trial, less than a 10 min delay in puncture time and a very low rate of procedural hypotension.[154] All three RCTs were single-centre studies with a high risk of bias deriving from local optimisation of GA protocols before the start of the RCT.[153–155] This is a limitation to the generalisability since many, if not most, 'z world' thrombectomy-capable centres do not have subspecialised anaesthesia teams readily available for stroke interventions and often rely on a pool of non-specialised anaesthesiologists. Hence, results from those RCTs may not be naturally transposable to other settings, with different neuroanaesthesiology approaches. Along, one may argue that non-neurological anaesthesia teams may not have similar attention to blood pressure management and fastpaced atmosphere of recanalisation procedure for AIS. Second, as demonstrated in this study, patients from RCT comparing GA with non-GA procedures significantly differ from patients from others larger studies, particularly from those included in the trials investigated in the HERMES collaboration, limiting the potential to clarify the controversy in clinical routine. To improve generalisability and determine the optimal anaesthetic management require large and

multicentric RCTs, but until these data are available the results of such aggregate-level analyses constitute the best available data to inform routine anaesthetic management of patients with AIS-LVO treated with MT.

Our study suffered from several limitations, some of which are inherent to the question under scrutiny. First, four included studies were not randomised by anaesthesia type and the reasons for GA use in these studies were not always known, resulting in a potential selection bias that may contribute to observed differences. Similarly, although prospective studies aimed to control for confounders, the difference in outcome between these two techniques in the pooled analysis could simply be explained by a selection bias, that is, patients who were more severely ill were more likely to receive GA, as the higher average baseline NIHSS scores in GA patients suggest. Adjustment for this variable was unlikely reliable because of the small number of studies with this information. However, a point difference of 1–2 in baseline NIHSS score is unlikely to account for the observed marked differences in favourable outcome and does not convincingly exclude an independent effect of GA management on outcomes. Of note, the data from the HERMES collaboration were able to be adjusted for the 1-point median difference in baseline NIHSS score and still showed better outcomes in non-GA. In addition, the pooled ORs found in this analysis are not marginal and attest for an ample effect size, which strongly suggest that non-GA is indeed associated with better functional outcome. Second, current definitions of GA and non-GA are heterogeneous and allow for a very diverse choice of drugs and measures. Third, in our systematic review, the comprehensive search was designed to include as many pertinent studies as possible; however, some publications may have been missed. Fourth, data presentation was not uniform among the source papers. Baseline characteristics and outcome events were often limited to the entire series, without details on subgroups. The lack of detailed information at baseline precluded meta-regression analyses, and none of our results could be corrected for confounders. Fifth, the time intervals that could be affected by anaesthesia techniques are seldom presented in studies, namely arrival-to-interventional-suite-to-groin puncture time (possibly longer for GA because of induction of anaesthesia and intubation) and groin puncture-to-recanalisation time (possibly shorter for GA because of better working conditions). Finally, we had prespecified a p value of <0.01 because of the multiplicity of analyses. We should keep in mind that all analyses remain exploratory and clinicians should be extremely cautious about using these data for decision-making.

D-IV-6 Conclusion

This systematic review and meta-analysis, pooling studies from the modern area including anterior circulation AIS-LVO and stent retriever/contact aspiration recanalisation techniques only, showed that patients treated under non-GA demonstrated a more favourable functional

non-GA when compared with those patients treated under GA. Notwithstanding, these results do not imply causality and should be interpreted with caution given the inevitable biases deriving from the pooling of heterogeneous sources and unaccounted biases especially in patient sampling. Given the conflicting results between large studies that did not randomise patients by anaesthesia type and small cohorts of randomised patients, a large multicentric RCT is needed to confirm whether first-line GA is associated with worse clinical outcome, perhaps comparing three groups (GA, sequential non-GA and no sedation). A pooled patient-level analysis would also enable to derive adjusted estimates and account for main confounders biasing outcome assessment across groups. In the meantime, when deemed safe and feasible, since non-GA is at least as safe as GA, and if immediate conversion to GA is possible, it is reasonable to favour non-GA in the setting of MT for anterior AIS-LVO.

E. Facteurs post thérapeutiques

E-I Le défaut de reperfusion tissulaire malgré succès de la recanalisation artérielle: l'hypothèse du no-reflow

Le phénomène de No-Reflow a été largement étudié en cas d'ischémie myocardique, défini par la persistance de zones du myocarde non perfusée malgré une désobstruction rapide de l'occlusion coronarienne[169]. Ce phénomène serait dû à une atteinte microcirculatoire induite par la séquence ischémie-reperfusion. Le phénomène du no-reflow est associé à un mauvais pronostic clinique malgré une recanalisation coronaire obtenue dans les meilleurs délais[170]. En cas d'AVC ischémique, plusieurs travaux sur des modèles animaux suggèrent l'existence d'un phénomène similaire au niveau du tissu cérébral. Toutefois, ce phénomène n'a jamais pu être démontré in-vivo, en cas d'AVCi et aucune donnée d'incidence n'est proposée. L'objectif de ce travail était donc d'essayer de mettre en évidence ce phénomène de no-reflow après recanalisation complète (TICI3) l'IRM de perfusion par marquage de spins artériels (ASL).

Tissue *no-reflow* despite full recanalization following thrombectomy for anterior circulation stroke with proximal occlusion: A clinical study

Adrien ter Schiphorst[1,2], Sylvain Charron[1,3], Wagih Ben Hassen[1,3], Corentin Provost[1,3], Olivier Naggara[1,3], Joseph Benzakoun[1,3], Pierre Seners[1,4], Guillaume Turc[1,4], Jean-Claude Baron[1,4,*] and Catherine Oppenheim[1,3,*]

JCBFM DOI: 10.1177/0271678X20954929

E-I-I Résumé Etude N°6

Le phénomène de no-reflow, c'est-à-dire l'altération de la reperfusion microvasculaire malgré une recanalisation complète, peut contribuer au mauvais pronostic fonctionnel malgré un succès de recanalisation. Bien que bien documenté sur des modèles animaux, le phénomène de non-reflux est encore mal caractérisé chez l'homme. Sur une grande base de données prospective de thrombectomie, nous avons inclus tous les patients présentant : *i)* une occlusion proximale intracrânienne, *ii)* une recanalisation complète (score 2c-3 de la thrombolyse modifiée dans l'infarctus cérébral) *iii)* disponibilité d'une IRM de base et d'une IRM de suivi de 24 heures comprenant un marquage de spin artériel. L'absence de reflux a été définie de manière opérationnelle comme *i)* une hypoperfusion de 40 % par rapport à la région homologue controlatérale évaluée à la fois par une analyse visuelle (deux investigateurs indépendants) et une analyse automatique des images, *ii)* présence d'un infarctus sur l'IRM de suivi. Trente-trois patients étaient éligibles (âge médian : 70 ans, NIHSS

: 18, délai entre le début de l'AVC et la recanalisation : 208 minutes). Les critères définissant le No-Reflow étaient présent que chez un seul patient, ce qui est cohérent avec les analyses visuelles et automatiques. Ce patient a été recanalisé 160 minutes après le début de l'AVC et a eu un excellent résultat fonctionnel. Dans notre cohorte de patients ayant bénéficié d'une recanalisation complète après thrombectomie pour une occlusion proximale intracrânienne, le phénomène d'hypoperfusion profonde post recanalisation était rare. Ainsi, le No-Reflow pourrait être un événement peu fréquent dans les accidents vasculaires cérébraux chez l'homme et peut ne pas contribuer de manière substantielle aux recanalisations futiles.

Ce travail

- Est le premier étudiant l'incidence in-vivo chez l'homme du phénomène de no-reflow

- Montre une incidence très faible, constaté chez un patient sur 33

- Rend improbable une implication majeure du no-reflow dans l'évolution clinique défavorable malgré une recanalisation

E-I-II Introduction

Stroke is the second most common cause of death and third most common cause of disability-adjusted life-years worldwide. Acute ischemic stroke (AIS), which represents 80% of all strokes, refers to blockage of an artery by a blood clot, in turn causing insufficient oxygen supply in the affected vascular territory. The longer this lasts, the larger the area of irreversible damage. To limit the size of infarction, therapeutic interventions aim to restore blood supply early enough to save areas in which neurons are “silent” but still viable (the ischemic penumbra). Early reperfusion by means of thrombolysis or mechanical thrombectomy salvages the penumbra, and in turn significantly improves patient’s outcome.[171] However, even with early recanalization, around half of the patients do not recover to an independent life.[19]Understanding the mechanisms underlying such so-called futile recanalizations may lead to novel therapies as adjuncts to thrombectomy.[172,173]

One potential mechanism for poor outcome despite full recanalization of proximal arterial occlusion is inadequate distal reperfusion. It is indeed well established that tissue reperfusion better predicts clinical outcome than recanalization.[174–176]Following thrombectomy, several adverse events may compromise tissue reperfusion, such as per-procedural embolization to distal arteries, early re-occlusion and cerebral hemorrhage, as well as the ‘no-reflow’ phenomenon.[177]

The no-reflow phenomenon, termed *no-reflow* in what follows, refers to the absence of reperfusion of brain tissue despite complete recanalization of the arterial occlusion, due to impaired microvascular perfusion. It was first described in rabbits following global cerebral ischemia[178], then in monkeys subjected to transient focal ischemia by occlusion of the proximal middle cerebral artery (MCA).[179–182] In the latter studies, the carbon black perfusion technique revealed wide MCA territory areas involving the striato-capsular regions but also cortical areas that exhibited absence of capillary filling despite fully recanalized MCA. *No-reflow* was subsequently described following transient MCA occlusion in rodents.[183–185] *No-reflow* is currently thought to be mainly due to narrowing of the capillary lumen secondary to pericyte contraction (as a result of reduced nitric oxide production) and possibly also to pre-capillary small muscle cell contraction[186] in the previously ischemic area, disrupting capillary flow and resulting in the formation of microvascular obstructs containing trapped erythrocytes and leukocytes, fibrin deposits and aggregated platelets.[47,183,187–189] Importantly, it appears possible to prevent or counter *no-reflow*, for instance by acting on the nitric oxide pathway.[183]

Despite these experimental data, the very existence of the no-reflow phenomenon in human remains controversial. This is mainly because reliably investigating *no-reflow* implies unequivocally documentable complete recanalization, which has been doable only once mechanical thrombectomy became clinical routine. In addition, until recently most imaging

techniques used to assess tissue reperfusion were affected by major technical limitations. Thus, although several studies carried out before the thrombectomy era reported rates of recanalization without reperfusion around 25%,[47] most assessed recanalization using magnetic resonance angiography (MRA) or computed tomography angiography (CTA), which are notoriously inadequate to detect distal occlusions, while in many studies reperfusion was assessed using conventional digital subtraction angiography (DSA), which does not provide reliable information on tissue perfusion. Thus, by design, these studies could not provide definitive evidence for the existence of *no-reflow* in human AIS. Two thrombectomy-era studies report on rates of *no-reflow*, but defined recanalization as either partial or complete,[190] therefore including persistent distal occlusions, or did not provide the actual number of assessed patients[191] (see Discussion for further details).

In summary, no study to date has evaluated the occurrence of *no-reflow* in AIS patients enjoying early thrombectomy with complete recanalization. Accordingly, the existence of this phenomenon in humans, its prevalence, location, and impact on functional outcome remain unknown. Documenting the existence and prevalence of *no-reflow* in humans could foster the search for specific therapies to limit its potentially deleterious consequences.

The main objective of the present prospective, mechanistic, proof-of-concept study was therefore to assess the prevalence of *no-reflow* after recanalization in a sizeable sample of AIS patients following early thrombectomy. Importantly, we directly assessed tissue perfusion by means of arterial spin labelling (ASL), which provides quantitative perfusion maps without the need for contrast agent[192,193] and has been validated against conventional methods in both healthy controls and AIS patients.[194–199]

E-I-III Methods

Operational definition of no-reflow

No-reflow by definition entails severe tissue hypoperfusion despite complete recanalization of the previously occluded territory;[47,178–180,182] For the present study, we therefore operationally defined *no-reflow* as ≥ 40% reductions in cerebral blood flow (CBF) affecting anatomical regions of the affected hemisphere on 24-hr ASL maps. This cut-off was chosen based on a previous ASL study in AIS patients that demonstrated that ≥ 40% CBF reduction relative to contralateral homologous region best identified critical hypoperfusion, with high correlation with standard first pass gadolinium perfusion-weighted sequence (PWI).[197] Anatomical regions were based on the ASPECTS (Alberta Stroke Programme Early CT Score) template[200], first because ASPECTS is the most standardized and widely used visual assessment method to assess ischemic tissue in AIS, and secondly because it was recently used by Yu et al to validate a score of ASL-based reperfusion after AIS.[201] Briefly, the ASPECTS score divides

the MCA territory in 10 regions[200] from two standard axial slices, one at the level of the thalamus and basal ganglia, and one just rostral to the ganglionic structures.

The other operational component to identify *no-reflow* here was tissue outcome. As *no-reflow* by definition leads to tissue infarction[47,179,180,182], we also considered *no-reflow* to be present only if the severely hypoperfused ASPECTS area as defined above also exhibited infarction on the 24hr follow-up MRI.

Study population

For the present single-centre study, we systematically reviewed the records retrieved from a prospective database of consecutive patients treated by mechanical thrombectomy (MT) for AIS at Sainte-Anne Hospital, which includes both patients directly admitted to Sainte-Anne (so called “mothership”) and patients referred for endovascular treatment from other centers lacking interventional neuroradiology facilities (“drip and ship”). As per current French regulations, prospective inclusion of patients in this database has received formal regulatory agreement (CNIL MR004).

Inclusion criteria for the present study were as follows: 1/ anterior circulation AIS treated between January 2014 and May 2019; 2/ acute occlusion of the intracranial internal carotid artery (ICA) or of the MCA in its first segment (i.e., proximal large vessel occlusion, the pre-clinical situation in which *no-reflow* has been documented;[179,180,182,185] 3/ successful recanalization by means of MT, defined as a modified treatment in cerebral ischemia (mTICI) score 2c or 3 according to an experienced neuroradiologist who reviewed all arteriographies blinded to the findings of the 24hr ASL (the mTICI score, which ranges from 0 to 3, is used to assess the degree of anterograde recanalization of the MCA territory; grade 3 correspond to a complete recanalization of the previously occluded territory with absence of visualized occlusion in all distal branches, while grade 2c corresponds to near complete recanalization except for slow flow or distal emboli in a few distal cortical vessels); and 4/ availability of MRI datasets both prior to MT (‘MRI-1’) and at ~24hr after mechanical thrombectomy including an ASL-sequence (‘MRI-2’). Eligible patients could receive thrombolysis prior to MT according to international guidelines.[202]

Exclusion criteria were as follows: 1/ presence of parenchymal hematoma (PH) 1 or 2 on MRI-2, according to the European Cooperative Acute Stroke Study (ECASS) classification[203], as ASL-CBF may be decreased within and around a PH[204]; 2/ re-occlusion or new occlusion of an intra-cranial artery on MRI-2; 3/ stenosis ≥ 50% of the ICA or MCA ipsi- or contralateral to the infarct, which may cause ipsilateral CBF decreases; however, a stenosis treated during the MT procedure without residual stenosis on follow-up imaging was not a cause of exclusion; 4/ delay between MRI-1 and groin puncture (start of thrombectomy) ≥ 3 hrs, in order to exclude

marked pre-recanalization infarct growth; and 5/ un-interpretable ASL images due to e.g., movements artefacts, technical problems, artefactually low whole brain CBF (<20 mL/100g/min).

MRI protocol

In France, MRI is recommended as first line diagnostic imaging work-up in candidates to recanalization, and is implemented 24/7 at the Sainte-Anne comprehensive stroke center. At Sainte-Anne hospital, a follow-up MRI (MRI-2) is carried out around 24hrs after treatment whenever feasible. All MRI data were acquired using a 1.5T MRI scanner (General Electric Healthcare). How as per the above inclusion criteria, patients were included in the present study if they had both the acute and follow-up MRI sessions, and the latter included ASL.

The following standard sequences were acquired: i) Diffusion-Weighted Imaging (DWI) with b=0 s/mm^2 and b=1000 s/mm^2 sequences.; ii) Fluid-Attenuated Inversion Recovery (FLAIR); iii) T2*, to determine the presence of haemorrhages; and iii) 3D Time-of-Flight (3D TOF) MR angiography (MRA), to determine the presence and localization of intracranial occlusion on MRI-1 and the absence of reocclusion on MRI-2. The ASL perfusion imaging obtained at MRI-2 was a 3D pseudo-continuous sequence acquired using the following parameters: 4.5 minutes duration, 3.5×3.5×4 mm resolution, TR/TE = 4600/10.5 ms, pairs of control/label 3; post-labeling delay 2000 ms, 40 slices with a 4.0 mm thickness with whole brain coverage and background suppression, in order to suppress signal from static tissue (background) and hence improve signal-to-noise ratio while reducing sensitivity to motion artifacts. ASL-CBF parametric perfusion maps were automatically calculated from the labelled and unlabelled ASL images (M0) with the READY VIEW® software (GE Healthcare).

