# Recanalisation artérielle précoce après thrombolyse intraveineuse d'un accident ischémique cérébral avec occlusion artérielle proximale : incidence, prédiction et physiopathologie

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## Incidence, prédiction et physiopathologie

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Thèse de doctorat de Neurosciences

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# Résumé

A la phase aigüe de l'accident ischémique cérébral (AIC) avec occlusion artérielle proximale, la cible thérapeutique principale est l'obtention d'une recanalisation artérielle la plus rapide possible. L'utilisation combinée de la thrombolyse intraveineuse (TIV) par alteplase et de la thrombectomie mécanique (TM), dénommée 'bridging therapy' et recommandée depuis 2015, est actuellement remise en question car i) en cas de faible probabilité de recanalisation précoce post-TIV, celle-ci pourrait être non seulement inutile, mais aussi délétère ; et ii) inversement, si la probabilité de recanalisation précoce est forte, un transfert en centre spécialisé pour TM pourrait s'avérer inutile. Une meilleure compréhension des mécanismes physiopathologiques sous-tendant la résistance à la TIV, et le développement d'outils prédictifs de la survenue de celle-ci, pourraient avoir des implications cliniques importantes, notamment le développement de thérapies intraveineuses plus efficaces ou l'avancée vers une médecine personnalisée sélectionnant le traitement de recanalisation (c'est-à-dire, TIV seule, bridging ou TM seule) le plus adapté à chaque patient.

Dans cette thèse, nous avons étudié l'incidence et les facteurs prédictifs de la recanalisation précoce post-TIV dans une large cohorte multicentrique française d'AIC avec occlusion proximale (n=1107), traités par TIV et adressés pour TM entre 2015 et 2017. La recanalisation était évaluée dans les 3h suivant la TIV, sur le premier jet de l'artériographie ou par imagerie vasculaire non-invasive.

Notre travail a montré que l'incidence de la recanalisation précoce post-TIV est relativement importante, survenant en moyenne chez 1 patient sur 5. L'analyse des facteurs prédictifs a montré que la localisation du thrombus dans l'arbre artériel, sa longueur, le délai entre la TIV et l'évaluation de la recanalisation, et la qualité du réseau artériel collatéral ou la sévérité de l'hypoperfusion cérébrale, sont associés de manière indépendante à la survenue d'une recanalisation précoce, contribuant de ce fait à la compréhension des mécanismes sous-tendant celle-ci. Un score prédictif original, créé par combinaison des trois premières variables, permettait de prédire l'absence de recanalisation avec une très grande spécificité, mais de façon insuffisamment fiable la survenue d'une recanalisation. Ce score devrait permettre à l'avenir d'aider à la sélection des patients pour des essais randomisés comparant bridging *vs.* TM seule, mais pas de limiter les « transferts futiles » en TM.

Dans le sous-groupe de patients avec déficit neurologique mineur (score NIHSS<6), situation dans laquelle le traitement optimal est actuellement incertain, nous avons montré que la longueur du thrombus est un facteur prédictif puissant de recanalisation, et qu'un seuil de 9mm permet de prédire l'absence de recanalisation avec un bon rapport sensibilité/spécificité, ce qui pourrait aider au dessin d'essais randomisés testant TIV seule *vs.* bridging dans cette population.

Enfin, dans un échantillon de patients nécessitant un transfert inter-hospitalier pour la réalisation de la TM, situation clinique la plus fréquente actuellement, l'incidence de recanalisation précoce n'était pas différente entre patients thrombolysés par tenecteplase (un nouveau thrombolytique prometteur) en comparaison à l'alteplase. La divergence de ce résultat avec ceux de l'essai randomisé de phase II EXTEND-IA TNK qui a rapporté une incidence deux fois plus élevée de recanalisation précoce après tenecteplase dans une population admise directement dans un centre de TM (chez qui le délai thrombolyse-thrombectomie était donc nettement plus court), s'expliquerait par une recanalisation plus précoce après tenecteplase, ce qui, en cas de confirmation par des études futures, pourrait avoir des conséquences cliniques importantes.

Dans l'objectif de développer de nouvelles thérapeutiques intraveineuses plus efficaces, des études prospectives ciblant spécifiquement l'effet de biomarqueurs d'hémostase spécialisée et de la composition du thrombus sur la recanalisation précoce post-thrombolyse, facteurs non étudiés dans cette thèse, sont à présent souhaitables.

# Abstract

In acute stroke patients with large-vessel occlusion (LVO), the goal of intravenous thrombolysis (IVT) is to achieve early recanalization. Whether all patients with LVO need to undergo intravenous thrombolysis (IVT) before mechanical thrombectomy (MT) – *i.e.* bridging therapy, which is standard-of-care since 2015 – is debated as: i) thrombolysis may be harmful in patients unlikely to recanalize following IVT; and, ii) conversely, transfer for MT may be unnecessary in patients highly likely to recanalize. It is therefore timely and important to investigate the mechanisms and predictors of post-IVT recanalization, since the findings could have major clinical implications, such as the development of more efficient intravenous therapies, as well as moving towards personalized medicine, involving the selection of individual patients for best therapy, *i.e.*, IVT alone, bridging, or MT alone.

In the present thesis, we studied the incidence and predictors of post-IVT early recanalization in a large French multicentric cohort of acute stroke with LVO (n=1107), where all patients were treated with IVT and referred for MT between 2015 and 2017. Recanalization was evaluated on first intracranial angiogram or non-invasive vascular imaging within the first 3h following IVT start.

The incidence of early recanalization following IVT was substantial in the overall cohort, occurring in ~1 in 5 patients. Thrombus site and length, time elapsed between IVT start and recanalization assessment, and quality of the leptomeningeal collateral flow or severity of hypoperfusion, were all independently associated with early recanalization occurrence. These findings are novel and important, and shed new light on the mechanisms underlying post-IVT recanalization. A six-point score derived from the three former variables afforded >90% specificity for no-recanalization, but did not reliably predict occurrence of early recanalization. This score should prove of value for patient selection into trials, testing *e.g.* bridging therapy *vs.* MT alone, but may not be used to support decisions to withhold referral for MT.

In the subgroup of LVO patients with minor neurological symptoms (NIHSS score <6), in whom the optimal treatment is unknown, we found that thrombus length was a powerful independent predictor of no-recanalization, and that the optimal cutoff (9mm) had a high sensitivity/specificity ratio for no-recanalization, which may help design randomized trials aiming to test bridging therapy *vs.* IVT alone in this population.

Lastly, unlike the EXTEND-IA TNK randomized trial which found 2-fold higher early recanalization rate before mechanical MT following IVT with tenecteplase as compared to alteplase in patients directly admitted to MT-capable centres, we found similar early recanalization rates with these two thrombolytic agents in patients transferred for MT from a non MT-capable centre (*i.e.,* with longer IVT-to-MT delays than in EXTEND-IA TNK), currently the most frequently encountered clinical situation. Taken together, these data suggest that recanalization may occur earlier with tenecteplase, which if confirmed would have clinical relevance.

Towards further clarifying the pathophysiology of post-thrombolysis early recanalization failure and develop more efficient intravenous therapies for acute ischemic stroke, specific studies will need to address two additional potentially important predictors of early recanalization, namely haemostatic biomarkers and thrombus composition.

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# Sommaire

**Liste des publications liées au travail de thèse (articles publiés ou soumis) :**

*signifie contribution équivalente

1) Indicidence and predictors of early recanalization following IV thrombolysis. A systematic review and Meta-Analysis. **Seners P***, Turc G*, Maïer B, Oppenheim C, Mas JL, Baron JC. Stroke 2016 Sep;47(9):2409-12.

2) Mechanical Thrombectomy After Intravenous Thrombolysis vs Mechanical Thrombectomy Alone in Acute Stroke. **Seners P**, Oppenheim C, Baron JC. *JAMA Neurol*. 2017;74:1014-1015 (lettre à l'éditeur)

3) Post-thrombolysis recanalization in stroke referrals for thrombectomy: Incidence, predictors and prediction scores. **Seners P**, Turc G, Naggara O, Henon H, Piotin M, Arquizan C, Cho TH, Narata AP, Lapergue B, Richard S, Legrand L, Bricout N, Blanc R, Dargazanli C, Gory B, Debiais S, Tisserand M, Bracard S, Leclerc X, Obadia M, Costalat V, Berner LP, Cottier JP, Consoli A, Ducrocq X, Mas JL, Oppenheim C*, Baron JC*, on behalf of the PREDICT-RECANAL collaborators. ***En révision dans Stroke.***

4) Better collaterals are independently associated with post-thrombolysis recanalization before thrombectomy. **Seners P**, Roca P, Legrand L, Turc G, Cottier JP, Cho TH, Arquizan C, Bracard S, Ozsancak C, Ben Hassen W, Naggara O, Lion S, Debiais S, Berthezene Y, Costalat V, Richard S, Magni C, Mas JL, Baron JC*, Oppenheim C*. ***En révision dans Stroke.***

5) Early recanalization in tenecteplase *vs.* alteplase-treated drip-and-ship patients referred for thrombectomy. **Seners P**, Chausson N*, Caroff J,* Turc G, Denier C, Piotin M, Aghasaryan M, Alecu C, Chassin O, Lapergue B, Naggara O, Ferrigno M, Arquizan C, Cho TH, Narata AP, Richard S, Bricout N, Mazighi M, Costalat V, Gory B, Debiais S, Consoli A, Bracard S, Oppenheim C, Mas JL, Smadja D**, Spelle L**, Baron JC**, on behalf of the PREDICT-RECANAL collaborators. ***Accepté dans Journal of Stroke (lettre à l'éditeur, sous presse).***

6) Relationships between brain perfusion and early recanalization after intravenous thrombolysis for acute stroke with large vessel occlusion. **Seners P**, Turc G, Lion S, Cottier JP, Cho TH, Arquizan C, Bracard S, Ozsancak C, Legrand L, Naggara O, Debiais S, Berthezene Y, Costalat V, Richard S, Magni C, Nighoghossian N, Narata AP, Dargazanli C, Gory B, Mas JL, Oppenheim C*, Baron JC*. ***Soumis au Journal of Cerebral Blood Flow and Metabolism le 20/08/2018***

7) Thrombus length predicts lack of post-thrombolysis early recanalization in minor stroke with large vessel occlusion. **Seners P**, Delepierre J, Turc G, Henon H, Piotin M, Arquizan C, Cho TH, Lapergue B, Cottier JP, Richard S, Legrand L, Bricout N, Mazighi M, Dargazanli C, Nighoghossian N, Consoli A, Debiais S, Bracard S, Naggara O, Leclerc X, Obadia M, Costalat V, Berthezène Y, Tisserand M, Narata AP, Gory B, Mas JL, Oppenheim C, Baron JC, on behalf of the PREDICT-RECANAL collaborators. ***Soumis à Stroke le 3/09/2018***

# Abréviations

AIC : Accident ischémique cérébral

ACI : Artère carotide interne

AOL : Arterial occlusive lesion score

ARM : Angiographie par résonnance magnétique

ASPECTS : Alberta Stroke Program Computerized Tomography Score

FLAIR : Fluid-Attenuated Inversion Recovery

HIR : Hypoperfusion intensity ratio

IC95% : Intervalle de confiance à 95%

IRM : Imagerie par résonnance magnétique

M1 : Premier segment de l'artère cérébrale moyenne

M2 : Deuxième segment de l'artère cérébrale moyenne

MIP : Maximum intensity projection

mTICI : Modified thrombolysis in cerebral infarction scale

NIHSS : National Institute of Health Stroke Scale

rtPA : Activateur tissulaire recombinant du plasminogène

SVS : Susceptibility vessel sign

TNK : Tenecteplase

TOF : Time of flight

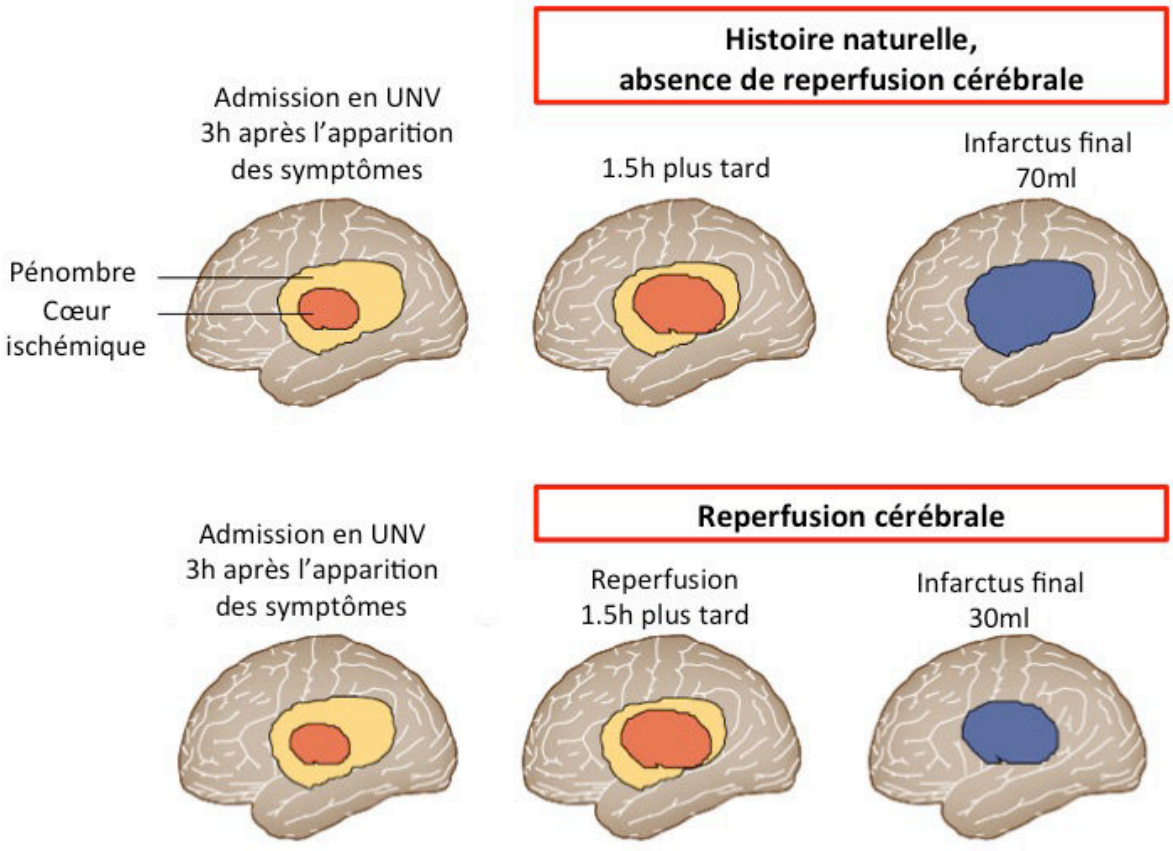
UNV : Unité neurovasculaire

# Introduction

## I. Accident ischémique cérébral : généralités

L'accident ischémique cérébral (AIC) est un problème majeur de santé publique, dont l'incidence annuelle est estimée à 12 millions dans le monde et environ 100 000 en France,[1,2] occasionnant de nombreux décès et handicaps. Il est lié à l'occlusion d'une artère cérébrale par un thrombus, à l'origine d'une ischémie cérébrale occasionnant un déficit neurologique variable dans sa nature et sa sévérité. Dans les premières heures suivant l'occlusion artérielle, le tissu ischémique peut être séparé en deux compartiments : le « cœur » ischémique (tissu en voie de nécrose ou infarctus), d'ores et déjà irréversiblement lésé même en cas de reperfusion rapide, et la pénombre, tissu sévèrement hypoperfusé et contribuant au déficit neurologique, mais encore viable et dont l'évolution vers la nécrose peut être évitée par une reperfusion cérébrale rapide (**Figure 1**).[3] La survie de la pénombre détermine la récupération neurologique initiale, et bien que du tissu pénombral puisse persister jusqu'à 24-48h heures chez certains patients, la majorité de la conversion du tissu pénombral vers l'infarcissement se produit au cours des premières heures suivant l'occlusion artérielle, avec une vitesse variable d'un patient à l'autre en fonction de différents facteurs au premier plan desquels la qualité du réseau artériel collatéral, notamment leptoméningé.[3,4]

**Figure 1.** Schéma illustrant l'évolution du cœur ischémique et de la pénombre ischémique selon la survenue ou non d'une reperfusion cérébrale, d'après Baron *et al*.[5]



En accord avec ces notions démontrées par de nombreuses études tant expérimentales que cliniques,[6-9] la survenue d'une reperfusion cérébrale est un puissant facteur prédictif d'amélioration clinique et de bon pronostic fonctionnel à long terme, principalement lorsque la pénombre est étendue.[7] Cependant, l'amélioration clinique et le pronostic fonctionnel à long terme sont fortement dépendants du délai de survenue de la reperfusion,[10] et une reperfusion trop tardive peut-être futile en cas d'absence de pénombre résiduelle. Ceci explique l'importance d'obtenir une reperfusion cérébrale rapide, pour sauver le maximum de pénombre et améliorer d'autant le pronostic fonctionnel.

**II. Reperfusion versus recanalisation**

Bien que souvent utilisés de façon interchangeable, les termes « reperfusion » et « recanalisation » ne sont pas synonymes. La reperfusion cérébrale correspond à la restauration du flux sanguin cérébral au niveau capillaire, tandis que la recanalisation correspond à la restauration de la lumière artérielle. Bien que les deux événements soient étroitement liés, la survenue de l'un n'entraîne pas nécessairement la survenue de l'autre.[11] En effet, une recanalisation peut ne pas induire de reperfusion en raison de micro-emboles distaux ou de lésions micro-vasculaires[12] – bien qu'il n'existe actuellement pas de preuve forte de l'existence de ce dernier phénomène chez l'homme. A l'inverse, une reperfusion efficace peut être observée malgré l'absence de recanalisation artérielle,[11] le mécanisme présumé étant une reperfusion rétrograde via les collatérales leptoméningées.[13]

L'évaluation de la reperfusion cérébrale nécessite la réalisation d'un scanner ou d'une IRM de perfusion pré- et post-traitement et n'est de ce fait pas évaluée en routine clinique. A l'inverse, la recanalisation, qui nécessite une imagerie vasculaire pré- et post-thérapeutique, est évaluée en routine dans la plupart des centres, notamment en cas de traitement endovasculaire. Nous utiliserons le terme de recanalisation artérielle dans la suite de ce travail.

**III. Prise en charge à la phase aigüe**

Il existe actuellement deux thérapeutiques efficaces à la phase aigüe de l'AIC visant à obtenir la recanalisation artérielle :

- Depuis 1996, la thrombolyse intraveineuse par l'activateur tissulaire recombinant du plasminogène (rtPA ou alteplase, à la dose 0.9mg/kg), un traitement pharmacologique visant à dissoudre le thrombus, a fait preuve de son efficacité en terme de pronostic fonctionnel à 3 mois dans un délai de 4,5 heures après l'AIC.[14,15] Le rtPA permet l'activation du plasminogène en plasmine, une enzyme protéolytique très puissante capable de dégrader la fibrine contenue dans le thrombus. La thrombolyse par rtPA a pour avantage d'être largement et rapidement disponible, pouvant être administrée dans toutes les unités neurovasculaires (UNV, 140 réparties sur l'ensemble du territoire français), mais également dans certains services d'urgences dotés de télémédecine ou de personnels formés à la thrombolyse. Cette facilité d'accès est d'autant plus importante que le délai entre l'apparition des symptômes et l'administration de la thrombolyse est un facteur pronostic important.[16] Malheureusement, plusieurs contre-indications empêchent sa

plus large utilisation, et son efficacité est limitée en cas d'occlusion artérielle proximale car elle ne permet l'obtention d'une recanalisation précoce que chez une minorité de patients.[6,17] Par ailleurs, elle expose à un risque d'hémorragie cérébrale symptomatique d'environ 6%.[15]

- Depuis 2015, la thrombectomie mécanique réalisée dans les 6 heures suivant l'apparition des symptômes (associée à une thrombolyse intraveineuse préalable si indiquée), qui permet un retrait mécanique du thrombus par voie endovasculaire, a fait preuve de sa nette supériorité en terme de recanalisation (environ 80%) et de pronostic fonctionnel en comparaison au traitement médical seul (incluant la thrombolyse intraveineuse si indiquée).[18-23] Cependant, plusieurs facteurs limitent actuellement son efficacité. Premièrement, la thrombectomie ne peut être réalisée qu'en cas d'occlusion proximale, qui représente une minorité des patients évalués à la phase aigüe d'un AIC (environ 35%).[24] Deuxièmement, elle ne peut être réalisée rapidement que chez une minorité des patients car seuls de rares centres spécialisés disposent du personnel et du plateau technique adapté (UNV dite « de recours », environ 25% des UNV en France et aux Etats-Unis).[25,26] Ce dernier point est particulièrement limitant car l'efficacité de la thrombectomie est fortement corrélée au délai de recanalisation.[10]

Les principaux avantages et inconvénients de la thrombolyse intraveineuse et de la thrombectomie mécanique sont résumés dans la **Table 1**.

**Table 1.** Avantages et inconvénients des deux traitements de recanalisation cérébrale

| | **Thrombolyse intraveineuse** | **Thrombectomie mécanique** |
|---|---|---|
| **Avantages** | • Largement et rapidement disponible sur l'ensemble du territoire<br>• Réalisable et utile en cas d'occlusion artérielle proximale ou distale | • Nettement supérieure à la thrombolyse intraveineuse seule (recanalisation/ pronostic fonctionnel) |
| **Inconvénients** | • Efficacité limitée (recanalisation/ pronostic fonctionnel) en cas d'occlusion proximale<br>• Nombreuses contre-indications<br>• Risque hémorragique | • Peu disponible rapidement<br>• Réalisable uniquement en cas d'occlusion proximale<br>• Risque hémorragique |

### III.1 Recommandations actuelles de prise en charge des AIC dans les 6 premières heures

#### III.1.1 Présence d'une occlusion proximale

En cas d'AIC avec occlusion proximale (terminaison de l'artère carotide interne et/ou premier segment de l'artère cérébrale moyenne [M1]), de déficit neurologique sévère (score National Institute of Health Stroke Scale [NIHSS] ≥6), de cœur ischémique de taille limitée (score Alberta Stroke Program Computerized Tomography [ASPECTS] ≥6) et d'absence de handicap antérieur à l'AIC (score de Rankin modifié 0-1), les organismes français et internationaux recommandent actuellement de réaliser une thrombectomie mécanique aussi vite que possible si le déficit neurologique est apparu il y a moins de 6h.[27,28] Celle-ci doit être précédée d'une thrombolyse intraveineuse par rtPA 0.9mg/kg si elle est indiquée (*cf.* paragraphe III.1.2), ou réalisée d'emblée en l'absence d'indication à la thrombolyse.[27,28] La thrombolyse intraveineuse ne doit pas retarder la réalisation de la thrombectomie, et il est recommandé de ne pas attendre une éventuelle amélioration clinique post-thrombolyse pour envisager la thrombectomie si elle est indiquée.[27]

En cas d'occlusion proximale et de déficit neurologique 'mineur' (score NIHSS <6), d'occlusion du deuxième segment de l'artère cérébrale moyenne (M2), de cœur ischémique étendu (score ASPECTS <6) ou de handicap antérieur à l'AIC, une thrombectomie mécanique « peut être envisagée » dans les 6h suivant l'apparition des symptômes (précédée d'une thrombolyse intraveineuse, si indiquée), bien que le bénéfice de celle-ci soit incertain dans ces situations car ces patients ont été majoritairement exclus des essais de thrombectomie.[27] Des essais randomisés seront nécessaires pour établir ces indications.

L'objectif « technique » du traitement de recanalisation est d'obtenir une recanalisation 2b ou 3 sur l'échelle mTICI (modified thrombolysis in cerebral infarction scale).[27]

#### III.1.2 Absence d'occlusion proximale

En l'absence d'occlusion proximale, seule la thrombolyse intraveineuse par rtPA 0.9mg/kg est recommandée, quelle que soit la sévérité du déficit neurologique (à condition qu'il soit considéré comme « invalidant »), si l'apparition des symptômes est inférieure à 4h30, et en l'absence de contre-indication.[27] Elle doit être réalisée le plus rapidement possible après l'instauration des symptômes.

Dans la suite de cette thèse, nous nous focaliserons sur les patients victimes d'AIC avec occlusion proximale, chez lesquels une indication de thrombolyse intraveineuse suivie d'une thrombectomie mécanique (« bridging therapy ») est retenue.

**IV. Organisation du système de soins à l'ère de la thrombectomie mécanique**

L'importance cruciale d'obtenir une recanalisation rapide – majoritairement obtenue par thrombectomie en cas d'occlusion proximale, et par thrombolyse intraveineuse seule en cas d'occlusion distale – pour améliorer le pronostic fonctionnel rend nécessaire de réduire au maximum le délai survenue des symptômes-recanalisation. L'amélioration à la fois des connaissances de la population générale concernant les symptômes évocateurs d'accident vasculaire cérébral, de la régulation téléphonique par le SAMU-centre 15, et de l'évaluation clinique par le personnel médical et paramédical arrivant au domicile du patient, sont autant de points potentiellement améliorables en vue de raccourcir l'arrivée du patient en UNV.

Si l'UNV la plus proche du lieu de survenue des symptômes évocateurs d'AIC ne dispose pas de la thrombectomie, la stratégie actuellement privilégiée en France consiste à adresser le patient vers l'UNV de proximité, où la thrombolyse intraveineuse est débutée si indiquée, et seuls les patients avec occlusion proximale démontrée par imagerie sont secondairement transférés vers l'UNV de recours pour réaliser une thrombectomie (paradigme « drip-and-ship »). Cependant, le bénéfice d'une stratégie consistant à adresser directement le patient vers une UNV de recours (en shuntant l'UNV de proximité) où la thrombolyse et/ou la thrombectomie sont réalisées, si indiquées, a été évoqué (paradigme « mothership »).[29,30] Le choix entre ces deux stratégies est rendu complexe notamment par le fait qu'il est impossible de manière fiable de différencier en pré-hospitalier un AIC de ses principaux diagnostics différentiels (hémorragie cérébrale notamment), et de déterminer la présence d'une occlusion artérielle proximale.[24] Ainsi, la stratégie drip-and-ship a pour avantages de débuter la thrombolyse intraveineuse plus rapidement et d'éviter de surcharger l'UNV de recours avec des patients (nombreux en pratique) qui ne nécessitent pas de thrombectomie (AIC sans occlusion proximale, autres diagnostics, *etc*...), tandis que la stratégie mothership permet de débuter la thrombectomie plus rapidement et de limiter les transferts secondaires. Les résultats des études observationnelles ayant comparé ces deux stratégies sont discordants,[29,30] et il n'existe actuellement pas d'étude randomisée permettant de répondre à cette question.

L'identification pré-hospitalière des patients victimes d'AIC à l'aide d'ambulances équipées d'un scanner, d'un laboratoire de première nécessité et de personnel formé à la prise en charge des AIC (« UNV mobiles »), a récemment fait preuve de son efficacité pour réduire le délai symptômes-thrombolyse.[31] Cette stratégie très prometteuse est toujours à l'étude dans de nombreux pays. En plus de la réduction du délai symptômes-thrombolyse, elle permettrait également de détecter en pré-hospitalier les patients avec occlusion proximale et ainsi organiser leur transfert immédiat vers l'UNV de recours la plus proche.

## V. Nouvelles questions à l'ère de la thrombectomie

### V.1 Thrombolyse et thrombectomie : l'association des deux traitements est-elle utile ?

Depuis la validation de la thrombectomie, l'intérêt de l'association thrombolyse intraveineuse et thrombectomie mécanique est remis en question pour deux raisons principales. Premièrement, une majorité de patients avec occlusion proximale traités par thrombolyse intraveineuse n'aura pas recanalisé avant la thrombectomie (~80%).[17] Ainsi, cette efficacité modeste de la thrombolyse dans cette population en termes de recanalisation pourrait-être contrebalancée par son surcoût financier et son possible sur-risque hémorragique et allongement du délai admission–thrombectomie.[32] Deuxièmement, à l'inverse, la survenue d'une recanalisation précoce post-thrombolyse chez environ 20% des patients adressés en thrombectomie a pour corollaire un nombre conséquent de transferts « inutiles » pour thrombectomie, celle-ci n'étant finalement pas nécessaire chez ces patients.[23,33] Ces « transferts futiles » sont couteux en moyens humains, matériels et financiers, particulièrement dans les situations de drip-and-ship, et exposent inutilement certains patients aux complications liées à l'artériographie cérébrale.[34]

Dans l'optique d'une médecine personnalisée visant à réduire les complications iatrogènes et les coûts matériels, humains et financiers, il serait utile de proposer un seul des deux traitements (thrombolyse intraveineuse ou thrombectomie mécanique) à chaque patient, en fonction des caractéristiques cliniques, biologiques et radiologiques individuelles. La suppression d'une des deux options thérapeutiques chez les patients candidats à un bridging devra cependant nécessairement passer par un essai randomisé comparant les différentes options thérapeutiques dans des populations préalablement sélectionnées selon l'un des deux dessins suivants : i) thrombolyse seule *vs*. bridging chez les patients à haute probabilité de recanalisation précoce post-thrombolyse, dans l'optique de réduire les « transferts futiles », ou ii) bridging *vs.* thrombectomie seule chez les patients à haute probabilité de non-recanalisation précoce post-thrombolyse, visant à réduire les complications potentielles de la thrombolyse intraveineuse. Il est ainsi important de déterminer les facteurs prédictifs mais aussi les mécanismes sous-tendant la recanalisation précoce après thrombolyse intraveineuse.

### V.2 Améliorer le taux de recanalisation par traitement intraveineux ?

La thrombolyse intraveineuse a pour avantage d'être plus largement disponible que la thrombectomie, et l'amélioration de l'efficacité du traitement intraveineux permettrait de réduire le délai symptômes-recanalisation et ainsi le handicap fonctionnel des patients. Les pistes thérapeutiques actuelles visant cet objectif sont principalement i) l'utilisation de traitements thrombolytiques ayant des propriétés pharmacocinétiques et pharmacodynamiques plus intéressantes que celui actuellement recommandé – le rtPA –, et ii) l'association à ce dernier d'un traitement adjuvant, principalement d'autres produits actifs sur la dégradation de la fibrine ou sur la dégradation d'autres constituants du thrombus.

### V.2.1 Nouveaux thrombolytiques

Le rtPA présente des limites pharmacocinétiques (courte demi-vie impliquant une perfusion continue sur une heure) et pharmacodynamiques (faible fibrino-spécificité, neuro-toxicité),[35] ayant motivé l'essai de nouveaux thrombolytiques à la phase aigüe de l'AIC : la tenecteplase et la desmoteplase.

***La tenecteplase*** est un mutant du rtPA obtenu par bio-ingénierie par la substitution d'acides aminés : la thréonine 103 a été remplacée par une asparagine, l'asparagine 117 par une glutamine, et 4 autres acides aminés du domaine protéase, en position 296-299, ont été substitués par 4 alanines.[36] Les deux premières substitutions ont aboutit au déplacement du site de glycosylation du domaine Kringle 1, permettant de diminuer la clairance plasmatique et ainsi de prolonger la demi-vie de la tenecteplase.[36] Cette augmentation de demi-vie (environ 18 minutes *vs*. 6-7 minutes pour le rtPA) permet une administration en un seul bolus intraveineux, conférant ainsi à la tenecteplase des avantages indéniables pour la pratique clinique.[35] Quant aux quatre dernières substitutions, elles ont permis d'augmenter la résistance du rtPA à l'activateur du plasminogène de type 1 (PAI-1) et de majorer la spécificité à la fibrine.[36] L'amélioration de ces propriétés intrinsèques ont confirmé leur intérêt chez l'animal, la tenecteplase permettant une recanalisation artérielle plus complète et plus rapide que l'alteplase dans un modèle d'occlusion carotide chez le lapin, sans augmentation du risque hémorragique.[36] Ces données pharmacologiques et expérimentales ont motivé l'essai de ce thrombolytique chez l'homme, à la phase aigüe de l'AIC, avec des résultats assez divergents en terme d'efficacité clinique (récupération neurologique précoce et handicap à 3 mois) et de recanalisation artérielle.[37-40] Les principaux résultats des 3 études ayant comparé la recanalisation par tenecteplase *vs.* alteplase avant la conception de cette thèse sont présentés dans la **Table 2**. Ces études ont utilisé des doses de tenecteplase (0,1 ; 0,25 et 0,4mg/kg) et des délais d'évaluation de la recanalisation différents, ce qui rend difficile leur comparaison directe. Les résultats des deux études utilisant la dose de 0,25mg/kg sont cependant discordants, l'une montrant une recanalisation à 24h plus fréquente après tenecteplase[38] et l'autre pas.[39]

***La desmoteplase*** est un activateur du plasminogène extrait de la salive de la chauve-souris Desmodus rotundus qui présente quelques différences structurales avec le tPA humain, lui conférant une spécificité nettement plus importante pour la fibrine et une demi-vie plus longue permettant son administration en bolus intraveineux.[35] Les effets neurotoxiques supposés de l'alteplase et de la tenecteplase semblent par ailleurs absents avec la desmoteplase. Compte-tenu de ces éléments, plusieurs essais thérapeutiques ont étudié son efficacité à la phase aigüe de l'AIC, en comparaison au placebo car utilisé dans des fenêtres horaires plus tardives que celle autorisée à l'époque pour l'alteplase (entre 3 et 9h après la survenue des symptômes), montrant une recanalisation artérielle à 12-24h plus fréquente après desmoteplase *vs.* placebo (49% *vs.* 38%), mais sans amélioration significative du handicap neurologique à 3 mois.[41-45] A ce jour, aucune étude n'a comparé l'efficacité sur le pronostic fonctionnel ou sur la recanalisation artérielle de la thrombolyse par desmoteplase *vs.* alteplase.

**Table 2.** Principales caractéristiques et principaux résultats des trois études publiées comparant le taux de recanalisation après thrombolyse intraveineuse seule par alteplase *vs*. tenecteplase.

| Etude | Dose de thrombolytique (nombre de patients) | Sites d'occlusion (méthode d'évaluation) | Délai d'évaluation de la recanalisation (méthode d'évaluation) | Incidence de recanalisation |
|---|---|---|---|---|
| **Parsons *et al.**[38] Essai randomisé Phase IIb** | TNK 0.1mg/kg (n=24) *vs.* rtPA 0.9mg/kg (n=23) | ACI-T/L 2% M1 81% M2 13% Autre 4% (CTA) | 24h (ARM) | Complète: 35% (TNK) *vs.* 36% (rtPA) *P*=0.91<br><br>Partielle ou complète: 78% (TNK) *vs.* 68% (rtPA) *P*=0.51 |
| **Parsons *et al.**[38] Essai randomisé Phase IIb** | TNK 0.25mg/kg (n=25) *vs.* rtPA 0.9mg/kg (n=23) | ACI-T/L 0% M1 77% M2 17% Autre 6% (CTA) | 24h (ARM) | Complète: 80% (TNK) *vs.* 36% (rtPA) *P*=0.002<br><br>Partielle ou complète: 96% (TNK) *vs*. 68% (rtPA) *P*=0.02 |
| **ATTEST†[39] Essai randomisé Phase II** | TNK 0.25mg/kg (n=35) *vs.* rtPA 0.9mg/kg (n=38) | ACI-T/L 29% M1 46% M2 17% Autre 9% (CTA) | 24-48h (CTA) | Partielle ou complète: 66% (TNK) *vs*. 74% (rtPA) *P*=0.38 |
| **Molina *et al.*[40]** Etude observationnelle** | TNK 0.4mg/kg (n=42) *vs.* rtPA 0.9mg/kg (n=80) | M1 69% M2 31% (DTC) | 2h (DTC) | Complète: 42% (TNK) *vs.* 32% (rtPA) *P*=0.014<br><br>Partielle ou complète: 69% (TNK) *vs.* 53% (rtPA) *P*=0.028 |

*: Exclusion de 3 patients sans occlusion visible. †: Exclusion de 21 patients sans occlusion visible.

** : Seul un résumé à été publié.

*Abréviations* : ACI-T/L : terminaison carotide en T ou L ; ACM : artère cérébrale moyenne ; ARM : angiographie par résonnance magnétique ; CTA : angioscanner ; DTC : doppler transcrânien ; M1 : premier segment de l'ACM ; M2 : deuxième segment de l'ACM ; rtPA : activateur tissulaire recombinant du plasminogène; TNK : tenecteplase.

### V.2.2 Thérapies adjuvantes à la thrombolyse intraveineuse

#### V.2.2.1 Thérapies actives sur la dégradation de fibrine

L'alpha-2-antiplasmine, le PAI-1, et l'inhibiteur de la fibrinolyse activé par la thrombine (TAFI) sont trois enzymes inhibant la voie de la fibrinolyse. Ainsi, leur inhibition thérapeutique pourrait permettre d'améliorer la fibrinolyse et, par conséquent, la recanalisation. Cependant, aucun travail publié – y compris pré-clinique – n'a étudié l'effet de l'inhibition de ces enzymes sur la recanalisation.

#### V.2.2.2 Thérapies actives sur d'autres constituants du thrombus

Le thrombus contient des proportions très variables en fibrine, plaquettes, globules rouges et globules blancs,[46] et le rtPA n'est actif que sur la lyse de fibrine. Ainsi, son association à d'autres produits, actifs sur les autres constituants du thrombus, ouvre des perspectives thérapeutiques intéressantes. Le facteur von Willebrandt (vWF) et les « *Neutrophil Extracellular Traps* » (NETs), deux constituants du thrombus récemment mis en évidence, présentent un intérêt particulier car accessibles à des thérapies.

*Les NETs* sont des réseaux de chromatine décondensée et de protéines granulaires, sécrétés par les polynucléaires neutrophiles dans l'espace extracellulaire. Ils sont impliqués, entre autres, dans les processus de thrombose. Leur présence en quantité variable dans les thrombi intracrâniens récupérés lors de procédures de thrombectomie a été récemment démontrée.[47,48] Dans ces études, l'application conjointe *in vitro* de rtPA et de DNAse (une enzyme catalysant l'ADN, et donc les NETs) améliorait la lyse des thrombi, en comparaison au rtPA seul,[47,48] ouvrant des perspectives thérapeutiques.

*Le vWF* est une glycoprotéine plasmatique jouant un rôle important dans la formation des thrombus artériels, en recrutant les plaquettes circulantes et en les liant entre-elles ou à l'endothélium environnant. Récemment, l'efficacité de l'administration de la protéase ADAMTS-13 ou de N-Acétyl-cystéine, deux agents permettant de cliver le vWF, a montré son efficacité sur la recanalisation dans des modèles murins d'AIC présentant des thrombi riches en plaquettes.[49,50]

#### V.2.2.3 Autres thérapies

La sonothrombolyse consiste à appliquer un faisceau d'ultrasons par voie transcrânienne au site du thrombus, en association ou non au rtPA, dans l'optique de favoriser la recanalisation. Cette procédure a fait l'objet de quelques études depuis le début des années 2000, montrant sa supériorité en comparaison au rtPA seul en termes de recanalisation précoce dans des essais de phase II.[51-53] Cependant, sa mise en œuvre nécessite des opérateurs très entrainés, limitant sa généralisation. Un casque de sonothrombolyse récemment développé pour tenter de pallier cette limite et utilisable par du personnel non formé au Doppler, permet de délivrer les ultrasons sur l'ensemble du territoire sylvien *via* plusieurs sondes.[54] Malheureusement, les résultats de l'essai randomisé de phase III testant son efficacité en comparaison à la thrombolyse intraveineuse seule semblent négatifs (résultats présentés en 2015 au congrès de *l'European Stroke Conference*, non publiés à ce jour).

### V.3 Intérêts de la prédiction de la recanalisation précoce et de la compréhension des mécanismes physiopathologiques sous-jacents

Le développement d'outils prédictifs de la survenue d'une recanalisation précoce post-thrombolyse intraveineuse, et parallèlement l'amélioration de la compréhension des mécanismes physiopathologiques sous-tendant celle-ci pourraient avoir des implications cliniques importantes. Premièrement, ces connaissances pourraient aider à la sélection des patients les plus adaptés dans des essais randomisés testant différentes stratégies thérapeutiques (thrombolyse seule *vs.* bridging ou bridging *vs.* thrombectomie seule ; voir ci-dessus), dans l'optique d'une médecine personnalisée permettant de réduire les complications iatrogènes et les coûts. Deuxièmement, elles pourraient orienter le développement de nouvelles thérapeutiques intraveineuses augmentant le taux de recanalisations précoces.

Les données disponibles lors de la conception de cette thèse sur les facteurs prédictifs de la recanalisation précoce post-thrombolyse intraveineuse sont présentées ci-après.

## VI. Facteurs prédictifs et mécanismes sous-tendant la recanalisation artérielle précoce

### VI.1 Données disponibles lors de la conception de la thèse

Les données disponibles lors de la conception de cette thèse sur les facteurs prédictifs et les mécanismes sous-tendant la recanalisation étaient majoritairement issues d'études évaluant la recanalisation 24 heures après la thrombolyse intraveineuse. En effet, à cette époque, le bridging n'avait pas encore fait preuve de sa supériorité en comparaison à la thrombolyse seule, et très peu d'études disposaient de données sur la recanalisation précoce (en pratique, dans les toutes premières heures suivant la thrombolyse). Si les données sur la recanalisation à 24h donnent des pistes de recherche pour l'étude des facteurs prédictifs et mécanismes sous-tendant la recanalisation précoce, elles ne sont plus pertinentes cliniquement à l'ère de la thrombectomie car elles incluent des recanalisations tardives, sans bénéfice clinique significatif.

La plupart des travaux disponibles sur la recanalisation *précoce* lors de la conception de la thèse combinaient thrombolyse intraveineuse et sonothrombolyse. Les rares études concernant la thrombolyse intraveineuse seule (sans sonothrombolyse associée) évaluaient la recanalisation précoce sur le premier jet de l'artériographie dans des populations de bridging réalisé à l'époque « hors AMM », volontiers biaisées (patients les plus sévères, les plus jeunes, *etc*...), ou à l'aide d'une imagerie non invasive mais incluant une proportion inconnue de patients qui, aujourd'hui, ne seraient pas candidats au bridging (occlusion trop distale, cœur ischémique très étendu, *etc*...).

Dans ce qui suit, nous détaillerons les principaux facteurs vasculaires et biologiques ayant montré une association avec la recanalisation post-thrombolyse à 24h, ou avec la recanalisation précoce post-thrombolyse associée à de la sonothrombolyse. Les données disponibles concernant la recanalisation précoce après thrombolyse intraveineuse seule seront détaillées dans la revue systématique avec méta-analyse présentée en **Partie 1** de la thèse.

### VI.2 Facteurs vasculaires

#### VI.2.1 Thrombus

Les caractéristiques du thrombus apparaissent comme un élément prédictif important de la survenue d'une recanalisation post-thrombolyse intraveineuse. Plusieurs études suggèrent que la localisation, la longueur ou la « charge » en thrombus, sont associées de manière forte et indépendante à la recanalisation évaluée 24h après la thrombolyse.[55-59] Ces données semblent robustes car montrées dans plusieurs cohortes indépendantes, quelle que soit la méthode d'imagerie utilisée pour l'évaluation des caractéristiques du thrombus (scanner sans injection, angioscanner ou séquence T2* en IRM).[55-59] Ainsi, la thrombolyse intraveineuse lyserait plus difficilement les thrombus les plus volumineux.

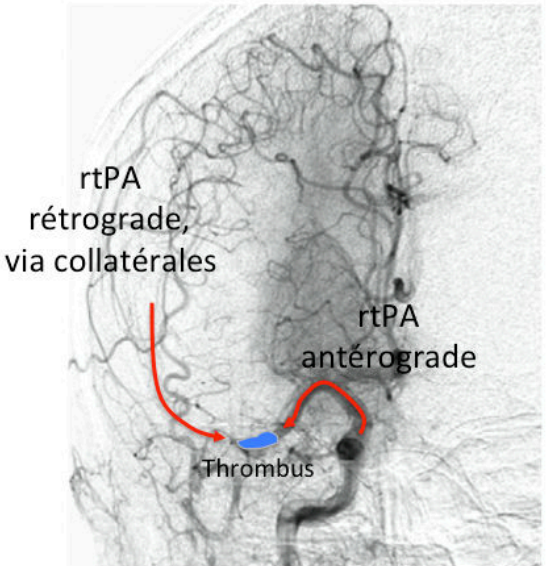
Par ailleurs, une étude a montré une association indépendante entre la présence d'un flux résiduel en aval du thrombus (évalué en Doppler transcrânien) et la survenue d'une recanalisation précoce après thrombolyse intraveineuse associée à la sonothrombolyse.[60] Ceci suggèrerait que le traitement thrombolytique lyserait plus facilement les thrombi partiellement perméables, en pénétrant dans ces derniers.[60]

Enfin, la forme du thrombus a également été rapportée comme associée à la recanalisation à 24h dans la seule étude s'y étant intéressé : les thrombi non rectilignes ou situés à cheval sur une bifurcation artérielle avaient une moindre probabilité de recanalisation post-thrombolyse.[59] Le(s) mécanisme(s) sous-tendant cette possible association restent cependant obscurs.

### VI.2.2 Perfusion cérébrale et collatérales

Deux études suggèrent qu'une hypoperfusion cérébrale moins sévère serait associée à la survenue d'une recanalisation artérielle évaluée 24h après thrombolyse intraveineuse.[61,62] Cependant, les caractéristiques du thrombus n'étaient pas prises en comptes dans les analyses statistiques, et il n'est pas certain que cette association soit indépendante des autres marqueurs d'intérêt. Même si parmi les différentes hypothèses évoquées pour expliquer cette association celle de collatérales leptoméningées de bonne qualité semble la plus séduisante, il n'existe aucune preuve de sa véracité à ce jour. La circulation collatérale leptoméningée, dont la qualité varie grandement d'un individu à l'autre, est le réseau vasculaire alternatif permettant d'apporter un flux sanguin résiduel aux régions ischémiques en aval d'une occlusion artérielle.[63] En effet, la présence de bonnes collatérales, et de là d'une hypoperfusion cérébrale moins sévère, favoriserait la recanalisation en facilitant l'accès du thrombolytique aux deux extrémités du thrombus (**Figure 2**).[64]

**Figure 2.** Illustration de l'hypothèse physiopathologique liant la présence d'un bon réseau artériel collatéral à la recanalisation : accès facilité du rtPA aux deux extrémités du thrombus.



### VI.3 Facteurs biologiques

Très peu d'études se sont intéressées aux facteurs biologiques associés à la recanalisation post-thrombolyse, les seules données disponibles étant issues de deux cohortes espagnoles incluant des patients traités par thrombolyse intraveineuse associée à une sonothrombolyse. Ces travaux ont montré une association entre les inhibiteurs de la fibrinolyse (alpha-2-antiplasmine,[65] PAI-1,[66] et TAFI[67]) et la survenue d'une recanalisation précoce. Malgré leur intérêt, ces résultats sont sujet à caution dans la mesure où les principaux facteurs confondants n'étaient pas pris en compte dans l'analyse multivariée de ces études, notamment les caractéristiques du thrombus.

## VII. Objectifs de la thèse, hypothèses de travail et plan de la thèse

Les deux objectifs principaux de cette thèse sont d'étudier l'incidence et les facteurs prédictifs vasculaires de la recanalisation précoce après thrombolyse intraveineuse d'un AIC avec occlusion artérielle proximale, et de là, d'éclaircir les mécanismes physiopathologiques sous-tendant la recanalisation précoce post-thrombolyse. A partir des facteurs prédictifs, un objectif supplémentaire est d'établir des scores (association de plusieurs facteurs indépendants) prédictifs de recanalisation précoce, utilisables en routine clinique, visant à aider à sélectionner les patients les plus adaptés pour des essais randomisés testant de nouvelles stratégies de prise en charge.

Les **hypothèses de travail** sont que les caractéristiques du thrombus (localisation, longueur, perméabilité) et la qualité du réseau collatéral (ou la sévérité de l'hypoperfusion cérébrale) sont associés de manière indépendante à la recanalisation précoce après thrombolyse intraveineuse.

La **première partie** de la thèse sera consacrée à une revue systématique des données de la littérature disponibles lors du commencement de celle-ci, sur l'incidence et les facteurs prédictifs de recanalisation précoce après thrombolyse intraveineuse.

La **deuxième partie** détaillera l'incidence et les facteurs prédictifs de recanalisation précoce dans une large cohorte multicentrique française d'AIC avec occlusion proximale, traités par rtPA et transférés pour thrombectomie depuis la validation du bridging en 2015 (cohorte PREDICT-RECANAL). Elle visera également à créer et valider des scores prédictifs de recanalisation précoce post-thrombolyse.

La **troisième partie** étudiera plus spécifiquement l'effet de la perfusion cérébrale et des collatérales sur la recanalisation précoce dans le sous-groupe de patients de la cohorte PREDICT-RECANAL pour lequel une IRM de perfusion était disponible à l'admission.

La **quatrième partie** sera consacrée à l'incidence et facteurs prédictifs de recanalisation précoce post-thrombolyse dans le sous-groupe de patients de la cohorte PREDICT-RECANAL avec déficit neurologique mineur et occlusion proximale.

La **cinquième partie** comparera l'incidence de la recanalisation précoce pré-thrombectomie, après thrombolyse intraveineuse par tenecteplase, en comparaison à l'alteplase.

Enfin, dans la **sixième partie**, nous présenterons une synthèse des résultats, des limites et des perspectives des travaux présentés dans les cinq parties précédentes.

# Première partie :
# Revue systématique et méta-analyse des données de la littérature sur l'incidence et les facteurs prédictifs de recanalisation précoce après thrombolyse intraveineuse

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Cette première partie a fait l'objet d'une publication dans *Stroke* en septembre 2016, dont le manuscrit est inséré ci-après. La version revue est également disponible en **Annexe 1**.

**Résumé :** L'objectif de cette étude était de faire une revue complète des données de la littérature publiées entre 1990 et 2016, associée à une méta-analyse, sur i) l'incidence de la recanalisation précoce après thrombolyse intraveineuse (définie comme survenant dans les 3h suivant le début de la thrombolyse) ; et ii) les facteurs prédictifs de l'absence de recanalisation précoce. Les études associant une sonothrombolyse au rtPA intraveineux étaient exclues. Au total, 26 études répondaient aux critères d'inclusion, incluant un total de 2063 patients.

*Incidence de recanalisation précoce :* L'incidence de recanalisation précoce complète était de 20% (IC95% 15-26), et variait de manière significative selon le site d'occlusion sur l'imagerie vasculaire pré-thrombolyse: 38% (IC95% 22-54) en cas d'occlusion M2-M3, 21% (IC95% 15-29) en cas d'occlusion M1, 4% (IC95% 1-8) en cas d'occlusion de la terminaison carotide, et 4% (IC95% 0-22) en cas d'occlusion basilaire. L'incidence de recanalisation complète était de 18% (IC95% 10-28) dans la méta-analyse incluant uniquement les patients avec intention de bridging (à savoir, avec évaluation de la recanalisation sur le premier jet de l'artériographie).

*Facteurs prédictifs de recanalisation précoce :* Un site d'occlusion très proximal (terminaison carotide ou M1) et la présence d'un score NIHSS élevé étaient les deux facteurs principaux associés à l'absence de recanalisation précoce. Plusieurs autres facteurs semblaient prometteurs pour la prédiction de l'absence de recanalisation précoce, mais n'ont été évalués que sur un faible nombre de patients et nécessitent donc d'être confirmés dans de plus larges cohortes : un thrombus de longue taille, le caractère totalement occlusif du thrombus, et un réseau artériel collatéral de mauvaise qualité.

*Conclusions*: L'incidence de recanalisation précoce après thrombolyse intraveineuse est loin d'être négligeable, et rend ainsi nécessaire sa prédiction, notamment pour limiter les transferts futiles en thrombectomie. Hormis le site d'occlusion et le score NIHSS, peu de données sont disponibles sur les facteurs prédictifs de recanalisation précoce. D'autres études sur de larges cohortes sont nécessaires.

**Indicidence and predictors of early recanalization following IV thrombolysis. A systematic review and Meta-Analysis.** Seners P*, Turc G*, Maïer B, Oppenheim C, Mas JL, Baron JC. Stroke 2016 Sep;47(9):2409-12.
*Equal contribution.


**Abstract**

**Background and purpose:** Following the demonstration of efficacy of bridging therapy, reliably predicting early recanalization (ER; ≤3hrs after start of intravenous thrombolysis; IVT) would be essential to limit futile, resource-consuming interhospital transfers. We present the first systematic review on the incidence and predictors of ER following IVT alone.

**Methods:** We systematically searched for studies including patients solely treated by IVT that reported incidence of ER and/or its association with baseline variables. Using meta-analyses we estimated pooled incidence of ER, including according to occlusion site, and summarized the available evidence regarding predictors of no-ER.

**Results:** We identified 26 studies that together included 2063 patients. The overall incidence of partial or complete ER was 33% (95%CI: 27-40). It varied according to occlusion site: 52% (39-64) for distal middle cerebral artery (MCA), 35% (28-42) for proximal MCA, 13% (6-22) for intracranial carotid artery, and 13% (0-35) for basilar occlusion. Corresponding rates for complete ER were 38% (22-54), 21% (15-29), 4% (1-8) and 4% (0-22), respectively. Proximal occlusion and higher NIHSS were the most consistent no-ER predictors. Other factors, such as long or totally occlusive thrombus and poor collateral circulation emerged as potential predictors but will need confirmation.

**Conclusion:** The overall incidence of ER following IVT is substantial, highlighting the importance of reliably predicting ER to limit futile inter-hospital transfers. Incidence of no-ER is particularly high for proximal occlusion and severe strokes. Given the scarcity of published data, further studies are needed to improve no-ER prediction accuracy.

## Introduction

Recent randomized trials demonstrated the superiority of bridging therapy (mechanical thrombectomy [MT] added on intravenous thrombolysis [IVT]) over IVT alone for the treatment of acute stroke due to large artery occlusion.[68] However, endovascular procedures can currently be provided in comprehensive stroke centers only. Therefore, candidates for MT admitted to primary stroke centers or general hospitals should urgently be transferred after initiation of IVT, and futile interhospital transfers (*i.e.*, patients who ultimately do not undergo MT) due to early recanalization (ER) are as high as 30%.[33] Consequently, it is essential to improve no-ER prediction based on admission data in order to limit futile, resource-consuming interhospital transfers. To date, two published meta-analyses have provided partial data on recanalization rates following IVT, but the first merged early- and later-assessed recanalization,[6] while the second included only sonothrombolysis trials.[69] Moreover, neither provided information on incidence of ER according to site of occlusion, nor on ER predictors.

We therefore performed a systematic review and meta-analysis of the incidence and predictors of ER following IVT.

## Methods

The manuscript was prepared in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines. Studies published between 1/01/1990 and 27/01/2016 were eligible for review if they: (1) enrolled ≥15 IVT-treated stroke patients; (2) confirmed the presence of arterial occlusion before IVT; and (3) reported data on incidence or predictors of ER. ER was defined as occurring ≤3hrs after initiation of IVT, regardless of the imaging method used. Details on search strategy, study exclusion criteria, data extraction, assessment of study quality, and definition of complete and partial ER are provided in the **Supplemental Methods** and **Supplemental Tables I-III**.

### Statistical analysis

Estimates of proportions (incidence) of ER were pooled after Freeman–Tukey double arcsine method and then back-transformed onto the original scale. Given the heterogeneity regarding modalities and timing of recanalization assessment across studies, we computed random-effects pooled ER incidences. The methods used to summarize available data on no-ER predictors are described in the **Supplemental Methods**. A meta-analysis was performed only for variables assessed in ≥4 studies.

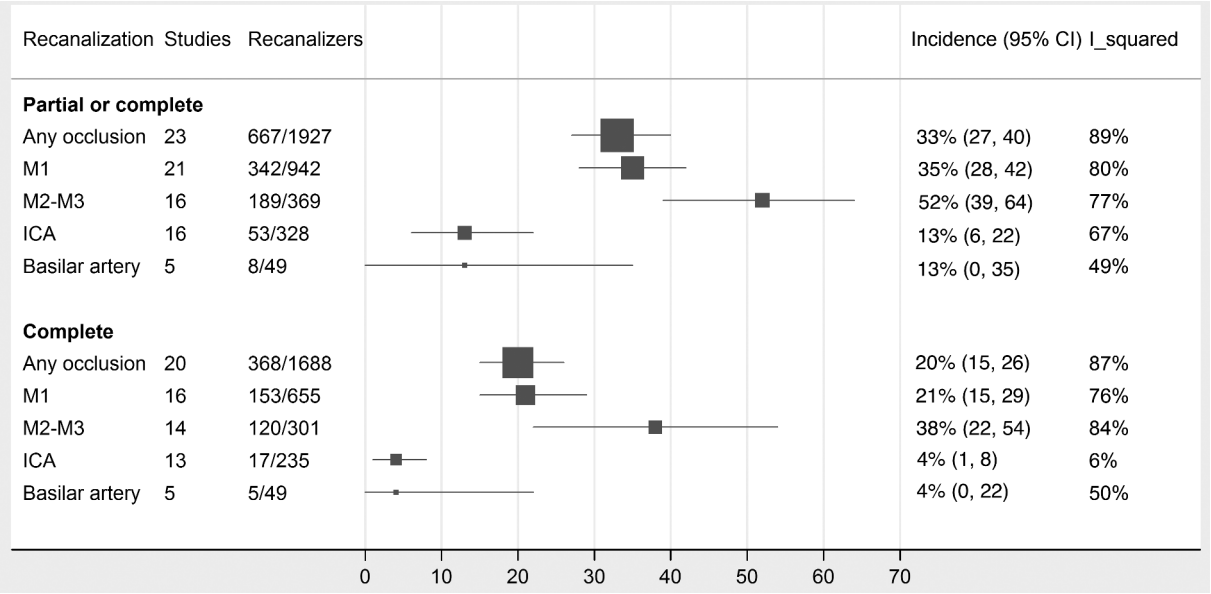
**Results**

Twenty-six studies were included in this review (**Supplemental Figure I**). The list and characteristics of the included studies (including imaging method and scale used) are summarised in **Supplemental Table IV**.

**Incidence of ER**

The overall incidence of *partial or complete* ER was 33% (95%CI: 27-40), and that of *complete* ER was 20% (15-26) (**Figure 1**). The incidence of *partial or complete* ER was 52% (39-64) for distal middle cerebral artery (MCA, M2-M3) occlusion, 35% (28-42) for proximal MCA (M1) occlusion, 13% (6-22) for intracranial carotid artery (ICA) occlusion, and 13% (0-35) for basilar artery (BA) occlusion. Corresponding incidence for *complete* ER were 38% (22-54), 21% (15-29), 4% (1-8) and 4% (0-22), respectively **(Figure 1)**. The details of each meta-analysis are presented in **Supplemental Figures II-XI**. Incidence of *partial or complete* ER was significantly lower in studies using digital subtraction angiography (DSA) compared with other methods, but complete ER rate was similar across imaging modalities (**Supplemental Results**). Funnel plots did not suggest publication bias (**Supplemental Figure XII**).

**Figure 1:** Incidence of ER according to occlusion site and degree of recanalization.

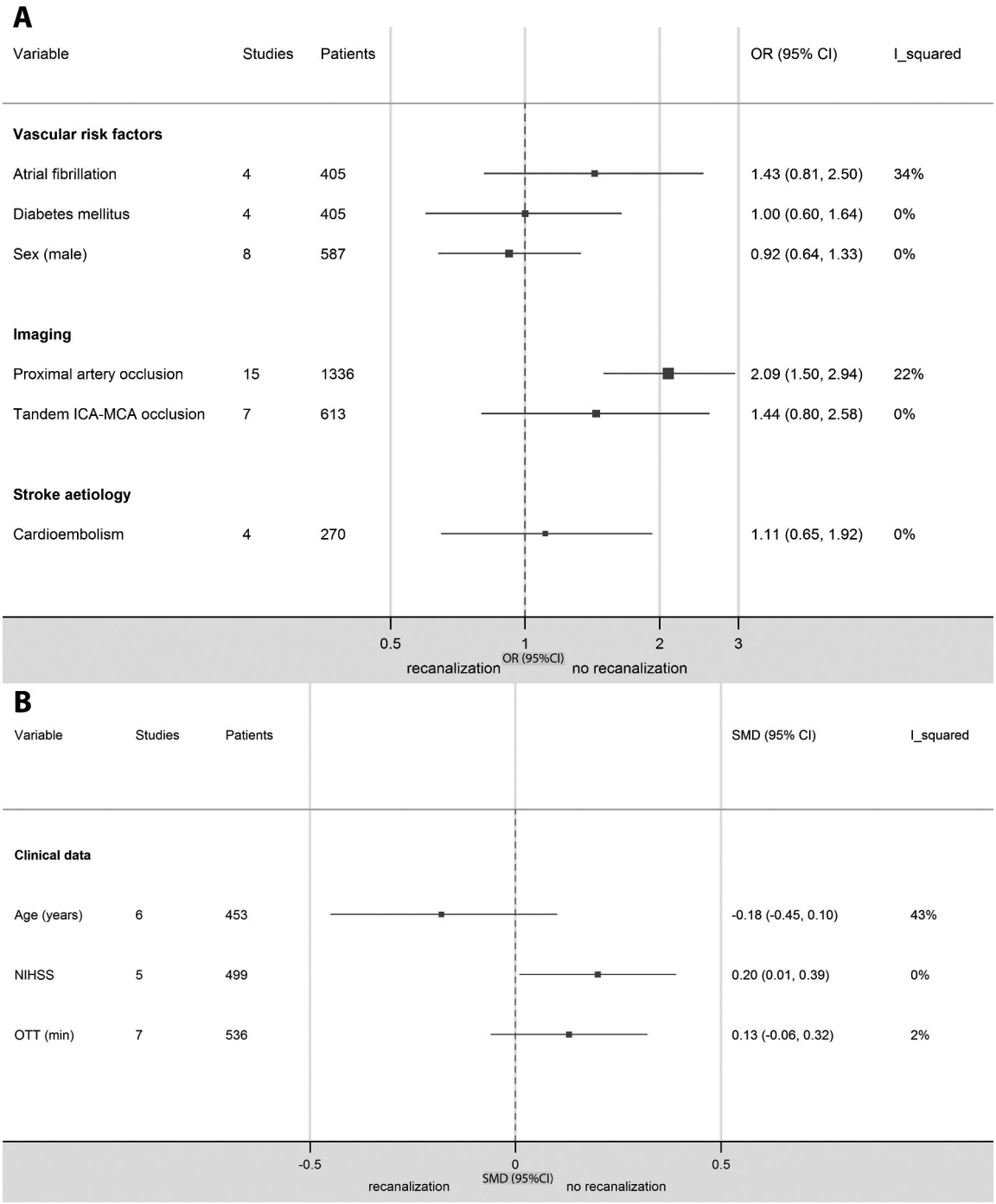



*Legend:* studies: number of studies included; recanalizers: number of patients with ER/total number.

**No-ER predictors**

For anterior circulation strokes, proximal occlusion (M1 or ICA) was a strong predictor of no-ER (OR=2.09; 95%CI 1.50-2.94, **Figure 2**). Higher admission NIHSS score was the only clinical variable associated with no-ER (Standardized mean difference=0.20; 95%CI 0.01-0.39, **Figure 2**).

**Figure 2:** Summary odds ratios and standardized mean differences for the associations between no-ER and (A) categorical and (B) continuous baseline variables measured in IVT-treated patients in ≥4 studies.




*Legend*: OTT: Onset-to-treatment time

The results of the systematic review regarding no-ER predictors assessed in less than 4 studies are presented in **Table 1** and **Supplemental Table VI**. Variables associated with no-ER were: poor arterial collaterals on arteriography; M1 susceptibility vessel sign on T2*-MR; clot located <10mm from MCA origin; long thrombus; no residual flow within the clot on CT-angiography (CTA); no anterograde flow beyond the clot on 4-dimensional CTA; and low HDL-cholesterol.

**Table 1:** Predictors of no-ER assessed in <4 studies.

| Predictor | Number of patients | OR (CI 95%) or P-value |
|---|---|---|
| **Poor collaterals**[70] | 32 | 5.33 (1.07-26.61)* |
| **Long thrombus**[71,72,73] | 228[71] | P<0.001 |
| | 96[72] | P=0.01 |
| | 41[73] | P=0.15 |
| **Thrombus location <10mm from MCA origin**[71] | 117 | 3.06 (1.22-7.69)* |
| **M1 Susceptibility Vessel Sign on T2*-MR**[74] | 132 | 7.16 (1.76-29.17)† |
| **No anterograde blood flow beyond the thrombus on 4D-CTA**[75] | 67 | 13.25 (2.08-84.52)* |
| **No residual blood flow in thrombus on CTA**[71] | 228 | 6.25 (3.03-14.29)* |
| **Low HDL-cholesterol**[76] | 70 | P=0.004† |

*Calculated from raw data. †Multivariable analysis.

**Discussion**

Here we focused on the incidence of ER following IVT and its predictors, with the objective to assist patient triaging for MT.

*Incidence of ER*

Overall, *partial or complete* ER occurred in 33%, and *complete* ER in 20% of patients. We found lower ER rates in ICA than M1, and even more so than M2-M3 occlusions. The overall rate of ER following IVT is consistent with the reported rate of futile inter-hospital transfers for MT,[33] with the majority of the latter representing ER.

*Predictors of no-ER*

Proximal occlusion site was the strongest no-ER predictor. Moreover, thrombus location within 10mm from MCA origin predicted higher no-ER rate.[71]

Several other potential radiological predictors of no-ER emerge from this systematic review but have been assessed in few studies. First, poor collaterals was predictive of no-ER in one angiography study,[70] consistent with another study reporting that MR-perfusion-based collaterals influenced recanalization rate 24hrs after IVT.[61] Good collaterals would facilitate retrograde access of the thrombolytic agent to the thrombus. Second, long thrombi, intuitively more resistant to IVT, appear predictive of no-ER.[71-73] Lastly, completely occlusive thrombi appear strongly associated with no ER,[71,75] as studied using standard CTA[71] or 4-dimensional CTA.[75] This association was also reported using a novel CT-perfusion-based evaluation of thrombus permeability, although ER was assessed at slightly later timepoints.[77] All the above points to the crucial role advanced imaging may hold in predicting no-ER following IVT. For instance, collaterals can now be evaluated using multiphase-CTA, CT-perfusion, perfusion-MRI or conventional MRI.[64] Among clinical factors, higher NIHSS was the only no-ER predictor. However, this may reflect the strong association between NIHSS and occlusion site.

The present meta-analysis has several limitations. First, a substantial heterogeneity between studies regarding ER incidence was observed. This can be explained by selection bias in DSA studies and variable recanalization scales, time of baseline and post-IVT imaging among studies. Moreover, the accuracy of recanalization assessment may vary among imaging methods. Second, as the majority of patients included in this systematic review had M1 occlusion, our findings regarding ER prediction mainly apply to this stroke subtype. Lastly, this systematic review was limited by the scarce data available for the majority of admission variables, preventing strong conclusions.

**In conclusion**, the incidence of ER following IVT is substantial, pointing to the importance of reliably predicting it to avoid futile interhospital transfers. Although proximal occlusion site was confirmed as the strongest no-ER predictor, this systematic review identified additional potential predictors from advanced imaging that may in the future improve ER prediction. Further studies are needed to confirm the latter and identify novel markers, aiming towards improved patient triaging for bridging procedures.

**Supplemental material**

## Supplemental Methods

The manuscript was prepared in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines.[78]

*Selection Criteria and Definition of ER*

We did not include studies that combined intravenous thrombolysis (IVT) with other therapeutic interventions, such as sonothrombolysis, considering their potential effects on recanalization rate.[69] Studies on bridging therapy were included only if the vascular status before the endovascular procedure was available, which ensured that early recanalization (ER) was solely due to IVT.