Whenever feasible, MRI-1 also included a PWI sequence and, whenever needed, a contrast-enhanced cervical MRA to guide decision-making regarding thrombectomy. If not obtained before treatment, contrast-enhanced cervical MRA was performed after treatment as part of the etiological work-up.

Identification of no-reflow

Visual analysis

To facilitate anatomical identification of the ASPECTS regions, which may be difficult to determine on CBF maps, a preliminary step involved for each patient rigid co-registration between the ASL-derived CBF maps and the 24hrs DWI and FLAIR images, using the General Electric Volume Viewer® software. Then, any ASPECTS region pair with significant hemorrhagic transformation on MRI-2 T2* imaging or with old infarction on FLAIR (MRI-1) on either hemisphere were excluded from further analysis, as it was considered these could

mislead image interpretation for *no-reflow*. With aid from the coregistered FLAIR and DWI images, two investigators with ASPECTS training (a stroke neurologist (ATS) and a neuroradiologist (CP)), blinded to all clinical information except stroke side, independently visually determined in each ASPECTS region the presence of severe hypoperfusion on ASL-derived CBF maps, as compared to the contralateral mirror ASPECTS region. To confirm any visually determined hypoperfusion in a given ASPECTS region, the investigator positioned on the co-registered DWI image a circular or elliptic two-dimensional region of interest (ROI) encompassing the hypoperfused region, and a mirror ROI in the contralateral homologous ASPECTS region. *No-reflow* was retained if i) the reduction of mean CBF in the affected ROI was ≥ 40% relative to that in the contralateral mirror ROI, and ii) the affected ASPECTS region displayed infarction on 24hr DWI. Any discrepancy between readers was resolved by consensus adjudication. Hypoperfused regions so identified were then retrospectively assessed for the presence of DWI lesion at MRI-1. Likewise, their perfusion status on admission PWI, whenever available, was assessed on Tmax images, based on the notion that *no-reflow* is expected to develop in initially ischemic areas.[47]

Automatic analysis

In order to confirm the results of the visual analysis, a fully automated analysis was carried out, which automatically calculated the mean CBF within each ASPECTS region and its contralateral mirror region across the entire patient dataset. To this end, we created an ASPECTS template similar to that developed by Yu et al.[201] using the MANGO® software, version 4.0.1 (Research Imaging Institute, University of Texas Health Science Center). Based on the Pick Atlas template and the study by Tatu et al.[205] the ASPECTS template was created in the T2 Montreal Neurological Institute MNI 152 space. ASPECTS regions were built on the two axial ASPECTS cuts, each with 6 mm thickness.

To apply the MNI-space ASPECTS template onto each patient's ASL images, the following procedure was applied using Matlab R2018b (The MathWorks, Inc., Natick, MA, USA) via SPM12. We chose as initial normalization step to normalize the b=0 maps into the Montreal Neurological Institute (MNI) space rather than directly the ASL into this space, because ASL maps are functional, as opposed to b=0 being anatomical, which is recommended for efficient normalization. To coregister the ASL maps into MNI space, we then registered the b=0 image with the M0 ASL sequence rather than the ASL derived CBF maps, as the former contain greater anatomical information.

Thanks to this automatic analysis, regional perfusion values were extracted automatically for the 10 ASPECTS brain regions and their contralateral mirror regions for each patient. As with

the visual analysis, the presence of *no-reflow* was retained whenever the mean CBF in an ipsilateral ASPECTS region was ≥ 40% lower than that in the contralateral mirror region.

Clinical and imaging variables

The following data were collected:

- Demographic characteristics: age, sex, vascular risk factors, history of atrial fibrillation, pre-stroke modified Rankin scale (mRS, a disability scale ranging from 0 (no disability) to 6 (death));

- Admission clinical AIS data: time of last seen well, time of admission, National Institutes of Health Stroke Scale (NIHSS), a validated stroke severity scale ranging from 0 (no deficit) to 42 (death);

- Admission imaging data: presence and location of arterial occlusion (ICA, proximal or distal MCA-M1, tandem), presence and imaging features of the ischemic stroke (localization: deep or cortical);

- DWI lesion volume: using MANGO ® software, DWI lesions were semi-automatically segmented for both MRI sessions, and volumes were extracted;

- Treatment: thrombolysis and time of start of thrombolysis when performed, time of start of thrombectomy, mTICI score;

- Cause of stroke according to the TOAST (trial of ORG 10172 in acute stroke treatment) criteria[206]

- Follow-up data during hospital stay: NIHSS at 24hrs. Early neurological improvement was defined as a ≥8-point decrease in 24hr NIHSS relative to baseline, or 24hr NIHSS ≤ 4; early neurological deterioration was defined as as ≥4-point increase on 24hr NIHSS[207,208]

- 3-month follow-up data: mRS. Favourable outcome was defined as mRS≤2.

Statistical analysis

Data were analysed using SPSS Statistics Version 25 (IBM, Armonk, NY). Kappa coefficients were calculated to characterize the agreement between investigators for the visual analysis. To analyse the difference between included and non-included patients, continuous variables were compared using the Wilcoxon rank-sum test, and categorical data were analysed by means of Fisher exact test. Tests were bilateral and acceptable type I error was set a priori at $\alpha=0.05$. Means are presented as mean±SD, medians as median (IQR).

Data availability

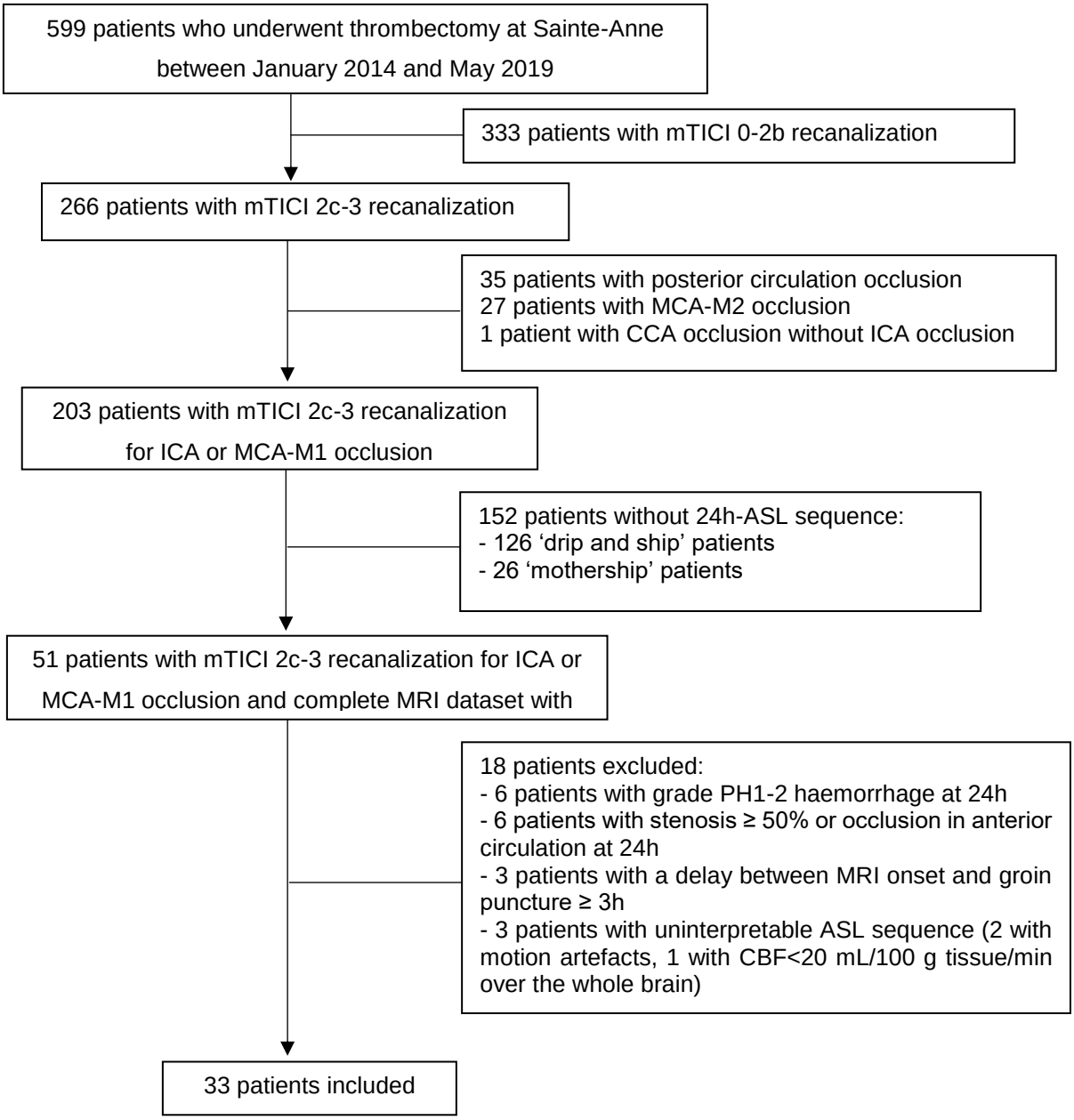
The data that support the findings of this study are available from the corresponding author upon reasonable request.

E-I-IV Results

Study population

Out of 599 patients who underwent thrombectomy at Sainte-Anne Hospital during the study period, 33 patients fulfilled the inclusion criteria for the present study. **Figure E-I-1** presents the study flow-chart including all the causes for exclusion. Because most drip and ship patients return to their referring stroke center immediately following the procedure, only three drip and ship patients had MRI-2 with ASL in the whole Sainte-Anne registry. However, they were not eligible for the present study because in all the delay between the initial MRI (not repetead on arrival to our hospital) and groin puncture was >3 hrs. Consequently, the present study included only mothership patients.

Figure E-I-1: Flowchart of study population



The baseline characteristics, clinical and imaging data, treatment received and outcome data are summarized in **Tables E-I-1 and 2**.

Table E-I-1: Clinical and radiological characteristics.

Variable	Patients (n=33)
History and characteristics at admission	
Age, years, median (IQR)	70 (61-79)
Male gender	21 (64)
Pre-stroke mRS ≤ 2	31 (94)
History of hypertension	18 (55)
Current smoking	6 (18)
Atrial fibrillation	19 (58)
Stroke cause	
- Cardio-embolic	23 (70)
- Atherothrombotic	1 (3)
- Undetermined	9 (27)
Known time of symptoms onset	26 (79)
Initial NIHSS score, median (IQR)	18 (12-21)
Imaging	
Stroke onset* to admission MRI delay (mins), median (IQR)	94 (72-135)
Last-time-seen-well to admission MRI delay (mins), median (IQR)	104 (72-233)
Initial perfusion imaging	23 (70)
Initial DWI lesion volume, mL, median (IQR)	10 (4-26)
Thrombus localization (DSA)	
- Intracranial ICA occlusion (+/- MCA or ACA)	8 (24)
- Tandem occlusion	2 (6)
- Isolated proximal MCA-M1 occlusion	14 (42)
- Isolated distal MCA-M1 occlusion	9 (27)
Right-sided thrombus	16 (49)

*Values shown are numbers (percentages), unless stated otherwise.mRS=modified Rankin Scale, IQR=Interquartile range; NIHSS=National Institutes of Health Stroke Scale, DWI=Diffusion Weighted Imaging, ASPECTS=Alberta Stroke Program Early CT score, ICA=Internal Carotid Artery, ACA=Anterior Carotid Artery, MCA=Middle Cerebral Artery, M1=First segment of MCA; DSA: digital subtraction angiography. *Onset of symptoms: for stroke with unknown time, time when the patient was found symptomatic.*

Median age was 70yrs (IQR 61-79). Before treatment, median NIHSS was 18, mean DWI lesion volume was 10 mL and mean DWI ASPECTS score was 7.5. Twenty-one patients (64%) were administered intravenous thrombolysis.

Table E-I-2: Treatment and follow-up data.

Variable	Patients (n=33)
Treatment-related data	
Intravenous thrombolysis	21 (64)
Stroke onset* to thrombolysis delay (min), median (IQR)	110 (95-144)
Stroke onset* to groin puncture delay (min), median (IQR)	150 (124-202)
Admission MRI to groin puncture delay (min), median (IQR)	52 (39-66)
First pass thrombectomy method	
- Contact aspiration	32 (97)
- Combined (contact aspiration and stent retriever)	1 (3)
Final recanalization score	
- mTICI 2c	22 (67)
- mTICI 3	11 (33)
Groin puncture to recanalization delay (min), median (IQR)	30 (16-46)
Admission MRI to recanalization delay (min), median (IQR)	84 (55-101)
Stroke onset* to recanalization delay (min), median (IQR)	196 (154-230)
Last-time-seen-well to recanalization delay (min), median (IQR)	208 (154-337)
Follow-up data	
Recanalization to follow-up MRI delay (hours), median, IQR	24 (20-27)
NIHSS at 24 hours	4 (1-9)
$\Delta NIHSS_{24h\text{-}initial}$	11 (5-14)
Early neurological improvement†	26 (79)
Early neurological deterioration‡	0
24-hr follow-up DWI-lesion volume (mL), median (IQR)	13 (6-32)
Admission to follow-up DWI lesion volume change (mL), median (IQR)	2 (0-8)
Favorable outcome (mRS≤2) at 3-months	21 (68)

Values shown are numbers (percentages), unless stated otherwise.

*IQR=Interquartile range; mTICI= modified Treatment In Cerebral Ischemia; NIHSS=National Institutes of Health Stroke Scale; mRS=modified Rankin Scale; *Onset of symptoms: for stroke with unknown time, time when the patient was found symptomatic; †: ≥8-point decrease in 24hr NIHSS relative to baseline, or 24hr NIHSS ≤ 4; ‡: ≥4-point increase on 24hr NIHSS.*

The mean delay between onset of symptoms and groin puncture was 150 mins, and was 52 mins between start of MRI-1 and groin puncture. Twenty-two patients (67%) had TICI 2c recanalization and 11 had TICI 3. Median NIHSS score at 24hrs was 4, with a median pre-thrombectomy to 24-hrs NIHSS decrease of 11. Follow-up DWI-lesion volume was 13 mL, with a median change in DWI-lesion volume between baseline and 24hrs of +2mL.

Twenty-six mothership patients with TICI 2c-3 recanalization for ICA – M1 occlusion did not undergo follow-up ASL imaging, of whom 14 fulfilled all the inclusion criteria for the present study apart from ASL availability. None of the baseline and follow-up characteristics of these 14 patients significantly differed from those of the 33 included patients.

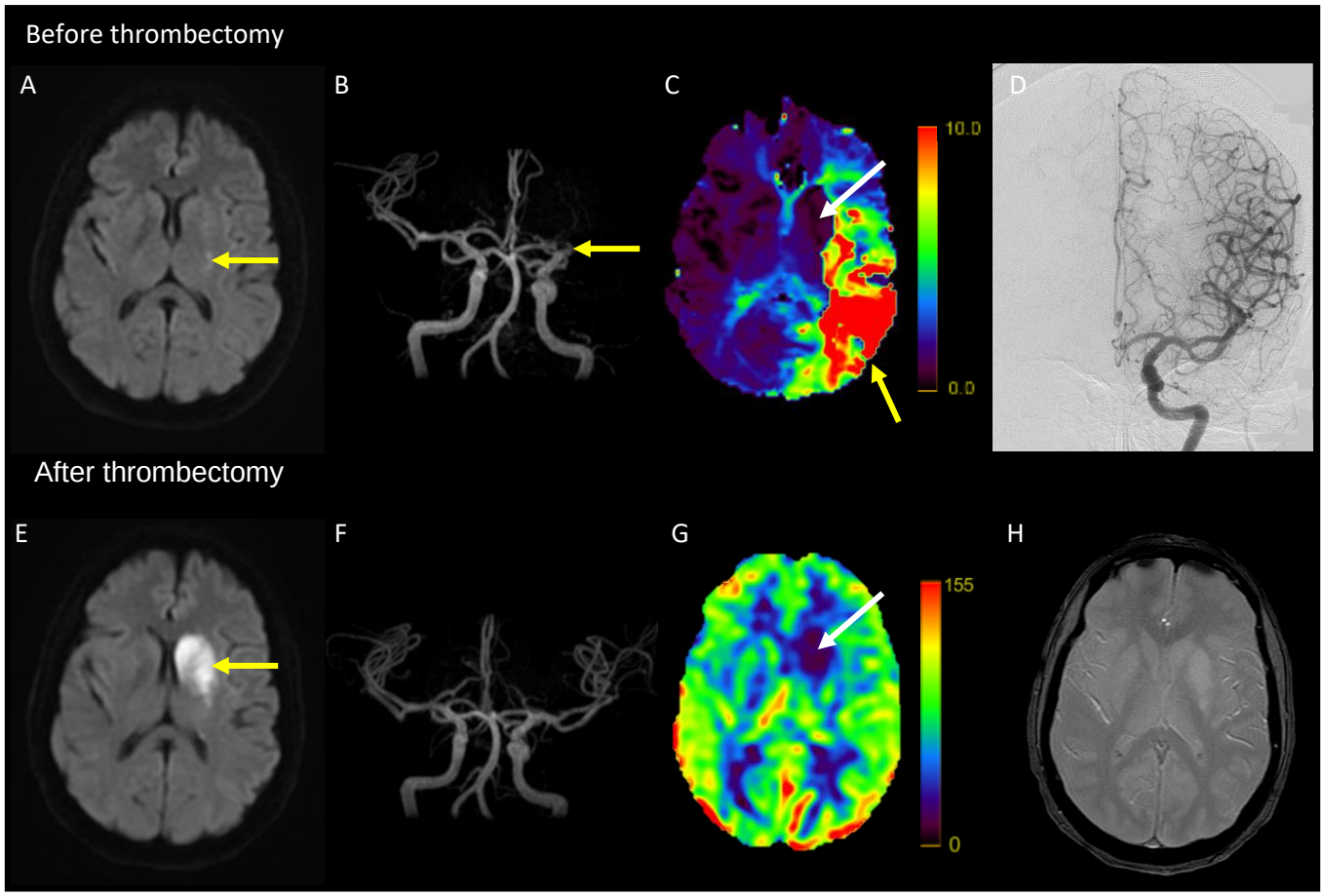
No-reflow analysis

Across the 33 patients, eight ASPECTS region values were excluded *a priori* from the analysis: three because of haemorrhage, three because of ipsilateral old infarct, and two because of contralateral old infarct. Accordingly, 322 ASPECTS regions values (with their mirror region values) were available for final analysis.