ER was defined as occurring ≤3hrs after initiation of IVT, which seems a reasonable upper limit to start endovascular procedures following IVT. ER was considered as *complete* if reaching grade 4-5 on the Thrombolysis in Brain Infarction (TIBI) scale, 3 on the Arterial Occlusive Lesion (AOL) and Thrombolysis in Myocardial Infarction (TIMI) scales, 2b-3 on the Thrombolysis in Cerebral Infarction (TICI) or modified-TICI (mTICI) scales, or 3-4 on the Mori scale (**Supplemental Table I**).[79] We also considered a second category combining *partial or complete* recanalization, defined as grade ≥2 on AOL, TIMI, TICI, mTICI, or Mori's scales, or as improvement in flow signal by ≥1 TIBI grade.

*Search Strategy*

We searched Medline and Embase for articles published between 1/01/1990 and 27/01/2016, using the terms detailed in **Supplemental Table II**. We also hand-searched the reference lists of all included articles, any relevant review articles, and books of abstracts from recent international stroke conferences. A first reviewer was responsible for the entire selection process. From a random sample (10%) of all articles, a second reviewer assessed the reproducibility of the process. When two or more articles from the same group used an expanded cohort, we included only the article reporting the largest sample.

*Data Extraction and Evaluation of Study Quality*

Using a standardized form (**Supplemental table III**), two readers independently extracted data from selected articles. All discrepancies were resolved by consensus. Whenever appropriate, authors were contacted to obtain further information. For the three studies that assessed the incidence of ER at two different timepoints after IVT in the same cohort, only the data pertaining to 3hrs were used.

The quality of included studies was scored using items derived from the STROBE checklist (**Supplemental Table IV**).[80]

*Statistical Analysis*

Incidence of ER

Estimates of proportions (incidences) of ER were pooled after Freeman–Tukey double arcsine method and then back transformed onto the original scale.[81] 95% confidence intervals (CIs) around these estimates were calculated using the Wilson method. Heterogeneity across studies was assessed using Cochran's Q (reported as a P-value) and the $I^2$ statistics. Given the heterogeneity regarding the modalities and timing of recanalization assessment across studies, we decided *a priori* to compute random-effects rather than fixed-effect pooled incidences of ER. Potential sources of heterogeneity were investigated by stratifying studies according to potentially relevant variables, such as the dose of alteplase or the imaging method used for recanalization assessment, and by meta-regression. Publication bias was investigated using funnel plots.

Associations between baseline variables and no-ER

Given the heterogeneity regarding the modalities of recanalization assessment across studies, we decided to compute random-effects rather than fixed-effect meta-analysis of potential predictors of no-ER. However, because the between-study heterogeneity may only be accurately estimated in a random-effects model including more than 3 studies[6], we performed a meta-analysis for potential predictors assessed only in case at least 4 studies were available. For each binary predictor assessed in at least 4 studies, crude Odds Ratios (OR) and 95%CI were recorded or calculated in each study, and pooled as a global OR (95%CI) in a random-effects meta-analysis. For each continuous predictor assessed in at least 4 studies, mean, standard deviation and sample size were recorded in each study, and summarized as pooled standardized mean difference (SMD) and its 95%CI in a random-effects meta-analysis. Statistical analysis and plots were done using STATA 11.0 (Statacorp) and SAS 9.4 (SAS Inc).

**Supplemental Results**

*Incidence of ER according to imaging modality*

Analysis of ER incidence according to imaging modality (DSA *vs* others) was only performed for M1 occlusions because the other subgroups were too small. Incidence of *partial or complete* ER was significantly lower in studies using DSA compared with other methods (27%, 95%CI 20-35, $I^2$=69% *vs* 46%, 95%CI 35-57, $I^2$=75%, respectively; P=0.01). However, *complete* ER rate was similar (18%, 95%CI 10-28 and 25%, 95%CI 14-37, respectively; P=0.46).

*Incidence of ER according to alteplase dose*

Most studies used alteplase at the dose of 0.9 mg/kg, except 6 using the 0.6 mg/kg dose, and one using a fixed dose of 100 mg. Analysis of ER incidence according to alteplase dose was feasible for M1 occlusions only. Incidence of *partial or complete* ER was similar for the two doses, namely 34% (95%CI 22-47, $I^2$=86%) and 38% (95%CI 25-51, $I^2$=73%) for 0.9mg/kg and 0.6mg/kg, respectively (P=0.65). The results were similar for *complete* ER: 22% (95%CI 12-33) and 23% (95%CI 13-35), respectively (P=0.88).

**Supplemental Table I:** Recanalization scales used in the included studies.

| Scale | Details |
|---|---|
| **TIMI**[82] | **0:** No perfusion<br>**1:** Perfusion past the initial occlusion, but no distal branch filling<br>**2:** Perfusion with incomplete or slow distal branch filling<br>**3:** Full perfusion with filling of all distal branches, including M3-4 |
| **TICI**[83] | **0:** No Perfusion (No antegrade flow beyond the point of occlusion)<br>**1:** Penetration With Minimal Perfusion (The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run)<br>**2:** Partial Perfusion (The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, eg, the opposite cerebral artery or the arterial bed proximal to the obstruction).<br>**2a:** Only partial filling (<2⁄3) of the entire vascular territory is visualized.<br>**2b:** Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.<br>**3:** Complete Perfusion. Anterograde flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery. |
| **mTICI**[84] | **0:** No perfusion<br>**1:** Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion<br>**2a:** Perfusion of less than half of the vascular distribution of the occluded artery (eg, filling and perfusion through 1 M2 division)<br>**2b:** Perfusion of half or greater of the vascular distribution of the occluded artery (eg, filling and perfusion through 2 or more M2 divisions)<br>**3:** Full perfusion with filling of all distal branches |
| **TIBI**[85] | **0:** Absent (Absent flow signals)<br>**1:** Minimal (Systolic spikes of variable velocity and duration. Absent diastolic flow during all cardiac cycles)<br>**2:** Blunted (Flattened systolic flow acceleration of variables duration compared to control. Positive end diastolic velocity and pulsatility index<1.2)<br>**3:** Dampened (Normal systolic flow acceleration. Positive end diastolic velocity. Decreased mean flow velocities (MFV) by>30% compared to control)<br>**4:** Stenotic (MFV of >80cm/s and velocity difference of >30% compared to the control side)<br>**5:** Normal (<30% mean velocity difference compared to control. Similar waveform shapes compared to control) |
| **AOL**[86] | **0:** No recanalization of the occlusion<br>**1:** Incomplete or partial recanalization of the occlusion, with no distal flow<br>**2:** Incomplete or partial recanalization of the occlusion, with any distal flow<br>**3:** Complete recanalization of the occlusion with any distal flow |
| **Mori**[87] | **0:** Unchanged<br>**1:** Movement of thrombus not associated with any improvement of perfusion<br>**2:** Partial (branch) recanalization with reperfusion in less than 50% of ischemia-related area<br>**3:** Partial (branch) recanalization with reperfusion in more than 50% of ischemia-related area<br>**4:** Complete or near-complete recanalization with full return of perfusion |

AOL: Arterial occlusive lesion ; TIBI: Thrombolysis in Brain Ischemia ; TICI: Thrombolysis in Cerebral Infarction ; mTCI: modified TICI ; TIMI: Thrombolysis in Myocardial Infarction.

**Supplemental Table II:** Search terms in MEDLINE and EMBASE

| | |
|---|---|
| MEDLINE search | ("Recanalization" [All Fields] OR "Reperfusion" [Mesh]) AND ("Thrombolysis" [All Fields] OR "Fibrinolysis" [All Fields] OR "Thrombolytic therapy" [Mesh]) AND ("Stroke" [Mesh] OR "Cerebrovascular disorders" [Mesh] OR "Ischemic stroke" [All Fields]) AND ("1990/01/01" [PDAT] : "2016/01/27" [PDAT]) AND "humans" [MeSH Terms] AND English [lang] |
| EMBASE search | 'recanalization'/exp OR 'reperfusion'/exp AND ('thrombolysis'/exp OR 'thrombolytic therapy'/exp) AND ('ischemic stroke'/exp OR 'stroke'/exp OR 'cerebrovascular disorders'/exp) AND [english]/lim AND [humans]/lim AND [embase]/lim AND [1-1-1990]/sd NOT [27-01-2016]/sd |

**Supplemental Table III:** Standardized form used for data extraction

| | |
|---|---|
| General information | Publication year |
| | Journal of publication |
| | Abstract only (Yes/No) |
| | First author name |
| Study location, relevant dates | Study location |
| | Mono/Multicentric |
| | Dates of patients inclusion |
| Methods of patients selection | Onset-to-IVT inclusion time |
| | Type of cerebral admission imaging |
| | Type of vascular admission imaging |
| | Dose of Alteplase used |
| Information on ER evaluation | Type of ER imaging |
| | Timing of ER evaluation |
| | Scale used for ER evaluation |
| | Definition used for partial ER |
| | Definition used for complete ER |
| Characteristics of included patients | Total number of patients |
| | Number of patients with ICA occlusion |
| | Number of patients with proximal MCA occlusion (M1) |
| | Number of patients with distal MCA occlusion (M2-M3) |
| | Number of patients with tandem occlusion |
| | Number of patients with anterior cerebral artery occlusion |
| | Number of patients with basilar artery occlusion (BA) |
| | Number of patients with vertebral artery occlusion |
| | Number of patients with posterior cerebral artery occlusion |
| | Number of patients with other site of arterial occlusion |
| Data on ER incidence | Total number of patients with *partial or complete* ER |
| | Total number of patients with *complete* ER |
| | Number of *partial or complete* ER in patients with ICA occlusion |
| | Number of *complete* ER in patients with ICA occlusion |
| | Number of *partial or complete* ER in patients with M1 occlusion |
| | Number of *complete* ER in patients with M1 occlusion |
| | Number of *partial or complete* ER in patients with M2-M3 occlusion |
| | Number of *complete* ER in patients with M2-M3 occlusion |
| | Number of *partial or complete* ER in patients with tandem occlusion |
| | Number of *complete* ER in patients with tandem occlusion |
| | Number of *partial or complete* ER in patients with BA occlusion |
| | Number of *complete* ER in patients with BA occlusion |
| General information on study of ER prediction | Study of ER prediction (Yes/No) |
| | Number of predictors studied |
| | Name of predictor (repeated for each predictor) |
| | Number of patients studied for this predictor (repeated for each predictor) |
| Data on ER prediction, for categorical variables | Number of patient with presence of predictor and ER |
| | Number of patient with presence of predictor and no-ER |
| | Number of patient with absence of predictor and ER |
| | Number of patient with absence of predictor and no-ER |
| Data on ER prediction, for continuous variables | Predictor mean (or median), in patients with ER |
| | Predictor standardized deviation (or interquartile range), in patients with ER |
| | Predictor mean (or median), in patients with no-ER |
| | Predictor standardized deviation (or interquartile range), in patients with no-ER |

IVT: intravenous thrombolysis; ER: early recanalization; ICA: intracranial internal carotid artery; MCA: middle cerebral artery; BA: basilar artery.

**Supplemental Table IV:** Characteristics of the 26 studies included in the Systematic Review

| Study | Onset to IVT time | Arterial imaging on admission | Occlusion sites | ER imaging method | Timing of ER evaluation† | ER scale used‡ | N |
|---|---|---|---|---|---|---|---|
| **Von Kummer 1992**[70] | ≤6h | DSA | ICA,MCA | DSA | 90min | TIMI | 32 |
| **Alexandrov 2004**[51] | ≤3h | TCD | MCA | TCD | 60 and 120min | TIBI | 63 |
| **Wunderlich 2005**[88] | ≤6h | TCDD | ICA | TCDD | 90min | TIBI | 15 |
| **Lee 2007**[89] | ≤3h | CTA | ICA,MCA,BA | DSA | M=120min | TICI | 31 |
| **Wunderlich 2007**[90] | ≤6h | TCDD | MCA | TCDD | 90min | TIBI | 99 |
| **Eggers 2008**[52] | ≤3h | TCDD | MCA | TCDD | 60min | TIBI | 18 |
| **Jeong 2009**[91] | ≤3h | CTA | ICA,MCA,VA,BA,PCA | DSA | M≈90min | TIMI | 32 |
| **Mazighi 2009**[92] | ≤3h | CTA/MRA/TCD | ICA,MCA,BA,PCA | DSA | NP | TIMI | 53 |
| **Kawakami 2010**[93] | ≤3h | MRA | ICA,MCA,BA | DSA | 60min | TIMI | 18 |
| **Smadja 2011**[94] | ≤4.5h | MRA | MCA | MRA | 90min | TIMI | 40 |
| **Ernst 2011**[95]* | NP | CTA | MCA | DSA | M=142min | TIMI | 27 |
| **Kimura 2011**[74] | ≤3h | MRA | ICA,MCA | MRA | 120min | S.-M. | 132 |
| **Garcia-Bermejo 2012**[96] | ≤6h | TCDD/TCD | MCA | TCDD/TCD | 60 and 120min | TIBI | 122 |
| **Sanak 2012**[97] | ≤4.5h | CTA/MRA | MCA | TCD/DSA | <180min | TIBI/TICI | 146 |
| **Frölich 2013**[75]* | M≈150min | CTA | ICA,MCA | DSA | M≈85min | TICI | 67 |
| **Koga 2013**[76] | ≤3h | MRA | ICA,MCA | MRA | M≈65min | Mori | 70 |
| **Uzuner 2013**[98] | ≤4.5h | TCD | MCA | TCD | 60min | TIBI | 90 |
| **Behrens 2014**[72] | M=119min | CTA/MRA | ICA,MCA,BA,PCA | DSA | M=98min | TICI | 96 |
| **Yoshimura 2014**[99] | ≤3h | CTA/MRA | ICA,MCA,BA | DSA | 60-180min | mTICI | 194 |
| **Kim 2014**[100]* | NP | CTA/MRA | ICA,MCA | DSA | M=75min | AOL | 118 |
| **Luby 2014**[101] | ≤3h | MRA | ICA,MCA,ACA, BA,VA,PCA | MRA | 180min | S.-M. | 45 |
| **Mishra 2014**[71] | M=120min | CTA | ICA,MCA | DSA | M=70min | TICI | 228 |
| **Von Kummer 2014**[102]* | ≤3h | CTA | ICA,MCA,BA,VA | DSA | NP | NP | 189 |
| **Fjetland 2015**[103] | ≤4.5h | CTA | ICA,MCA,BA | DSA | M=75min | mTICI | 57 |
| **Campbell 2015**[104] | ≤4.5h | CTA | ICA,MCA | DSA | M=74min | mTICI | 35 |
| **Ritzenthaler 2015**[73] | ≤4.5h | MRA | ICA,MCA | MRA | <180min | AOL | 41 |

*Abstract only. †: Timing between initiation of IVT and evaluation of ER. ‡: Details of each scale a presented in supplemental Table 1.

ER: early recanalization. IVT: Intravenous thrombolysis. N: Number of patients. M: mean. NP: Non-precised. TCDD: transcranial duplex Doppler. TCD: transcranial Doppler. CTA: computed tomography angiography. MRA: magnetic resonance angiography. DSA: digital subtracted angiography. ICA: internal carotid artery. MCA: middle cerebral artery. ACA: anterior cerebral artery. PCA: posterior cerebral artery. BA: Basilar artery. VA: vertebral artery. TICI: Thrombolysis in cerebral infarction. mTICI: modified TICI. TIMI: Thrombolysis in myocardial infarction. AOL: Arterial occlusive lesion. TIBI: Thrombolysis in brain ischemia. S-.M: self-made scale.

**Supplemental Table V:** Quality assessment of included studies

| | **Methods** | | | | **Results** | | | |
|---|---|---|---|---|---|---|---|---|
| | Location, relevant dates | Sources and methods of selection of participants | Specified criteria of ER | Specified timing of ER evaluation | Characteristics of patients† | Data on arterial occlusion sites | Incidence of ER | Uni or multivariate analysis of ER predictors |
| **Von Kummer 1992**[70] | Yes | yes | yes | yes | no | yes | yes | yes |
| **Alexandrov 2004**[51] | No | yes | yes | yes | no | yes | yes | yes |
| **Wunderlich 2005**[88] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Lee 2007**[89] | No | yes | yes | yes | no | yes | yes | yes |
| **Wunderlich 2007**[90] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Eggers 2008**[52] | No | yes | yes | yes | no | yes | yes | yes |
| **Jeong 2009**[91] | No | yes | yes | yes | yes | yes | yes | yes |
| **Mazighi 2009**[92] | Yes | yes | yes | no | yes | no | yes | no |
| **Kawakami 2010**[93] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Smadja 2011**[94] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Ernst 2011**[95]* | Yes | No | yes | yes | yes | yes | yes | yes |
| **Kimura 2011**[74] | Yes | yes | no | yes | yes | yes | yes | yes |
| **Garcia-Bermejo 2012**[96] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Sanak 2012**[97] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Frölich 2013**[75]* | No | yes | no | yes | no | no | yes | yes |
| **Koga 2013**[76] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Uzuner 2013**[98] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Behrens 2014**[72] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Yoshimura 2014**[99] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Kim 2014**[100]* | No | No | yes | yes | no | yes | yes | yes |
| **Luby 2014**[101] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Mishra 2014**[71] | Yes | yes | yes | yes | no | yes | yes | yes |
| **Von Kummer 2014**[102]* | Yes | yes | no | no | yes | yes | yes | yes |
| **Fjetland 2015**[103] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Campbell 2015**[104] | Yes | yes | no | yes | yes | yes | yes | no |
| **Ritzenthaler 2015**[73] | Yes | yes | yes | yes | yes | yes | yes | yes |
| Number of « yes » answers | 20/26 (77%) | 24/26 (92%) | 22/26 (88%) | 24/26 (92%) | 19/26 (73%) | 24/26 (92%) | 26/26 (100%) | 21/26 (81%) |

For each study, one reader (PS) scored each item as "Yes" or "No" according to the definition of the quality item. We considered items separately and calculated a global score for each item (corresponding to the proportion of "Yes" answers).

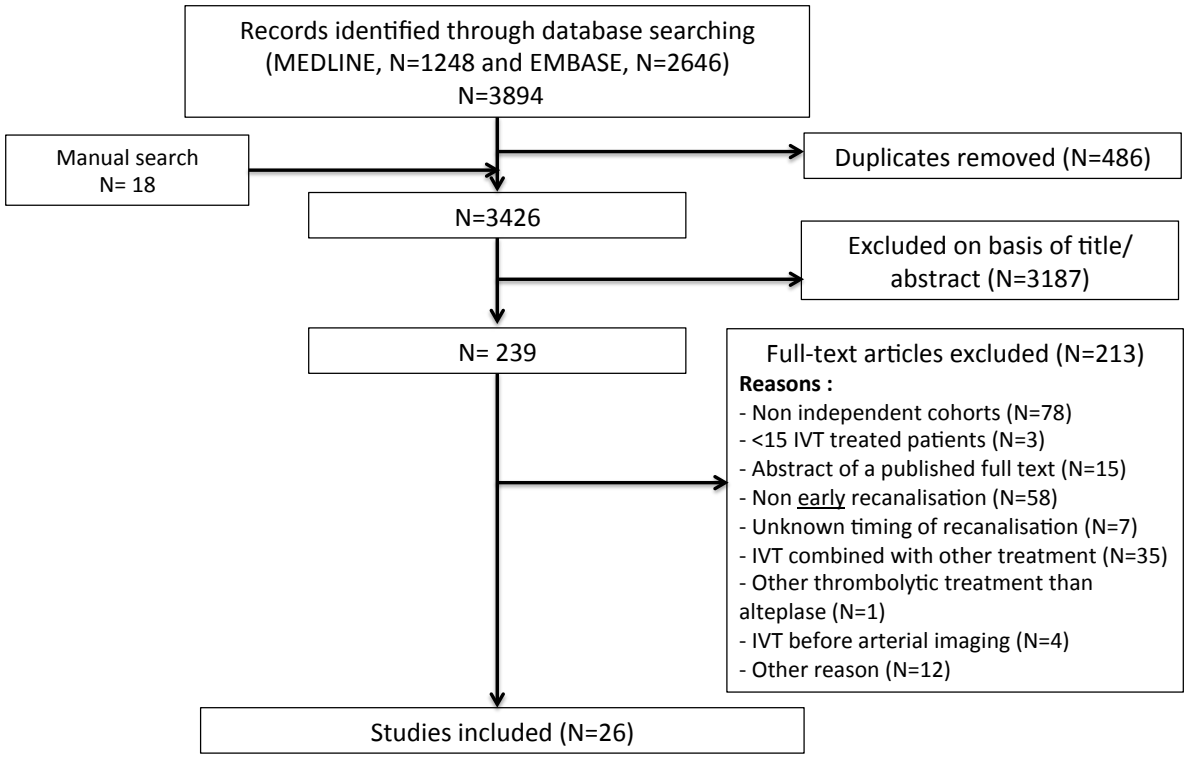
*Abstract only. ER: Early recanalisation. † Characteristics of study patients: number of eligible, included and analysed patients.

**Supplemental Table VI:** Variables without consistent association with no-ER, assessed in less than 4 studies.

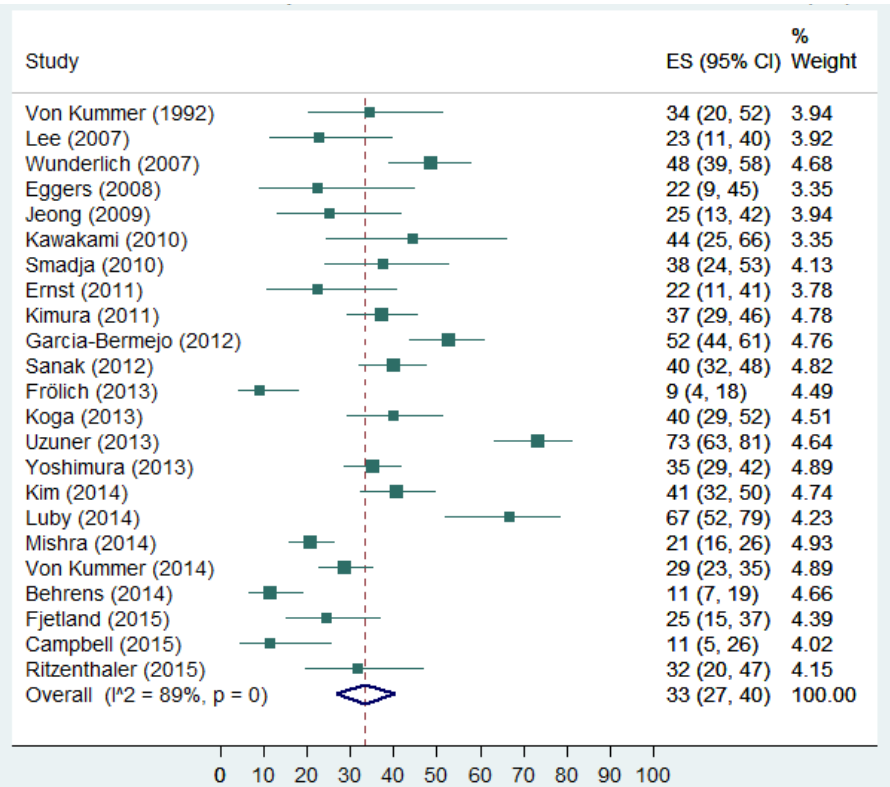
| Variable | Number of studies (number of patients) |
|---|---|
| **Vascular risk factors** | |
| Hyperlipidemia | 2 (202) |
| Hypertension | 3 (259) |
| Current smoking | 2 (202) |
| **Past medical history** | |
| Coronary heart disease | 2 (127) |
| Congestive heart failure | 1 (70) |
| Previous stroke | 1 (57) |
| **Previous treatment** | |
| Antiplatelets* | 2 (278) |
| Anticoagulant | 1 (132) |
| Statin | 1 (146) |
| **Clinical data on admission** | |
| Systolic blood pressure | 3 (348) |
| Diastolic blood pressure | 2 (278) |
| Heart rate | 1 (70) |
| **Imaging** | |
| Susceptibility Vessel Sign (any artery) | 1 (41) |
| Hyperdense MCA sign | 1 (27) |
| DWI-ASPECTS | 1 (70) |
| DWI volume | 1 (132) |
| **Biological parameters** | |
| Leucocyte count | 2 (202) |
| Erythrocyte count | 1 (132) |
| Hemoglobin | 1 (70) |
| Platelets count | 2 (202) |
| INR | 2 (202) |
| Fibrinogen | 1 (70) |
| Antithrombin III | 1 (70) |
| D-dimers | 2 (202) |
| Fibrin degradation product | 1 (70) |
| Total cholesterol level | 1 (70) |
| LDL cholesterol level | 1 (70) |
| Triglyceride level | 1 (70) |
| Glucose level | 3 (348) |
| HbA1c | 2 (202) |
| C-reactive protein* | 2 (202) |
| Creatinine | 2 (202) |
| Brain natriuretic peptide | 1 (70) |
| **Stroke aetiology** | 1 (132) |
| Large artery atherosclerosis | 2 (168) |

* Discordant results between the two studies.

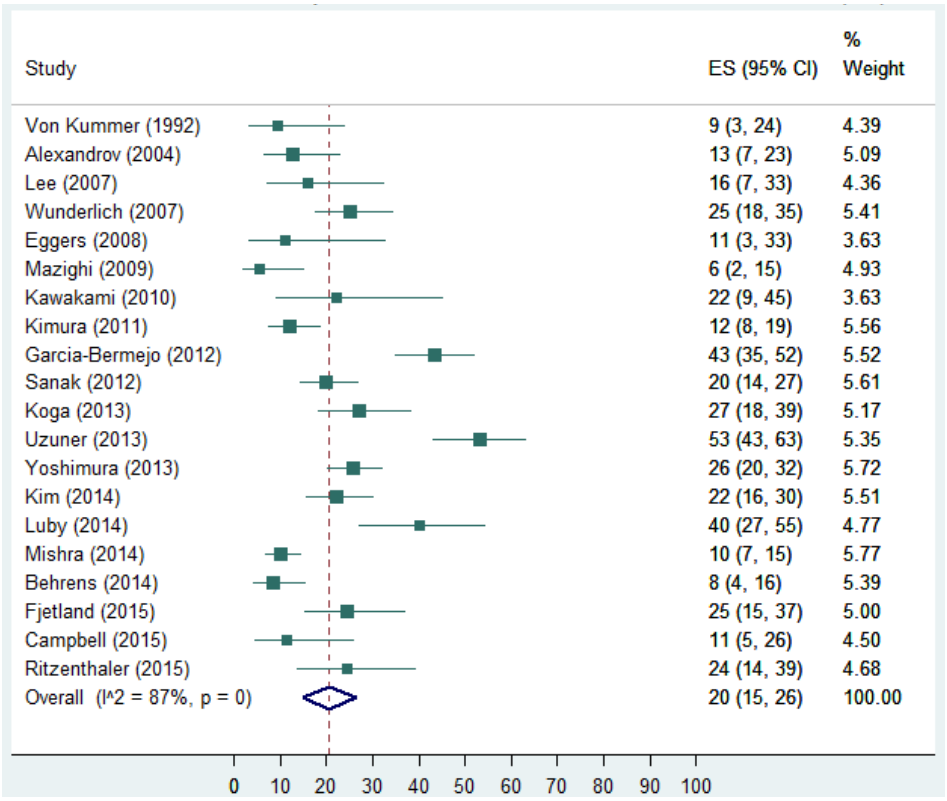
**Supplemental Figure I:** Flow chart of the selection process.



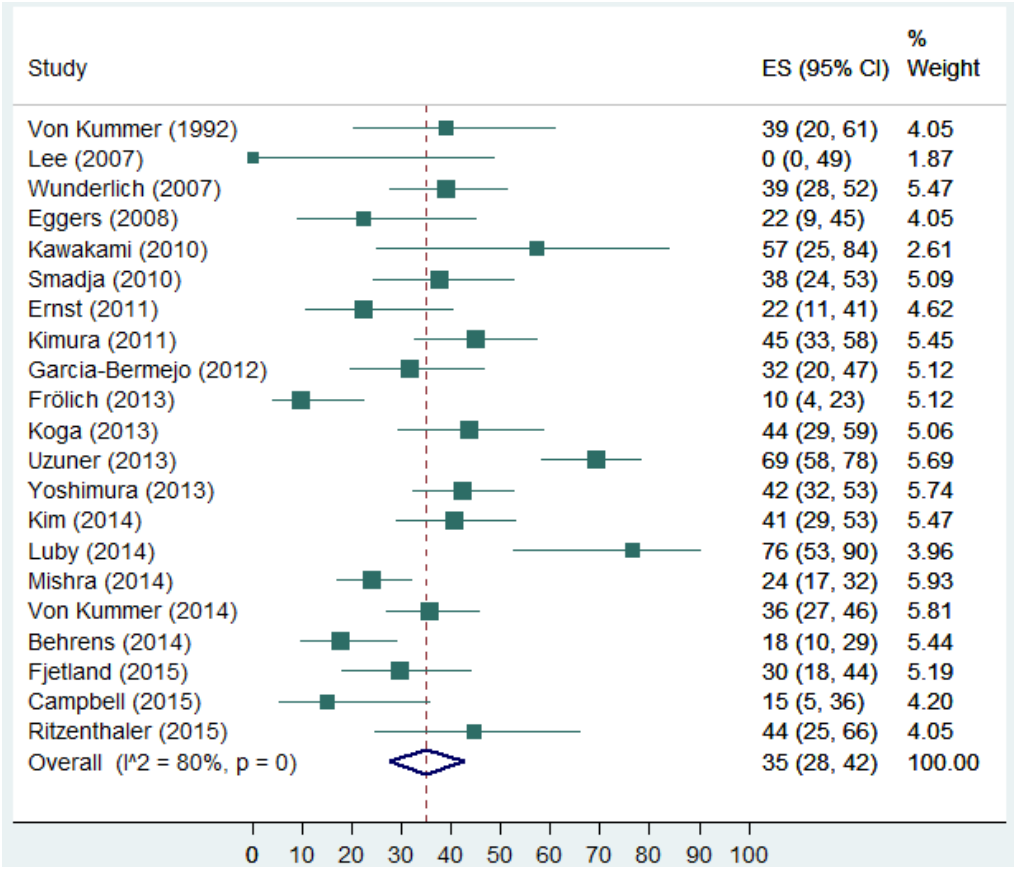
**Supplemental Figure II:** Meta-analysis of incidence of early *partial or complete* recanalization regardless of occlusion site.[70-76,89-91,93,96-104]



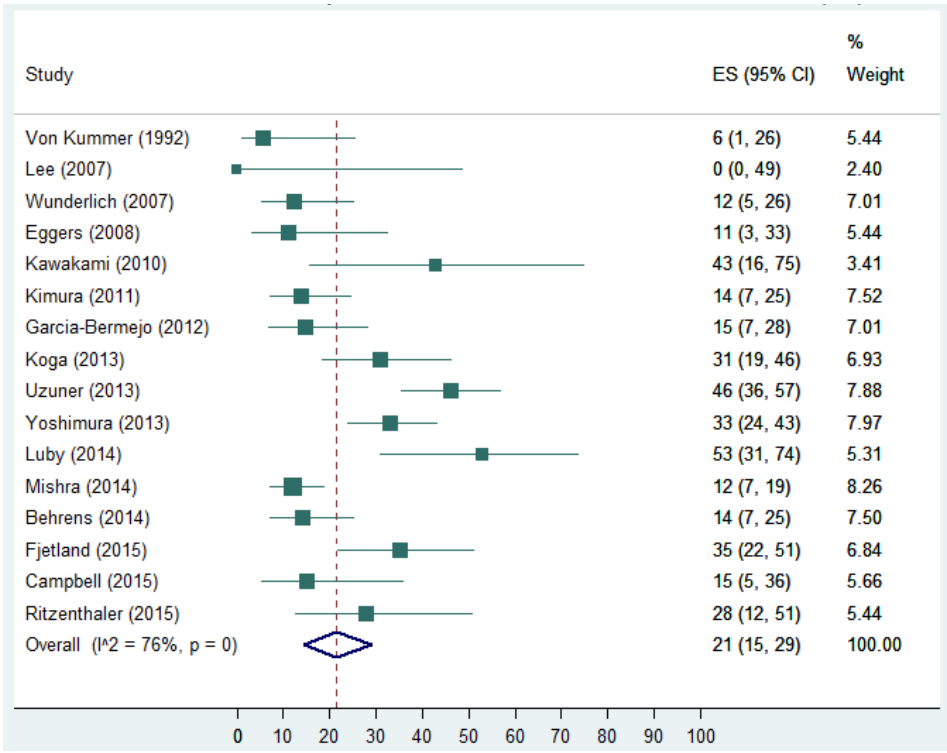

**Supplemental Figure III:** Meta-analysis of incidence of early *complete* recanalization regardless of occlusion site. [51,70-74,76,89,90,92,93,96-101,103,104]