Visual analysis

No-reflow was not identified in 32 of the 33 patients. In the remaining patient, both investigators independently identified *no-reflow* in the same two regions, namely the caudate and lentiform regions (average CBF decrease of -63% and -55% relative to mirror region, respectively). (**Figure E-I-2**).

Figure E-I-2: Co-registered imaging data for the single patient in whom no-reflow was identified.



The patient had sudden-onset severe hemiparesis (three levels) and global aphasia. On admission to our hospital, the neurological deficit had partly resolved and the patient had mild three-level hemiparesis and non-fluent dysphasia (NIHSS.4). She was treated with thrombectomy 160 min after symptom onset. (a–c) MRI-1 obtained 84 min after symptom onset, showing a small, faint DWI lesion involving the posterior-most lentiform nucleus (a, arrow), an MCA-M1 occlusion on time-of-flight angiogram (b, yellow arrow) distal to the lenticulo-striate arteries (blue arrow), and on PWI (Tmax; the pseudo-color scale ranges from 0 to 10 s) an extensive area of severe hypoperfusion covering a large part of the left cortical MCA territory (yellow arrow), but sparing the deep MCA territory (white arrow) (c). (d) Digital subtraction arteriography obtained immediately following thrombectomy, showing mTICI 3 recanalization. (e–h) Twenty-four-hour MRI-2 showing extension of the DWI lesion to the entire caudate and lentiform nuclei (e), without re-occlusion on time-of-flight MRA (f). These newly infarcted areas are severely hypoperfused on 24 h ASL-CBF maps (g; the pseudo-color scale is in milliliters/100 g/min), fulfilling the operational criteria for no-reflow for both regions (CBF relative to mirror region: –63% and –55%, respectively). No hemorrhage was present across the MCA territory on T2 MRI-2 (h). (a, c, e, g, and h) Images co-registered using GE Volume Viewer (see Methods). Stroke etiology was atrial fibrillation. This patient enjoyed early neurological recovery (24-h NIHSS.1) and excellentoutcome (three-month mRS.0).*

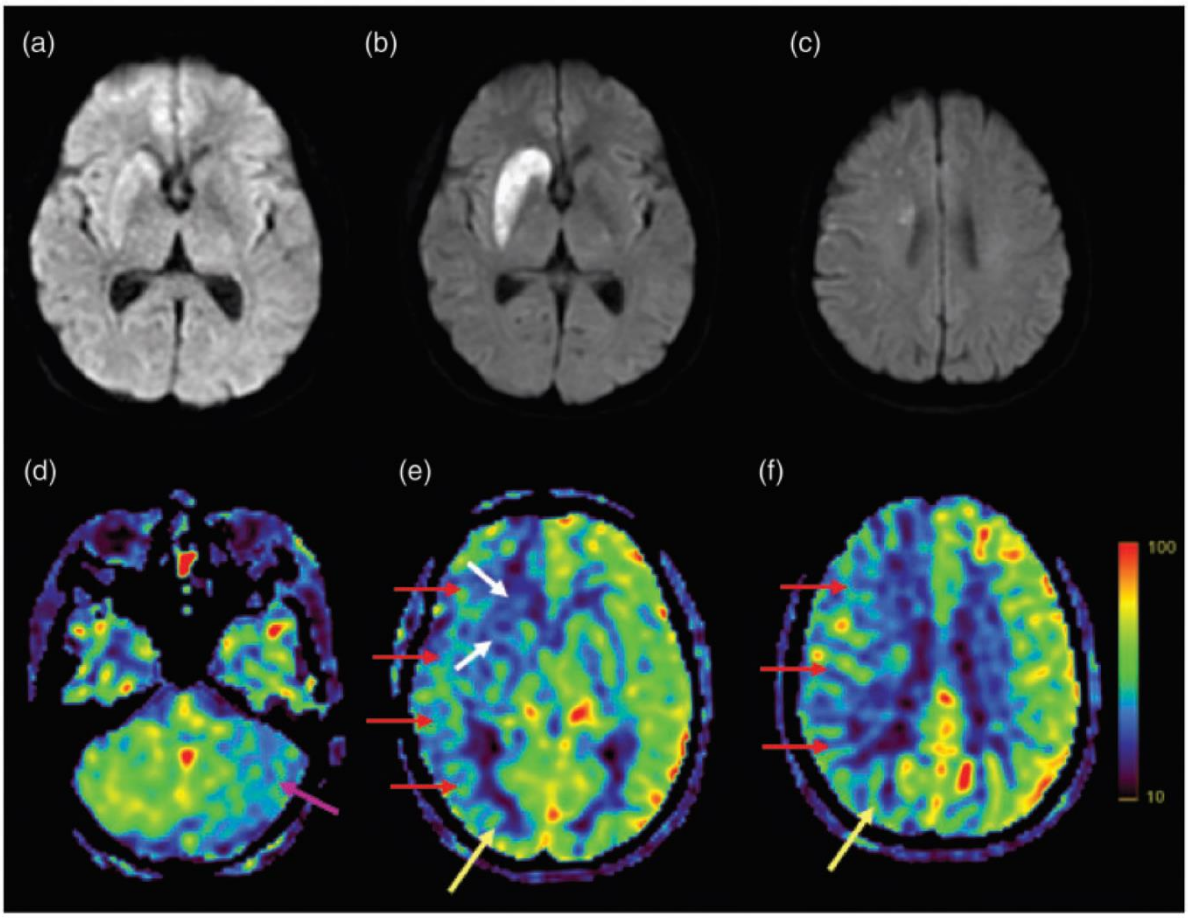
The kappa coefficient for *no-reflow* was therefore 1. As per the operational criteria for *no-reflow* defined above, both regions exhibited infarction on MRI-2 (**Figure E-I-3**), but not on MRI-1. Of note, neither region exhibited hypoperfusion on Tmax-derived PWI in MRI-1 (**Figure E-I-3**).

Automatic analysis

Entirely consistent with the visual analysis, no ASPECTS region mean CBF fulfilled our operational definition for *no-reflow* in any patient save for the same patient as with the visual

analysis, involving the caudate nucleus only (a decrease of -73% relative to contralateral region; see **Figure E-I-3** for further detail).

Figure E-I-3: Illustrative image dataset of the patient with mild hypoperfusion associated with infarction.



This 66-year-old patient presented with acute-onset moderate deficit (NIHSS score.11) and was treated with IV thrombolysis followed by thrombectomy for right terminal ICA occlusion, with mTICI 2c recanalization obtained 215 min after symptom onset. Perfusion MRI was carried out prior to thrombolysis in this patient but unfortunately the data were not interpretable due to marked head motion and technical errors. (a–c) Illustrative DWI b.1000 s/mm2 sequences obtained (i) on admission (68 min after symptom onset) (a), and at 24 h follow-up (b and c), showing a stable DWI lesion in the striato-capsular area (i.e. deep MCA territory); (d–f) 24 h follow-up ASL-CBF maps, showing mild hypoperfusion within the DWI lesion (15% and 17% reduction in the caudate and lenticular nuclei, respectively, relative to contralateral ASPECTS regions; white arrows), but also cortically at distance from the DWI lesion (20–35% reduction relative to contralateral ASPECTS regions; red arrows), spreading beyond the ICA territory (i.e. posterior circulation, yellow arrows; note that in this patient both posterior cerebral arteries originated from the basilar artery on MRA, data not shown). The left cerebellar hemisphere, i.e. contralateral to the stroke, also shows mild hypoperfusion compared to the right cerebellum (purple arrow), reflecting crossed cerebellar diaschisis. The patient made a good recovery (24 h NIHSS score.1, three-month mRS.1).

E-I-V Discussion

This study is the first to assess the incidence of *no-reflow* in human stroke using perfusion mapping in a sizeable sample of patients strictly selected for successful recanalization following thrombectomy for intracranial proximal arterial occlusion. Applying our operational definition, *no-reflow* was present on 24hrs follow-up ASL CBF maps in one out of 33 patients only, consistently so using the visual or the automatic analysis. This unexpected finding suggests that *no-reflow* is at best a rare phenomenon, unlikely to substantially contribute to the frequently observed poor outcomes following successful recanalization.

A detailed discussion of the actual findings in this particular patient is in order. The basal ganglia, which were not initially hypoperfused and exhibited only a faint and very small diffusion abnormality, displayed severe hypoperfusion in the follow-up ASL maps, satisfying the *no-reflow* criteria (**Figure E-I-3**). This lack of initial hypoperfusion comes however as a surprise, as *no-reflow* is expected to develop in ischemic tissue.[47] One could hypothesize that the basal ganglia were indeed initially ischemic but, due to distal migration of the clot, had reperfused by the time of MRI-1 without causing extensive irreversible damage.[209] Two different, and more likely, hypotheses to explain the severe hypoperfusion and secondary infarction affecting these brain regions are, first, inadvertent occlusion of small lenticulostriate arteries during the thrombectomy procedure, and, second, a new embolic event in this patient with atrial fibrillation. Either of the latter two scenarios would imply that the severe hypoperfusion present on 24-hr ASL may not represent genuine *no-reflow*, but merely a new ischemic event. In turn, the rate of *no-reflow* in our population of AIS patients with large vessel occlusion experiencing full and permanent recanalization within a median of 3-4hrs after stroke onset was at best 3%, and possibly even less.

Interestingly, there was a discrepancy between the visual and automatic analyses in this patient with respect to the lenticular nucleus, which was categorized *no-reflow* with the former but not with the latter (**Figure E-I-3**). This is likely because the severe hypoperfusion affecting the lenticular nucleus spared its postero-lateral part (**Figure E-I-3**), and was therefore not fully captured by the automatic template-based analysis, which samples the entire, bounded ASPECTS region, at variance with the visual analysis. Importantly, full validation of the visual analysis of follow-up ASL perfusion maps by the automatic, template-based analysis has been previously reported.[201] Our data suggest the former is more sensitive to focal hypoperfusion not affecting entire ASPECTS regions, which may be missed by the automatic analysis due to "dilution" by normoperfused, or potentially hyper-perfused, portions of the ASPECTS region.

To compare our findings with the literature, we analyzed all 13 published clinical studies that assessed the perfusion status of AIS patients following recanalization, even though *no-reflow* wasn't necessarily their focus and the relevant data may appear somewhere in the article

without being commented upon. This literature is summarized in **Table E-I-3.** Although most mention a rate of recanalization without reperfusion of ~25-40%, potentially reflecting *no-reflow*, several recent studies - including some carried out after thrombectomy became standard-of-care - have reported much lower rates. Below we will examine why this change in reported rates may have occurred. In their systematic review on *no-reflow* published in 2012, Dalkara and Arsava[47] assessed all seven studies published until then[174,210–214] and found across these studies an average rate of poor reperfusion despite recanalization of 26%. Note that regarding one of these seven studies,[213] we were unable to find the data referring to the cited *no-reflow* rate of 19% in the published article, and accordingly it is omitted from **Table E-I-3.** However, as detailed in **Table E-I-3**, all these studies in fact had methodological shortcomings, calling into question their reported *no-reflow* rate. As major shortcomings, most evaluated recanalization using MRA or CTA, which is inadequate to detect distal occlusions, and/or assessed reperfusion using conventional digital subtraction angiography (DSA), which does not provide reliable information on tissue perfusion. Furthermore, they all used as endpoint “partial or complete recanalization” instead of complete recanalization, a serious issue when assessing *no-reflow*.

Even though - at variance with our study - most of the six studies published after 2012 still only included patients treated with IV t-PA, they were of much improved methodology (**Table E-I-3**). Similar to the older studies above, three reported substantial rates (>20%) of *no-reflow*[175,190,215] evaluated reperfusion using 24hrs CT perfusion following IV t-PA and thrombectomy, respectively, and found a rate of recanalized patients with persistent hypoperfusion of 24% and 38%, respectively; however both studies used CTA to assess recanalization, and included both partial and complete recanalization, severely limiting interpretation. Horsch et al.[215] studied 178 patients (2/3 treated with IV tPA, the rest not receiving reperfusion therapy) with perfusion defect in the MCA territory on admission imaging, of whom 152 had initial occlusion; of the latter, 83 had complete recanalization on 24hrs follow-up imaging, with 33 (40%) having incomplete reperfusion. However, recanalization was again assessed by CTA, so ‘missed’ distal occlusions may have caused at least some of the observed reperfusion defects. In sum, none of these three studies was designed to formally assess *no-reflow*. Because the imaging tools are close to those used in the present study, a final study[201] deserves mention even though data on *no-reflow* are not presented - explaining why it does not appear in **Table E-I-3**. These authors report that 11 patients out of 23 with successful post-thrombectomy recanalization (determined with DSA) had poor “reperfusion score” (determined on 24hrs follow-up ASL imaging), which however included both hypo- and

Table E-I-3. Previously published articles (listed in chronological order) on cerebral hypoperfusion in recanalized stroke patients, and present study.

First author, year	Acute revascularization treatment	Stroke onset-to-treatment delay (h)	Recanalization assessed with	Recanalization assessment time	Definition of recanalization	Imaging modality used to assess reperfusion	Reperfusion assessment time	Number of recanalized patients	Number of recanalized patients with hypoperfusion (%)
Baird, 1994[45]	IA SK	4–24	DSA	24 h	***Partial***[a] or complete	SPECT	24 h	4	1 (25%)
Yasaka, 1998[46]	IV SK or placebo	<4	***Transcranial Doppler***[b]	24 h	***Partial***[a] or complete	SPECT	24 h	8	4 (50%)
Khatri, 2005[47]	IV + IA t-PA	<3	DSA	On completion of DSA	Complete (AOL III)	***DSA (TIMI)***	On DSA completion	32	26 (81%)
Albers, 2006[51]	IV t-PA	3–6	***MRA***[b]	3–6 h after t-PA	***Partial***[a] or complete	PWI	3–6 h after t-PA	19	4 (21%)
De Silva, 2009[5]	IV t-PA	3–6	***MRA***[b]	3–5 days	***Partial***[a] or complete (TIMI 2–3)	PWI	3–5 days	13	4 (31%)
Soares, 2010[48]	IV t-PA ± MT, or no treatment	<6	***CTA***[b]	24 h	***Partial***[a] or complete	CTP	24 h	13	5 (38%)
Bivard, 2013[25]	IV t-PA or no treatment	<6	***MRA***[b]	24 h	Complete	ASL	24 h	48	0%
Eilaghi, 2013[6]	IV t-PA or no treatment	<4.5	***CTA***[b]	≤24 h	***Partial***[a] or complete (TIMI 2–3)	CTP	≤24 h	59	14 (24%)
Horsch, 2015[49]	IV t-PA or no treatment	<9	***CTA***[b]	3 days	Complete	CTP	3 days	83	33 (40%)
Cho, 2015[7]	IV t-PA or no treatment	<6	***MRA***[b]	<6 h after stroke onset	***Partial***[a] or complete (AOL II–III)	PWI	<6 h of symptoms onset	13	0 (0%)
Carbone, 2019[50]	IV t-PA ± MT, or no treatment	<8	***CTA***[b]	24 h	***Partial***[a] or complete (TIMI 2–3)	CTP	24 h	39	15 (38%)
Present study	MT ± t-PA	<24	DSA[c]	On completion of DSA	Complete (mTICI 2c–3)	ASL	24 h	33	1 (3.3%)

IA: intra-arterial; IV: intravenous; t-PA: tissue plasminogen activator; SK: streptokinase; MT: mechanical thrombectomy; DSA: digital subtraction angiography; SPECT: single-photon emission computed tomography; AOL: arterial occlusive lesion score; TIMI: thrombolysis in myocardial infarction score; mTICI: modified thrombolysis in cerebral infarction score; PWI: perfusion-weighted imaging; MRA: magnetic resonance angiography; CTA: computed tomography angiography; CTP: CT perfusion.