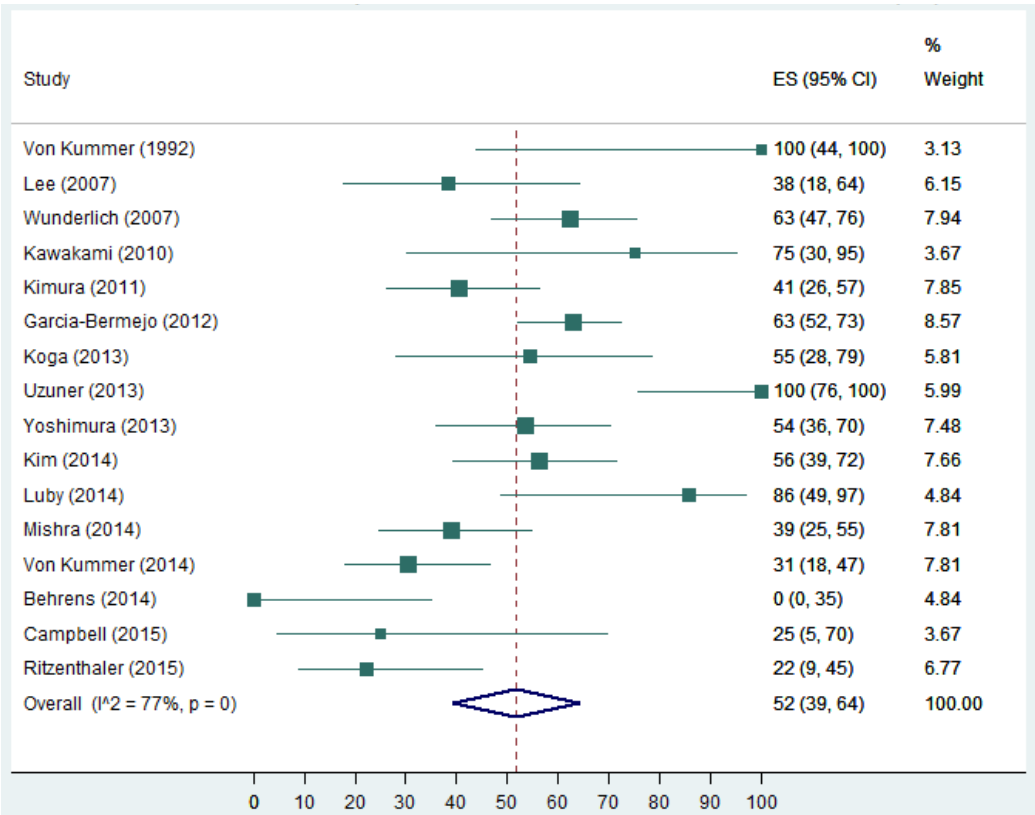
**Supplemental Figure IV:** Meta-analysis of incidence of early *partial or complete* recanalization in M1 occlusion.[52,70-76,89,90,93-96,98-104]



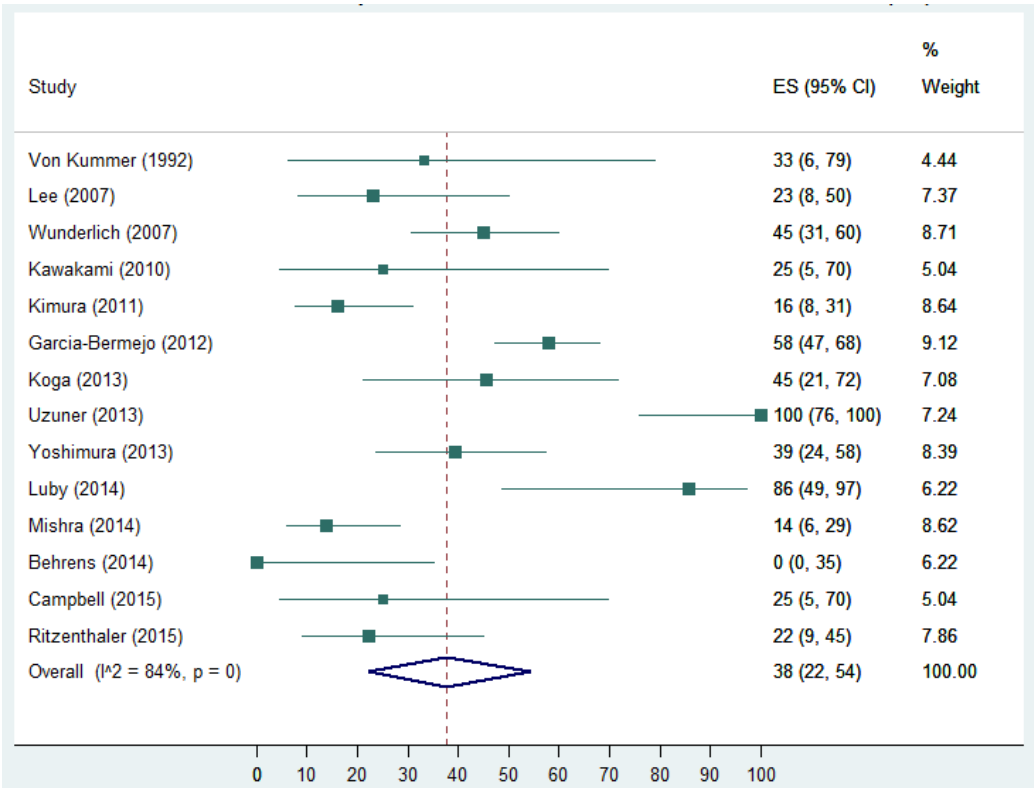

**Supplemental Figure V:** Meta-analysis of incidence of early *complete* recanalization in M1 occlusion.[52,70-74,76,89,90,93,96,98,99,101,103,104]



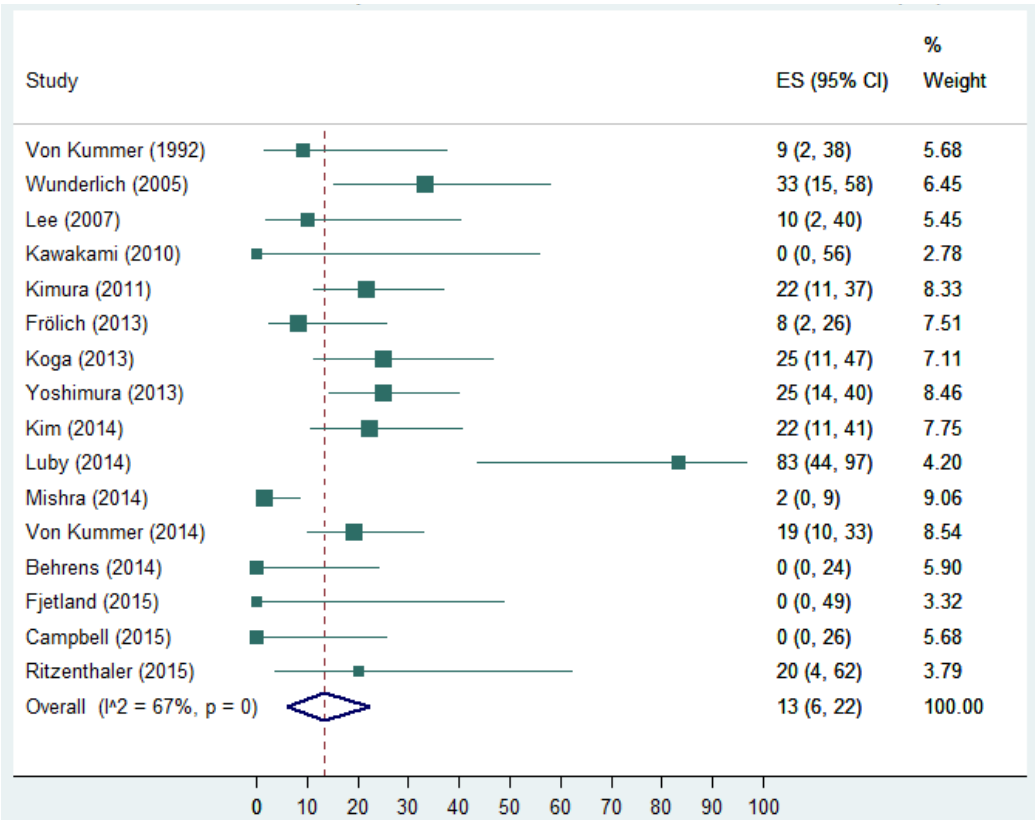
**Supplemental Figure VI:** Meta-analysis of incidence of early *partial or complete* recanalization in M2-M3 occlusion.[70-74,76,89,90,93,96,98-101,104]



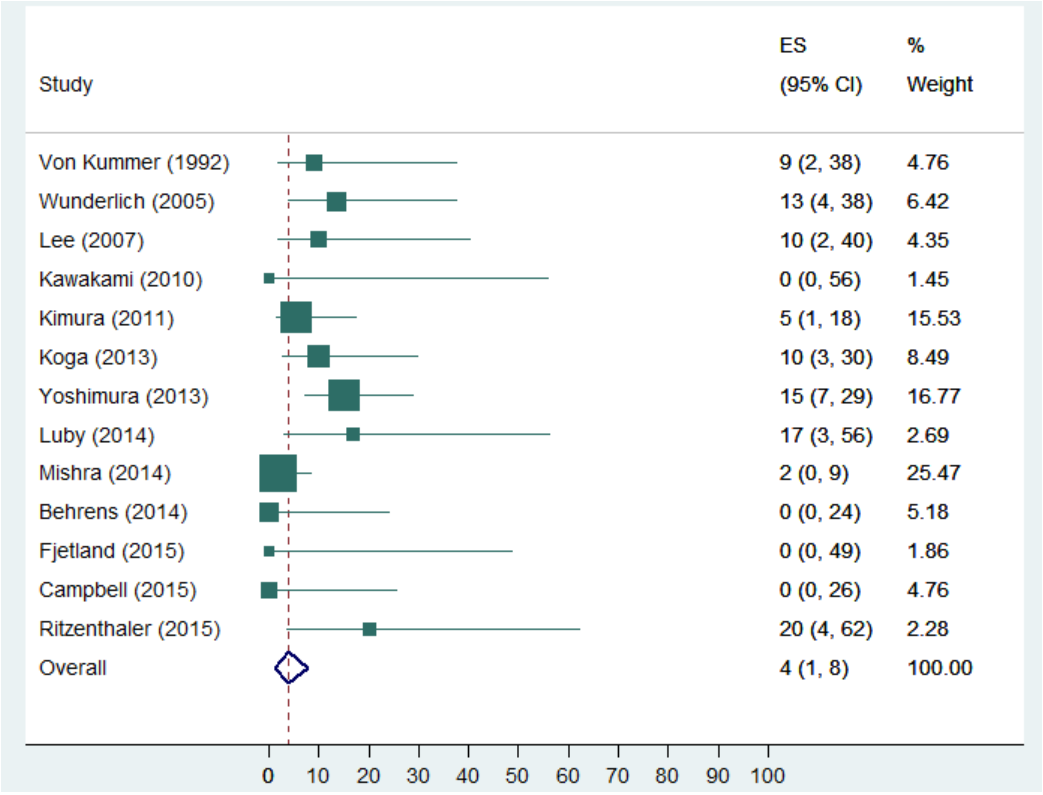

**Supplemental Figure VII:** Meta-analysis of incidence of early *complete* recanalization in M2-M3 occlusion.[70-74,76,89,90,93,96,98,99,101,104]



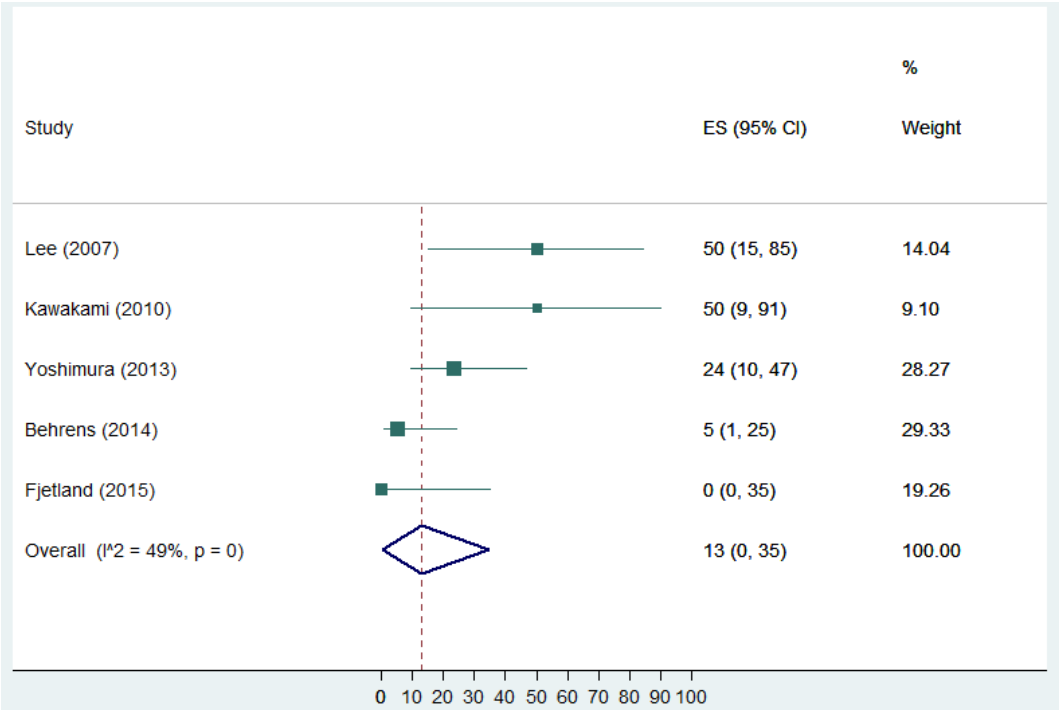
**Supplemental Figure VIII:** Meta-analysis of incidence of early *partial or complete* recanalization in intracranial carotid artery occlusion.[70-76,88,89,93,99-104]



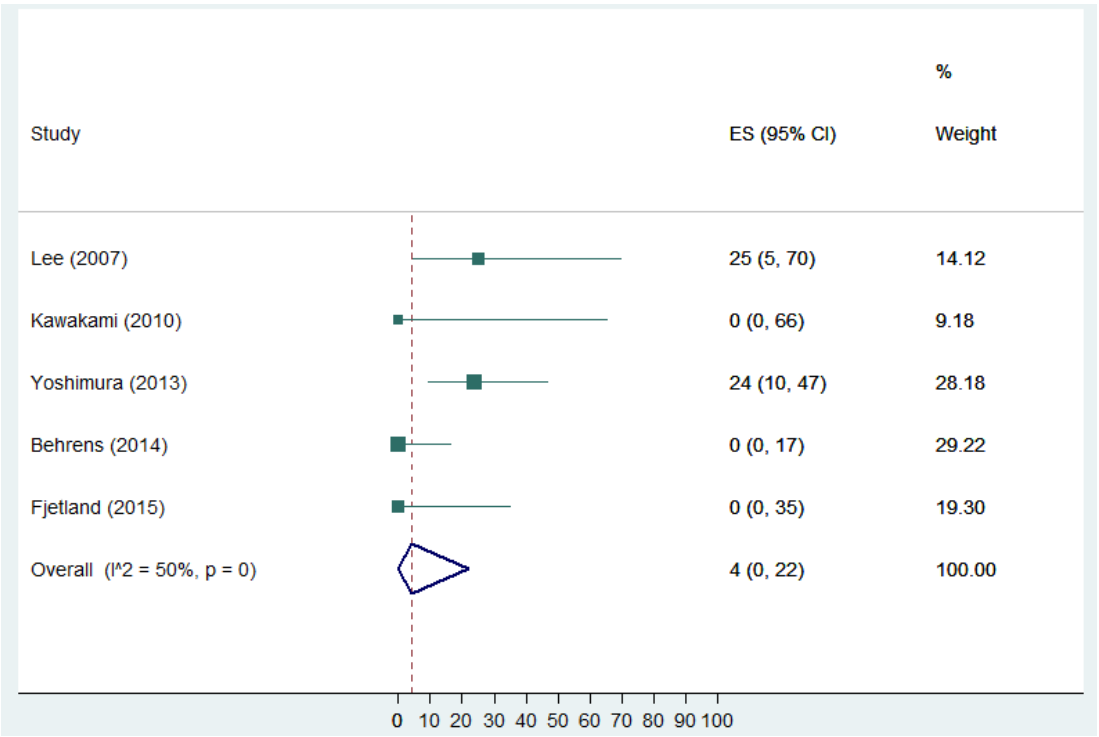

**Supplemental Figure IX:** Meta-analysis of incidence of early *complete* recanalization in intracranial carotid artery occlusion.[70-74,76,88,89,93,99,101,103,104]



**Supplemental Figure X:** Meta-analysis of incidence of early *partial or complete* recanalization in basilar artery occlusion.[72,89,93,99,103]

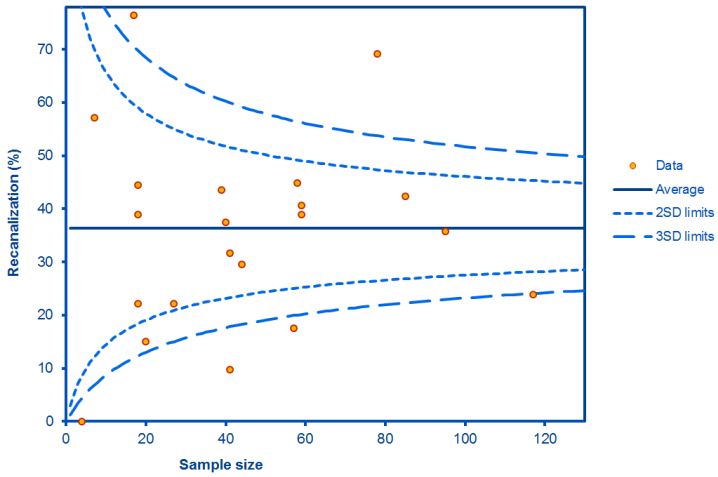



**Supplemental Figure XI:** Meta-analysis of incidence of early *complete* recanalization in basilar artery occlusion.[72,89,93,99,103]

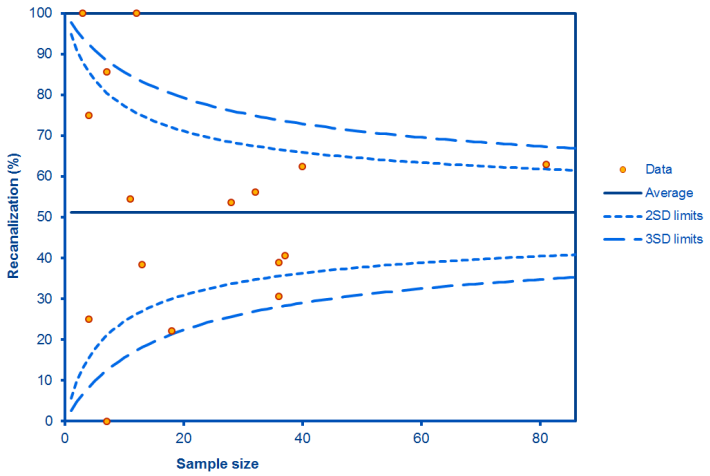


**Supplemental Figure XII:** Funnel plots assessing potential publication bias for assessment of incidence of early recanalisation.

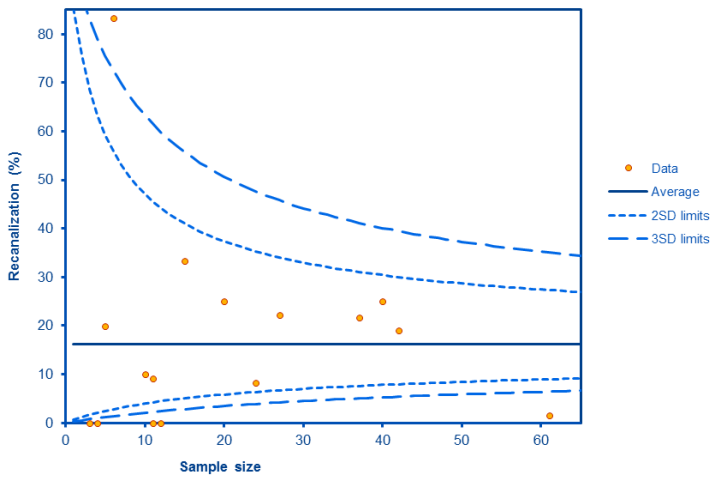
**A :** Proximal MCA occlusions (M1)




**B :** Distal MCA occlusions (M2-M3)




**C :** Intracranial ICA occlusions




Funnel plots are based on raw proportions. 2 SD and 3 SD limits are calculated using Wilson's method.

# Deuxième partie :
# Incidence et facteurs prédictifs de recanalisation précoce après thrombolyse intraveineuse : cohorte PREDICT-RECANAL

Le manuscrit de cette étude, actuellement soumis après révision dans *Stroke*, est inséré ci-après. Les supplemental figures 1, 3, 4, 5 et 6 n'ont pas été insérées dans la version soumise pour une raison de place, mais ont été ajoutées ici pour faciliter la compréhension.

**Résumé :** Les objectifs de cette étude observationnelle (PREDICT-RECANAL) étaient, dans une large population de patients chez lesquels une indication de bridging était retenue après 2015 : i) de déterminer l'incidence de recanalisation précoce survenant avant la réalisation de la thrombectomie ; ii) de déterminer les facteurs prédictifs indépendants de non-recanalisation précoce ; et iii) d'établir des scores prédictifs, utilisables en pratique clinique, qui aideraient à la sélection des patients dans de futurs essais randomisés.

Les données cliniques et radiologiques des patients issus du registre de thrombectomie de 4 UNV de recours françaises entre 2015 et 2017 ont été collectées, incluant les patients « mothership » et « drip-and-ship » (cohorte de dérivation, n=633). Les critères d'inclusion étaient i) présence d'une occlusion proximale de la circulation antérieure sur l'imagerie pré-thrombolyse ; ii) thrombolyse intraveineuse par alteplase 0.9mg/kg ; et iii) évaluation de la recanalisation dans les 3h suivant la thrombolyse (évaluée sur le premier jet de l'artériographie ou sur une imagerie vasculaire non-invasive). La recanalisation a été définie comme un score mTICI 2b-3 pour les occlusions terminaison carotide ou M1, et AOL 3 pour les occlusions M2. Une seconde cohorte similaire, issue du registre de 4 autres UNV de recours françaises, a été constituée pour validation externe des résultats issus de la cohorte de dérivation (cohorte de validation, n=474).

*Incidence de la recanalisation précoce :* L'incidence de recanalisation précoce était respectivement de 20% et 18% dans les cohortes de dérivation et validation, et était deux fois plus élevée chez les patients « drip-and-ship » que chez les patients « mothership » (cohorte de dérivation: 26% *vs.* 10%, respectivement; cohorte de validation: 22% *vs.* 12%). Le taux de recanalisation variait selon le site d'occlusion, avec des chiffres très similaires à ceux décrits dans la méta-analyse présentée dans la première partie: cohorte de dérivation: respectivement 6%, 16%, 30% et 34% en cas d'occlusion termino-carotide, M1 proximal, M1 distal et M2; cohorte de validation: respectivement 1%, 14%, 31% et 34%.

*Facteurs prédictifs de l'absence de recanalisation précoce :* En analyse multivariable (réalisée sur la cohorte de dérivation, n=498 patients chez qui toutes les variables étaient disponibles), trois variables étaient indépendamment associées à l'absence de recanalisation : un thrombus de longue taille (« susceptibility vessel sign » [SVS] sur la séquence T2* en IRM), un site d'occlusion proximal, et

traitement selon le paradigme « mothership ». Cette dernière association était liée au délai plus court entre la thrombolyse et l'évaluation de la recanalisation chez les patients mothership *vs*. drip-and-ship.
Une deuxième analyse multivariable a été réalisée, excluant cette fois les caractéristiques du SVS (cette variable n'étant pas toujours disponible), et a montré trois variables indépendamment associées à l'absence de recanalisation : un site d'occlusion proximal, un score NIHSS élevé, et un traitement selon le paradigme « mothership ».

*Score prédictif de l'absence de recanalisation précoce :* Un score prédictif sur 6 points a été déterminé à partir des résultats de la première analyse multivariable : score FIRE-6, comportant 3 items : 1) longueur du SVS : ≤7.0mm = 0pt, >7.0 et ≤10.0mm = 1pt, >10.0mm et ≤14.0mm = 3pts, >14.0mm = 4pts; 2) site d'occlusion: M1 distal ou M2 = 0pt, terminaison carotide ou M1 proximal = 1pt ; 3) paradigme de traitement: drip-and-ship = 0pt, mothership = 1pt. Ce score permettait une prédiction précise de l'absence de recanalisation précoce, que ce soit dans la cohorte de dérivation ou celle de validation (c-statistique= 0.854 et 0.888, respectivement).
Un score prédictif sur 4 points a été créé à partir des résultats de la seconde analyse multivariable : score FIRE-4, comportant 3 items : 1) score NIHSS : ≤12 = 0pt, >12 = 1pt ; 2) site d'occlusion: M1 distal ou M2 = 0pt, M1 proximal = 1pt, terminaison carotide = 2pts; 3) paradigme de traitement: drip-and-ship = 0pt, mothership = 1pt. Ce score permettait une prédiction moins précise de l'absence de recanalisation précoce que le score FIRE-6 dans les deux cohortes, mais celle-ci restait néanmoins très satisfaisante (c-statistique= 0.746 et 0.752, respectivement).
Les grades élevés des deux scores permettaient de prédire l'absence de recanalisation avec une spécificité >90%, mais les grades bas ne permettaient pas de prédire de manière fiable la survenue d'une recanalisation.

*Conclusions :* L'incidence de la recanalisation précoce après thrombolyse intraveineuse est loin d'être négligeable dans cette large cohorte multicentrique de patients avec intention de bridging, renforçant l'intérêt de la thrombolyse dans cette population. La recanalisation précoce dépend principalement de la longueur du SVS, du site d'occlusion et du délai entre la thrombolyse et l'artériographie (équivalent au paradigme de traitement, drip-and-ship *vs.* mothership). Les scores prédictifs créés ont une spécificité >90% pour prédire l'absence de recanalisation précoce, et devraient trouver une utilité pour le dessin d'essais randomisés futurs comparant bridging *vs*. thrombectomie seule. En revanche, ces scores ne permettent pas de prédire de manière suffisamment fiable la survenue d'une recanalisation, et ne devraient pas aider à limiter le nombre de « transferts futiles » en thrombectomie.

**Post-thrombolysis recanalization in stroke referrals for thrombectomy: Incidence, predictors and prediction scores.** Seners P, Turc G, Naggara O, Henon H, Piotin M, Arquizan C, Cho TH, Narata AP, Lapergue B, Richard S, Legrand L, Bricout N, Blanc R, Dargazanli C, Gory B, Debiais S, Tisserand M, Bracard S, Leclerc X, Obadia M, Costalat V, Berner LP, Cottier JP, Consoli A, Ducrocq X, Mas JL, Oppenheim C*, Baron JC*, on behalf of the PREDICT-RECANAL collaborators. *Stroke*, in revision.
*Equal contribution


**Abstract**

**Background and purpose:** Whether all acute stroke patients with large-vessel occlusion (LVO) need to undergo intravenous thrombolysis before mechanical thrombectomy (MT) is debated as i) the incidence of post-thrombolysis early recanalization (ER) is still unclear; ii) thrombolysis may be harmful in patients unlikely to recanalize; and, conversely, iii) transfer for MT may be unnecessary in patients highly likely to recanalize. Here we determined the incidence and predictors of post-thrombolysis ER in patients referred for MT, and derive ER prediction scores for trial design.

**Methods:** Registries from 4 MT-capable centres gathering patients referred for MT and thrombolyzed either on site (mothership) or in a non MT-capable centre (drip-and-ship) following MR- or CT-based imaging between 2015 and 2017. ER was identified on either first angiographic run or non-invasive imaging. In the MRI subsample, thrombus length was determined on T2*-based susceptibility vessel sign (SVS). Independent predictors of no-ER were identified using multivariable logistic regression models, and scores were developed according to the magnitude of regression coefficients. Similar registries from 4 additional MT-capable centres were used as validation cohort.

**Results:** In the derivation cohort (n=633), ER incidence was 20%. In patients with SVS (n=498), no-ER was independently predicted by long thrombus, proximal occlusion and mothership paradigm. A six-point score derived from these variables showed strong discriminative power for no-ER (c-statistic: 0.854) and was replicated in the validation cohort (n=353; c-statistic: 0.888). A second score derived from the whole sample (including negative T2* or CT-based imaging) also showed good discriminative power and was similarly validated. Highest grades on both scores predicted no-ER with >90% specificity, while low grades did not reliably predict ER.

**Conclusions:** The substantial ER rate underlines the benefits derived from thrombolysis in bridging populations. Both prediction scores afforded high specificity for no-ER, but not for ER, which has implications for trial design.

**Introduction**

In stroke patients with large vessel occlusion (LVO), mechanical thrombectomy (MT) added on intravenous thrombolysis with alteplase (IVT), so-called 'bridging therapy', is standard-of-care since early 2015.[105] However, whether all LVO patients need to undergo IVT before MT is currently debated.[32] First, the incidence of post-IVT early recanalization (ER) in the bridging-eligible population is still a matter of controversy.[23,106-109] Second, a rare occurrence of post-IVT ER would raise the issues of IVT-related delays and potential harm,[32] while conversely a substantial rate would point to both unnecessary transfers from primary to MT-capable centers ('drip-and-ship' paradigm)[33] and arteriography-related complications. In addition, there is some *post-hoc* evidence suggesting similar benefits from MT alone in patients with contra-indications to IVT.[32,68]

To address these issues, randomized trials formally testing MT alone versus bridging therapy are underway or in the planning stage.[32] However, how to select the best candidates for such trials is a key issue. Accordingly, identifying strong predictors of post-IVT ER would have major implications.

The strongest predictor of post-IVT ER reported to date is occlusion site: according to our recent meta-analysis,[107] ER within 3hrs is rare in intracranial internal carotid artery T or L occlusions (ICA-T/L, 4%), but more frequent in occlusions of the first (M1) or second (M2) segment of the middle-cerebral artery (21% and 38%, respectively). Additional potential radiological predictors of no-ER include long and/or totally occlusive thrombi.[71,72,77,107] However, previous studies had limitations such as small sample size precluding multivariable analysis, or merging of partial and complete ER as unique endpoint[71,72,77] even though these are in principle managed differently. Furthermore, all the above studies were published before licensing of bridging therapy, and consequently included selected populations. For these reasons, the predictors of early post-IVT recanalization in patients eligible for bridging therapy have not been established so far.

Here we aimed to determine, in a large dataset of stroke patients referred for MT after bridging therapy became standard-of-care: i) the incidence; and ii) the clinical, biological and radiological predictors of post-IVT ER. Based on these data, our second main aim was to develop and validate prediction scores for optimizing design of and patient recruitment in randomized trials.

**Methods**

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

*Study design and data sources*

*Derivation cohort*

We used the database of four MT-capable centres, two prospectively and two retrospectively gathered, collecting data from all stroke patients referred for MT (drip-and-ship or mothership) (**supplemental Table 1**). Inclusion criteria for the present collaborative registry (PREDICT-RECANAL) were (1) acute stroke with LVO of the anterior circulation identified before IVT using MR or CT between May 2015 and March 2017, (2) IVT with alteplase 0.9mg/kg, and (3) evaluation of ER before MT (see below).

*Validation cohort*

We used the prospectively gathered databases of four additional MT-capable centres (**supplemental Table 1**). To construct this cohort, the same inclusion criteria as above were applied.

In accordance with French legislation, each patient was informed of his/her participation in this study, and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required.

*Clinical data*

The following variables were extracted from the registries for both cohorts: age, sex, vascular risk factors and past medical history, pre-stroke medication, NIHSS score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time elapsed between start of IVT and evaluation of ER (IVT-to-$ER_{eval}$ time; see below).

*Imaging*

In France, MRI is first-line in candidates for reperfusion therapy, and accordingly was implemented in all centers of the present study. CT and CT angiography (CTA) is performed in case of contraindication to MRI. The acute stroke MRI protocol includes diffusion-weighted imaging (DWI), T2*, and intracranial MR angiography (MRA).

A stroke neurologist reviewed the pre-IVT imaging of all included patients from both cohorts, blinded to recanalization status. To assess reproducibility, a neuroradiologist independently reviewed a random subset (n=100) of pre-IVT imaging. The following variables were collected: (1) occlusion site, divided into 4 categories: ICA-T/L, M1 proximal, M1 distal and M2, where the M1 segment was defined as the first portion of the middle cerebral artery up to the main bifurcation, and dichotomized as proximal or distal based on the middle cerebral artery origin-to-clot interface distance (<10mm and ≥10mm, respectively, see

**supplemental Fig 1**);[71,110] (2) length of the susceptibility vessel sign (SVS), a specific marker of thrombus on T2*-MRI, based on previously published methodology: the in-plane length (M1 segment) was the distance between the proximal and distal parts of the SVS, and the length in the z-axis (supraclinoid ICA, M2) was the number of slices where the SVS was visible times slice thickness (see **supplemental Fig 2**);[111] and (3) DWI lesion extent using the Alberta Stroke Program Early CT score (DWI-ASPECTS, see **supplemental Fig 3**). Thrombus length and infarct size were not measured on CT considering, first, the small number of patients who underwent CT in our cohorts, and, second, that merging these CT-based variables with corresponding MR-based variables (namely, SVS and DWI-ASPECTS) in the same statistical analysis was deemed inappropriate.

*ER evaluation*

ER was evaluated ≤3hrs after initiation of IVT, a delay that includes typical 'drip-and-ship' situations.[108] In all participating centres, patients were referred for MT as soon as possible after start of IVT. Consequently, ER was evaluated on the first intracranial angiographic run for intended MT. However, in some patients with neurological improvement or deterioration, ER was evaluated using non-invasive vascular imaging (MRA or CTA). Two readers independently evaluated ER, blinded to clinical and imaging data. Discrepancies were resolved by consensus. In patients with conventional angiography, ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction scale for ICA-T/L or M1 occlusions, and 3 on the Arterial Occlusive Lesion scale for M2 occlusions (**Supplemental Figure 4 and 5**).[110] In the remaining patients, ER was defined as 3 (Arterial Occlusive Lesion scale) on CTA/MRA respectively.

*Statistical analysis*

Continuous variables were described as mean±standard deviation or median (interquartile range, IQR), as appropriate. Univariable comparison of both cohorts was performed using Student *t* or Mann-Whitney *U* tests for continuous variables, and Chi-square test for categorical variables. Inter-observer agreement was measured using intraclass correlations coefficients for quantitative variables and overall weighted Kappa for categorical variables.

To determine the independent predictors of no-ER, derive a predictive score and validate this score, the following steps were performed:

1. *Selection of independent predictors in the derivation cohort*. Univariable relationships between pre-IVT variables and no-ER were assessed. To adjust for potential confounders, multivariable binary logistic regression analysis was subsequently conducted, with no-ER as dependent variable. Variable selection was performed stepwise, whereby candidate variables entered the model at $P<.20$ and were retained only if they remained associated at $P<.10$ with the dependent variable. Covariates were assessed for collinearity and interaction effects.

2. *Development of a score (derivation cohort).* A score was developed based on the final multivariable model above, based on the magnitude of regression coefficients, with FIRE as acronym (*i.e.,* score **F**or **I**ntravenous thrombolysis **Re**sistance). Continuous variables independently associated with no-ER were

split according to cut-offs based on the c-statistic (*i.e*. the area under the receiver operating characteristic curve, see Results). Discrimination of the score to predict no-ER was assessed using c-statistic with 95% confidence interval (95%CI).

3. *Score validation*. Internal cross-validation was performed using the bootstrap method on the derivation cohort, and external validation was performed on the validation cohort. To check for significant differences between the observed and predicted risks of no-ER in the validation cohort, calibration of the FIRE score was assessed using the Hosmer-Lemeshow test.

In order to develop a similar score for use in patients without visible SVS on T2*-MRI or in whom CT/CTA is available instead of MRI, the above procedures were repeated, this time without the SVS characteristics.

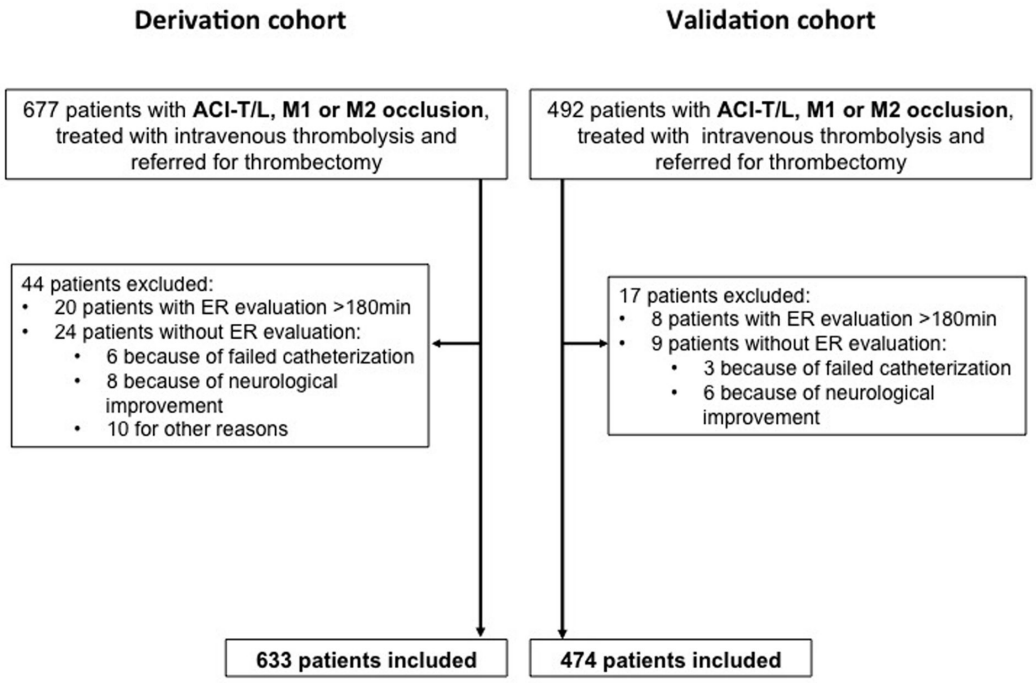
Statistical analyses were performed using SPSS 16.0 (SPSS Inc) and SAS 9.4 (SAS Institute, Inc). Two-tailed $P<.05$ was considered statistically significant.

**Results**

*Study population*

Six hundred and thirty three patients and 474 patients were included for the final analysis in the derivation and validation cohorts, respectively (see **Figure 1**). Inter-observer agreement for imaging data analysis is presented in **Supplemental Results.**

**Figure 1 –** Study flow chart.




*Legend*: ER indicates early recanalization.

*Characteristics of the derivation and validation cohorts and incidence of ER*

Baseline characteristics of patients from the derivation and validation cohorts are presented in **Table 1**. Both cohorts had ~60% drip-and-ship patients. The derivation cohort had more frequent hypertension, lower NIHSS, longer onset-to-IVT time, more proximal occlusions, higher DWI-ASPECTS, longer SVS, ER status less frequently evaluated on angiography, and longer IVT-to-$ER_{eval}$ time than the validation cohort. As expected, the median IVT-to-$ER_{eval}$ time was shorter in mothership than drip-and-ship patients in both cohorts (derivation cohort: 53min [IQR 29-81] *vs.* 124min [100-149], respectively, $P<0.01$; validation cohort: 45min [34-62] *vs.* 112min [93-137], $P<0.01$).

ER occurred in 19.6% (95%CI 16.7-22.9) and 17.9% (14.7-21.6) of patients in the derivation and validation cohorts, respectively ($P=.49$), and was twice larger in drip-and-ship as compared to mothership patients in both cohorts (derivation cohort: 25.9% *vs.* 10.4%, respectively; validation cohort: 22.0% *vs.* 12.0%). The ER rate was consistently markedly lower with more proximal occlusions (derivation cohort: 6.4%, 16.1%, 30.3% and 33.7% in ICA-T/L, M1 proximal, M1 distal and M2, respectively; validation cohort: 1.0%, 13.7%, 30.7% and 34.0%).

*Univariable analysis for lack of ER in the derivation cohort*

The univariable analyses with no ER as depending variable are presented in **supplemental Table 2**. The following variables were associated with no ER: mothership paradigm, higher baseline NIHSS, shorter IVT-to-$ER_{eval}$ time, more proximal occlusions, and longer SVS.

To illustrate the association between recanalization and continuous variables, ER rates as a function of SVS length, IVT-to-$ER_{eval}$ time and NIHSS are presented in **Figures 2A**, **2B**, and **2C**, respectively. Fig 2A shows initially precipitous ER rate decline with increasing thrombus length, followed by near-zero rate; Fig 2B shows initially increasing ER rate with IVT-to-$ER_{eval}$ time then plateauing for IVT-to-$ER_{eval}$ time longer than 90min; and Fig 2C shows decreasing ER rate with higher NIHSS, plateauing for NIHSS≥16.

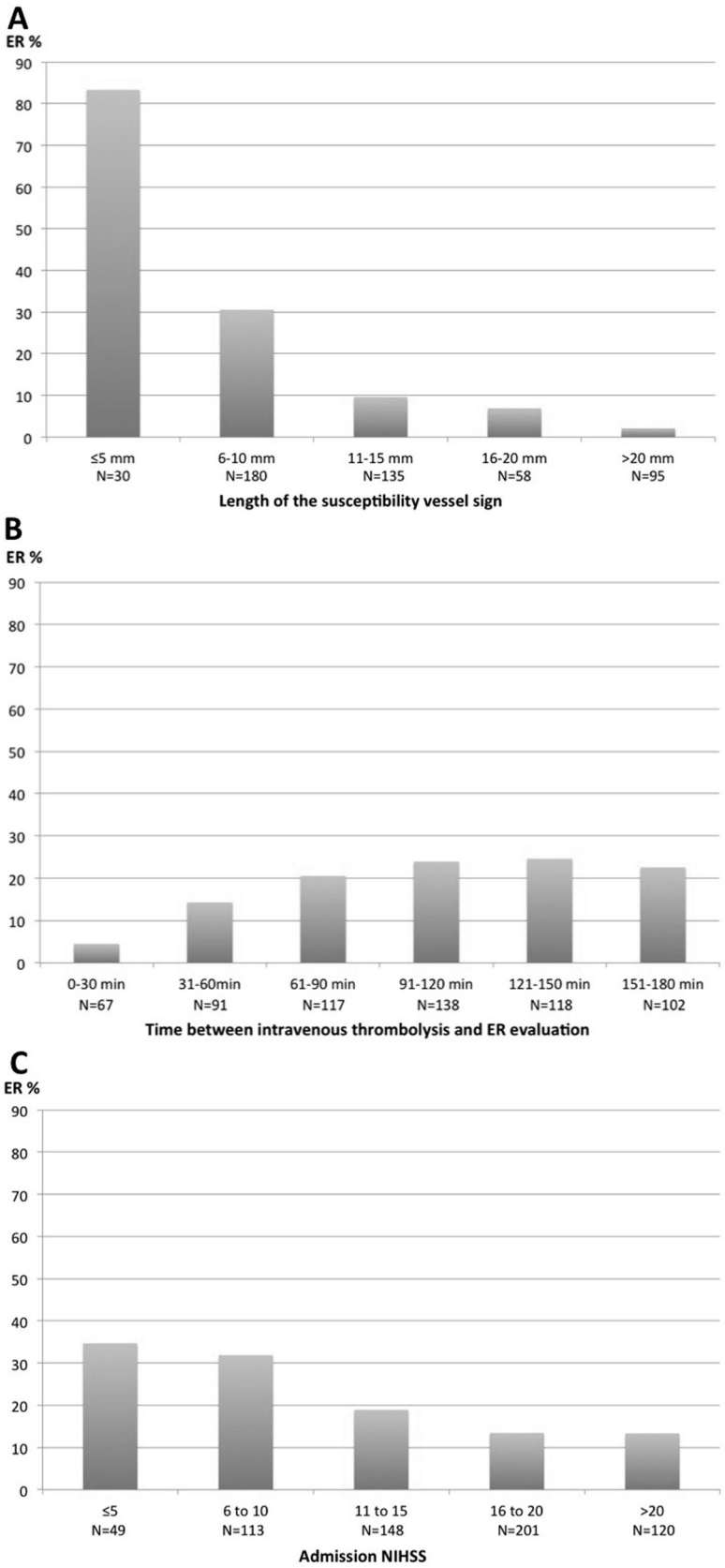
**Table 1** – Characteristics of, and comparison between the two cohorts*

| | **Derivation cohort N=633** | **Validation cohort N=474** | ***P* value** |
|---|---|---|---|
| **Patient history** | | | |
| Age (years) | 71.8 (60.7-80.3) | 70.2 (60.7-80.3) | 0.62 |
| Men | 310 (49.0) | 251 (53.0) | 0.19 |
| Hypertension | 381 (60.4) | 250 (53.2) | **0.01** |
| Diabetes mellitus | 91 (14.6) | 83 (17.7) | 0.17 |
| Current smoking | 104 (16.7) | 79 (16.8) | 0.95 |
| Antiplatelet use | 211 (33.8) | 146 (31.1) | 0.35 |
| Statin use | 179 (28.7) | 121 (28.3) | 0.88 |
| **Pre-IVT characteristics** | | | |
| Mothership | 259 (40.9) | 192 (40.5) | 0.89 |
| NIHSS | 16 (10-19) | 16 (11-21) | **0.03** |
| Onset-to-IVT time (min) | 150 (120-182) | 139 (120-165) | **<0.01** |
| **Pre-IVT imaging** | | | |
| MRI | 592 (93.5) | 424 (89.5) | **0.02** |
| Occlusion site | | | **0.02** |
| ICA-T/L | 141 (22.3) | 105 (22.2) | |
| Proximal M1 | 261 (41.2) | 190 (40.1) | |
| Distal M1 | 142 (22.4) | 82 (17.3) | |
| M2 | 89 (14.1) | 97 (20.5) | |
| DWI-ASPECTS† | 8 (6-9) | 7 (6-8) | **0.01** |
| SVS visible‡ | 498 (84.8) | 353 (84.0) | 0.75 |
| SVS length§ (mm) | 12.0 (9.2-17.6) | 11.6 (8.3-16.3) | **0.04** |
| **ER evaluation** | | | |
| Arteriography | 555 (87.7) | 460 (97.0) | **<0.01** |
| IVT-to-$ER_{eval}$ time (min) | 100 (61-134) | 87 (49-116) | **<0.01** |
| **ER occurrence** | 124 (19.6) | 85 (17.9) | 0.49 |

*Legend*: *: Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). †: Missing values: 41 in the derivation cohort and 50 in the validation cohort (patients with CT and CTA). ‡: Missing values: 47 in the derivation cohort (41 with CT and 6 without T2*-MRI) and 55 in the validation cohort (50 with CT and 5 without T2*-MRI). §: Missing values: 135 in the derivation cohort (41 with CT, 6 without T2*-MRI and 88 without SVS) and 121 in the validation cohort (50 with CT, 5 without T2*-MRI and 66 without SVS).

Abbreviations: ASPECTS indicates Alberta Stroke Program Early CT score; DWI, diffusion-weighted imaging; ER, early recanalization; IVT-to-$ER_{eval}$ time, time between thrombolysis start and evaluation of early recanalization; SVS, susceptibility vessel sign.

**Figure 2** – Rate of early recanalization as a function of (**A**) SVS length, (**B**) time between start of thrombolysis and evaluation of early recanalization, and (**C**) NIHSS strata in the derivation cohort.



*Multivariable analysis, derivation and validation of the FIRE score including SVS*

The multivariable model (n=498 patients with visible SVS) using the variables with *P*<.20 from supplemental Table 2 resulted in the following independent no-ER predictors: SVS length (*P*<.01), occlusion site (*P*=.01) and mothership paradigm (*P*<.01). Note that due to collinearity between the mothership and IVT-to-$ER_{eval}$ time variables, only the former was included in the model because in real life the IVT-to-$ER_{eval}$ time can be difficult to accurately anticipate due to unpredictable ambulance arrival time and transport delays; in other words, the care paradigm is more operationally relevant than time for clinical use.

Considering the high c-statistic of SVS length for no-ER, for clinical score derivation SVS length was split into 4 classes according to 3 cutoffs: i) the >95% sensitivity cutoff for no-ER prediction, found to be 7.0mm; ii) the >90% specificity cutoff for no-ER prediction (14.0mm); and iii) 10.0mm, as intermediate value between 7.0 and 14.0mm. The occlusion sites M2 and distal M1, and proximal M1 and ICA-T/L, were merged as their odds ratios were very similar in the multivariable model; this did not modify the c-statistic (data not shown). The multivariable model with split SVS length and dichotomized occlusion site used to derive the clinical score is presented in **Table 2** (model 1).

The integer-based FIRE score (range: 0-6 points, accordingly named FIRE-6) was constructed according to the magnitude of the regression coefficients in the latter multivariable model (**Table 3**). The distribution of no-ER per FIRE-6 incremental point is shown in **Fig 3A**: the higher the score, the greater the likelihood of no-ER, with no-ER probability ranging from ~20% to 98% for grades 0 and 6, respectively. The c-statistic was 0.854 (95%CI 0.813-0.895). The internal cross-validation based on 1,000 bootstrap replicates showed a similar c-statistic (0.854, 95%CI: 0.810-0.894). Typical patients with various FIRE-6 grades are shown in **supplemental Fig 6**.

FIRE-6 was successfully validated in the validation cohort (n=353 patients with visible SVS, **Fig 3A**), with a c-statistic of 0.888 (95%CI 0.848 - 0.928). The Hosmer-Lemeshow test did not suggest lack of calibration (*P*=.68).

*Derivation and validation of the FIRE score without SVS*

The multivariable model without SVS – *i.e.*, using the whole derivation cohort including patients without SVS on T2*-MRI or in whom MRI was not available; n=631 –, resulted in the following independent no-ER predictors: mothership paradigm (*P*<.01), occlusion site (*P*<.01) and NIHSS (*P*<.01).

For clinical score derivation, admission NIHSS was dichotomized using as cutoff the Youden index for no-ER prediction (namely, NIHSS≤12 and >12). Again, M2 and distal M1 occlusion sites were merged as their odds ratios were very close in the multivariable model; this did not modify the c-statistic of the model (data not shown). The multivariable model with dichotomized NIHSS is presented in **Table 2** (model 2).

The FIRE score without SVS ranged from 0 to 4 points (accordingly named FIRE-4, **Table 3**). The distribution of no-ER rates per incremental point is shown in **Fig 3B**. No-ER rates ranged from ~40% to 100% for grades 0 and 4, respectively. The c-statistic was 0.746 (95%CI 0.701-0.790). The internal cross-validation based on 1,000 bootstrap replicates showed a similar c-statistic (c= 0.746, 95%CI: 0.701-0.789). FIRE-4 was successfully validated in the validation cohort (**Fig 3B**), with a c-statistic of 0.752 (95%CI 0.704-0.800); the Hosmer-Lemeshow test did not suggest lack of calibration (*P*=.16).

**Table 2** – Variables independently associated with no recanalization in multivariable logistic regression in the derivation cohort, including (model 1) or excluding (model 2) SVS characteristics.

| **Model 1, including SVS characteristics* (**n=498; patients with visible SVS) | | |
|---|---|---|
| | **Adjusted OR (95%CI)** | ***P* value** |
| SVS length | | **<0.001** |
| ≤7.0mm | Reference | |
| >7.0 and ≤10.0mm | 4.6 (2.2-9.6) | |
| >10.0mm and ≤14.0mm | 20.1 (8.5-47.6) | |
| >14.0mm | 36.3 (14.4-91.8) | |
| Paradigm | | **<0.001** |
| Drip-and-Ship | Reference | |
| Mothership | 3.3 (1.8-6.0) | |
| Occlusion site | | **0.002** |
| M2 or M1 distal | Reference | |
| M1 proximal or ACI-T/L | 2.5 (1.4-4.4) | |

| **Model 2, excluding SVS characteristics**† (n=631 with available NIHSS) | | |
|---|---|---|
| | **Adjusted OR (95%CI)** | ***P* value** |
| Paradigm | | **<0.001** |
| Drip and ship | Reference | |
| Mothership | 3.76 (2.29-6.15) | |
| Occlusion site | | **<0.001** |
| M2 or M1 distal | Reference | |
| M1 proximal | 2.40 (1.56-3.75) | |
| ACI-T/L | 6.24 (2.91-13.41) | |
| NIHSS | | **<0.001** |
| ≤12 | Reference | |
| >12 | 2.42 (2.29-6.15) | |

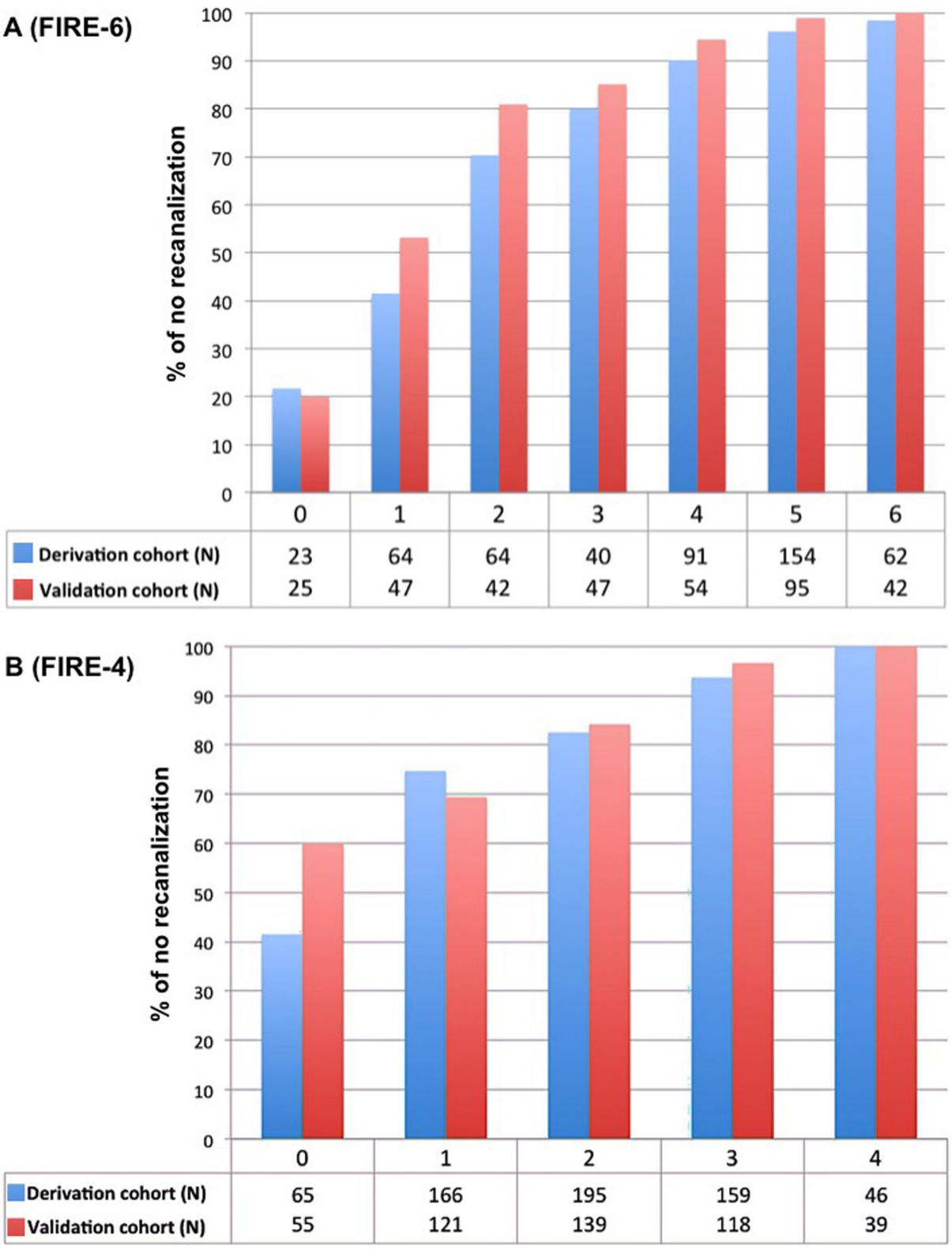
*Legend:* *: Including both SVS length and occlusion site in the model did not induce notable multi-collinearity. †: Including both occlusion site and NIHSS in the model did not induce notable multi-collinearity. Abbreviations: CI indicates confidence interval; ER, early recanalization; OR, odds ratio; SVS, susceptibility vessel sign.

**Table 3** – FIRE-6 and FIRE-4 scores for prediction of no recanalization

| **FIRE-6 score** | | | **FIRE-4 score** | |
|---|---|---|---|---|
| **Category** | **Points** | | **Category** | **Points** |
| SVS length | | | NIHSS | |
| ≤7.0mm | 0 | | ≤12 | 0 |
| >7.0 and ≤10.0mm | 1 | | >12 | 1 |
| >10.0mm and ≤14.0mm | 3 | | Occlusion site | |
| >14.0mm | 4 | | M2 or M1 distal | 0 |
| Occlusion site | | | M1 proximal | 1 |
| M2 or M1 distal | 0 | | ACI-T/L | 2 |
| M1 proximal or ACI-T/L | 1 | | Paradigm | |
| Paradigm | | | Drip and ship | 0 |
| Drip and ship | 0 | | Mothership | 1 |
| Mothership | 1 | | | |

Abbreviations: SVS indicates susceptibility vessel sign.

**Figure 3** – Probability of no early recanalization according to incremental points for the (**A**) FIRE-6 score, and (**B**) FIRE-4 score, applied to the derivation (blue bars) and validation (red bars) cohorts (see Table 3 and Results for details).




*Legend:* Incremental FIRE grades are presented in the x-axis, and probability of no-recanalization in the y-axis.

**Discussion**

Our aim in this study was to determine the incidence and identify independent predictors of post-thrombolysis ER in a large sample of patients eligible for bridging therapy, and therefrom derive ER prediction scores intended for optimizing design and patient recruitment in randomized trials. Based on two large multicentric cohorts of LVO patients treated after bridging therapy became standard-of-care, this study disclosed three key findings: i) the incidence of post-thrombolysis ER was substantial, namely ~20% on average, both in the derivation and validation cohorts; ii) on multivariable analysis, long SVS, mothership paradigm and proximal occlusion independently predicted no-ER; and iii) both the MR-based and MR-independent derived scores (*i.e.* FIRE-6 and FIRE-4, respectively) had strong discriminative power, with high grades on either scores reliably predicting no recanalization.

*ER incidence*

One strength of our study is that three key methodological measures were implemented to limit selection bias. First, patient inclusion in the study started only after bridging therapy became clinical routine in all participating centres. Second, both drip-and-ship and mothership patients were included, reflecting everyday practice. And third, patients with early neurological improvement in whom ER was evaluated using non-invasive vascular imaging were included in the study.

Documenting substantial (namely, ~20%) rates of post-thrombolysis ER in mix drip-and-ship and mothership populations is highly relevant to current debates regarding whether or not IVT should be skipped in candidates for MT.[32] Although a recent meta-analysis of bridging studies[106] reported a much lower rate of pre-MT ER than here (namely, 11%, 95%CI 7-16), this figure likely was underestimated – as acknowledged –, because in several of the included primary studies the vascular imaging used for patient enrolment was mainly performed *after* start of IVT: in other words, instances of ER occurring *before* vascular imaging were excluded *a priori.*[106,109] In our meta-analysis of pre-thrombectomy era studies implementing pre-IVT vascular imaging – from which therefore the above-mentioned biased studies were excluded –, the post-IVT ER rate in patients intended for MT was 18% (95%CI 10-28),[107] consistent with that found here despite the different populations. This substantial ER rate underlines the essential clinical role of IVT in candidates for MT in current practice, particularly regarding the drip-and-ship paradigm.

*Independent no-ER predictors*

In the multivariable model that included SVS, we found that long thrombi (>10mm) strongly predicted no-ER (Figure 2A). This finding is consistent with two smaller-scale studies,[71,72] which however did not report multivariable analyses.

The second independent no-ER predictor was occlusion site, such that the more proximal the occlusion, the lower the probability for ER. This finding is consistent with both previous work[71,108,112] and our meta-analysis.[107] Interestingly, even though occlusion site and thrombus length were to a degree inter-related (**supplemental Figure 7**), including both in the multivariable model did not induce notable multi-

collinearity, and both were effectively independently associated with no-ER. This may suggest that thrombus volume, rather than just length, is a key underlying no-ER predictor.

The third, and final, independent predictor found in our study was care paradigm. This likely reflects the shorter IVT-to-$ER_{eval}$ delay inherent to the mothership, as compared to the drip-and-ship, paradigm, as also found in our cohorts. As mentioned in Results, the variables IVT-to-$ER_{eval}$ time and care paradigm could not be entered together in the multivariable model due to multi-collinearity. Nevertheless, a *post-hoc* sensitivity analysis replacing care paradigm by IVT-to-$ER_{eval}$ time as expected yielded SVS length, occlusion site and IVT-to-$ER_{eval}$ time as independent predictors (**supplemental Table 3**). In terms of mechanism, drip-and-ship patients are more likely than mothership patients to receive full-dose alteplase – the infusion of which lasts one hour – as well as to benefit from longer overall alteplase exposure, in turn increasing the probability of ER. Importantly, consistent with one previous report,[108] ER occurrence increased up to 90-120min after IVT-start (Figure 2B), suggesting alteplase possesses more prolonged pharmacodynamics than widely believed. This in turn implies that a substantial fraction of drip-and-ship patients will have recanalized by the time they reach the MT-capable centre. Note that the association between IVT-to-ER evaluation delay and ER should not be interpreted as an encouragement for delaying transfer for MT.

*Score derivation and validation*

Based on the above results, we derived two clinical scores – one MR-based and another MR-independent – intended to reliably predict ER, or no ER, following admission imaging, with the aim to help design randomized trials testing thrombolysis alone *vs.* bridging in patients highly likely to recanalize, as well as direct referral for thrombectomy *vs.* bridging therapy in patients at high risk of no ER.

We found that even the lowest grades on either score did not reliably predict ER (Figure 3). This is particularly true for FIRE-4, as roughly one in two patients with grade 0 will not experience ER, but also applies to FIRE-6, where even for grade 0 the risk of no-ER is still substantial (~20%). Thus, neither score may be used to support decisions to withhold referral for MT in clinical routine. Our finding that the lowest FIRE-6 grade (which refers to drip-and-ship patients with M1-distal or M2 occlusion and thrombus ≤7.0mm) predicts high ER rate (~80%) is in line with a *post-hoc* analysis of the THERAPY trial that found lower benefits from bridging therapy *vs.* thrombolysis alone with decreasing thrombus length, being neutral for thrombi <10mm.[113] Although testing thrombolysis alone *vs.* bridging therapy in such patients could be considered, such trial would seem hard to carry out given the very small proportion (~5%) of patients with grade 0 on FIRE-6 in our cohorts.

Conversely, high grades on either score predicted lack of recanalization with near-perfect specificity. As both scores should be easily obtainable on hospital admission following assessment with either MR (FIRE-6 for patients with visible SVS; FIRE-4 otherwise) or CT (FIRE-4), they should prove of value for patient selection into trials, *e.g.* testing bridging therapy *vs.* MT alone. Although some advocate withholding IVT

in LVO patients arguing the high odds of no-ER and the potential harmful effects of prior IVT,[32] based on our study showing a 20% average incidence of ER this approach appears too radical, and at any rate should be formally tested in randomized trials ideally recruiting only patients with very high probability of no-ER. This patient selection could be based on high FIRE grades, given their >90% specificity for no-ER (*e.g.*, FIRE-6 ≥4 or FIRE-4 ≥3, representing ~60% and ~30% of our cohorts, respectively). Note however that, owing to the potential benefits of alteplase over and above recanalization *per se,* such as reduced risk of embolization in a new territory and improved microcirculation after thrombectomy,[32,114,115] withholding IVT might be detrimental even in case of high FIRE grades, and should not be implied for routine care from our results.

Importantly, as they provide reference ER rates for each incremental point, our scores could also be valuable to calculate sample size for trials testing new approaches to enhance ER rates with thrombolytic therapy, *e.g.* tenecteplase,[116] DNAse-1[48] or N-acetylcysteine.[50]

Notably, both scores were externally validated using the validation cohort. In addition, their generalizability would if anything be strengthened by the small differences in clinical-radiological variables present between the derivation and validation cohorts (Table 1).

*Limitations*

The decision to refer patients for MT in our study was under the treating physician, which might have induced selection bias. That said, our populations do reflect current routine care of acute stroke patients with LVO. Second, patient workup before reperfusion therapy in our cohorts mainly relied on MR, CT being used in case of contra-indication to MR. Acknowledging that in many countries CT is first-line admission imaging, we derived a second score (FIRE-4) not relying on MR and applicable to CT-assessed patients. Note that the sub-sample of CT-assessed patients in our cohorts was too small to derive a reliable score including CT-based thrombus length or thrombus perviousness, which may also influence ER.[71,77] Third, the proximal end of ICA-T/L thrombi can sometimes be difficult to delineate, however such clots are expected to belong to the longest length category.[71]

**Conclusion**

In conclusion, our study documents a substantial rate of ER in IVT-treated patients with LVO referred for additional MT in routine day-to-day care, underlining the important benefits derived from IVT in current stroke management. Second, we show that post-alteplase recanalization mainly depends on thrombus length, but also on occlusion site and time elapsed between IVT and thrombectomy, which largely translates into care paradigm. Finally, the straightforward MR-based and MR-independent scores derived from these associations afford very high specificity for no-ER, which has implications for trial design.

**Supplemental material**

**Supplemental Results**

The intra-class correlation coefficient between observers was high for SVS length and DWI-ASPECTS (0.95 [95%CI: 0.93-0.97] and 0.94 [0.92-0.96], respectively), and the overall weighted Kappa showed almost perfect inter-observer concordance for occlusion site, and SVS visibility (0.95 [95%CI: 0.91-0.99], and 0.88 [95%CI: 0.64-1.11], respectively).

**Supplemental Table 1.** List of including centres of both derivation and validation cohorts

| **Primary stroke centers** | **Corresponding thrombectomy-capable centres** |
|---|---|
| **Derivation cohort** | |
| Orléans hospital | Tours hospital |
| Perpignan hospital<br>Nîmes hospital<br>Béziers hospital<br>Narbonne hospital | Montpellier hospital |
| Valenciennes hospital<br>Lens hospital<br>Douai hospital<br>Maubeuge hospital<br>Arras hospital<br>Cambrai hospital | Lille hospital |
| Metz hospital | Nancy hospital |
| **Validation cohort** | |
| Fleyriat Hospital, Bourg-en-Bresse<br>Valence Hospital<br>Lucien Hessel Hospital, Vienne | Hospices Civils de Lyon, Lyon |
| Saint-Antoine Hospital, Paris<br>Saint-Denis Hospital<br>Gonesse Hospital<br>Robert Ballanger Hospital, Aulnay<br>François Quesnay Hospital, Mantes-la-Jolie | Fondation A. de Rothschild, Paris |
| Intercommunal Poissy/St-Germain Hospital<br>André Mignot Hospital, Versailles | Foch Hospital, Suresnes |
| Saint-Joseph Hospital, Paris | Sainte-Anne Hospital, Paris |

**Supplemental Table 2.** Univariable relationships with lack of early recanalization (derivation cohort).[a]

| | ER N=124 | No ER N=509 | *P* value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 70.8 (58.8-79.9) | 72.1 (58.8-80.4) | 0.41 |
| Male gender | 66 (53.2) | 244 (47.9) | 0.29 |
| Hypertension | 69 (57.5) | 312 (61.9) | 0.37 |
| Diabetes mellitus | 23 (19.2) | 68 (13.5) | 0.11 |
| Current smoking | 21 (17.5) | 83 (16.5) | 0.79 |
| Antiplatelet use | 45 (37.5) | 166 (32.9) | 0.34 |
| Statin use | 40 (33.3) | 139 (27.6) | 0.21 |
| **Pre-IVT characteristics** | | | |
| Mothership | 27 (21.8) | 232 (45.6) | <0.01 |
| NIHSS | 11 (7-17) | 16 (12-20) | <0.01 |
| Admission glucose[b] (mmol/l) | 6.9 (5.9-8.3) | 6.7 (5.9-8.0) | 0.44 |
| Onset-to-IVT time (min) | 155 (125-190) | 150 (120-180) | 0.11 |
| **Pre-IVT imaging** | | | |
| MRI and MRA | 119 (96.0) | 473 (92.9) | 0.22 |
| Occlusion site | | | <0.01 |
| ICA-T/L | 9 (7.3) | 132 (25.9) | |
| Proximal M1 | 42 (33.9) | 219 (43.0) | |
| Distal M1 | 43 (34.7) | 99 (19.4) | |
| M2 | 30 (24.2) | 59 (11.6) | |
| DWI-ASPECTS[c] | 8 (6-9) | 8 (6-8) | 0.11 |
| SVS visible[d] | 99 (85.3) | 399 (84.9) | 0.90 |
| SVS length[e] (mm) | 7.6 (5.9-9.9) | 13.6 (10.2-20.2) | <0.01 |
| **ER evaluation** | | | |
| IVT-to-$ER_{eval}$ time (min) | 115 (89-137) | 95 (54-133) | <0.01 |
| **TOAST classification**[f] | | | 0.57 |
| Atherosclerosis | 14 (12.1) | 64 (12.6) | |
| Cardioembolic | 57 (49.1) | 241 (47.4) | |
| Other | 4 (3.4) | 35 (6.9) | |
| Undetermined | 41 (35.3) | 168 (33.1) | |

*Legend*: a: Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). b: 36 missing values. c: 41 missing values (patients with CT and CTA). d: 47 missing values (41 patients with CT and CTA and 6 patients without T2*-MRI). e: 135 missing values (41 patients with CT, 6 patients without T2*-MRI and 88 patients without SVS). f: 9 missing values.