Methodological limitations that affect interpretation regarding the presence and reported rate of *no-reflow* appear in bold and italics.

[a]Inclusion of partial recanalization could in part account for some of the reported hypoperfusions.

[b]These techniques are inadequate to identify distal occlusions, which could in turn have caused some of the observed hypoperfusions.

[c]Lack of re-occlusion was verified in each patient using the 24 h follow-up MRA.

hyper-perfusions, with no breakdown between the two being presented; furthermore, information on arterial re-occlusion or hemorrhagic transformation is missing.

In contrast with the three recent studies on *no-reflow* just discussed, the data reported in three additional recent studies[176,191,194] point to low incidence or complete absence of *no-reflow*, consistent with our findings. Of note, none of these studies addresses the *no-reflow* issue in their discussion. Bivard et al[194] studied 100 patients (most treated with IV t-PA; none with thrombectomy), of whom 41 had hypoperfusion on 24hr ASL. However, none of these latter patients had complete recanalization on 24hr MRA, pointing to a complete absence of bona fide *no-reflow*. Likewise, in 13 patients showing full recanalization on early (≤ 12hrs) follow-up MRI, Cho et al.[176] found no instance of *no-reflow*; as a caveat, however, their patients had mostly distal occlusions (second segment of the MCA), a situation where *no-reflow* could be difficult to detect. Finally, in an imaging substudy of the SWIFT PRIME thrombectomy trial[191], 7% of the mTICI3 thrombectomized patients in whom 27-hr follow-up CT perfusion or PWI was performed did not show successful reperfusion. Overall, therefore, the upper rate of 3% potential *no-reflow* in our study is entirely consistent with the latter three studies. Yet, as detailed in **Table C-I-3**, these three earlier studies did have significant methodological shortcomings, making their assessment of *no-reflow* not entirely reliable.

Further evidence mitigating against a high prevalence or significant extent of *no-reflow* in our population was the negligible average increase in infarct volume between MRI-1 and MRI-2 (median = 2 mL), consistent with another recent thrombectomy study which reported a median DWI lesion growth of 0.9 mL 24hrs after complete recanalization.[216] These findings indeed speak against *no-reflow*, the definition of which implies irreversible tissue damage and infarct growth.

Taken together with these recent studies, it therefore appears that *no-reflow* is rare in human stroke. How can this be reconciled with its established status from pre-clinical stroke models? A number of possibilities will be considered below in succession.

Given the animal, including primate, literature,[47,178–180,182] we considered severe hypoperfusion as a key criterion in the operational definition of *no-reflow*. To this end, we applied a 40% threshold relative to contralateral mirror region, based on earlier ASL studies that showed it correlates well with PWI Tmax >6s, the well validated penumbra threshold.[192,197] In their seminal report in rabbits, Ames et al described *no-reflow* not only as large confluent no-perfusion areas, but also as 'mottled' areas where non-perfused brain regions interspersed with perfused areas.[178] It must be noted however that these authors studied global complete cerebral ischemia, not focal stroke, and, furthermore, mottled *no-reflow* was as a rule associated with confluent *no-reflow*. Were such mottled form of *no-reflow* to occur in human stroke, and given the limited spatial resolution of ASL, it might indeed translate as only mildly reduced average perfusion over a whole ASPECTS region and be missed by our operational

criteria. However, only limited functional impact would be expected as one would not anticipate mottled *no-reflow* to cause frank infarction, perhaps just selective neuronal loss.[217]

To address this issue, we assessed *post hoc* the presence of mild hypoperfusion in our population as a marker of mottled *no-reflow*. In our setting of complete recanalization without proximal hemodynamic carotid stenosis, mild hypoperfusion might however also result from diaschisis, i.e., coupled hypoperfusion/hypometabolism remote from damaged areas as a result of disconnection.[218–222] Using the same MRI-2 dataset and procedure as with the pre-planned visual analysis, each ipsilateral ASPECTS region was independently classified by two investigators in four categories, based on the presence or absence of hypoperfusion not fulfilling the criteria for severe hypoperfusion (see Methods) and whether or not the affected area was infarcted on concomitant DWI. As with the main analysis, the inter-observer reproducibility for these assessments was very good (data not shown). Of the 33 patients, 11 had at least one mildly hypoperfused ASPECTS region, consistently in conjunction with deep MCA territory infarcts, with associated cortical infarcts in four patients. In total, 43/320 ASPECTS regions displayed mild hypoperfusion, two of which only were infarcted on MRI-2 DWI, both involving the basal ganglia in the same patient. The latter may therefore represent a milder form of *no-reflow*, of sufficient severity to cause frank tissue infarction despite partial tissue reperfusion. Assuming this interpretation is correct, the incidence of *no-reflow* would increase to 6% at most in our sample, still far below clinical relevance. The remaining 41 mildly hypoperfused but non-infarcted ASPECTS regions were all cortical, apart from two involving the caudate nucleus. Whether these mild hypoperfusions represent mottled *no-reflow* not causing infarction would be difficult to ascertain. To indirectly tackle this issue, we then assessed whether such mild hypoperfusions could be ascribed to ipsilateral cortical diaschisis. To this end, we took advantage of its frequent association with crossed cerebellar diaschisis (CCD).[221,223,224] Accordingly, after excluding patients with vertebral stenosis, cerebellar infarct or cerebellum beyond the field of view of ASL, the two investigators assessed CCD on the ASL maps, independently from mild supratentorial hypoperfusions, as reported earlier[225,226]. CCD was present in 6/28 patients, and was significantly more frequent in patients with, as compared to without, mildly hypoperfused cortical regions ($p=0.038$, Fisher exact test). Thus, most if not all ipsilateral cortical mild hypoperfusions present in our population may be secondary to intra-hemispheric diaschisis. The wide prevalence of subcortical infarcts in all patients with mild cortical hypoperfusion is also consistent with this interpretation.[219,221]

An entirely different hypothesis to account for our negative findings would posit that *no-reflow* may well exist, but mainly in patients with longer occlusion times. In monkeys, Crowell et al noted that the longer the duration of temporary proximal MCA occlusion, the higher the incidence of severe, extensive *no-reflow*, which became prominent only after 4hrs occlusion.[179]

From the same group, Morawetz et al[227] consistently observed full restoration of perfusion immediately following clip removal after 2-3 hrs proximal MCA occlusion, even in subsequently infarcted areas, although in one animal perfusion fell to very low levels at the 24hrs follow-up assessment. Also in monkeys, Little et al observed that only mild *no-reflow* was present with MCA occlusions up to 3hrs.[181,182] A rat study failed to detect *no-reflow* following 2hrs MCA occlusions.[228] Our patients received thrombectomy as per the mothership paradigm, and accordingly the median delay between last-time-seen-well and recanalization was relatively short, namely 208mins, although the range was wide (112 to 750min except one outlier at 1325min). Conversely, some studies have observed *no-reflow* very early after occlusion, for instance permanent nodal microvascular constrictions affecting half of the microvessels was found to start as early as 1hr after ischemia onset.[183,186] Acknowledging this caveat, it remains that *no-reflow* was a rare occurrence in our standard population of mothership patients and in turn would not account for the poor outcomes that affected one-third of our sample despite complete recanalization (**Table E-I-2**).

As almost two-thirds of our patients received thrombolysis (**Table E-I-1**), one might wonder whether IV t-PA might decrease the incidence of *no-reflow*, which is known to be preventable by various ways in animal models.[179,183,229,230] However, Horsch et al. reported a *no-reflow* incidence of 22%, despite a high thrombolysis rate of 68%.[215] We are not aware of any pre-clinical studie that has investigated this issue.

One might also argue that *no-reflow* may be common only in association with incomplete recanalization. Arsava et al. retrospectively evaluated the presence of contrast stasis and absence of capillary blush, taken to indicate microcirculatory obstructions, on angiograms obtained during endovascular treatment for acute MCA occlusion, by injection into the distal site of occlusive thrombi prior to stent-retriever deployment.[231] All seven out of 34 patients (21%) found to have this pattern subsequently had incomplete (i.e., <TICI 2b–3) recanalization. Accordingly, these authors speculate that impaired microcirculatory flow could impact recanalization *per se*, and that patent flow in microcirculation downstream of an occlusion would be crucial for obtaining and sustaining proximal patency. However post-thrombectomy perfusion status was not assessed in these patients, and the above pattern was not seen in patients who fully recanalized, making these observations of unclear relevance to the *no-reflow* phenomenon *per se*.

Our study has limitations. The relatively small sample size and retrospective design make this study hypothesis-generating, and its findings will need to be confirmed in larger prospective cohorts. However, it is the first to assess *no-reflow* using a true perfusion imaging technique and stringent operational criteria, and the data were extracted from a large prospective database. Although some mothership patients with TICI 2c/3 recanalization did not have ASL

on follow-up imaging, their general characteristics were similar to those of the included patients. As *no-reflow* was evaluated only in ASPECTS regions, we cannot rule out that it may have been present in other regions and outside the two ASPECTS axial planes. Finally, our results are only applicable to mothership patients with thrombectomy-treated intracranial ICA or proximal MCA occlusions.

E-I-VI Conclusion

This retrospective clinical study of the *no-reflow* phenomenon, the first to apply a stringent operational definition to evaluate recanalization by means of DSA and to assess true tissue perfusion, provided evidence that, in patients with proximal arterial occlusion who enjoyed early, complete and stable post-thrombectomy recanalization, the *no-reflow* phenomenon appears a rare event. In turn, it may not contribute substantially to the frequently observed poor outcomes despite successful early recanalization, and hence does not stand as an important therapeutic target. These findings will need replication in larger, prospective cohorts.

E-II L’hémorragie intra-crânienne symptomatique

L’hémorragie intra-crânienne symptomatique (HICs) est une complication redoutée après traitement de recanalisation d’un accident vasculaire ischémique. L’HICs est associée à un mauvais pronostic fonctionnelle et une mortalité élevée[232] et identifiée dans notre première étude sur la cohorte MR-CLEAN comme un des prédicteurs les plus puissants de mauvais pronostic après recanalisation réussie.

La survenue d’une HICs reste un événement rare (entre 2 et 8% selon les définitions), dont l’incidence survient à 24-48h de la survenue de l’AVCi. Plusieurs facteurs ont été déjà identifiés comme fortement corrélés à la survenue d’une HICs, en particulier un gros volume d’AVC, une pression artérielle systolique élevée et non contrôlée, une hyperglycémie, ces deux derniers facteurs pouvant amener à une correction rapide, après découverte de l’AVC et avant l’apparition de l’HICs. L’identification de biomarqueurs en imagerie, plus fins que le simple volume de tissu infarci, permettrait de déployer des thérapeutiques de prévention plus aggressives.

Dans ce contexte nous avons choisi d’étudier un biomarqueur d’imagerie récemment décrit en lien avec la survenue d’un HICs : l’opacifation veineuse précoce, visualisée pendant le geste thrombectomie après obtention d’une recanalisation complète. Nos objectifs étaient de :

- préciser si les différents phénotypes de l’opacification veineuse précoce après thrombectomie avaient une corrélation avec la survenue d’une HICs. **(Étude N°7)**

- développer un score clinique intégrant l’opacification veineuse précoce pour améliorer la prédiction de l’HICs. **(Étude N°8)**

E-II-I Relation entre opacification veineuse précoce et hémorragie intra-crânienne

Pour ce travail numéro VII, les données de l'essai randomisé français THRACE et du registre prospectif de Sainte-Anne ont été poolées, permettant d'évaluer les différents phénotypes de ce nouveau signe d'imagerie chez plus de 460 patients.

Early Venous Filling Patterns after Endovascular Ischemic Stroke Treatment Predict Reperfusion Hemorrhage. *(En Révision)*

Mohamed AlOtaibi*, MD; Wagih Ben Hassen*,MD-MSc; Alice Le Berre, MD; Joseph Benzakoun, MD-MSc; Grégoire Boulouis, MD-MSc; Basile Kerleroux, MD-MSc; Frédéric Clarencon, MD-PhD; François Lun, MD; Christine Rodriguez-Regent, MD-MSc; Olivier Heinzlef, MD; Wassim Farhat, MD; Guillaume Turc, MD-PhD; Pierre Seners MD-PhD; Catherine Oppenheim, MD-PhD; Serge Bracard, MD-PhD; Jean-Claude Baron, MD-PhD; Olivier Naggara, MD-PhD

E-II-I-1 Résumé Étude N°7

Une opacification veineuse précoce sur l'angiographie après recanalisation est corrélée à un risque plus élevé d'hémorragie post-reperfusion. Nous avons cherché à décrire les différents types d'opacification veineuse précoce et leur relation avec la transformation hémorragique. Les données proviennent de l'essai randomisé THRACE et d'un registre prospectif multicentrique de patients consécutifs atteints d'un AVC par occlusion artérielle proximale traités par thrombectomie mécanique et ayant obtenu une recanalisation réussie. Les caractéristiques cliniques et d'imagerie ont été extraites, y compris la transformation hémorragique, classée selon ECASSII sur l'imagerie post-traitement et l'opacification veineuse précoce, définie comme un remplissage d'une veine cérébrale avant la phase artérielle tardive après opacification sélective de la carotide interne initialement occluse. Les différents modes de présentation de l'opacification veineuse précoce ont été classés en fonction de leur localisation anatomique (système veineux superficiel, profond ou mixte) et de leur nombre (unique ou multiple). Les associations statistiques entre les différents types d'opacification veineuse précoce et le type de transformation hémorragique ont été testées. Sur 462 patients (54,1% de sexe masculin, âge moyen 68,3±15,9 ans), 127 (27,5%) avaient une opacification veineuse précoce, 73 (15,8%) ont développé une transformation hémorragique parenchymateuse (PH) dont 16 (3,5%) une hémorragie intracrânienne symptomatique. La présence d'une opacification veineuse précoce était un facteur prédictif indépendant d'une transformation hémorragique de type PH lors de l'analyse multivariable (OR ajusté = 4,07 [1,96-8,46], P<10-4). Les types de localisation profonde et multiples étaient associés à un risque de PH cinq et sept fois plus élevé, respectivement, et à des valeurs de spécificité et de prédiction négative accrues de la prédiction de PH (toutes deux ≥0,90). Les modèles

d'opacification veineuses multiples et profonds sont hautement prédictifs d'une hémorragie de reperfusion ultérieure de type PH, avec une spécificité et des valeurs prédictives négatives accrues par rapport à un critère unique de présence d'une opcafication veineuse précoce.

Les résultats de ce travail sont :

- L'identification de l'existence de plusieurs phénotypes d'opacification veineuse précoce (unique ou multiple, superficiel, profond ou mixte)

- La présence de ce signe chez plus d'un quart des patients, avec une excellente reproductibilité dans son identification

- Une forte valeur prédictive négative de ce signe

E-II-I-1 Introduction

Restitution of adequate cerebral perfusion is the primary target of mechanical thrombectomy (MT) in patients with acute ischemic stroke due to large vessel occlusion (AIS-LVO), as it reduces the odds of poor outcome by hindering brain damage extension.[232] However, despite successful mechanical reperfusion achieved in >80% (modified Thrombolysis in Cerebral Infarction score [mTICI] 2b-3), less than half of AIS-LVO patients achieve 3-month favorable outcome.[19,48] Recanalization may result in harmful reperfusion-mediated injury to the ischemic tissue, leading to parenchymal hemorrhage (PH), a potentially severe complication. The early detection of patients at high risk of PH after MT is an unmet need, to better adapt current therapeutic strategies and develop new approaches aimed to minimize PH risk.

Several risk factors for post-treatment PH have been identified, including intravenous thrombolysis (IVT), age, increased time to treatment, higher baseline National Institutes of Health Stroke Scale (NIHSS) score, high systolic blood pressure, high white matter hyperintensity burden, large ischemic core, severe hypoperfusion and blood-brain barrier disruption.[233–236]Additional imaging biomarkers derived from magnetic resonance imaging (MRI) or computed tomographic (CT) might also be of use but require advanced image post-processing that is not widely available.[237] An easily identifiable biomarker of post-reperfusion PH, immediately available after recanalization on Digital Subtraction Angiography (DSA) would therefore be of considerable use. Two previous studies have found the presence of an early venous filling (EVF) on DSA to be a marker of subsequent PH.[238,239] However, neither location (deep or superficial venous system), nor the number of visible EVFs were reported in these studies. In the present study, we aimed to investigate whether a specific EVF pattern (anatomical location or number) could enhance the prediction of hemorrhagic transformation occurrence.

E-II-I-2 Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Data was extracted from the THRombectomie des Artères CErebrales (THRACE; ClinicalTrials.gov, number NCT01062698), a randomized controlled trial with 26 recruiting centers in France,[18] and from a prospective multicentric registry including all consecutive AIS-LVO patients treated by MT between January 2015 and 2019 in a large comprehensive stroke center. Written informed consent was obtained from all patients or their legal representatives in the THRACE trial after approval of the CPP (Comité de Protection des Personnes) III Nord-Est Ethics Committee. Prospective registry was held in accordance with local ethic committee

approval (CNIL-MR004) and patients were informed they could oppose the use of their routine clinical care data for research purposes. This manuscript was prepared according to the Standards for Reporting Diagnostic accuracy studies (STARD) statement.[240]

Specific inclusion criteria for both THRACE trial and prospective registry for this study were: 1/ anterior circulation AIS-LVO treated by MT for internal carotid artery (ICA) and/or M1 occlusion or tandem occlusions; 2/ mTICI score 2b-3; 3/ follow-up brain CT or MRI obtained within 3 days after MT. Clinical and demographic data, admission NIHSS score, occlusion site, IVT, and time metrics were prospectively recorded. Favorable outcome was defined as modified Rankin Scale (mRS) ≤2 at 90-days.

Imaging

Parenchymal hemorrhage identification.

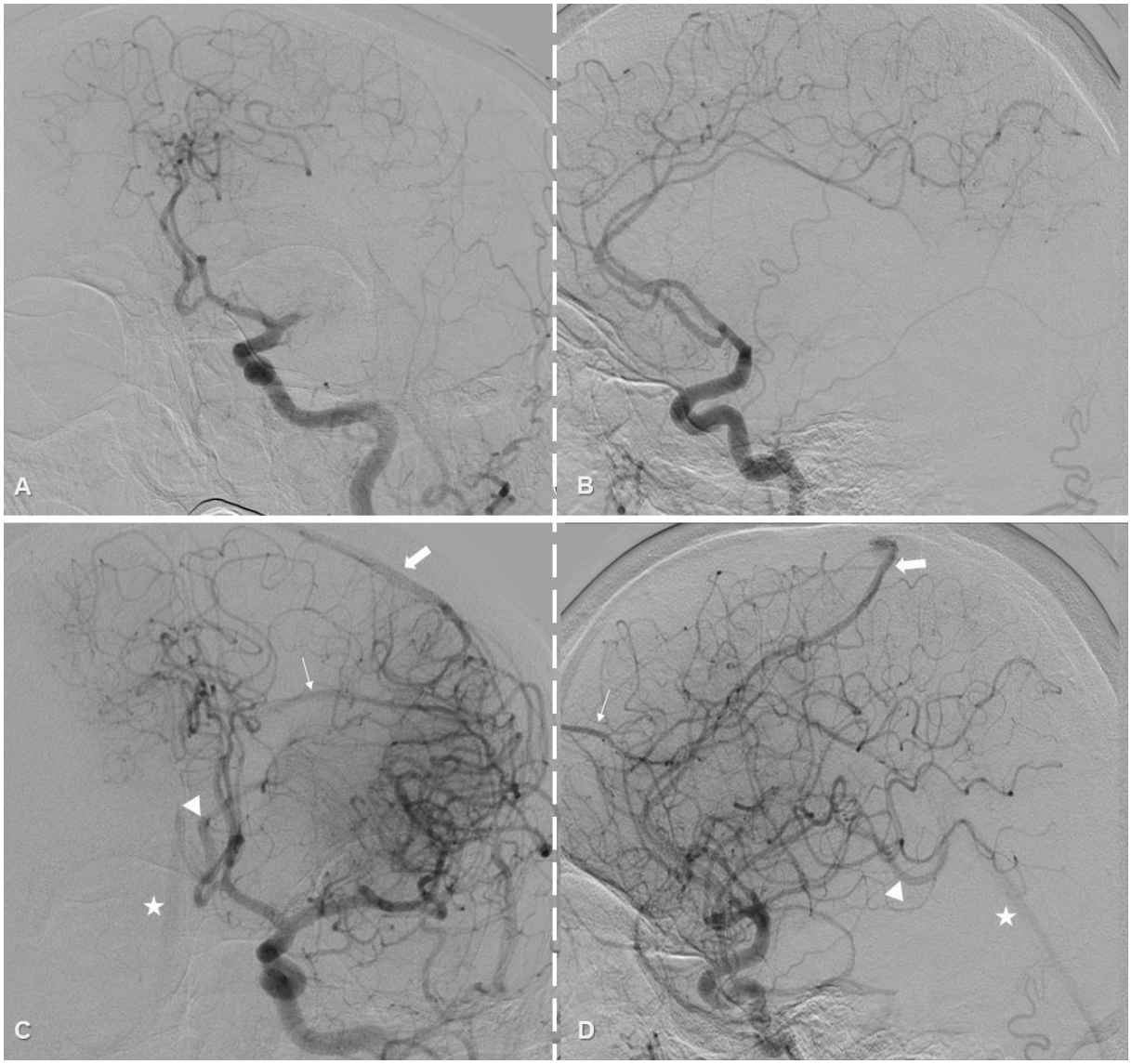
For the THRACE trial, the CT and MRI images were reviewed by an independent core lab of four experienced neuroradiologists blinded to any clinical data. In the prospective registry, all exams were reviewed by two additional senior neuroradiologists blinded to clinical info and outcome. The presence of prior intracranial hemorrhage (ICH) was determined on admission CT or MRI examination, the latter defines as showing blooming artifact within the brain parenchyma >5 mm diameter. Punctate foci of blooming artifact were not considered to represent clinically important prior ICH. Reperfusion hemorrhage was noted on imaging performed within 72hrs post-treatment and graded as HI1, HI2, PH1, or PH2 as per the ECASS II criteria.[241] In case of both CT and MRI being available following EVT, the presence of ICH was scored from the MRI given the superior sensitivity of gradient-echo MRI. Hemorrhagic infarction 1 (HI1) was defined as small petechiae along the margins of the infarct; hemorrhagic infarction 2 (HI2) as confluent petechiae within the infarcted area but no space occupying effect; parenchymal hematoma 1 (PH1) as involving ≤30% of the infarcted area with mild space-occupying effect; and parenchymal hematoma 2 (PH2) as involving >30% of the infarcted area with substantial space-occupying effect. Symptomatic intra-cerebral haemorrhage (sICH) was defined using The ECASS II[241] definition as any hemorrhage with neurological deterioration, as indicated by an NIHSS score higher by ≥4 points than the value at baseline or the lowest value before worsening. Patients without PH (i.e., with either no HI or with HI1/HI2) were labelled PH-.

Early venous opacification identification.

Both THRACE trial and prospective registry cases were reviewed by 2 experienced independent interventional neuroradiologists (7 and 15 years' experience) blinded to all patients' clinical outcome and other imaging data. Readers consensually reviewed the per procedure angiograms before and after mechanical thrombectomy and provided a consensus

evaluation regarding thrombus location on the pre-treatment angiogram and assessed final eTICI and EVF on post-treatment angiogram. EVF was evaluated on the post recanalization angiogram (anterior and lateral views) with selective contrast injection in the ICA. Readers were blinded to any clinical or radiological outcome. EVF was defined an early opacification of a cerebral vein concomitant to the arterial or capillary phase **(Figure E-II-I-1)**. EVF patterns were categorized depending on : i) anatomical venous territory: Superficial in case of early filling of a cortical vein, Deep in case of early filling of internal cerebral vein, basal vein of Rosenthal and/or their tributaries, or Mixed in case of early filling of both superficial and deep veins, and ii) number of veins with early filling **(Figure E-II-I -1)**.

Figure E-II-I-1: Illustration of Early Venous Filling (EVF) patterns categorization
Frontal (A) and Lateral (B) views on left internal carotid opacification showing a proximal M1 occlusion. Post Mechanical Thrombectomy frontal (C) and lateral (D) views angiograms showing multiple EVF, with a mixed venous drainage (both superficial and deep venous territory): early filling at the capillary phase of superficial cortical veins (Bold Arrows: Trolard cortical vein, Thin Arrows: Frontal cortical vein) and deep venous system (Arrowhead: internal cerebral vein, Star: straight sinus).



Statistical Analysis

Baseline variables, procedural variables and clinical outcome were compared between the PH+ and PH- cohorts. Variables were described as absolute number (percentage) for discrete variables and mean (Standard Deviation) or median and interquartile range [IQR] as appropriate. Chi-square, Fisher exact, Student's t-test, and Mann-Whitney tests were used as appropriate for the univariate analyses, with a two-tailed p-value <0.05 as the threshold for statistical significance. All variables with P<0.1 association in the univariable analyses were

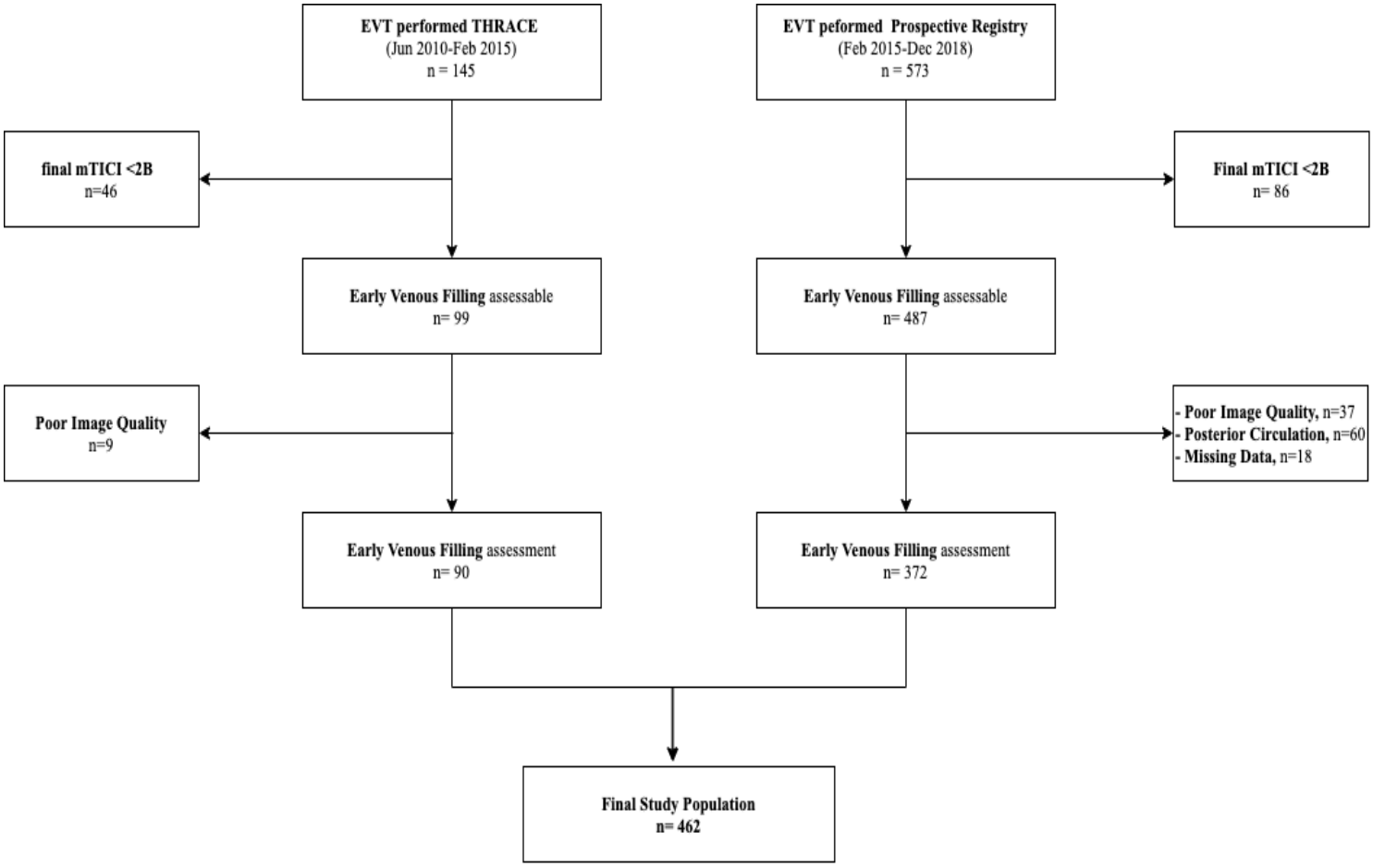
used into a multivariable analysis using binary logistic regression models to assess the demographic, clinical, and angiographic predictors of PH. To investigate the power of EVF in predicting symptomatic PH, we computed Sensitivity, Specificity, Positive (PPV), Negative Predictive value (NPV) and accuracy. Statistical analysis was performed using SPSS (SPSS V24, IBM, Chicago, IL).

E-II-I-3 Results

Population

A total of 462 patients (54.1% male sex, mean age 68.3±15.9 years) were included (**Flow-Chart in Figure E-II-I-2**).

Figure E-II-I-2 : Flowchart of study population



Baseline characteristics of study population and its stratification per PH status are summarized in **Table E-II-I-1**.

Table E-II-I-1: Predictors and outcome of post-reperfusion hemorrhage

	PH- (%)	**PH+ (%)**	***Univariable P value***	***Multivariable odd-ratio (95% CI)***	***Multivariable P value***
N of patients (n=462)	389 (84.2)	73 (15.8)	_		
THRACE (n=90)	77 (85.5)	13 (14.5)	_		
Characteristics					
Male	206 (53.0)	44 (60.3)	0.31	_	
Age, mean (SD), years	68.0 (15.9)	69.6 (16.0)	0.46	_	
Risk factors					
Hypertension	194 (49.9)	38 (52.0)	0.80	_	
Current smoking	70 (18.0)	16 (21.9)	0.42	_	
Dyslipidemia	114 (29.3)	19 (26.0)	0.67	_	
Diabetes mellitus	44 (11.3)	6 (8.2)	0.54	_	
Antiplatelet or Anticoagulation	139 (35.7)	38 (52.1)	**0.018**	2.4 (0.94-6.38)	0.068
Baseline blood glucose, mean (SD)	6.6 (2.4)	7.0 (2.1)	0.24	_	
Baseline NIHSS*, median [IQR]	16 [12-21]	18 [14-22]	**0.004**	1.03 (0.95-1.13)	0.49
<8	44 (11.3)	2 (2.7)	_		
8-15	110 (28.3)	18 (24.7)	_		
>15	235 (60.4)	53 (72.6)	_		
Treatment with IV-tPA	277 (71.2)	51 (69.6)	0.67	_	
Workflow, median [IQR], min					
Onset-to-Imaging	121.1 [85-150]	124.5 [89-144]	0.70	_	
Onset-to-IV-tPA	154 [112-179]	147.3 [116-178]	0.81	_	
Onset-to-groin puncture†	208 [161-250]	231.5 [186-283]	**0.06**	1.004 (0.99-1.01)	0.14
Onset-to-recanalization	260 [205-310]	281 [233-338]	0.65	_	
Imaging					
EVF	87 (22.3)	40 (54.8)	**$<10^{-4}$**	3.65 (1.57-8.52)	**0.003**
DWI-ASPECTS*, median [IQR]	7 [5-8]	6 [3-7]	**$<10^{-4}$**	0.73 (0.61-088)	**0.001**
Thrombus location					
M1	322 (82.8)	52 (71.2)	_	_	
ICA±M1	67 (17.2)	21 (28.8)	**0.033**	1.8 (0.7-4.68)	0.22
Post treatment imaging modality (MRI)	170 (43.7)	29 (39.7)	0.73	_	
Outcome					
3-months mRS ≤ 2	173 (44.5)	14 (19.2)	**$<10^{-4}$**	NA	
Death	38 (9.8)	28 (38.4)	**$<10^{-4}$**	NA	

*PH= Parenchymal Hematoma type 1 (PH1) or 2 (PH2) on 24H MRI; NIHSS=National Institutes of Health Stroke Scale; IV-tPA= intravenous tissue plasminogen activator; EVF=Early Venous opacification; DWI-ASPECTS=Diffusion-Weighted Imaging Alberta Stroke Program Early CT Score; mRS=modified Rankin Scale; ICA=Internal Carotid Artery; M1: First segment of Middle-Cerebral Artery. * Continuous variable, Per 1-point increase. † Continuous variable, per 1-minute increase. Variables with p<0.1 significance in univariable analysis were included in multivariable analysis.*

Reperfusion hemorrhage

Of the 462 patients, 198 (42.9%) developed post-reperfusion hemorrhage, including HI (n=125; 27.1%) and PH (PH+ group, n=73; 15.8%). Symptomatic intra-cranial hemorrhage (sICH) was encountered in 16 patients (3.5%). Outcome was significantly worse in PH+ patients relative to PH- patients, both for 3-month mRS≤2 (19.2% vs 44.5%; $P<10^{-4}$) and mortality (38.4% vs 9.8%; $P<10^{-4}$).