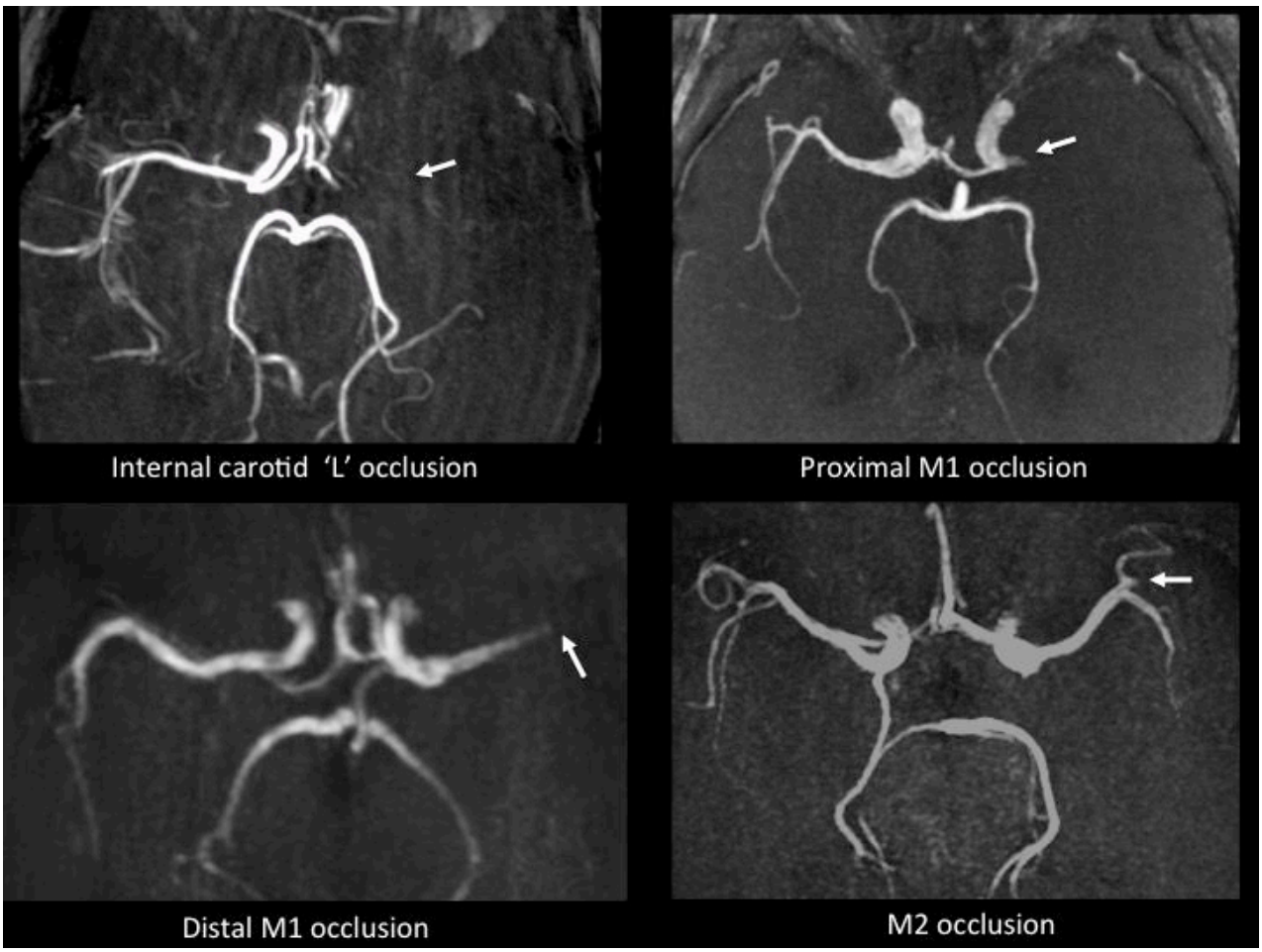
Abbreviations: ASPECTS indicates Alberta Stroke Program Early CT score; DWI, diffusion-weighted imaging; ER, early recanalization; ICA T/L, intracranial internal carotid; IVT, intravenous thrombolysis; IVT-to-$ER_{eval}$ time, time between intravenous thrombolysis start and evaluation of early recanalization; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; MRI; magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; SVS, susceptibility vessel sign.

**Supplemental Table 3**. Variables independently associated with no recanalization in multivariable logistic regression in the derivation cohort, replacing care paradigm by IVT-to-$ER_{eval}$ time*

| | **Adjusted OR (95%CI)** | ***P* value** |
|---|---|---|
| SVS length | | **<0.001** |
| ≤7.0mm | Reference | |
| >7.0 and ≤10.0mm | 5.0 (2.4-10.3) | |
| >10.0mm and ≤14.0mm | 22.5 (9.5-53.3) | |
| >14.0mm | 42.4 (16.7-107.5) | |
| IVT-to-$ER_{eval}$ time, per each 30min increase | 0.7 (0.6-0.9) | **<0.001** |
| Occlusion site | | **0.004** |
| M2 or M1 distal | Reference | |
| M1 proximal or ACI-T/L | 2.3 (1.3-3.9) | |

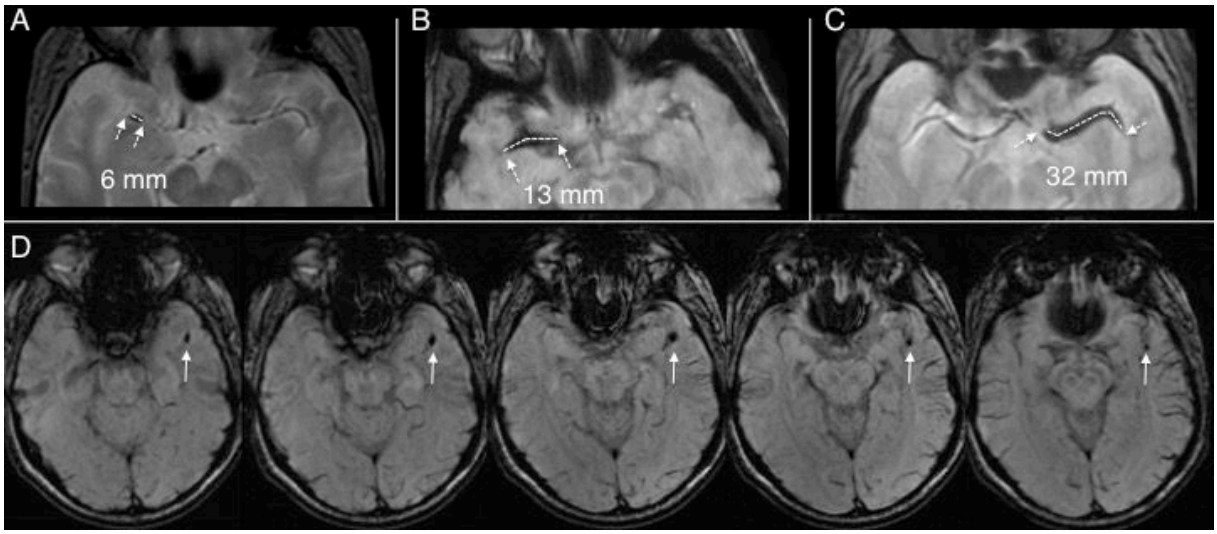
*Legend:* *498 patients with visible SVS were included in this analysis. Abbreviations: CI indicates confidence interval; ICA T/L, intracranial internal carotid; IVT-to-$ER_{eval}$ time, time between intravenous thrombolysis start and evaluation of early recanalization; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; OR, odds ratio; SVS, susceptibility vessel sign.

**Supplemental Figure 1**. Representative images of occlusion site in 4 patients.




*Legend:* Illustrative patients with the 4 different occlusion sites on intracranial MRA. The M1 segment was defined as the first portion of the middle cerebral artery up to the main bifurcation, and dichotomized as proximal or distal based on the middle cerebral artery origin-to-clot interface distance (<10mm and ≥10mm, respectively.

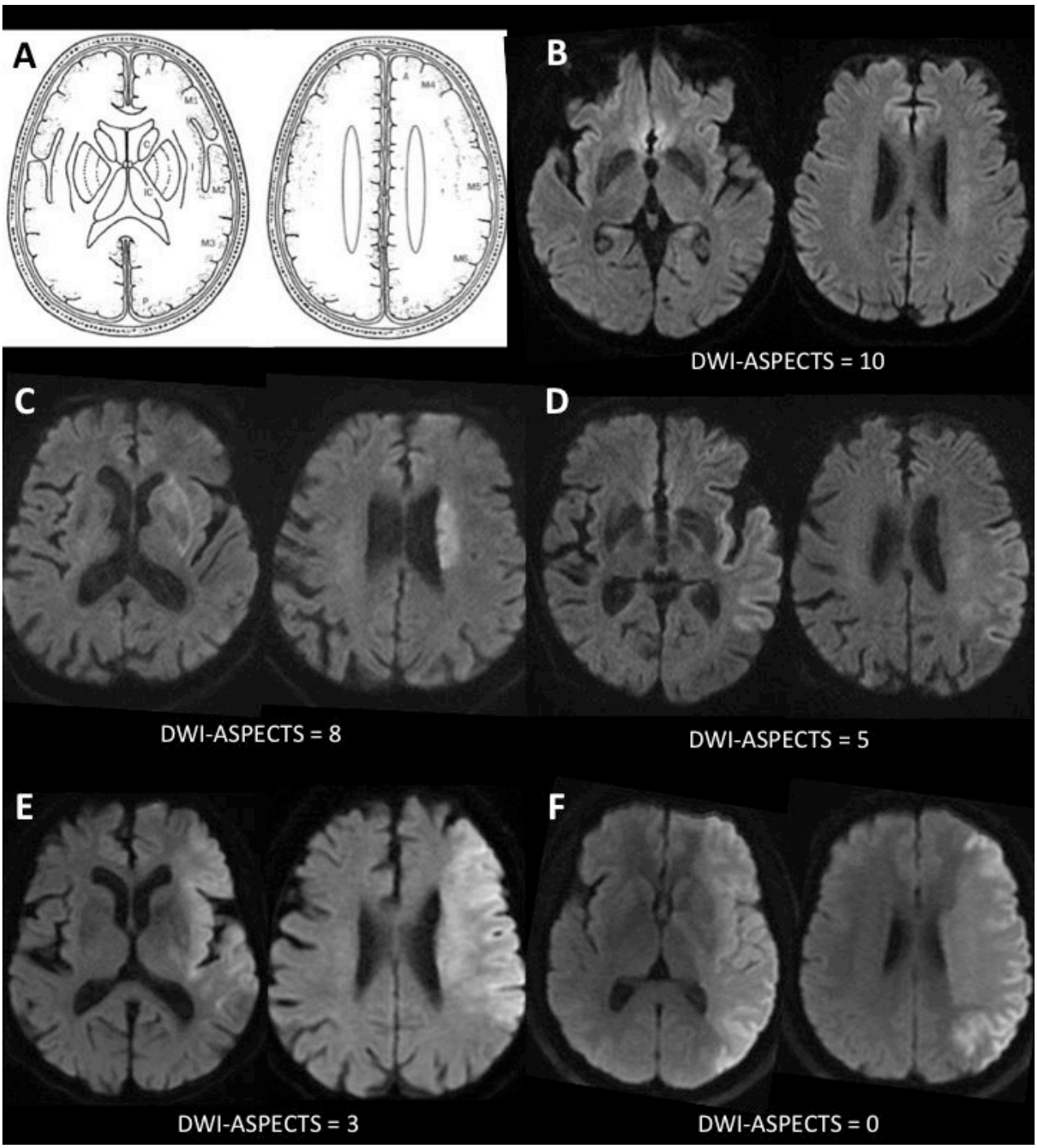
**Supplemental Figure 2**. Representative images of SVS length evaluation on T2*-MRI (white arrows) in 4 patients.




*Legend:* **A**, **B**, **C** and **D**: The in-plane length (M1 segment) was the distance between the proximal and distal parts of the SVS, and the length in the z-axis (supraclinoid ICA, M2) was the number of slices where the SVS was visible times the slice thickness. **A**, 6mm M1 SVS; **B**, 13mm M1 SVS; **C**, 32 mm M1 SVS. **D**: M2 SVS perpendicular to the axial acquisition plane (z-axis), visible on 5 consecutive slices (2mm thickness): SVS length is 5×2mm=10mm.

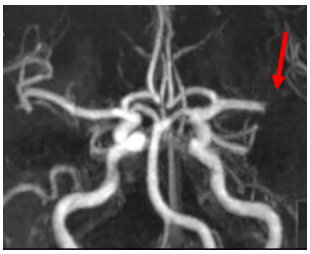
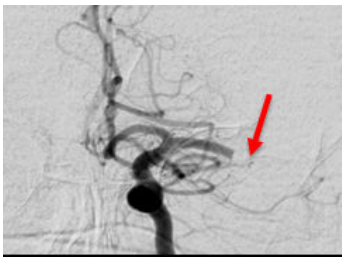
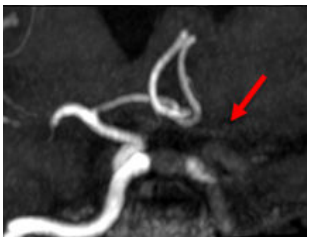
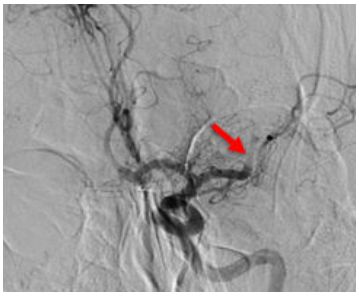
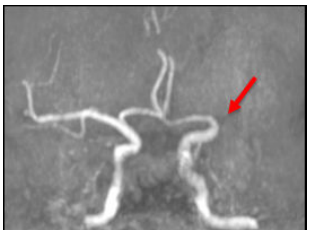
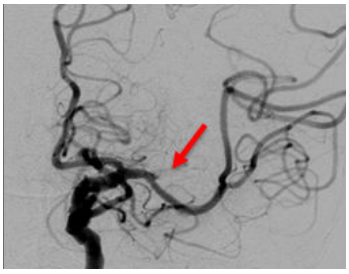
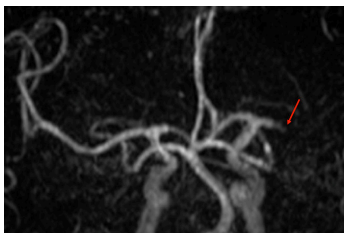
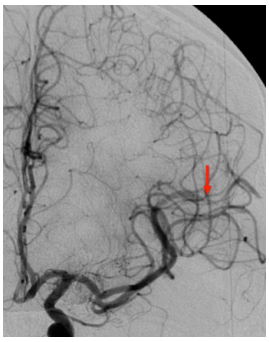
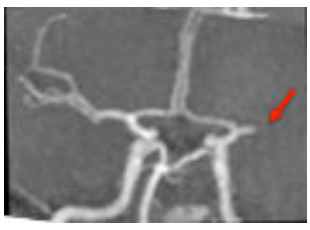
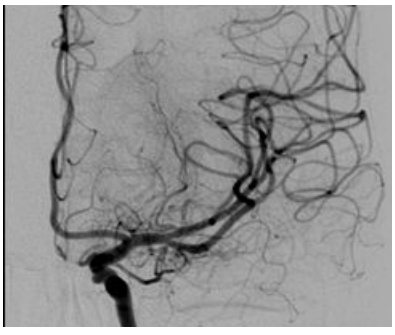
Abbreviations: M1 indicates, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; SVS, susceptibility vessel sign.

**Supplemental Figure 3**. Representative images of DWI-ASPECTS evaluation in 5 patients.

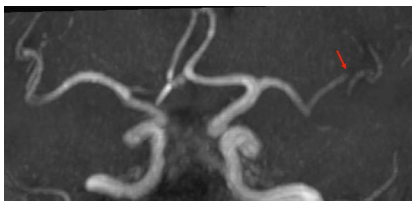
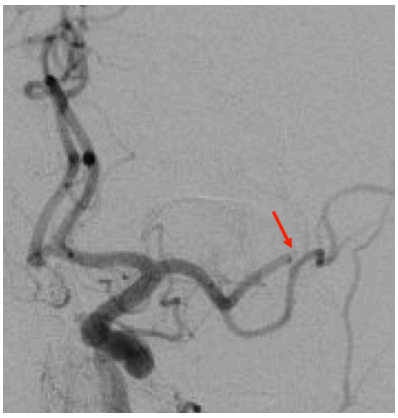
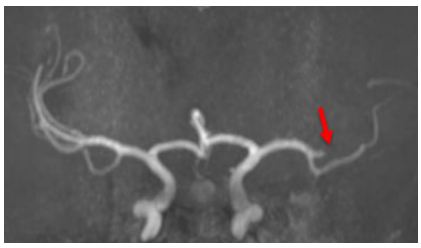
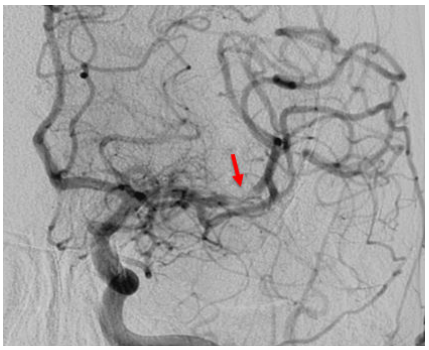
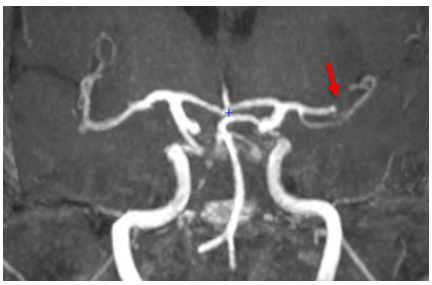
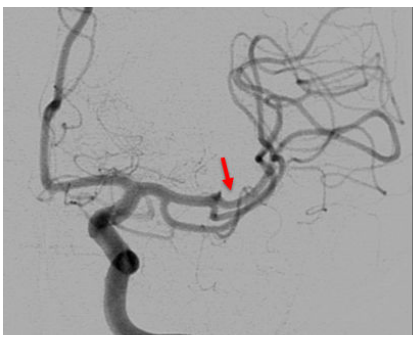



*Legend:* A: the middle cerebral artery (MCA) territory is divided into 10 regions on two standard axial sections on DWI: 1 at the level of the thalamus and basal ganglia, and the other just rostral to the ganglionic structures. Subcortical structures are allotted 3 points (C: caudate nucleus, L: lenticular nucleus, and IC: internal capsule). MCA cortex is allotted 7 points (I: insular cortex, M: anterior MCA cortex; M2: MCA cortex lateral to insular ribbon; M3: posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.). One point is subtracted for each of the defined regions with DWI abnormality. A score of 10 indicates the absence of MCA territory infarction, and a score of 0, complete infarction throughout this territory. B-F: five illustrative patients with DWI-ASPECTS 0 to 10.

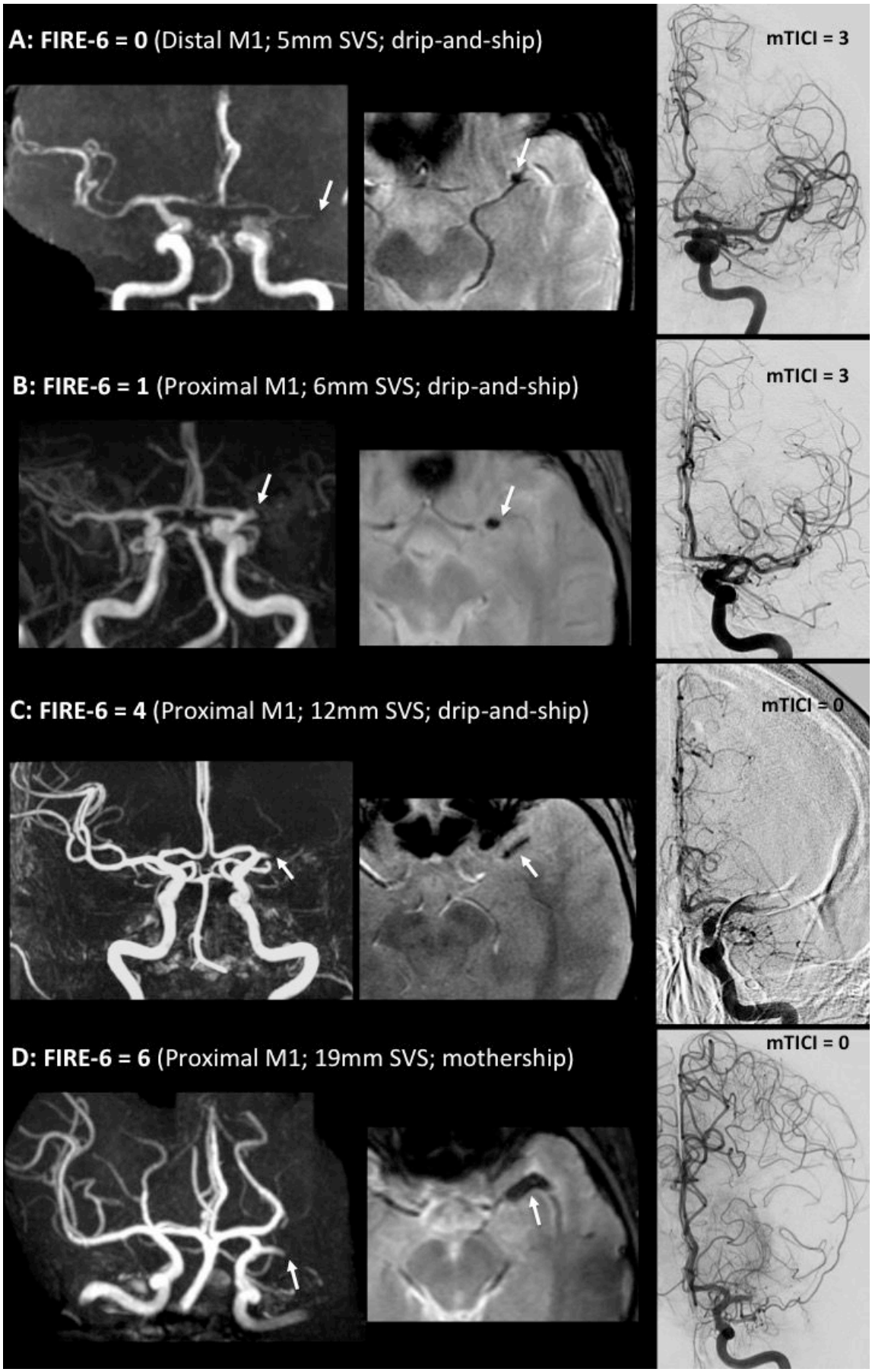
**Supplemental Figure 4.** Five typical patients with different modified thrombolysis in cerebral infarction (mTICI) scale.[110]

| Baseline MRI | First angiographic run | Classification |
|---|---|---|
|  |  | **mTICI 0**<br>No perfusion |
|  |  | **mTICI 1**<br>Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion |
|  |  | **mTICI 2a**<br>Perfusion of less than half of the vascular distribution of the occluded artery |
|  |  | **mTICI 2b**<br>Perfusion of half or greater of the vascular distribution of the occluded artery |
|  |  | **mTICI 3**<br>Full perfusion with filling of all distal branches |

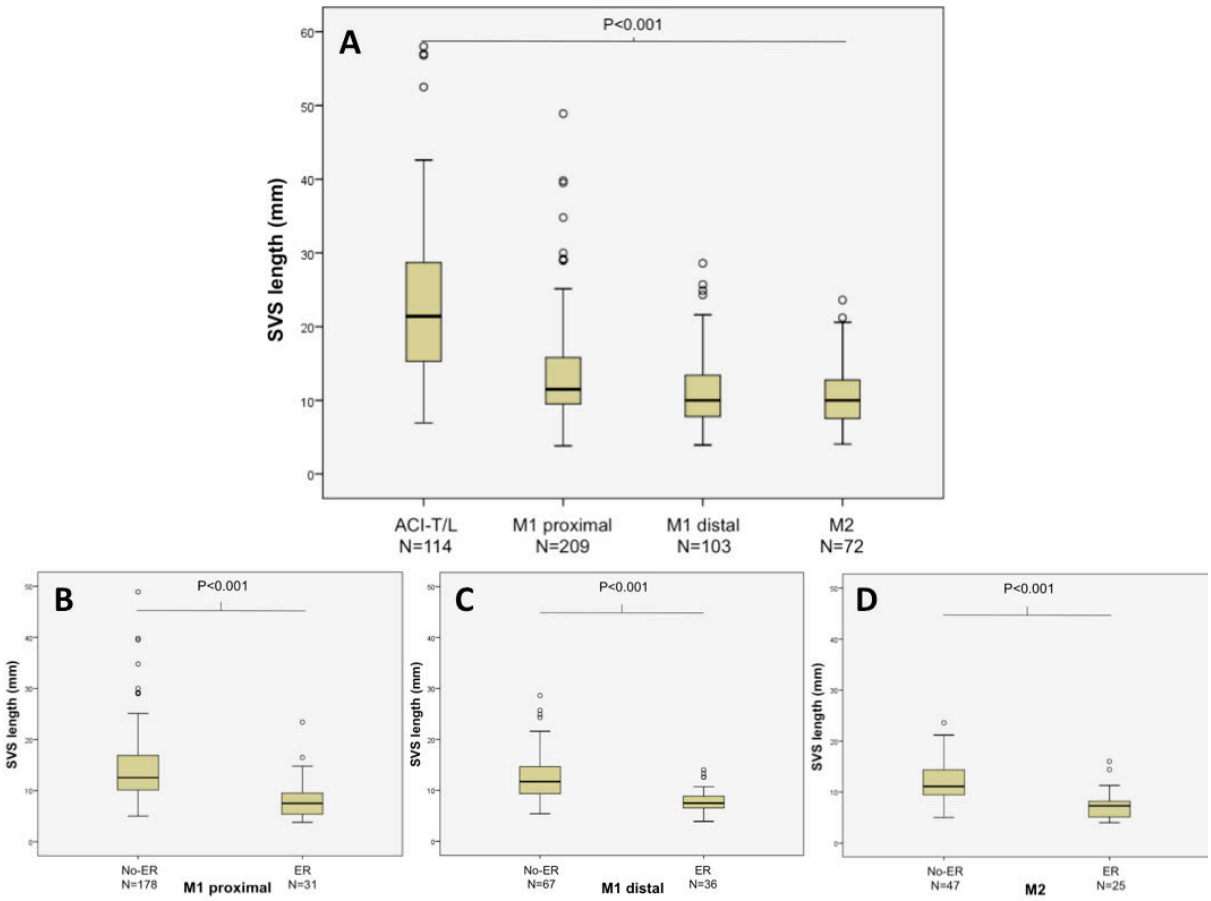
**Supplemental Figure 5.** Three typical patients with different Arterial occlusive lesion (AOL) scale.[110]

| Baseline MRI | First angiographic run | Classification |
|---|---|---|
|  |  | **AOL 0/1**<br>No recanalization of the occlusion or incomplete/partial recanalization of the occlusion, with no distal flow |
|  |  | **AOL 2**<br>Incomplete or partial recanalization of the occlusion, with any distal flow |
|  |  | **AOL 3**<br>Complete recanalization of the occlusion with any distal flow |

**Supplemental Figure 6**. Typical patients with left M1 occlusion and various FIRE-6 grades, and the corresponding first angiographic run (left: MRA showing occlusion site; middle: T2* showing SVS; right: first angiographic run).



**Supplemental Figure 7.** Box-and-whiskers plot of susceptibility vessel sign (SVS) length according to site of occlusion and early recanalization (ER) status.




*Legend:* (**A**): SVS length according to arterial occlusion site; (**B**), (**C**) and (**D**): SVS length according to ER status for proximal M1 (**B**), distal M1 (**C**) and M2 (**D**) occlusion subsets. The number of patients with ER in the ICA-T/L occlusion subset was too small for a reliable analysis. Abbreviations: ICA-T/L, T or L shape internal carotid terminus; IVT, intravenous thrombolysis; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery. Boxes indicate interquartile range; horizontal lines, median; whiskers, 5$^{th}$ and 95$^{th}$ percentiles, and points, extreme values.

# Troisième partie :
# Relations entre perfusion cérébrale, circulation collatérale et recanalisation artérielle précoce après thrombolyse intraveineuse

## Chapitre 1 : Perfusion cérébrale

Cette étude a été soumise pour publication fin août 2018 dans le *Journal of Cerebral Blood Flow and Metabolism*. Le manuscrit est inséré ci-après.

**Résumé :** L'objectif de cette étude était d'étudier si les données de l'imagerie de perfusion cérébrale, et notamment la sévérité de l'hypoperfusion cérébrale, apportaient des informations utiles à la prédiction de la recanalisation précoce post-thrombolyse intraveineuse, indépendamment des données déjà rapportées (à savoir, principalement la longueur et la localisation du thrombus).

Dans cette sous-étude de la cohorte PREDICT-RECANAL (présentée dans la deuxième partie), seuls les patients chez lesquels une IRM de perfusion a été réalisée à l'admission (n= 218 patients issus de 6 centres réalisant de l'IRM de perfusion en routine clinique) ont été inclus. Les séquences de diffusion et perfusion étaient ont été traitées à l'aide du logiciel Olea Sphere. Les volumes de cœur ischémique et de mismatch perfusion-diffusion ont été mesurés, ainsi que l'*Hypoperfusion Intensity Ratio* (HIR, défini comme la proportion de Tmax>6sec avec Tmax>10sec, un HIR bas indiquant une hypoperfusion moins sévère).

Sur les 218 patients inclus, 34 (16%) ont présenté une recanalisation précoce. En analyse multivariable, un HIR bas, un court thrombus et une occlusion artérielle distale (M1distale/M2) étaient les trois facteurs associés de manière indépendante à la survenue d'une recanalisation précoce. Il existait une interaction entre la longueur du thrombus et le HIR, à savoir, plus le thrombus était de petite taille, plus l'effet du HIR était important.

*Conclusion* : La sévérité de l'hypoperfusion exprimée sous la forme du HIR est un marqueur indépendant de survenue d'une recanalisation précoce dans cette population. Cette association pourrait être principalement liée i) à la présence d'un réseau artériel collatéral de bonne qualité, favorisant l'accès du thrombolytique aux deux extrémités du thrombus, ou ii) à des thrombi partiellement occlusifs. L'imagerie de perfusion pourrait être utile pour sélectionner les patients tirant le bénéfice le plus important de la thrombolyse intraveineuse avant transfert pour thrombectomie.

**Relationships between brain perfusion and early recanalization after intravenous thrombolysis for acute stroke with large vessel occlusion.** Seners P, Turc G, Lion S, Cottier JP, Cho TH, Arquizan C, Bracard S, Ozsancak C, Legrand L, Naggara O, Debiais S, Berthezene Y, Costalat V, Richard S, Magni C, Nighoghossian N, Narata AP, Dargazanli C, Gory B, Mas JL, Oppenheim C*, Baron JC*. ***Soumis au Journal of Cerebral Blood Flow and Metabolism le 20/08/2018***

*Equal contribution


**Abstract**

In large vessel occlusion (LVO) stroke, it is unclear whether severity of ischemia is involved in early post-thrombolysis recanalization over and above thrombus site and length. Here we assessed the relationships between perfusion parameters and early recanalization following intravenous thrombolysis administration in LVO patients. From a multicenter registry, we identified 218 thrombolysed LVO patients referred for thrombectomy with both i) pre-thrombolysis MRI, including diffusion-weighted imaging (DWI), T2*-imaging, MR-angiography and dynamic susceptibility-contrast perfusion-weighted imaging (PWI); and ii) evaluation of recanalization on first angiographic run or non-invasive imaging ≤3hrs from thrombolysis start. Infarct core volume on DWI, PWI-DWI mismatch volume and Hypoperfusion Intensity Ratio (HIR; defined as the proportion of Tmax>6s volume with Tmax>10sec, low HIR indicating milder hypoperfusion) were determined using a commercially available software. Early recanalization occurred in 34 (16%) patients, and was independently associated with lower HIR ($P$=0.006), shorter thrombus on T2*-imaging ($P$<0.001) and more distal occlusion ($P$=0.006). There was a significant interaction between thrombus length and HIR such that the smaller the thrombus the stronger the effect of HIR. This study disclosed an independent association between lower HIR and early post-thrombolysis recanalization. Perfusion imaging may help to identify LVO patients most likely to benefit from thrombolysis before thrombectomy.