EVF was more frequent in PH+ (40/73, 54.8%) than in PH- patients (87/389, 22.3%; $P<10^{-4}$). PH+ patients had higher prevalence of prior anti-aggregant or anticoagulant treatment, higher initial NIHSS, longer onset-to-arterial puncture delay, higher ICA+/- M1 occlusion and lower initial ASPECTS score (P≤0.004 for all, **Table E-II-I-1**). In multivariable analysis, EVF was independently associated with PH+ (adjusted OR=4.07 [1.96-8.46], $P<10^{-4}$].

In univariable analysis, sICH was associated with onset-to-arterial puncture and onset-to--recanalization delays, EVF, intracranial carotid occlusion and lower initial ASPECTS score. In multivariable analysis, low ASPECT and EVF were significant predictors of subsequent sICH. (**Table E-II-I-2**).

Table E-II-I-2. Analysis of symptomatic Intra-Cranial Hemorrhage (sICH) Predictors and outcome

	Non-Symptomatic ICH (%)	sICH (%)	*Univariable P value*	Multivariable Odd-Ratio (95%CI)	*Multivariable P value*
No. of patients	446(96.5)	16(3.5)	_		
No. of THRACE patients	88 (97.8)	2(2.2)	_		
Characteristics					
Male	242(96.8)	8(3.2)	0.80		_
Age, mean (SD), years	68.3(15.9)	66.9(16.0)	0.78		_
Risk factors					
Hypertension	227 (52)	5(31.2)	0.13		_
Current smoker	80(18.0)	6(37.5)	0.21		_
Dyslipidemia	130(29.1)	3 (18.8)	0.57		_
Diabetes mellitus	49(11.0)	1(6.3)	0.98		_
Prior stroke	53(11.9)	0(0)	0.24		_
Antiplatelet or anticoagulation	169(37.9)	8(50.0)	0.43		_
Baseline Glycemia, mean (SD)	6.7(2.3)	7.1(1.9)	0.42		_
Baseline NIHSS, median [IQR]	17(12-21)	17(10.8-20.5)	0.82		_
<8	45	1	_		
8-15	123	5	_		
>15	278	10	_		
Treatment with IV-tPA	319(71.5)	9(56.2)	0.14		_
Workflow, median [IQR], min					
Onset-to-Imaging	109.5(85-147)	167(102-223)	**0.02**	1.01 (0.99-1.03)	0.24
Onset-to-IV-tPA	140(113-178)	189(127-241)	0.19		_
Onset-to-groin puncture*	202.5(75-250)	267.5(188-324)	**0.015**	_	_
Onset-to-recanalization	255(206-313)	309(257-369)	**0.019**	1.004 (0.98-1.02)	0.6
Imaging					
EVF	117(26.2)	10(62.5)	**0.003**	7.42 (1.11-49.6)	**0.039**
DWI-ASPECTS, median [IQR]	7(5-8)	5.5(1-6.5)	**0.004**	0.59 (0.41-0.84)	**0.004**
Thrombus location*					
M1	368(82.8)	6(37.5)	_		_
ICA±M1	78 (17.2)	10(62.5)	**0.038**	2.17 (0.36-13.1)	0.39
Post treatment imaging modality (MRI)	176(43.7)	3(39.7)	0.12		_
Outcome					
3-months mRS ≤ 2	186(41.7)	1(6.3)	**<0.0001**		NA
Death	59(13.2)	7(43.8)	**0.011**		NA

sICH: ECASII definition as any hemorrhage with an increase ≥4 points in NIHSS score more than the value at baseline or the lowest value before worsening; NIHSS=National Institutes of Health Stroke Scale; IV-tPA= intravenous tissue plasminogen activator; EVF=Early Venous Shunting; DWI-ASPECTS=Diffusion-Weighted Imaging Alberta Stroke Program Early CT Score; mRs=modified Rankin Scale; ICA=Internal Carotid Artery; M1: First segment of Middle Cerebral Artery. All variables with P<0.1 association in the univariable analyses were used into a multivariable analysis using binary logistic regression.: Onset to groin puncture was not entered in the multivariable analysis due to a high collinearity with onset to recanalization variable.*

Early venous filling prevalence, location and number

EVF was present (EVF+) in 127/462 (27.5%) patients, with a strong inter-readers agreement (κ=0.89). Superficial location was found in 83 (65.3%) of EVF+ patients, deep in 67 (52.7%) and mixed in 30 (23.6%) patients **(Table E-II-I-3).** EVF+ was significantly associated with PH+, for all EVF patterns (**Table E-II-I-3**). Multiple EVF and deep location were associated with highest risk of PH+ (Adjusted OR = 7.08 [2.9-17.3] and 5.01 [2-12.3]; $P<10^{-4}$ respectively) **(Table E-II-I-3)**.

Table E-II-I-3: Early venous opacification presence, location and number distribution and prediction of Parenchymal Hemorrhage

	All	PH- (%) **N=389**	PH+ (%) **N=73**	OR (95%CI)	*P* value	*Adjusted OR (95% CI)*	*P* value
Presence of EVF	127	87(22.4)	40(54.8)	4.21 (2.50-7.07)	$<10^{-4}$	4.07 (1.96-8.5)	$<10^{-4}$
EVF Location:							
Any Deep	67/127 (52.7%)	40 (10.3)	27 (37)	5.12 (2.9-9.1)	$<10^{-4}$	5.01 (2-12.3)	$<10^{-4}$
Any Superficial	83/127(65.3%)	56 (14.4)	27 (37)	3.49 (2-6.07)	$<10^{-4}$	2.96 (1.32-6.7)	0.01
Mixed	30/127 (23.6%)	16 (4.1)	14 (19.2)	5.5 (2.5-11.9)	$<10^{-4}$	3.5 (1.02-12.4)	0.04
EVF Number							
Multiple	56/127 (44.1%)	25 (6.4)	31(42.5)	9.16 (5-16.7)	$<10^{-4}$	7.08 (2.9-17.3)	$<10^{-4}$
Unique	71/127 (55.9%)	62 (15.9)	9 (12.3)	ref	_	_	

EVF=Early Venous Filling; Mixed: Deep+Superficial; PH=Parenchymal Hemorrhage; OR= Univariable binary logistic regression Odds Ratio of parenchymal hemorrhage. Adjusted OR: Multivariable model analysis, adjustment for prior anti-aggregant or anticoagulant treatment, initial NIHSS, onset-to-arterial puncture delay (min), iV-tPA and initial ASPECTS.

The sensitivity, specificity, PPV, NPV and accuracy of any EVF to predict PH+ was 54.8% (43.4-66.2), 77.6% (73.5-81.8), 0.32, 0.90 and 0.74, respectively. Higher specificity was seen in case of multiple EVF (92.4%[89.5-95.2]) and deep location (90%[86.9-92.7])**(Table E-II-I-4)**.

Table E-II-I-4: Early Venous Filling patterns diagnostic accuracy for Parenchymal Hemorrhagic prediction (PH)

	Sensitivity	*Specificity*	*PPV*	*NPV*	*Accuracy*
Any EVF	54.8(43.4-66.2)	77.6(73.5-81.8)	0.32	0.90	0.74
Mixed location EVF	30.0(16.7-42.9)	95.0(92.6-97.4)	0.47	0.90	0.87
Any Deep EVF	45.0(32.4-57.6)	90 (86.9-92.7)	0.40	0.90	0.88
Any superficial	45.0(32.4-57.6)	84.4(80.6-88.1)	0.33	0.90	0.79
Multiple EVF	48.4(36.2-60.7)	92.4(89.5-95.2)	0.55	0.90	0.85

PPV: Positive Predictive Value; NPV: Negative Predictive Value

E-II-I-4 Discussion

The present study confirmed the association between EVF present on DSA after successful MT (mTICI 2B or 3) for AIS-LVO and PH-type reperfusion hemorrhage. EVF was present in 27.5% of the population, similar to previously reported rates.[238,239] A novel finding of this study is the definition of EVF patterns immediately available on post-recanalization DSA. EVF number and deep location (early filling of deep venous system) patterns were the strongest predictors of PH+. Thus, taking EVFs patterns in consideration enhanced PH+ prediction accuracy, with specificity and NPV consistently ≥0.90. EVF presence and pattern are therefore important imaging biomarkers, reproducible between different readers, with potential therapeutic implications. For instance, EVF presence, particularly deep location or multiplicity, suggests that additional intra-arterial infusion of thrombolytic agents, which is considered reasonable as a salvage adjunct to achieve mTICI 2b/3,[242] may be detrimental. Although the optimal blood pressure target during and after MT is still unclear, the presence of EVF would suggest a strict blood pressure control is in order to prevent PH. As an illustration, in Ohta et al study,[238] of 7 patients with failure to strictly control blood pressure, all 4 patients who had EVF died as a result of massive intracerebral hematoma, while the remaining 3 patients without EVF did not develop PH. The loss of local cerebrovascular autoregulation in acutely reperfused tissue; compounded by wide fluctuations in systemic blood pressure; would make EVF+ patients at

high risk of PH. The findings from the present study also have implications regarding antiplatelet therapy initiation or anticoagulation continuation after recanalization. Biomarkers with high specificity and NPV for PH would help to characterize PH risk, in concert with other risk factors for PH such as low initial DWI-ASPECTS, or poor collateral status.[235]

The mechanistic relationship between EVF and PH is however not completely clear. EVF is widely considered to reflect an acute elevation in regional cerebral blood flow and blood volume (i.e., true "hyperemia") due to vasoplegia,[243,244] i.e., lack of vasoconstriction upon re-establishment of normal cerebral perfusion pressure - also called the "luxury perfusion syndrome"- rather than the existence of true arteriovenous shunting.[245] Impaired cerebrovascular autoregulation is probably caused by ischemia-induced endothelial dysfunction, which can also contribute to the development of PH via blood-brain barrier disruption and extravasation.[246] Accordingly, the presence of EVF could point to brain tissue at risk of bleeding.

Our study has several limitations. The retrospective design exposes to confounding effects. Missing variables, such as precise post EVT blood pressure time-course, may influence PH risk. It is also unknown whether the exact time onset of EVF occurrence during the MT procedure influences the development of PH.

In conclusion, identification of EVF patterns, and particularly of multiple or deep location patterns, upon completion of MT implies a high risk of reperfusion-related PH. In such case, blood pressure control should be discussed, and any ongoing intra-arterial fibrinolysis should probably be discontinued. More generally, knowledge regarding presence of EVF may be important to determine optimal blood pressure targets after thrombectomy. Conversely, the absence of EVF has a strong negative predictive value, pointing to a reduced risk of PH.

La localisation profonde et le nombre de veines opacifiées précocement après succès de recanalisation sont fortement associés à une transformation hémorragique parenchymateuse à 24h. Si ce signe d'imagerie a une forte valeur prédictive négative, il est également important de signaler sa présence pour alerter sur le risque de survenue d'une hémorragie symptomatique et adapter la thérapeutique, la surveillance et les objectifs tensionnels en post procédure.

E-II-II Prédiction de l'hémorragie intra-crânienne symptomatique après succès de recanalisation par thrombectomie mécanique

Dans les suites du travail précédent, montrant le lien fort entre opacification veineuse précoce constaté après recanalisation d'une occlusion artérielle proximale, nous avons souhaité élaborer un score prédictif d'HICs incluant ce biomarqueur d'imagerie.

TAGE Score for Symptomatic Intracranial Hemorrhage Prediction in Acute Ischemic Stroke treated by Mechanical Thrombectomy *(En soumission)*

Paul Janvier, Basile Kerleroux, Guillaume Turc, Marco Pasi, Wassim Farhat, Nicolas Bricout, Joseph Benzakoun, Laurence Legrand, Frédéric Clarençon, Serge Bracard, Catherine Oppenheim, Grégoire Boulouis, Hilde Henon, Olivier Naggara*, Wagih Ben Hassen*

E-II-II-1 Résumé Étude N°8

Un score prédictif de l'hémorragie symptomatique a été développé sur deux cohortes une de dérivation (Issue du registre prospectif Sainte Anne) et une deuxième (Registre prospectif du CHU de Lille). Les données cliniques et radiologiques ont été collectées de façon prospective puis analysées de façon rétrospective. Un modèle multivarié a été utilisé sur la cohorte de dérivation afin d'établir le score prédictifs d'hémorragie intracrânienne symptomatique (HCIS), validé ensuite sur la cohorte de validation. Sur les 402 et 507 patients des cohortes de dérivation et de validation, nous avons observé une HICS chez 9.9% et 8.9% d'entre eux respectivement. Le temps jusqu'à la recanalisation > 270 min (OR 7.8, 95% IC 2.5-24), le score ASPECTS ≤5 (OR 2.49, 95% IC 1.8-8.1) ou de 6-7 (OR 1.15, 95% IC 1.03-4,46), la glycémie > 7 mmol/L (OR 2.92, 95% IC 1.26-6.7) et la présence d'une opacification veineuse précoce (OR 11.9, 95% IC 3.8-37.5) étaient des facteurs indépendants de risque d'HICS. Le score TAGE ainsi constitué était associé à un risque d'HICS dans la cohorte de dérivation (OR augmentation par une unité du score : 1.99, [1.53-2.59], p<0.001) avec une AUC=0.832, 95%CI [0.77-0.90] et dans la cohorte de validation avec une AUC= 0.801, 95%CI [0.69-0.91]. Le score TAGE obtenu est un score prédisant la survenue d'une transformation hémorragique symptomatique, développé et validé chez des patients recanalisés avec succès par thrombectomie mécanique pour un AVC aigu par occlusion des gros vaisseaux.

Les résultats de ce travail sont :

- La confirmation de l'opacification veinneuse précoce comme un marqueur de l'hémorragie symptomatique

- La constitution d'un score clinique simple (Temps jusqu'à recanalisatio, Aspect, Glycémie et Opacificationn veineuse précoce) prédictif de l'hémorragie symptomatique dans le groupe de patients bien recanalisés

- La validation de ce score sur une large cohorte externe.

E-II-II-2 Introduction

Symptomatic intra-cranial hemorrhage (sICH) after reperfusion therapy in acute ischemic stroke is an omnious event, correlated with poor functional outcome and high mortality.[247] Several risk factors of sICH for patients treated with modern mechanical thrombectomy (MT) were identified[248–251] and integrated into predictive scores (ASIAN[252], TAG[253], IER-SICH nomogram[254]). Early venous filling (EVF) is a new imaging biomarker which has been reported as a strong predictor of sICH after mechanical thrombectomy (MT)[238,239]. EVF can be detected after successful recanalization on digital subtraction angiography (DSA); consisting of an early opacification at the arterial phase of a cortical or deep vein[238]. This early filling is potentially linked to local capillary dysfunction in the infarcted area leading to focal hyperemia (also called luxury perfusion) and blood-brain barrier disruption[243,245], which contributes to the development of reperfusion hemorrhage[239,238,255]. No predictive score have yet integrated EVF for sICH prediction. The aim of our study was to determine in a large successfully recanalized population, if EVF was an independent predictor of sICH and derive a score for sICH prediction with an external validation on a population issued from a prospective registry and THRACE trial[256].

E-II-II-3 Methods

Participants and clinical assessments

Data were retrospectively extracted from two prospective registries including consecutive acute ischemic stroke with large vessel occlusion (AIS-LVO) treated by mechanical thrombectomy (MT) between January 2015 and December 2020. Derivation cohort was issued from a prospective registry from a first comprehensive stroke center (Center 1: Centre Hospitalier Sainte-Anne, Paris, France). Validation cohort was issued from a prospective registry from a second comprehensive stroke center (Center 2: Centre Hospitalo-Universitaire de Lille, France) and from the randomized therapeutic THRACE trial[256].

Inclusion criteria for all cases were: age ≥ 18, anterior circulation LVO treated by MT +/- Intravenous thrombolysis (IV-tPA) with successful recanalization defined by a final expanded treatment in cerebral ischemia (mTICI)≥2B; post reperfusion digital subtracted angiography (DSA) of sufficient quality for EVF assessment. Exclusion criteria were: no available control imaging (CT scan or MRI) or NIHSS evaluation at least 24h after MT.

Standard Protocol Approvals, Registrations, and Patient Consents

Data was extracted from prospective registries held after approval of national ethic committee (CNIL, MR004). Written informed consent was obtained from all patients or their legal representatives in the THRACE trial (THRACE; ClinicalTrials.gov, number NCT01062698) after approval of the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee. This manuscript was prepared according to the Standards for Reporting Diagnostic accuracy studies (STARD) statement[240].

Clinical and radiological outcomes assessment

Stroke severity was assessed at admission by trained vascular neurologists with the National Institutes of Health Stroke Scale (NIHSS) score (range 0-42, with higher scores indicating greater stroke severity). Clinical and biological variables such as age, gender, NIHSS, blood pressure, dyslipidemia, current smoking status, diabetes mellitus, pre-stroke modified Rankin Score, serum glucose level before treatment, administration of IV-tPA were extracted.

Symptomatic intracranial hemorrhage

Hemorrhagic transformation was evaluated on the 24h control imaging (CT-scan or MRI) and classified into 4 following subtypes according to ECASS[241] classification: HI-1: Hemorrhagic infarction small petechial hemorrhages, HI-2: Hemorrhagic infarction with confluent petechial hemorrhages. PH-1: Parenchymal hematoma < 30% of the infarcted area with minor mass effect attributable to the hematoma. PH-2: Parenchymal hematoma > 30% of the infarcted area with substantial mass effect attributable to the hematoma. The primary endpoint was sICH

defined by modified ECASS-II[241]: any intracranial hemorrhage on imaging control performed 24 hours after MT, associated with neurologic deterioration (increase of 4 points or more on NIHSS from baseline).

Early venous filling identification.

All digital subtraction angiography were reviewed by 2 independent experienced interventional neuroradiologists (7- [WBH] and 15-years' experience [ON]) blinded to all patients' clinical outcome and other imaging data. Readers provided a consensus evaluation regarding thrombus location on the pre-treatment angiogram and assessed final mTICI and EVF on post-treatment angiogram. EVF presence was assessed on the post recanalization angiogram, defined by an early opacification of a cerebral vein concomitant to the arterial or capillary phase as previously described[238].

Statistical Analysis

Score Derivation

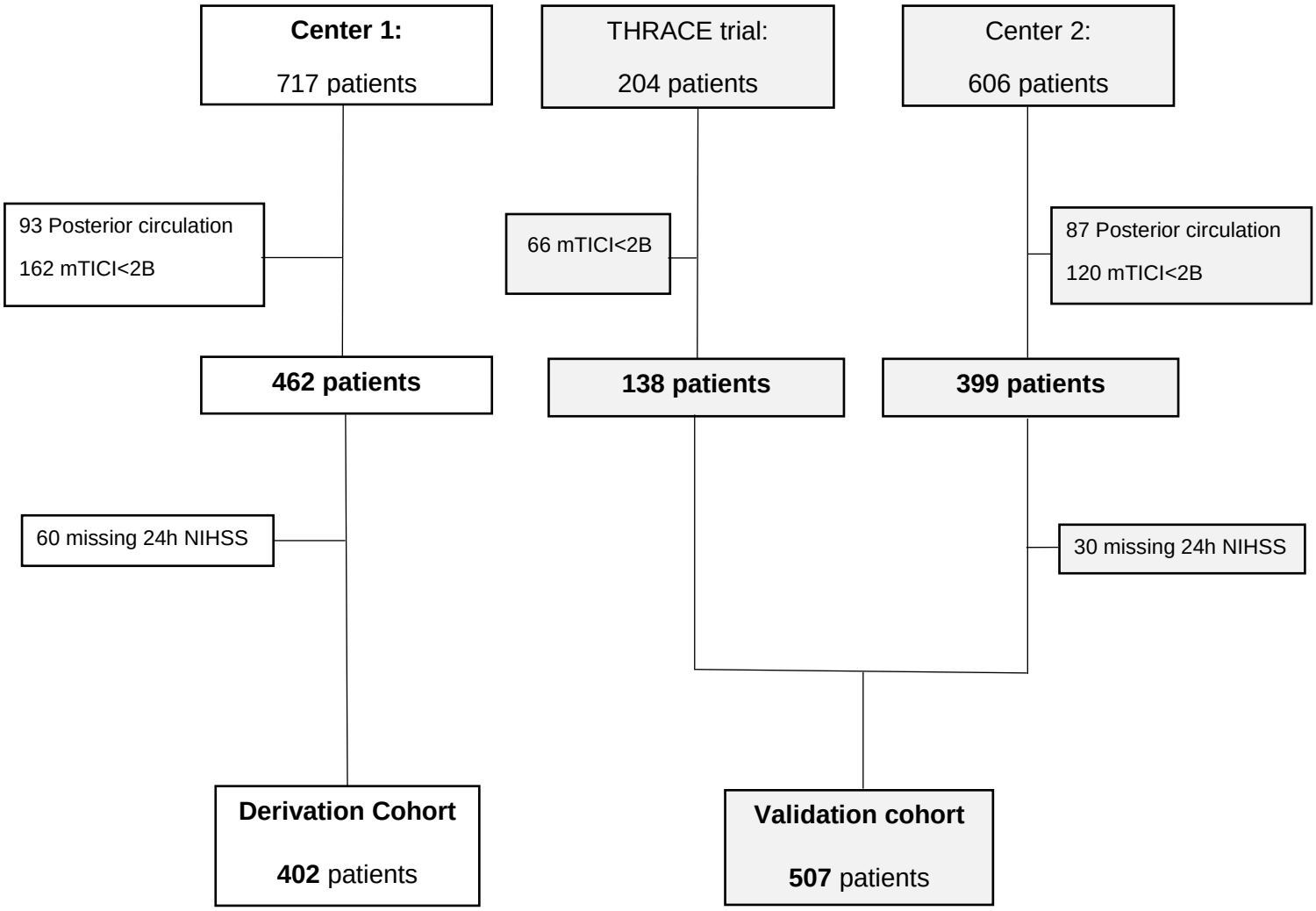
Continuous variables with a normal distribution were described as mean±SD and non-normally distributed variables were described as median and interquartile range. Univariable analysis was used to compare demographic, clinical and radiological factors between patients with and without sICH. Multivariable logistic regression was then performed with factors associated with sICH with p<0.1 in the univariate analysis. Continuous variables such as time from onset to successful reperfusion, ASPECTS and glycemia were categorized using previously defined cut-offs[253]. The scoring system was constructed by assigning points to the variables according to the value of the multivariable model regression coefficients: 1 point for regression coefficient >1 and ≤2, 2 points for variables with a *regression coefficient* > 2 and ≤3 and 3 points for variables with *a regression coeffecient*>3. Area under the receiver operating characteristic curve (ie, c-statistics) was calculated as a measure of predictive ability of the model. The calibration of the score for sICH prediction was assessed with Hosmer-Lemeshow test and a graphical plot. External validation was performed on population issued from center 2 and THRACE trial.

E-II-II-4 Results

Baseline characteristics

Four hundred and two patients (Center 1) were included in the derivation cohort and 507 patients (138 from THRACE trial and 369 from Center 2) in the validation cohort *(***Figure E-II-II-1***).*

Figure E-II-II-1: Flowchart of study population



Baseline characteristics of derivation and validation groups are presented in **Table E-II-II-1.** When compared to the derivation cohort, patients of the validation group had higher rates of hypertension, active smoking, prior anticoagulant treatment and dyslipidemia, lower rates of treatment with IV-tPA, pre-stroke mRS>1, M2 thrombus location and longer onset-to-IV-tPA delay. The rate of sICH was similar between the derivation and validation groups (8.9 % versus 9.9% respectively, p=0,9). Favorable outcome (90-days mRS≤2) was similar between derivation and validation groups (47.3 % versus 45.3 % respectively, p=0.47) *(***Table E-II-II-1***)*.

Table E-II-II-1: Baseline characteristics Derivation and Validation cohorts

	Derivation cohort (n=402)	Validation cohort (n=507)	P value
Male gender (%)	207 (51.5)	262 (51.7)	0.78
Age, mean±SD, years	71±16	67±16	0.19
Baseline NIHSS, median [IQR]	16 [16 – 17]	17 [17 – 18]	0.65
Comorbidities and risk factors (%)			
Hypertension	215 (53.5)	317 (62.5)	**0.002**
Current smoke	64 (16)	189 (37.3)	**10^{-4}**
Dyslipidemia	112 (27.9)	211 (41.6)	**10^{-4}**
Diabetes mellitus	55 (13.9)	72 (14.2)	0.8
mRS pre-stroke >1	25 (6.2)	66 (13)	**<10^{-4}**
Antiplatelet therapy* (%)	116/389 (29.8)	158/465 (34)	0.11
Anticoagulation therapy* (%)	46/389 (11.8)	98/465 (21)	**3.10^{-4}**
Serum glucose level, mean±SD, mmol/L	6.87±2.45	7.2±2.47	0.22
Imaging			
ASPECTS, median [IQR]	7 [7 – 8]	7 [6 – 8]	0.78
Thrombus location (%)			
ICA termination +/- M1	123 (30.6)	174 (34.3)	0.17
M1	211 (52.5)	304 (60)	0.01
M2	68 (16.9)	29 (5.7)	**10^{-4}**
Collateral status (ASITN)*			
Poor (%)	185/300 (61.7)	157/280 (56)	0.16
Good (%)	115/300 (38.3)	123/280 (44)	0.16
Treatment with IV-tPA (%)	316 (78.6)	334 (65.9)	**10^{-4}**
Workflow duration, min, median [IQR]			
Onset-to-imaging	111 [105-120]	125 [108-144]	0.2
Onset-to-IV-tPA	130 [120-140]	150 [137-163]	**0.04**
Onset-to-groin puncture	221 [210-240]	225 [218-236]	0.32
Onset-to-reperfusion	280 [260-300]	294 [281-307]	0.4
Outcome			
sICH (%)	40 (9.9)	45 (8.9)	0.9
Hemorrhagic Transformation (ECASS) (%)			
0	207 (51.5)	278 (54.8)	0.27
HI 1	43 (10.7)	63 (12.4)	0.34
HI 2	64 (16)	98 (19.4)	0.14
PH 1	50 (12.4)	39 (7.7)	**0.006**
PH 2	38 (9.4)	29 (5.7)	**0.02**
Good functional outcome* (mRS≤2)	183/387 (47.3)	211/466 (45.3)	0.47

Values are numbers (percentages), unless stated otherwise

SD=Standard derivation; NIHSS=National Institutes of Health Stroke Scale; IQR=Interquartile range; ASPECTS= Alberta Stroke Program Early Computed Tomography Score; ICA=internal carotid artery; M1=proximal segment of the middle cerebral artery; M2: second segments of middle cerebral artery; Collateral status according to ASITN: Poor 0-1-2 categories, good: 3 or 4 categories; IV-tPA=intravenous tissue plasminogen activator; sICH: symptomatic intra-cerebral hemorrhage (ECASS II); ECASS: European-Australian Cooperative Acute Stroke Study; HI: hemorrhagic infarction; PH: parenchymal hematoma; mRS=modified Rankin Scale. * : missing data

Predictors of sICH

sICH was present in 40 patients (9.9%) in the derivation cohort. In univariate analysis, factors associated with sICH compared to no sICH group were EVF presence (72.5% versus 32.3% respectively, $p<10^{-4}$), admission glucose level (mean 7.74 versus 6.74mmol/L respectively; *P*=0.03), ASPECT score (median, 5 versus 7 respectively; *P*=0.003), onset-to-imaging (median, 161 versus 109 minutes; *P*=0.001), onset-to-groin puncture (median, 270 versus 204 minutes; *P*=0.02), onset-to-successful recanalization (median, 319 versus 247 minutes; *P*=0.004) *(***Table E-II-II-2***).*

Table E-II-II-2: Univariable comparison between sICH and no sICH groups in the derivation Cohort

	sICH (n=40)	**No sICH (n=362)**	**P value**
Male gender (%)	18 (45)	167 (46.1)	0.89
Age, mean±SD, years	74±13	70±16	0.12
Baseline NIHSS, median [IQR]	16 [15 – 19]	17 [17 – 18]	0.19
Comorbidities and risk factors (%)			
Hypertension	27 (67.5)	200 (55.2)	0.14
Current smoke	8 (20)	68 (18.8)	0.85
Dyslipidemia	10 (25)	101 (27.9)	0.7
Diabetes mellitus	7 (17.5)	53 (14.6)	0.6
Antiplatelet therapy* (%)	10 (25)	106 (29.3)	0.57
Anticoagulation therapy* (%)	4 (10)	42 (11.6)	0.76
Serum glucose level, mean±SD, mmol/L	7.74 (3.75)	6.74 (2.05)	**0.03**
Imaging			
ASPECTS, median [IQR]	5 [5-6]	7 [7-8]	**0.003**
Thrombus location (%)			
ICA termination +/- M1	11 (27.5)	72 (19.9)	0.26
M1	21 (52.5)	232 (64)	0.15
M2	8 (20)	58 (16.1)	0.53
Early Venous Filling	29 (72.5)	117 (32.3)	**10^{-4}**
Poor ASITN Collateral Status* (%)	24/34 (70.6)	159/266 (60)	0.23
Treatment with IV-tPA (%)	22 (55)	214 (59.1)	0.61
Workflow duration, min, median [IQR]			
Onset-to-imaging	161 [120-247]	109 [100-115]	**0.001**
Onset-to-IV-tPA	161 [145-180]	126 [115-136]	0.24
Onset-to-groin puncture	270 [260-293]	204 [192-220]	**0.02**
Onset-to-reperfusion	319 [304-366]	247 [233-262]	**0.004**
Outcome			
Good functional outcome* (mRS≤2)	8/38 (21)	204/350 (45.3)	**0.003**

Values are numbers (percentages), unless stated otherwise

*SD=Standard derivation; NIHSS=National Institutes of Health Stroke Scale; IQR=Interquartile range; ASPECTS= Alberta Stroke Program Early Computed Tomography Score; ICA=internal carotid artery; M1=proximal segment of the middle cerebral artery; M2: second segments of middle cerebral artery; IV-tPA=intravenous tissue plasminogen activator; mRS=90 days modified Rankin Scale. * Missing data*

In the binary logistic regression model, independent predictor of sICH included : EVF presence (OR=11.9 [3.8-37.5], p<10-3), admission glucose level >7mmol/L (OR=2.92 [1.26-6.7], p<0.03), ASPECTS ≤5 (OR=2.49 [1.8-8.1], p=0.014), 6-7 (OR=1.15 [1.03-4,4], p=0.046) and onset to successful recanalization ≥270min (OR=7.8 [2.5-24], p<10-3). The onset-to-groin puncture time ≥270min was not independently associated with poor outcome after multivariate adjustment (**Table E-II-II-3**).

Table E-II-II-3: Multivariable analysis of association between predictors and sICH in the derivation cohort

	sICH	**No sICH**	**Multivariable Analysis**	
	n= 40 (8.9%)	n= 362 (91.1%)	Adjusted OR (95% CI)	P value
TAGE score items				
***T**ime-to successful recanalization*				
< 270min	7 (17.5%)	205 (56.6%)	ref	-
≥ 270min	33 (82.5%)	157 (43.4%)	7.8 [2.5-24]	$<10^{-3}$
***A**SPECTS*				
8-10	7 (17.5%)	163 (45%)	ref	-
6-7	13 (32.5%)	100 (27.6%)	1.15 [1.03-4.42]	0.046
0-5	20 (50%)	99 (27.4%)	2.49 [1.8-8.1]	0.014
***G**lucose level, mmol/L*				
< 7	15(37.5%)	245 (67.7%)	ref	
≥ 7	25 (62.5%)	117 (32.3%)	2.92 [1.26-6.7]	0.03
***E**arly Venous Filling*				
No	15 (33.3%)	317 (68.8%)	ref	
Yes	29 (72.5%)	117 (32.3%)	11.9 [3.8-37.5]	$<10^{-3}$

Successful recanalization defined as a mTICI score≥2B; ASPECTS= Alberta Stroke Program Early Computed Tomography Score

The Time-ASPECTS-Glycemia-Early venous filling (TAGE) score

Predictors for sICH were weighted (points assigned) based on their respective regression coefficient in the multivariable analysis. The TAGE score was the sum of the points of each of the predictors (**Table E-II-II-4**).