**Introduction**

Perfusion imaging is of considerable interest in the acute stroke setting as it allows one to measure the presence and volume of infarct core – the already irreversibly injured tissue – and penumbra – the severely hypoperfused but still salvageable tissue –, and thereby brings on powerful information on patient's response to reperfusion therapies such as intravenous thrombolysis (IVT) and mechanical thrombectomy, that may in turn help decision-making.[117-119] Regarding IVT, perfusion imaging may improve the identification of patients likely to benefit.[120,121] Regarding thrombectomy, several reports have shown that infarct core volume, assessed using either MR-[122] or CT-based approaches,[123] as well as penumbral volume[124,125] strongly predict 3-month functional outcome within early time windows, *i.e.*, ≤6hrs, and that the clinical benefit of adding thrombectomy to medical therapy (including IVT or not) is related to the former.[122,126] Moreover, perfusion imaging also guides thrombectomy decisions beyond 6hrs, and based on the results of the DAWN and DEFUSE-3 trials,[127,128] infarct core measurement is now recommended for thrombectomy eligibility in LVO patients seen 6-24hrs from last known normal.[27] Consequently, perfusion imaging is used in some centers to guide thrombectomy decisions both within and beyond the 6-hr time window.[129]

The main therapeutic target of reperfusion therapies in acute stroke with LVO is early recanalization (ER; *i.e.*, within the very first few hours), because ER is strongly associated with smaller infarct growth,[7,128] and consequently with improved functional outcome.[6,7,125] However, IVT has limited efficacy to induce ER (10-20% ER rate in LVO patients[106,107]), which has led to the testing and subsequent licensing of thrombectomy added on IVT (so-called 'bridging therapy'). Yet, the mechanisms underlying failure of ER following IVT, *i.e.*, clot resistance, remain inadequately understood. Thrombus site is one key factor explaining resistance to IVT,[107] while thrombus length, as determined on admission T2*-weighted MR or CT angiography (CTA),[71,72,107,130] as well as thrombus perviousness on CTA, may also help predict recanalization.[71,77,131] Finally, thrombus composition may also be involved.[46,74] Due to the low ER rate following IVT together with its potential harmful effects, some authors have even called into question its use before thrombectomy in LVO patients.[32,132] For these reasons, it is timely and important to further investigate the predictors of post-IVT ER. Identifying strong predictors may eventually help to select individual LVO patients for best therapy, *i.e.*, IVT alone, bridging, or thrombectomy alone,[117] and for recruitment into trials comparing these options.

Perhaps surprisingly, the potential predictive value of perfusion parameters for ER in LVO patients has been little studied so far. One study found that core volume was not associated with ER.[74] Two studies investigated the relationship between severity of hypoperfusion and recanalization, but both assessed the latter at 24hrs[61,62] which is not relevant to the current thrombectomy paradigm, and in addition such late assessment includes futile reperfusion, *i.e.*, occurring too late to save sizeable penumbral volume.

In the present study, we assessed the relationships between core volume and markers of hypoperfusion severity on one hand, and occurrence of post-IVT ER on the other hand, in LVO patients undergoing multimodal admission MRI. In order to assess ER, we exploited a large multi-centric sample of LVO patients intended for thrombectomy since bridging therapy became standard-of-care, *i.e*. in whom ER is routinely assessed on first-run conventional angiography.

**Methods**

Patients

We analyzed the registries of six French stroke centers (Sainte-Anne [Paris], Hospices civils [Lyon], Orléans, Tours, Montpellier and Nancy university hospitals), collecting data prospectively (n=3) or retrospectively (n=3) from all consecutive stroke patients referred for thrombectomy. All centers had on-site endovascular capabilities except one, whose eligible patients were transferred to the nearest thrombectomy capable center (*i.e.*, drip-and-ship, as opposed to mothership, paradigm). In line with French recommendations,[133] MRI was implemented as first-line imaging in candidates for reperfusion therapy in all centers of the present study. CT and CTA was performed in case of contraindication to MRI. The stroke MRI protocol in the participating centers included diffusion-weighted imaging (DWI), T2*, intracranial MR angiography (MRA) and dynamic susceptibility-contrast perfusion-weighted imaging (PWI), whenever feasible with no delay. The PWI acquisition parameters used in each participating center are presented in **supplemental Table 1**. The PWI data were not a basis for decision-making in routine except in borderline cases.

Inclusion criteria for the present study were (1) patient admitted for acute stroke with LVO of the anterior circulation between May 2015 (when thrombectomy became routine care in these centers) and March 2017; (2) pre-IVT imaging with MRI, including DWI, T2*, MRA and PWI; (3) IVT with alteplase 0.9mg/kg; and (4) evaluation of ER before thrombectomy (see below).

In accordance with French legislation, each patient was informed of his/her participation in this study, and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required.

Clinical data

The following variables were extracted from the registries: age, sex, vascular risk factors and past medical history, pre-stroke medication, National Institutes of Health Stroke Scale (NIHSS) score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time elapsed between start of IVT and evaluation of ER (IVT-to-$ER_{eval}$ time; see below).

Imaging data

A stroke neurologist with experience in neuroimaging (PS) reviewed the pre-IVT anonymised imaging of all included patients, blinded to recanalization status. The following variables were collected: (1) occlusion site, according to 4 categories: intracranial internal carotid artery T or L (ICA-T/L), M1 proximal, M1 distal and M2, where the M1 segment was defined as the first portion of the MCA up to the main bifurcation, and dichotomized as proximal or distal based on the MCA origin-to-thrombus distance (<10mm and ≥10mm, respectively);[71,110] (2) length of the susceptibility vessel sign (SVS), a marker of thrombus on T2*, based on previously published methodology;[111] (3) DWI lesion volume, semi-

automatically segmented by means of Olea Sphere software (Olea Medical SAS, La Ciotat, France) after applying a threshold of $620\times10^{-6}$ $mm^2/s$ on apparent diffusion coefficient maps,[134] with manual correction when necessary; (4) PWI-DWI mismatch volume, calculated as the volumetric difference between the time-to-maximum (Tmax) ≥6s volume and the DWI lesion volume, the Tmax≥6s volume being automatically segmented from PWI using Olea Sphere[135] with manual correction whenever necessary; and (5) severity of hypoperfusion, assessed using the hypoperfusion intensity ratio (HIR),[136] defined here as the proportion of the Tmax≥6s volume with Tmax≥10s (*i.e.* HIR = [Tmax≥10s volume / Tmax ≥6s volume] ×100), low HIR indicating milder hypoperfusion.[137] Note that the HIR is derived only from perfusion maps, *i.e.* the Tmax volumes do not take into consideration the DWI lesion.

ER evaluation

ER was defined as recanalization occurring within 3hrs after initiation of IVT, a delay that includes typical 'drip-and-ship' situations.[108] In all participating centers, eligible patients were referred for thrombectomy as soon as possible after start of IVT. Consequently, ER was evaluated on the first angiographic run carried out as part of intended thrombectomy. However, in some patients with significant improvement in neurological status before reaching the angiosuite, recanalization was evaluated using non-invasive vascular imaging (MRA or CTA). Two readers independently evaluated recanalization, blinded to clinical and imaging data. Discrepancies were resolved by consensus. On conventional angiography, ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction scale for ICA-T/L or M1 occlusions, and 3 on the Arterial Occlusive Lesion scale for M2 occlusions.[110] Otherwise, ER was defined as 3 on the Arterial Occlusive Lesion scale on CTA or MRA.

Statistical analysis

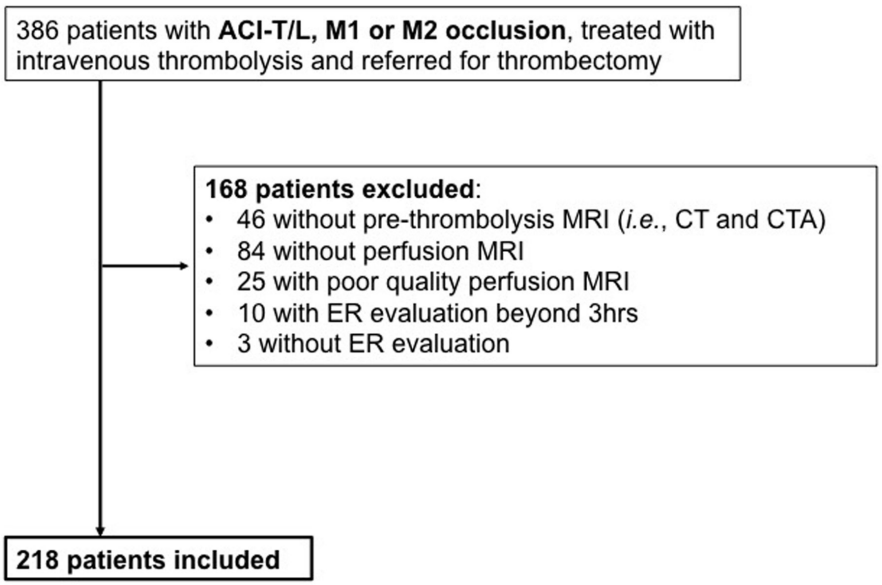
Continuous variables were described as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as number (percentage). Univariable comparison of ER and no-ER patients was performed using Student *t* or Mann-Whitney *U* tests for continuous variables, and Chi-square or Fisher exact test for categorical variables, as appropriate. Baseline variables associated with ER in univariable analysis at a level of $P<0.20$ were candidates for inclusion into a multivariable binary logistic regression model, with ER as dependent variable. Variable selection was performed stepwise, whereby candidate variables entered the model at $P<0.20$ and were retained only if they remained associated at $P<0.05$ with the dependent variable. Covariates were assessed for potential collinearity and interaction effects. Probability curves and contour plots were created based on the predictions of the final multivariable logistic model. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC) and SPSS 16.0 (SPSS Inc). Two-tailed $P<0.05$ was considered statistically significant.

**Results**

Patients' characteristics

Across the six participating centers, 386 patients with ACI-T/L, M1 or M2 occlusion and eligible for thrombectomy received IVT during the study period. Of these, 168 were excluded (see **Figure 1** for the reasons for exclusion), leaving 218 patients for the final analysis. Excluded patients with baseline MRI but without PWI or with poor quality PWI (n=109) had similar age (*P*=0.66), sex (*P*=0.27), NIHSS score (*P*=0.08), occlusion site (*P*=0.57) and ER rate (*P*=0.60) than included patients.

**Figure 1** – Study flow chart




*Abbreviations*: CT indicates computerized tomography; ER, early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; MRI, magnetic resonance imaging.

The baseline characteristics of included patients are presented in **Table 1**. Patients were managed according to the mothership or drip-and-ship paradigms in 88% (191/218) and 12% (27/218), respectively. ER was evaluated on first angiographic run in 207/218 (95%) patients, and on non-invasive imaging in the remaining. ER occurred in 34/218 (16%) patients, with rates of 3% (1/40), 7% (6/91), 28% (11/39) and 33% (16/48) in ACI-T/L, proximal M1, distal M1 and M2 occlusions, respectively. Considering the similar incidence of ER in ACI-T/L and proximal M1, and in distal M1 and M2 occlusions, respectively, these four subsets were collapsed into two categories for further analyses (distal M1 or M2 *vs.* ACI-T/L or proximal M1 occlusions).

**Table 1** – Baseline characteristics of the population and univariable relationships with ER*

| | Whole cohort n=218 | Early recanalization n=34 | No early recanalization n=184 | *P* value |
|---|---|---|---|---|
| **Patient history** | | | | |
| Age (years) | 72 (61-80) | 72 (59-83) | 72 (61-80) | 0.78 |
| Men | 120 (55) | 18 (53) | 102 (55) | 0.79 |
| Hypertension | 122 (56) | 19 (56) | 103 (56) | 0.99 |
| Diabetes mellitus | 35 (16) | 9 (27) | 26 (14) | 0.07 |
| Current smoking | 27 (12) | 5 (15) | 22 (12) | 0.66 |
| Antiplatelet use | 73 (34) | 13 (38) | 60 (33) | 0.52 |
| Statin use | 68 (31) | 14 (41) | 54 (29) | 0.17 |
| **Pre-IVT characteristics** | | | | |
| NIHSS score | 16 (10-20) | 12 (6-17) | 16 (10-20) | **<0.01** |
| Onset-to-IVT time (min) | 160 (130-192) | 163 (144-194) | 158 (129-192) | 0.48 |
| **Pre-IVT MRI** | | | | |
| Occlusion site | | | | **<0.01** |
| ICA-T/L | 40 (18) | 1 (3) | 39 (21) | |
| Proximal M1 | 91 (42) | 6 (18) | 85 (46) | |
| Distal M1 | 39 (18) | 11 (32) | 28 (15) | |
| M2 | 48 (22) | 16 (47) | 32 (17) | |
| SVS length† (mm) | 12.6 (9.2-17.6) | 7.2 (5.8-8.9) | 14.0 (10.2-19.7) | **<0.01** |
| DWI volume (ml) | 12 (5-23) | 9 (2-18) | 12 (5-29) | **0.04** |
| PWI-DWI mismatch volume (ml) | 62 (34-100) | 39 (17-63) | 71 (40-104) | **<0.01** |
| HIR (%) | 43 (30-53) | 31 (19-49) | 43 (32-54) | **<0.01** |
| **ER evaluation** | | | | |
| IVT-to-$ER_{eval}$ time (min) | 62 (37-97) | 61 (44-118) | 62 (35-97) | 0.68 |

*Legend*: *: Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). †: Missing values: 20 patients without visible SVS (4 with ER and 16 without ER). Abbreviations: DWI indicates diffusion-weighted imaging; ER, early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; IVT-to-$ER_{eval}$ time, time between thrombolysis start and evaluation of early recanalization; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; SVS, susceptibility vessel sign.

Variables associated with ER in univariable analysis

The univariable associations between ER and baseline variables are presented in **Table 1**. The following variables were significantly associated with ER occurrence: lower baseline NIHSS, more distal occlusions, shorter SVS, smaller DWI lesion and PWI-DWI mismatch volumes, and lower HIR.

Multivariable analysis with early recanalization as the dependent variable

The multivariable model (n=198 patients; 20 patients without SVS were excluded for this analysis) is presented in **Table 2**. Lower HIR (*P*=0.006), smaller SVS length (*P*<0.001) and more distal occlusion site (*P*=0.006) were independently associated with ER occurrence. Other candidate variables for the multivariable model (*i.e*., with *P*<0.20 in the univariable analysis), namely NIHSS score, DWI and PWI-DWI mismatch volumes, statin use and history of diabetes mellitus, were not retained in the multivariable model. As there was a significant (*P*=0.02) interaction between SVS length and HIR, such that the smaller the thrombus the stronger the effect of HIR, the HIR*SVS length interaction term was also included in the multivariable model.

**Table 2** – Variables independently associated with early recanalization in multivariable logistic regression*

| | **β coefficient** | **Standard error** | **P value** |
|---|---|---|---|
| **HIR**, per 10% increase | -1.19 | 0.43 | **0.006** |
| **SVS length**, per 1mm increase | -0.78 | 0.22 | **<0.001** |
| **Occlusion site** | | | **0.006** |
| ACI-T/L or M1 proximal | 0 (Reference) | - | |
| M1 distal or M2 | 1.54 | 0.56 | |
| **Interaction term** (HIR*SVS length) | 0.09 | 0.04 | **0.02** |

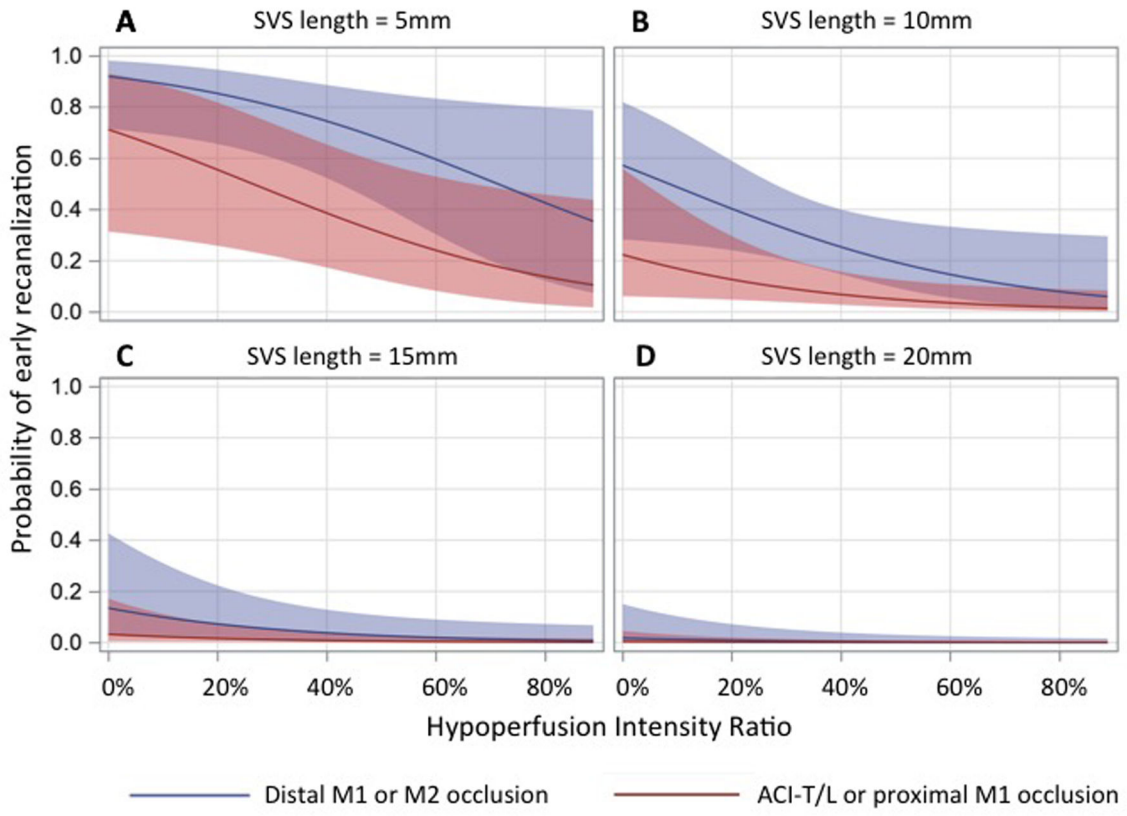
*Legend:* *20 patients without visible SVS were excluded from the model, which therefore included 198 patients (30 with early recanalization and 168 without).

Due to the presence of an interaction term in the logistic model, results are presented with beta coefficients and standard error rather than odds ratios and 95% confidence intervals.

Abbreviations: HIR indicates hypoperfusion intensity ratio; ICA-T/L, intracranial internal carotid artery occlusion; M1, first segment of the middle cerebral artery; M2, second segment of the cerebral artery; SVS, susceptibility vessel sign.

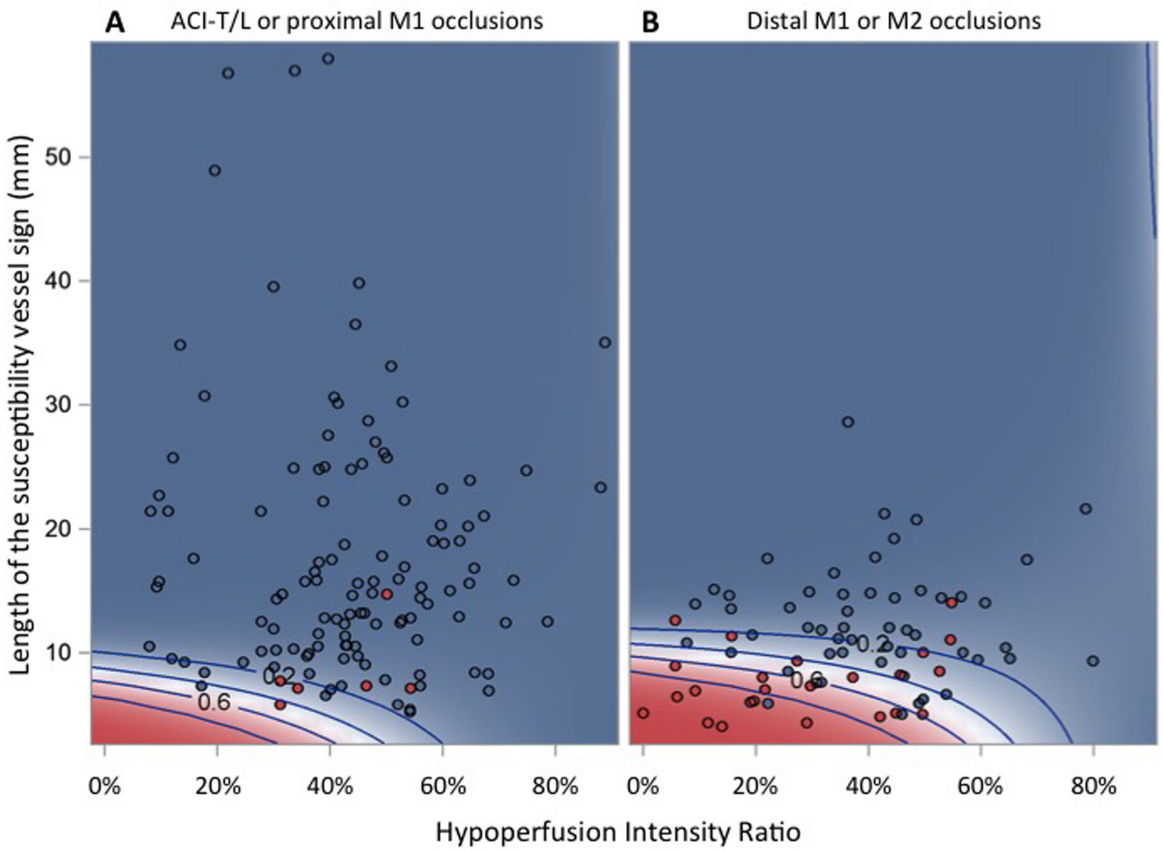
The predicted probability of post-IVT ER as a function of HIR and occlusion site, illustrated for different thrombus lengths, is presented in **Figure 2**. **Figure 3** represents the predicted probability of post-IVT ER according to thrombus length, HIR and occlusion site, taking into account the interaction between HIR and SVS. To allow individual assessment, each patient's data according to ER status is also plotted in the figure. Typical patients with and without ER are shown in **Figure 4** and **5**, respectively.

**Figure 2** – Probability of post-thrombolysis early recanalization according to Hypoperfusion Intensity Ratio, occlusion site and thrombus length.




*Legend:* The regression curves are estimates of the probability of post-thrombolysis early recanalization according to the Hypoperfusion Intensity Ratio for average patients with SVS lengths of (**A**) 5 mm, (**B**) 10 mm, (**C**) 15 mm and (**D**) 20 mm. The red curve corresponds to ACI-T/L/proximal M1 occlusions, and the blue curve to distal M1/M2 occlusions. The shaded area corresponds to the 95% confidence interval (logistic regression model). Regression curves for patients with SVS length >20 mm are not shown as no patient recanalized in this subgroup. Abbreviations: ICA-T/L indicates intracranial internal carotid artery occlusion; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; SVS, susceptibility vessel sign.

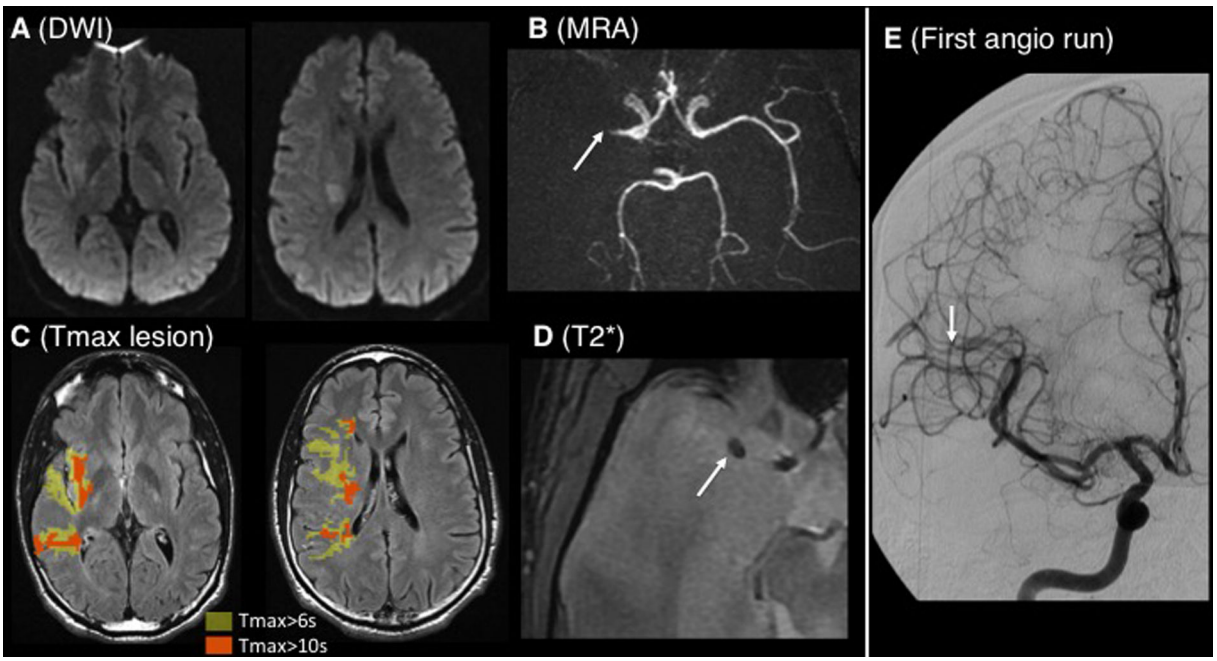
**Figure 3** – Contour plots showing post-thrombolysis early recanalization probability according to Hypoperfusion Intensity Ratio and thrombus length in patients with (**A**) ICA-T/L or proximal M1, and (**B**) distal M1 or M2 occlusions.




*Legend:* Red and blue dots correspond to individual patients with and without early recanalization, respectively. The shading and the concentric contour curves depict the probability of post-thrombolysis early recanalization predicted by the multivariable logistic regression model (Table 2), which includes HIR, thrombus length, occlusion site in two categories and the HIR*thrombus length interaction term. Red and blue shading corresponds to predicted probabilities of post-thrombolysis ER over or beyond 50%, respectively. The contour curves represent predicted probabilities of ER equal to 80%, 60%, 40% and 20%. The interaction term in the model causes the curvature of the contour lines and shows how the effect of HIR on the predicted probability of ER differs with thrombus length and vice versa.

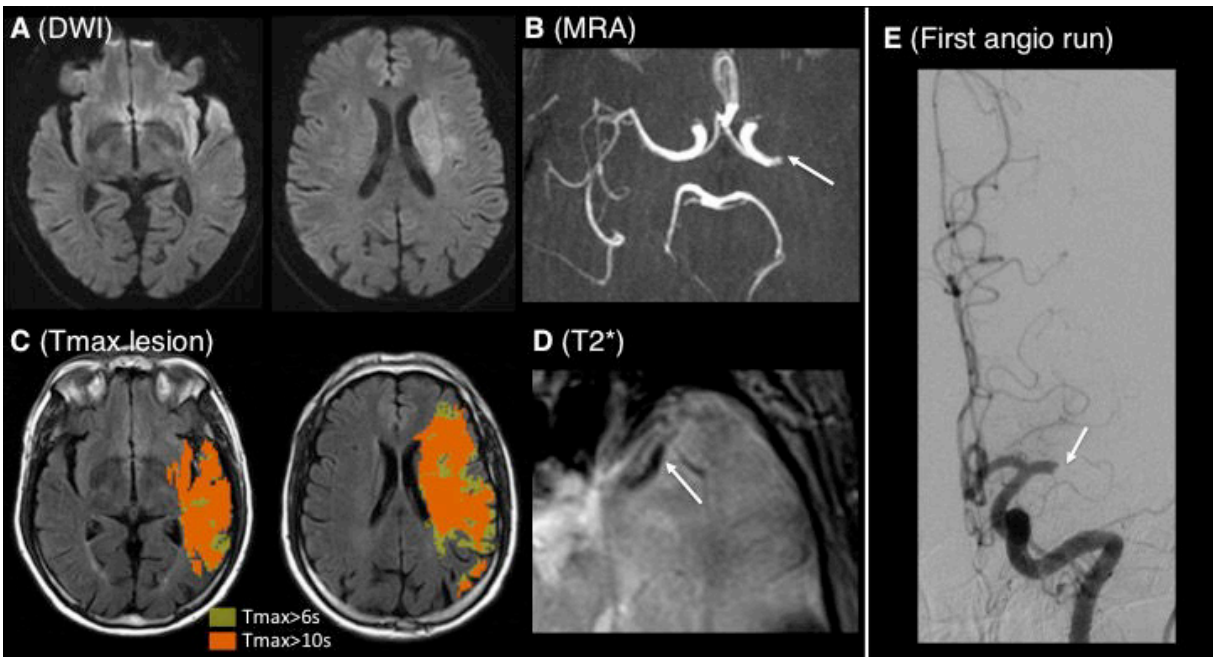
*Abbreviations:* ER, indicates early recanalization; HIR, hypoperfusion intensity ration; ICA-T/L, intracranial internal carotid artery occlusion; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery.

**Figure 4** – Typical patient with early recanalization.




*Legend:* Thirty-five years old patient with left hemiparesis; MRI obtained 180min after stroke onset (baseline NIHSS=8). **A**: Diffusion-weighted imaging showing a right-sided deep lesion in the middle cerebral artery territory (volume=4ml); **B**: MRA showing a right proximal M1 occlusion (arrow); **C**: Tmax>6sec lesion (yellow area, volume=61ml) and Tmax>10sec lesion (orange area, volume=19ml) projected onto the Fluid-Attenuated Inversion Recovery sequence; corresponding HIR=31%; **D**: T2*-imaging showing a small susceptibility vessel sign (arrow, 5mm). Intravenous thrombolysis was started 210min after stroke onset and the patient was immediately transported to the angiosuite, where the first angiographic run (**E**, performed 45min after thrombolysis start) showed early recanalization (mTICI score= 2b).

**Figure 5** – Typical patient without early recanalization




*Legend:* Sixty-six years old patient with right hemiparesis and dysphasia; MRI obtained 90min after stroke onset (baseline NIHSS=22). **A**: Diffusion-weighted imaging showing a left-sided deep and superficial lesion in the MCA territory (volume=28ml); **B**: MRA showing a left proximal M1 occlusion (arrow); **C**: Tmax>6sec lesion (yellow area, volume=176ml) and Tmax>10sec lesion (orange area, volume=109ml) projected onto the FLAIR sequence; corresponding HIR=62%; **D**: T2*-imaging showing a long susceptibility vessel sign (arrow, 14mm). IVT was started 115min after stroke onset and the patient was immediately transported to the angiosuite, where the first angiographic run (**E**, performed 70min after IVT start) showed persistent occlusion (mTICI score= 0).

**Discussion**

In this large multicenter cohort of LVO patients who underwent pre-IVT PWI and were then referred for thrombectomy following IVT, milder hypoperfusion severity –evaluated using the HIR– was independently associated with ER, together with smaller thrombus and more distal occlusion sites. Of note, other markers of ischemic severity, namely DWI lesion volume and mismatch volume, were not independently associated with ER, suggesting that the HIR is the most powerful among these markers. Interestingly, there was an interaction between HIR and thrombus length for ER probability, such that the smaller the thrombus the stronger the effect of HIR. As illustrated in Figure 3, we tend to interpret this interaction as due to the vastly predominant effect of thrombus length on ER, with substantial effects of HIR mostly present for smaller thrombi.

Our study is the first to report an association between ER and HIR. This finding is however consistent with two previous studies that reported an association between other indexes of hypoperfusion severity and post-IVT recanalization,[61,62] with the caveat that recanalization was evaluated at 24hrs, which therefore includes futile recanalization and is not relevant anymore in the thrombectomy era. In addition, neither study adjusted the observed association for occlusion site or thrombus length.

Several mechanisms might explain the association between lower HIR and ER. First, good collaterals, which are strongly associated with lower HIR,[136-138] may increase the odds of ER via enhanced delivery of the thrombolytic agent to both ends of the thrombus.[64,139,140] Second, non-fully occlusive thrombi, which also likely are associated with milder hypoperfusion and hence lower HIR, may enhance the odds of the thrombolytic agent permeating the thrombus.[71,77,131] Last, severe hypoperfusion might favor more organized thrombi, which might in turn be more resistant to alteplase.[62] The choice of Tmax cutoffs for the present study was based on Olivot *et al*,[137] who found the HIR to be strongly associated with infarct growth and functional outcome. As sensitivity analysis, we also assessed the HIR using Tmax ≥4s instead of 6s as it includes mild hypoperfusion and may better reflects good collaterals,[141] which was similarly independently associated (data not shown).

Perfusion imaging has been shown to bring powerful prognostic information for 3-month functional outcome after both IVT and thrombectomy, which may in turn help decision-making in early time windows,[117,120,125] while infarct core measurement is now recommended beyond 6hrs to guide the indication for thrombectomy.[27] Our results underline another potential utility of MR- or CT-based perfusion imaging, namely the use of HIR which may provide additional help towards selecting LVO patients most likely to benefit from IVT (see Introduction). This of particular interest since the HIR can now be quickly determined owing to automated software.[137]

Our study has several strengths. First, it is based on a large multicentric sample of LVO patients referred for thrombectomy since bridging therapy became standard of care, thereby limiting potential selection biases typical of the pre-thrombectomy era. Also, patients with early neurological improvement, in whom

ER was evaluated using non-invasive vascular imaging, were also included, again limiting potential bias. Second, the method used for HIR determination was mostly automatized and therefore objective, using a licensed and widely available software. Last, ER was assessed independently by two experienced raters, reducing the risk of classification errors.

This study also has limitations. First, the decision to refer patients for thrombectomy was under the treating physician, which might have induced bias. For instance, patients with large core volumes may less likely be referred for thrombectomy. That said, the median DWI volume in our population (Table 1) was similar to both DWI[122] and CT-perfusion[123] median core volumes reported in recent thrombectomy trials. Second, one-third of patients from our MR-assessed population were excluded because PWI was not performed or was of poor quality. Note however, that the included and excluded MRI populations had similar baseline characteristics.

**Conclusion**

This mechanistic study revealed an independent association between milder hypoperfusion severity, as assessed with the HIR, and early post-IVT recanalization. Perfusion imaging may play a role in the clinical setting by identifying LVO patients most likely to benefit from IVT according to the bridging paradigm.