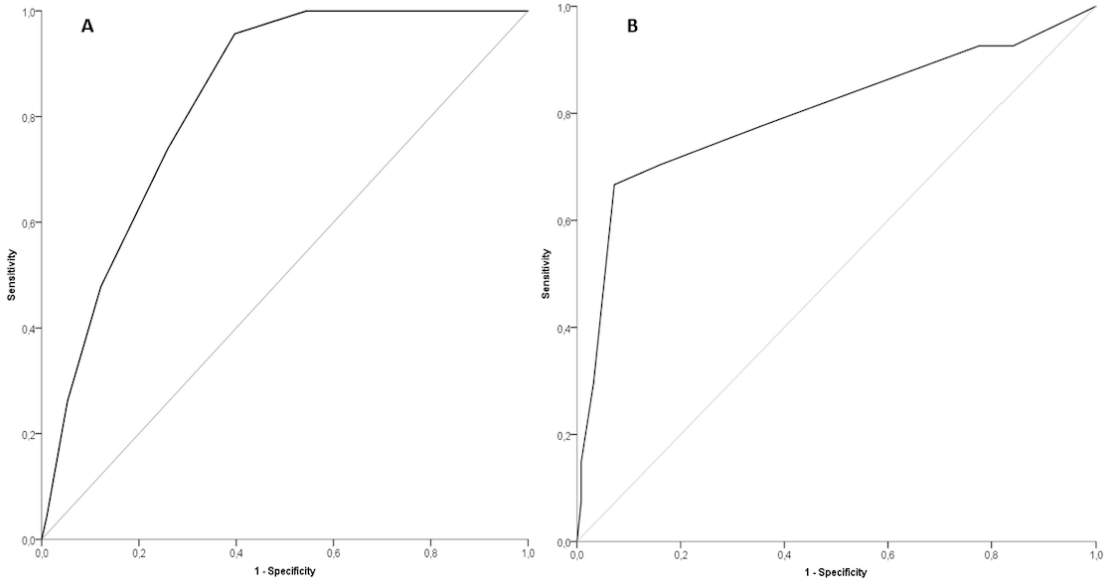
Table E-II-II-4: TAGE Score

ITEMS	POINTS /10
TIME TO SUCCESSFUL REPERFUSION	
≥270 min	3
<270min	0
ASPECTS	
0-5	2
6-7	1
8-10	0
GLUCOSE LEVEL (mmol/L)	
≥7 mmol/l	2
<7 mmol/l	0
EARLY VENOUS FILLING	
YES	3
NO	0

ASPECTS= Alberta Stroke Program Early CT Score

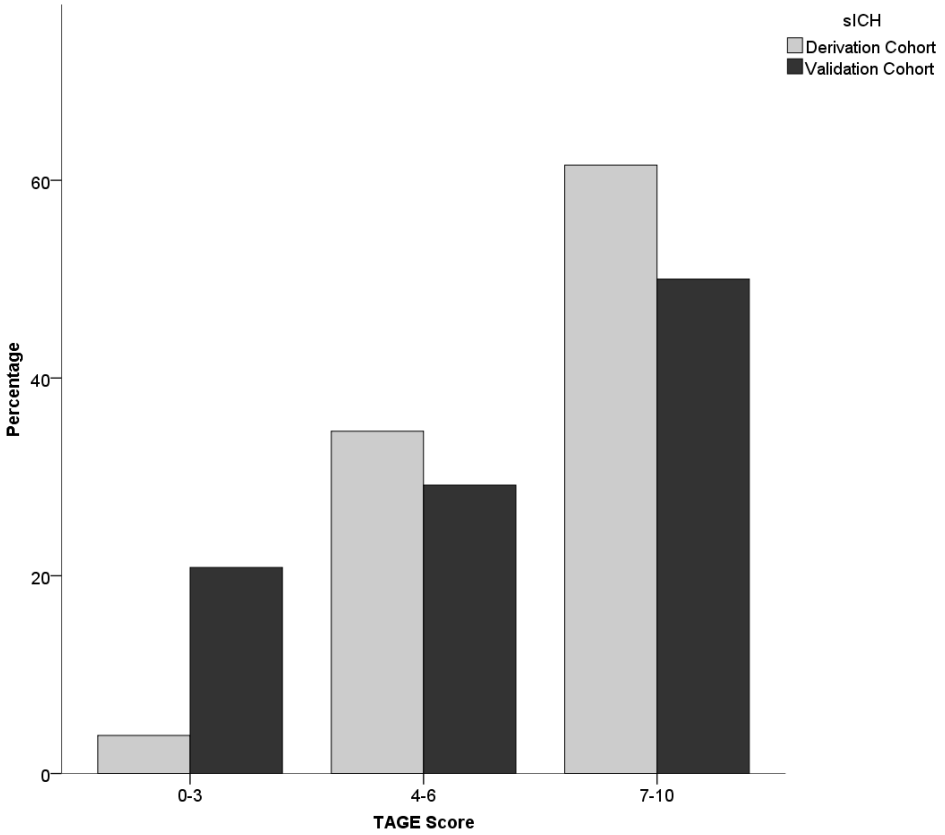
The TAGE score demonstrated an excellent ability (AUC=0.832, 95%CI [0.77-0.90], **Figure E-II-II-2A**) for sICH discrimination in the derivation cohort. The calibration of the total score was tested with hosmer-Lemeshow goodness-of-fit test comparing predicted and observed rates of sICH; showing a good calibration of the total score (Chi-square =3.05; P=0.88). There was an increasing risk of sICH with increasing TAGE score (OR per unit increase 1.99, [1.53-2.59], p<0.001). The addition of EVF significantly enhanced model prediction ability compared to a score with time to recanalization, ASPECT and glycemia alone (AUC= 0.832 [0.77-0.90] versus 0.686 [0.58-0.79], p<0.001). External validation in a cohort issued from the THRACE trial and a second comprehensive stroke center (N=507) was performed to assess the reliability of the TAGE score, showing consistent performance for sICH prediction with an AUC= 0.801, 95%CI [0.69-0.91] (**Figure E-II-II-2B**).

Figure E-II-II-2: Receiving operator characteristics (ROC) curve of TAGE Score performance.
sICH prediction in the derivation group (AUC=0.832 [0.77-0.90]) (A) and the external validation group (AUC= 0.801 [0.69-0.91]) (B).



The- calibration of the total score was tested with hosmer-Lemeshow goodness-of-fit test comparing predicted and observed rates of sICH; showing a good calibration of the total score (Chi-square =2.67; P=0.85) (**Figure E-II-II-3**).

Figure E-II-II-3: sICH distribution in derivation and validation cohorts by increasing TAGE score: low (0-3), moderate (4-6) and high (7-10) risk.



E-II-II-5 Discussion

We identified in this study independent predictors of sICH in patients achieving successful recanalization after MT for AIS-LVO. High delay from onset to successful recanalization, low ASPECTS, admission hyperglycemia and presence of an EVF after MT were strong predictors associated with sICH and constituted the TAGE score. This new score successfully predicted the occurrence of sICH in two large heterogeneous cohorts of successfully recanalized patients.

Time from stroke onset to recanalization was a strong independent predictor of sICH in the derivation cohort, consistent with previous studies highlighting the higher rates of sICH and a detrimental effect on functional outcome with increased time-to-treatment[257–260]. The time dependent effect of reperfusion therapies in acute stroke emphasizes the need for time saving policies[261] in order to reduce door to treatment timings.

Hyperglycemia and ASPECT score are also well-known predictors of sICH incorporated in the TAGE score. Hyperglycemia has a deleterious effect on blood-brain barrier during ischemic stroke[262,263] leading to increased infarct growth and higher risk of sICH[264,265]. Low ASPECT score is correlated to higher infarct burden and increased sICH rates explaining its routine use for patients' selection for reperfusion therapies[266].

The TAGE score is the first pragmatic tool for early and reliable prediction of sICH incorporation the EVF finding. This angiographic sign can be easily assessed on DSA after successful recanalization with mechanical thrombectomy with reproducible results[238,239,255,267]. The presence of EVF is probably linked to focal hyperhemia in the infarct territory, due to blood-brain barrier disruption and microcapillar dysfunction, leading to HT and unfavorable outcome[268]. EVF was a powerful predictor of sICH in the derivation cohort, consistent with previous studies, and its addition significantly enhanced the model prediction ability and allowed a good prediction performance of the TAGE score on the derivation and external validation cohorts. The other novelty of the TAGE score compared with previously available scores, is the target population consisting only of successfully recanalized (eTICI≥2B) patients. We chose to focus in this population since EVF cannot be reliably assessed when the angiogram is partially masked by persistent arterial occlusions. Nevertheless, successful recanalization is achieved in more than 70% of patients with proximal occlusion treated with modern MT techniques[19]. It seemed more relevant to develop the score on patients with successful recanalization, for whom a sICH would have a meaningful impact on functional outcome, rather than incorporate patients with unsuccessful MT for whom functional outcome is already heavily burdened by persistent arterial occlusion.

The strengths of our study included a relatively large sample size of successfully treated

patients in the derivation and external validation cohorts and the use of simple variables that can be quickly obtained in real-world conditions of acute stroke treatment. Nevertheless, several limitations should be noted. Presence of EVF can only be diagnosed once the therapeutic decision has been made and the reperfusion therapy performed, which greatly limits its impact on the therapeutic decision. Although the purpose of this kind of predictive scores is not to select patients for a particular treatment, but to alert the clinician to an increased risk of sICH, imposing a more severe control of blood pressure or glycemia. Another limitation is the lack of patients' hemodynamic data such as arterial pressure before and after MT that could contribute to sICH[269–271].

E-II-II-6 Conclusion

the TAGE score is a simple and accurate tool for sICH prediction, using Time-to-successful reperfusion, ASPECT score, level-blood-glucose and EVF presence, all easily available at an early phase of acute ischemic stroke management. Larger studies are warranted to estimate the efficiency and reproducibility of this score.

F. Conclusion et Perspectives

Nous avons identifié au travers des travaux présentés ici plusieurs facteurs associés au mauvais pronostic clinique malgré une bonne recanalisation après thrombectomie mécaniques. Les différents facteurs ; propres au patient (tel que l'âge, l'étendue de l'iscémie ou l'état de ses collatérales) ou inhérents à la procédure (nombre de passage, modalité anesthésique) sont imbriqués de façon complexe et il est impossible de tous les contrôler.

Le critère de jugement le plus communément utilisé, une évolution clinique mesurée à trois mois en utilisant le score du mRS, considérée favorable en cas de mRS≤2, ne rend pas compte du réel effet ou bénéfice éventuel du traitement réalisé.[272] En effet, l'échelle mRS comporte des limites et est impactée par les co-morbidités d'un patient (antécédents cardio-vasculaire, diabète, chirurgie…), par ses capacités cognitives ou son statut socio-économique.[273,274]

L'efficacité de la thrombectomie dans les essais thérapeutiques est illustrée par un nombre de sujets à traiter (NNT) de 2.6, un chiffre extrêmement bas, mais la sélection des malades pour la thrombectomie dans les conditions de la vie réelle dépasse celle du cadre strict des essais thérapeutiques. Les patients traités sont souvent âgés, avec plusieurs comorbidités qui affectent leur pronostic. La sélection des patients pour la thrombectomie mécanique peut être complexe car la décision doit être prise en urgence, ce qui limite le temps pour rechercher les informations pertinentes concernant les antécédents, l'état cognitif et général du patient. Même dans les situations ou toutes les données sont disponibles, un praticien peut quand même choisir de réaliser un geste dont la pertinence clinique est discutable, dans un cas de gros AVC chez un patient jeune par exemple. Un dernier point financier est également à signaler, puisque la majorité des malades candidats pour une thrombectomie mécanique sont transférés vers une unité dotée d'un service de neuroradiologie interventionnelle, générant des surcoûts de transport et de personnels au bloc opératoire. La sélection de candidats pour la thrombectomie pour éviter de sur-traiter les patients est donc un problème courant, complexe et justifie les efforts visant à trouver des approches de sélection des patients plus sophistiquées, avec une approche individuelle basée sur l'éloquence fonctionnelle du parenchyme à sauver et passe par une évaluation du parenchyme par des modalités d'imagerie avancées comme l'imagerie de perfusion.

Dans les suites de cette thèse, de nouveaux travaux sont actuellement en cours, s'intéressant à la fois à des facteurs propres aux patients comme à des facteurs liés à l'intervention. Ainsi, l'importance de la microangioangiopathie a été étudiée par notre équipe (Boulouis et al, Neurology 2019), sur une population d'AVC ischémique avec occlusion artérielle proximale. Toutefois, les données spécifiques concernant des patients avec succès de recanalisation et évolution clinique défavorable restent à analyser.

Un autre élément important démontré dans cette thèse consiste en l'impact négatif des embols distaux dans de nouveaux territoires, chez les patients recanalisés avec évolution défavorable. Une étude en cours cherche à montrer les déterminants de survenue de ces embols, liés à la fragmentation du thrombus principal lors de son retrait, en analysant la composition de celui-ci à la fois définie en IRM T2* (travail en cours de rédaction) qu'en analyse biologique (inclusions en cours, étude COMPOCLOT). La morphologie du thrombus en IRM sera également analysée, tant pour le succès de la recanalisation que pour la survenue des embols distaux.

Un autre facteur d'influence montrée par notre équipe (Kerleroux et al. Neurology 2021) dans l'évolution clinique des patients est la localisation des lésions hypoperfusées avant recanalisation. Ce travail a tout particulièrement concerné les patients avec un large volume d'ischémie (cœur de l'infarctus > 70ml) et donc avec une probabilité d'évolution défavorable plus importante. L'objectif du travail en cours sera d'identifier le poids de la localisation des lésions chez ces patients évoluant défavorablement, malgré une recanalisation, nonobstant le volume d'ischémie initiale.

Un axe de recherche actuellement très dynamique dans la littérature est celui de la neuroprotection. D'aucuns considèrent que la recanalisation rapide n'est qu'une étape précédent la lutte contre les effets ischémiques à l'échelle cellulaire. L'injection systémique ou intra-artérielle d'un agent thérapeutique est une piste (Verapamil intra-artériel : NCT03347786 ; Hypothermie intra-artérielle[275]…) . Plusieurs essais thérapeutiques sont en cours pour explorer l'effet neuroprotecteur de différentes molécules[276]. La recherche translationnelle jouera également un rôle fondamental pour la sélection sur des modèles animaux des meilleurs agents neuroprotecteurs. L'injection intra-artérielle à la fin de la thrombectomie d'un agent neuroprotecteur permettre aux médicaments d'atteindre des tissus auparavant inaccessibles et de réduire les effets de la dose systémique. Un agent permettant simplement de baisser le risque de transformation hémorragique serait déjà d'une valeur inestimable. Les neuroradiologues interventionnels seront donc aux premières loges pour l'installation et l'application de ces nouvelles thérapies prometteuses.

G. Publications :

En rapport avec la thèse

- Ben Hassen, W ; Touloupas, C ; Benzakoun, J ; Boulouis, G ; Bretzner, M ; Bricout, N & al, Impact of Repeated Clot Retrieval Attempts on Infarct Growth and Outcome After Ischemic Stroke. **Neurology.** 2021
- Ben Hassen, W ; Tordjman, M ; Boulouis, G ; Bretzner, M ; Bricout, N ; Legrand, L & al, Benefit of first-pass complete reperfusion in thrombectomy is mediated by limited infarct growth. **Eur J Neurology.** 2021
- van de Graaf, RA ; Samuels, N ; Chalos, V ; Lycklama A Nijeholt, GJ ; van Beusekom, H ; Yoo, AJ & al. Predictors of poor outcome despite successful endovascular treatment for ischemic stroke: results from the MR CLEAN Registry. **JNIS.** 2021
- Ter Schiphorst, A ; Charron, S ; Ben Hassen, W ; Provost, C ; Naggara, O ; Benzakoun, J & al. Tissue no-reflow despite full recanalization following thrombectomy for anterior circulation stroke with proximal occlusion: A clinical study. **JCBFM.** 2021
- Zhu, F ; Ben Hassen, W ; Bricout, N ; Kerleroux, B ; Janot, K ; Gory, B & al. Effect of Operator''s Experience on Proficiency in Mechanical Thrombectomy: A Multicenter Study. **Stroke.** 2021
- Ben Hassen, W ; Raynaud, N ; Bricout, N ; Boulouis, G ; Legrand, L ; Ferrigno, M & al , MT-DRAGON score for outcome prediction in acute ischemic stroke treated by mechanical thrombectomy within 8 hours., J Neurointerv Surg, **2020**
- Girot, JB ; Richard, S ; Gariel, F ; Sibon, I ; Labreuche, J ; Kyheng, M & al , Predictors of Unexplained Early Neurological Deterioration After Endovascular Treatment for Acute Ischemic Stroke., **Stroke,** 2020
- Boulouis, G ; Bricout, N ; Benhassen, W ; Ferrigno, M ; Turc, G ; Bretzner, M & al , White matter hyperintensity burden in patients with ischemic stroke treated with thrombectomy., **Neurology,** 2019.
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AVC et Thrombectomie (2018-2021)

- Happi Ngankou, E ; Gory, B ; Marnat, G ; Richard, S ; Bourcier, R ; Sibon, I & al, Thrombectomy Complications in Large Vessel Occlusions: Incidence, Predictors, and Clinical Impact in the ETIS Registry. Stroke 2021
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