## Supplemental material

**Supplemental Table 1:** Parameters of the dynamic susceptibility-contrast perfusion-weighted imaging sequence in the six participating centres.

| **Parameters** | **Sainte-Anne** | **Lyon** | | **Montpellier** | | **Tours** | **Nancy** | **Orléans** |
|---|---|---|---|---|---|---|---|---|
| Magnetic field strength | 1.5T | 3T | 1.5T | 3T | 1.5T | 3T | 1.5T | 1.5T |
| Echo time (ms) | 60 | 40 | 30-40 | 38 | 38 | 29 | 46 | 30 |
| Repetition time (ms) | 2000 | 1600 | 1550-2260 | 1800 | 1800 | 1750 | 2325 | 1650 |
| Number of phases | 25 | 40 | 40-60 | 100 | 100 | 60 | 30 | 60 |
| Field of view (cm) | 24×24 | 23×23 | 23×23 | 24×24 | 24×24 | 24.5×24.5 | 23×23 | 23×23 |
| Matrix | 64×96 | 112×108 | 212×139 | 100×100 | 108×108 | 128×128 | 96×128 | 128×128 |
| Slice thickness (mm) | 6 | 3.5 | 5 | 5 | 5 | 4 | 5 | 5 |

# Chapitre 2 : Collatérales

Cette étude est actuellement en cours de révision dans *Stroke* ; le manuscrit est inséré ci-après. Les figures 1, 2 et 4 n'ont pas été insérées dans la version soumise, mais sont ajoutées ici pour faciliter la compréhension.

**Résumé :** L'objectif de cette étude était d'étudier si la présence d'un bon réseau artériel collatéral est un facteur prédictif indépendant de recanalisation précoce après thrombolyse intraveineuse. Dans cette sous-étude de la cohorte PREDICT-RECANAL (présentée dans la deuxième partie), seuls les patients chez lesquels une IRM de perfusion a été réalisée à l'admission (n= 224 patients issus de 6 centres réalisant de l'IRM de perfusion en routine clinique) ont été inclus. Une cartographie des collatérales a été générée automatiquement à partir des données sources de l'IRM de perfusion, répliquant une méthode préalablement validée par une équipe Coréenne.

Sur les 224 patients inclus, 37 (16%) ont présenté une recanalisation précoce, et celle-ci est survenue chez 10/83 (12%), 17/116 (15%) et 10/25 (40%) patients avec grade de collatérales mauvais/modéré, bon et excellent, respectivement. En analyse multivariable, de meilleures collatérales, un court thrombus et une occlusion artérielle distale (M1distale/M2) étaient les trois facteurs associés de manière indépendante à la survenue d'une recanalisation artérielle.

*Conclusion* : Un bon réseau collatéral est un marqueur indépendant de survenue d'une recanalisation précoce dans cette population. Cette association pourrait être liée à l'accès du thrombolytique aux deux extrémités du thrombus. L'évaluation de la collatéralité pourrait être utile pour sélectionner les patients tirant le bénéfice le plus important de la thrombolyse intraveineuse avant un transfert en thrombectomie.

**Better collaterals are independently associated with post-thrombolysis recanalization before thrombectomy.** Seners P, Roca P, Legrand L, Turc G, Cottier JP, Cho TH, Arquizan C, Bracard S, Ozsancak C, Ben Hassen W, Naggara O, Lion S, Debiais S, Berthezene Y, Costalat V, Richard S, Magni C, Mas JL, Baron JC*, Oppenheim C*. *Stroke, in revision.*
*Equal contribution

**Abstract**

***Background and purpose*:** In acute stroke patients with large-vessel occlusion (LVO), the goal of intravenous thrombolysis (IVT) is to achieve early recanalization (ER). Apart from occlusion site and thrombus length, predictors of early post-IVT recanalization are poorly known. Better collaterals might also facilitate ER, for instance by improving delivery of the thrombolytic agent to both ends of the thrombus. In this proof-of-concept study, we tested the hypothesis that good collaterals independently predict post-IVT recanalization before thrombectomy.

***Methods*:** Patients from the registries of 6 French stroke centres with the following criteria were included: (1) acute stroke with LVO treated with IVT and referred for thrombectomy between May 2015 and March 2017; (2) pre-IVT brain MRI, including diffusion weighted imaging, T2*, MR-angiography and dynamic susceptibility-contrast perfusion-weighted imaging (PWI); and (3) ER evaluated ≤3hrs from IVT start on either first angiographic run or non-invasive imaging. A collateral flow map derived from PWI source data was automatically generated, replicating a previously validated method. Thrombus length was measured on T2*-based susceptibility vessel sign.

***Results*:** Of 224 eligible patients, 37 (16%) experienced ER. ER occurred in 10/83 (12%), 17/116 (15%) and 10/25 (40%) patients with poor/moderate, good and excellent collaterals, respectively. In multivariable analysis, better collaterals were independently associated with ER ($P$=0.029), together with shorter thrombus ($P$<0.001) and more distal occlusion site ($P$=0.010).

***Conclusions*:** In our sample of stroke patients imaged with PWI before IVT and intended for thrombectomy, better collaterals were independently associated with post-IVT recanalization, supporting our hypothesis. These findings strengthen the idea that advanced imaging may play a key role for personalized medicine in identifying LVO patients most likely to benefit from IVT in the thrombectomy era.

**Introduction**

In acute stroke patients with large vessel occlusion (LVO), early recanalization (ER) is the mainstay of therapy as it strongly predicts clinical outcome.[6] Whenever indicated, intravenous thrombolysis with alteplase (IVT) followed by mechanical thrombectomy, *i.e.* 'bridging therapy', is currently recommended to achieve recanalization as early as possible.[27] Although it has the distinct advantage of being widely and quickly available, IVT on the other hand results in a limited (10-20%) rate of ER before thrombectomy,[106,107] and furthermore exposes to the risk of intracranial hemorrhage. Its utility before thrombectomy has therefore been recently questioned, and randomized trials testing bridging therapy *vs*. thrombectomy alone are underway.[32] With the aim to select patients for individualized therapy, namely IVT alone, bridging therapy, or thrombectomy alone, some advocate imaging-guided personalized therapy.[32,117] Along this line, identifying predictors of post-IVT ER may ultimately help to select those patients most likely to benefit from IVT before thrombectomy.

The strongest predictors of post-IVT ER reported to date are distal occlusion site (*i.e.*, second segment of the middle cerebral artery, MCA), lower admission National Institutes of Health Stroke Scale (NIHSS), and short and non-totally occlusive thrombi.[71,72,77,107,131] It has been suggested that collateral circulation, *i.e.* the alternative vascular network that provides residual blood flow to ischemic areas downstream of an arterial occlusion,[63] is also associated with ER.[64,142] However, support to this hypothesis is limited. Although a classic angiographic study showed higher rates of IVT-induced ER with better collaterals,[70] it was limited by the small sample size and an unusual alteplase dose. Three recent studies reported a similar association, but recanalization was assessed at 24hrs, which is not relevant in the thrombectomy era.[61,139,140] Thus, the association between collateral grade and post-IVT ER in patients with LVO has not been established thus far.

In the present proof-of-concept, mechanistic study, we tested the hypothesis that post-IVT ER occurring before thrombectomy is independently associated with better collaterals.

**Methods**

Study design, data sources and inclusion criteria

The registries of six French stroke centres (Sainte-Anne hospital in Paris, Hospices civils de Lyon, Orléans hospital, and university hospitals of Tours, Montpellier and Nancy), collecting data prospectively (n=3) or retrospectively (n=3) from all stroke patients referred for thrombectomy, were analysed. All centres had on-site endovascular capabilities except one center, whose eligible patients were transferred to the nearest endovascular capable centre for thrombectomy. According to the French recommendations,[133] MRI was implemented as first-line imaging in candidates for reperfusion therapy in all centers of the present study. CT and CT angiography (CTA) was performed in case of contraindication to MRI or restlessness. The stroke MRI protocol in the participating centres included diffusion-weighted imaging (DWI), T2*, intracranial MR angiography (MRA) and dynamic susceptibility-contrast perfusion-weighted imaging (PWI) whenever feasible with no delay. The PWI acquisition parameters used in each participating centre are presented in **supplemental Table 1**. The PWI-DWI patterns were not a basis for clinical decision-making except in borderline cases. Inclusion criteria for the present retrospective study were (1) acute stroke with LVO of the anterior circulation identified before IVT between May 2015 and March 2017; (2) baseline imaging with MRI, including at least DWI, T2*, MRA and PWI; (3) IVT with alteplase 0.9mg/kg; and (4) evaluation of ER before thrombectomy (see below). In accordance with French legislation, each patient was informed of his/her participation in this study, and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required.

Clinical data

The following variables were extracted from the registries: age, sex, vascular risk factors and past medical history, pre-stroke medication, NIHSS score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time between start of IVT and evaluation of ER (IVT-to-$ER_{eval}$ time; see below).

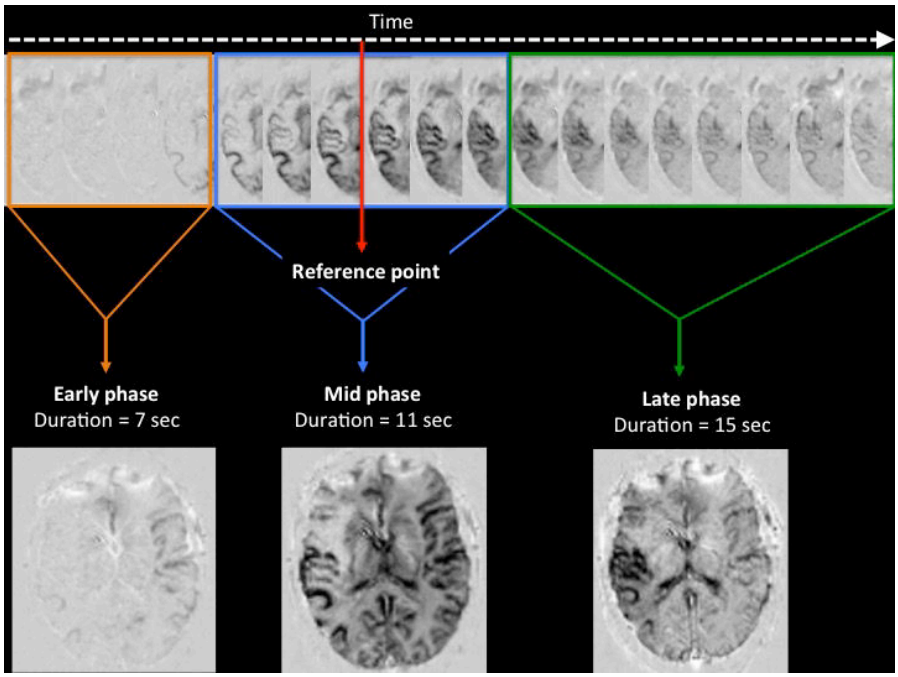
Imaging data

A stroke neurologist (P.S.) reviewed the pre-IVT imaging of all included patients, blinded to recanalization status. The following variables were collected: (1) occlusion site, according to 4 categories: intracranial internal carotid artery T or L (ICA-T/L), M1 proximal, M1 distal and M2, where the M1 segment was defined as the first portion of the MCA up to the main bifurcation, and dichotomized as proximal or distal based on the MCA origin-to-thrombus distance (<10mm and ≥10mm, respectively);[71,110] (2) length of the susceptibility vessel sign (SVS), a marker of thrombus on T2*, based on previously published methodology;[111] and (3) DWI lesion volume, semi-automatically segmented by means of Olea Sphere (Olea Medical SAS, La Ciotat, France) after applying a threshold of $620\times10^{-6}$ $mm^2/s$ on apparent diffusion coefficient maps,[134] with manual correction when necessary.

*PWI collateral flow maps generation and grading*

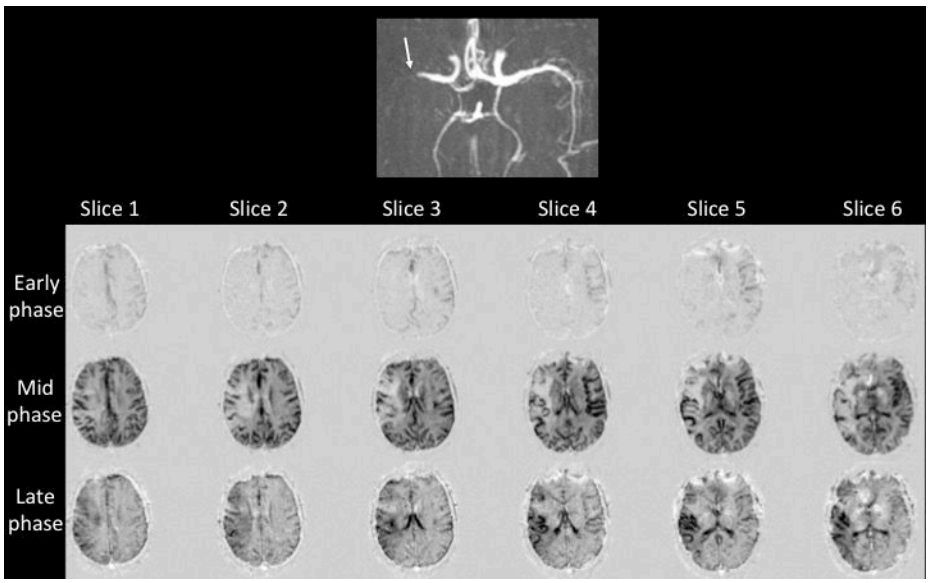
In the present study, we used the method previously published and validated against formal angiography, the gold-standard collateral grading technique, by Kim *et al.*[143] This method uses the PWI raw dataset to automatically generate three sets of maps covering the MCA territory, namely one early phase map, one mid-phase map and one late-phase map –corresponding to the arterial, capillary and venous phase of angiography, respectively–, from which collaterals are visually graded from 1 to 4 based on the ASITN/SIR angiographic classification.[110,143] To replicate the Kim *et al.* method for the present study, post-processing of the PWI dataset was performed using an in-house Nipype workflow in Python, implementing the following steps: (1) inter-frame rigid registration to correct for patient motion; (2) subtraction of the first frame from all consecutive frames to enhance the visualization of the contrast agent; (3) for 6 axial slices covering the MCA territory, summing the R2* values across all voxels of each slice and each time point; (4) automatic determination of the reference time point, defined as the average of the time points with the maximal summated R2* value for each slice, and assumed to be the midpoint of the midphase; and (5) generation of collateral flow maps by summing up adjacent time frames, divided into an early, mid and late phase with a duration of 7, 11 and 14 seconds, respectively (**see Figure 1 and 2**).[143]

**Figure 1 –** Processing of collateral flow maps.



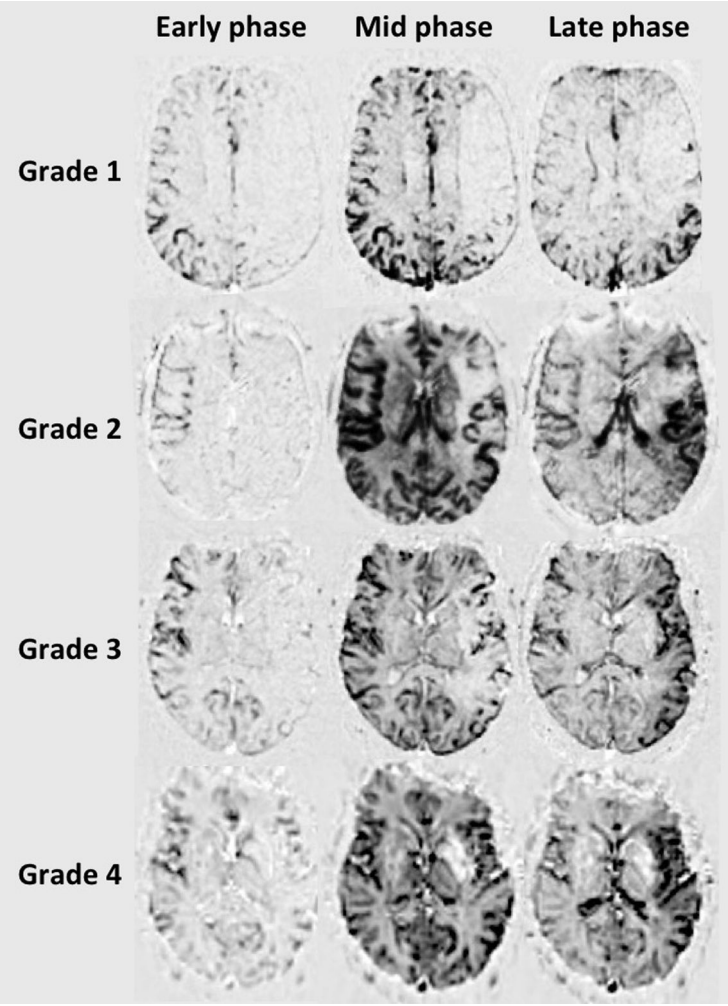

*Legend*: The upper panel shows one slice over time, after inter-frame rigid registration and substraction of the first frame from all consecutive frames to enhance the visualization of the contrast agent. The automatic determination of the R2* value maximum (see Methods for details), was considered as the reference time point (red line) and assumed to be the midpoint of the midphase. Then, the collateral flow maps was generated by summing up adjacent frames, which were divided into an early (orange box), mid (blue box) and late phase (green box) with a duration of 7, 11 and 14 seconds, respectively, as in Kim *et al.*

**Figure 2** – Illustrative example of collateral flow maps of the 6 contiguous slices covering the middle cerebral artery territory (lower panel) in a patient with a right proximal M1 occlusion (upper panel), as presented to the readers for collateral grading.



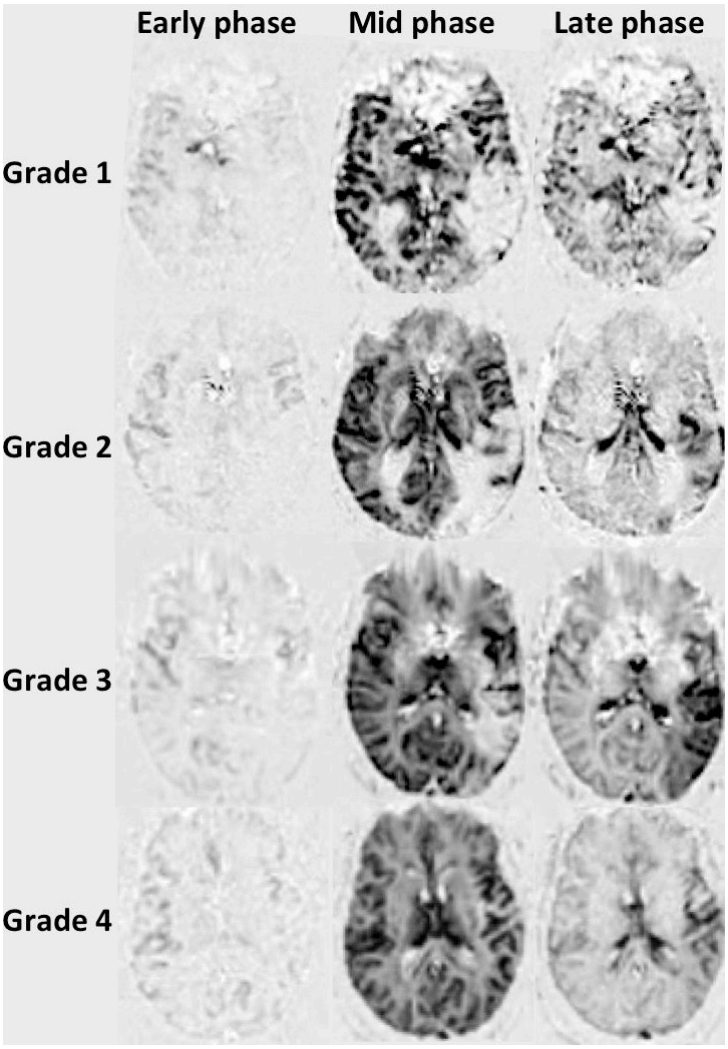
One reader (P.S.) reviewed all collateral flow maps, blinded to clinical and imaging data including recanalization status, except for the symptomatic side and site of occlusion. To assess reproducibility, an experienced neuroradiologist (L.L.) independently reviewed a random subset (n=100) of the sample. Discrepancies were resolved by consensus. For each patient, the raters visually assessed the affected MCA territory save for the striato-capsular region. As per the Kim *et al.* method, Grade 1 was defined as no collaterals or slow collaterals (visible only in the late phase) with persistence of some of the parenchymal contrast defect; Grade 2 as rapid collaterals (visible in the mid-to-late phase) with persistence of some defect; Grade 3 as slow but eventually complete collateral flow; and Grade 4 as rapid and complete collateral flow (see **Figure 3** and **4** for an illustration).[143]

**Figure 3** – Grading of collaterals on subtracted dynamic susceptibility-contrast perfusion imaging maps, illustrated in 4 different patients with left **M1** occlusion (see Methods for details).




*Legend*: For each patient, the territory of the affected middle cerebral artery was assessed, save for the striato-capsular region. Grade 1: no collaterals visible on the midphase and slow collaterals visible only in the late phase, with persistence of some parenchymal defect; Grade 2: rapid collaterals visible in the mid phase, with persistence of some parenchymal defect; Grade 3: slow but eventually complete collateral flow; and Grade 4: rapid and complete collateral flow.

**Figure 4** – Grading of collaterals on subtracted dynamic susceptibility-contrast perfusion imaging maps, illustrated in 4 different patients with left **M2** occlusion (see Methods for details).




*Legend*: For each patient, the territory of the affected M2 territory was assessed. Grade 1: no collaterals visible on the midphase and slow collaterals visible only in the late phase, with persistence of some parenchymal defect; Grade 2: rapid collaterals visible in the mid phase, with persistence of some parenchymal defect; Grade 3: slow but eventually complete collateral flow; and Grade 4: rapid and complete collateral flow.

ER evaluation

In all participating centres, eligible patients were referred for thrombectomy as soon as possible after start of IVT. Consequently, ER was evaluated on first angiographic run for intended thrombectomy. However, in some patients with significant change in neurological status before reaching the angiosuite, recanalization was evaluated using non-invasive vascular imaging (MRA or CTA). Two readers independently evaluated recanalization, blinded to clinical and imaging data. Discrepancies were resolved by consensus. ER was defined as recanalization occurring within 3hrs after initiation of IVT, a delay that includes typical 'drip-and-ship' situations.[108] On conventional angiography, ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction scale for ICA-T/L or M1 occlusions, and 3 on the Arterial Occlusive Lesion scale for M2 occlusions.[110] Otherwise, ER was defined as 3 on the Arterial Occlusive Lesion scale on CTA or MRA.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median (interquartile range), as appropriate. Inter-observer agreement of collateral grade was measured using weighted-Kappa. Correlation between collateral grade and pre-specified variables of interest (namely, baseline NIHSS, DWI volume, SVS length and occlusion site) was assessed using Spearman (Rho) coefficient. Univariable comparison of ER and no-ER patients was performed using Student *t* or Mann-Whitney *U* tests for continuous variables, and Chi-square or Fisher exact test for categorical variables, as appropriate. Baseline variables associated with ER in univariable analysis at a level of $P<0.20$ were candidates for inclusion into a multivariable binary logistic regression model, with ER as dependent variable. Variable selection was performed stepwise, whereby candidate variables entered the model at $P<0.20$ and were retained only if they remained associated at $P<0.05$ with the dependent variable. Covariates were assessed for collinearity and interaction effects. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC) and SPSS 16.0 (SPSS Inc). Two-tailed $P<0.05$ was considered statistically significant.

**Results**

Patients' characteristics

During the study period, 386 patients eligible for thrombectomy with ACI-T/L, M1 or M2 occlusion received IVT in the six participating centers. Among them, 162 patients were excluded for the following reasons: no MRI (*i.e.*, CT and CTA, n= 46), PWI not performed (n=84) or of poor quality (n=19), ER assessed beyond 3hrs after IVT start (n=10), or no-ER assessment (n=3), leaving 224 patients for the final analysis. Patients with baseline MRI but without or with inadequate quality PWI had similar age (*P*=0.53), sex (*P*=0.13), NIHSS (*P*=0.06), occlusion site (*P*=0.20) and ER rate (*P*=0.83) than included patients.

The baseline characteristics of included patients are presented in **Table 1**. ER was evaluated on first angiographic run in 213/224 (95%) patients. ER occurred in 37/224 (16%) patients. Grade 1 collaterals was present in 6/224 (3%) patients, Grade 2 in 77/224 (34%), Grade 3 in 116/224 (52%), and Grade 4 in 25/224 (11%). The weighted-kappa value for inter-rater agreement in grading PWI collateral flow maps was 0.85 (95% confidence interval: 0.76-0.93). Given the very small number of patients with Grade 1 collaterals, Grades 1 and 2 –both of which represent inadequate collaterals– were merged for subsequent analyses.

**Table 1** – Baseline characteristics of the population and univariate relationships with ER*

| | Whole cohort n=224 | Early recanalization n=37 | No early recanalization n=187 | *P* value |
|---|---|---|---|---|
| **Patient history** | | | | |
| Age (years) | 71 (61-80) | 74 (61-83) | 71 (61-80) | 0.49 |
| Men | 125 (56) | 21 (57) | 104 (56) | 0.90 |
| Hypertension | 124 (55) | 21 (57) | 103 (55) | 0.85 |
| Diabetes mellitus | 36 (16) | 9 (24) | 27 (14) | 0.14 |
| Current smoking | 28 (13) | 6 (16) | 22 (12) | 0.45 |
| Antiplatelet use | 75 (34) | 15 (41) | 60 (32) | 0.32 |
| Statin use | 70 (31) | 17 (46) | 53 (28) | **0.04** |
| **Pre-IVT characteristics** | | | | |
| NIHSS | 16 (9.5-19.5) | 12 (7-17) | 16 (10-20) | **0.02** |
| Onset-to-IVT time (min) | 160 (129-194) | 165 (145-200) | 155 (126-192) | 0.25 |
| **Pre-IVT MRI** | | | | |
| Occlusion site | | | | **<0.01** |
| ICA-T/L | 41 (18) | 1 (3) | 40 (21) | |
| Proximal M1 | 93 (42) | 7 (19) | 86 (46) | |
| Distal M1 | 40 (18) | 12 (32) | 28 (15) | |
| M2 | 50 (22) | 17 (46) | 33 (18) | |
| DWI volume (ml) | 12 (5-24) | 11 (2-18) | 12 (6-29) | **0.05** |
| SVS visible | 203 (91) | 33 (89) | 170 (91) | 0.75 |
| SVS length† (mm) | 12.6 (9.2-17.6) | 7.3 (5.8-8.9) | 14.0 (10.2-19.2) | **<0.01** |
| Collateral grade | | | | **<0.01** |
| Grade 1-2 | 83 (37) | 10 (27) | 73 (39) | |
| Grade 3 | 116 (52) | 17 (46) | 99 (53) | |
| Grade 4 | 25 (11) | 10 (27) | 15 (8) | |
| **ER evaluation** | | | | |
| IVT-to-$ER_{eval}$ time (min) | 62 (37-97) | 61 (45-118) | 61 (35-94) | 0.28 |

*Legend*: *: Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). †: Missing values: 21 patients without visible SVS. Abbreviations: DWI indicates diffusion-weighted imaging; ER, early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; IVT-to-$ER_{eval}$ time, time between thrombolysis start and evaluation of early recanalization; M1, first segment of the middle cerebral artery; M2, second segment of the cerebral artery; SVS, susceptibility vessel sign.

Correlation between collateral grade and other variables

As expected, collateral grade was negatively correlated with admission NIHSS (Rho = -0.29, $P<0.01$) and DWI lesion volume (Rho = -0.64, $P<0.01$), that is, the better the collaterals the lower the NIHSS and DWI lesion volume. Collateral grade was not correlated with SVS length (Rho= -0.07, $P=0.35$) or occlusion site (Rho= 0.10, $P=0.13$).

Variables associated with ER in univariable analysis

The univariable analysis with ER as the dependent variable is presented in **Table 1**. The following variables were significantly associated with ER: use of statins before stroke, lower baseline NIHSS, more distal occlusions, shorter SVS, smaller DWI lesion volume, and higher collateral grade. ER occurred in 1/41 (2%), 7/93 (8%), 12/40 (30%) and 17/50 (34%) patients with ACI-T/L, proximal M1, distal M1 and M2 occlusions, respectively, and in 10/83 (12%), 17/116 (15%) and 10/25 (40%) patients with collaterals Grades 1-2, 3 and 4, respectively.

Multivariable analysis with early recanalization as the dependent variable

The multivariable model (n=203 patients, excluding 21 patients without visible SVS) is presented in **Table 2**. Variables independently associated with ER were SVS length ($P<0.001$), occlusion site ($P=0.010$) and collateral grade ($P=0.029$).

**Table 2** – Variables independently associated with early recanalization in multivariable logistic regression*

| | **Adjusted OR (95%CI)** | ***P* value** |
|---|---|---|
| **SVS length**, per 1mm increase | 0.67 (0.56-0.80) | **<0.001** |
| **Occlusion site** | | **0.010** |
| ACI-T/L | Reference | |
| M1 proximal | 1.20 (0.40-3.55) | |
| M1 distal or M2 | 7.45 (1.57-35.32) | |
| **Collateral grade** | | **0.029** |
| Grade 1-2 | Reference | |
| Grade 3 | 1.06 (0.10-11.49) | |
| Grade 4 | 5.39 (0.56-51.47) | |

*Legend*: * 21 patients without visible SVS were excluded from the model, which therefore included 203 patients (33 with ER and 170 without). Statins use, diabetes mellitus, NIHSS, and DWI volume were candidate variables as their *P* value was less than 0.20 in univariable analysis (see Table 1), but were not retained in the multivariable model. Abbreviations: CI indicates confidence interval; ER, early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; M1, first segment of the middle cerebral artery; M2, second segment of the cerebral artery; OR, odds ratio; SVS, susceptibility vessel sign.

**Discussion**

Based on a large multicentric population of stroke patients referred for thrombectomy who underwent MR imaging with PWI before IVT, the present proof-of-concept study showed that a better collateral grade was independently associated with ER occurrence. As expected, smaller thrombus and more distal occlusion sites were also independently associated with ER.

Consistent with our observation, in a seminal study from 1992 on 32 LVO patients in whom conventional angiography was performed before and 90 minutes after IVT, good collaterals were associated with higher ER rate at the end of IVT infusion.[70] However, this result was not adjusted on other key variables now known to be associated with ER, and cannot be transposed to current practice since the dose of alteplase in this study was higher than currently recommended (100mg for all patients *vs.* 0.9mg/kg with a maximum of 90mg, respectively). Also in line with our results, three recent studies reported an association between post-IVT recanalization in LVO patients and i) lower normalized index derived from Tmax maps of PWI[61] –a surrogate marker of good collateral circulation–; ii) good collaterals evaluated on CT-perfusion source images;[140] and iii) rapid collateral filling evaluated on PWI, respectively.[139] These studies however had two major limitations. First, in all studies recanalization was evaluated at 24hrs after IVT, which includes futile recanalization and is not anymore relevant in the era of bridging therapy. Second, they all used small samples, precluding adjustment on two key confounders of post-IVT recanalization, namely occlusion site (except in Zhang *et al*.[139]) and thrombus length.

Regarding mechanisms, one attractive hypothesis to explain the relationship between collaterals and ER is that good collaterals may improve delivery of (endo- and exogenous) thrombolytics to both ends of the thrombus.[64,142] Another, not mutually exclusive, hypothesis, posits that rapid collateral flow may apply higher shear stress on the thrombus and thereby facilitate thrombus dissolution.[139] In support of the latter, Zhang *et al*. found that the velocity – but not the extent – of collateral filling was associated with ER.[139] Our findings showing a 2.5-fold higher ER rate in Grade 4 as compared to Grade 3 collaterals would also be consistent with this hypothesis. Indeed, both grades entail collaterals eventually covering the entire MCA territory, but they more rapidly do so in Grade 4 *vs*. 3 (see Figure 1). As a word of caution, however, association does not prove causality, and some as yet unidentified confounding factors might account for both ER and high collateral grade.

The 16% incidence rate of post-thrombolysis ER before thrombectomy present in our cohort is in line with the available literature.[106,107] Considering both these relatively limited rates of post-IVT ER and the potential harm from IVT in thrombectomy candidates, the utility of IVT before thrombectomy has been recently questioned.[32] However, the option of skipping IVT should be formally tested in randomized trials, which should ideally recruit patients with very low ER probability only. More generally, our results highlight the potential utility of advanced imaging for personalized medicine, and suggest that collateral imaging, together with thrombus imaging, may help to select patients most likely to benefit from IVT in the thrombectomy era.

Our study has several strengths. First, it is based on a large multicentric sample of LVO patients treated with IVT and referred for thrombectomy since bridging therapy has become standard of care. Also, patients with early neurological improvement, in whom ER was evaluated using non-invasive vascular imaging, were also included, therefore limiting selection bias. Second, the method used for collateral flow grading has been previously validated with angiography-based collateral grading.[143] Last, ER was assessed by two independent raters, reducing the risk of classification errors, and inter-rater agreement for collateral grading was very good.

This study also has limitations. First, the decision to refer patients for thrombectomy was under the treating physician, which might have induced selection bias. For instance, the presence of a large DWI lesion may have reduced patient's eligibility for thrombectomy, which in turn may explain why only few patients in our sample had Grade 1 collaterals. That said, the median DWI volume in our population (Table 1) was similar to both CT-perfusion[123] and DWI[122] median core volumes reported in recent thrombectomy trials. Second, 31% (103/327) of patients from our MR-assessed population were excluded because PWI was not performed or was of poor quality, which might have induced selection bias. Note however, that the included and excluded MRI populations were similar in terms of age, NIHSS, occlusion site and ER rate. Last, despite the large sample size and the substantial ER rate, the absolute number of patients who recanalized within 3hrs of IVT was relatively low, precluding subgroup analysis.

**Conclusion**

This mechanistic study in patients eligible for thrombectomy revealed an independent association between better collaterals and early post-IVT recanalization, supporting the idea that delivery of thrombolytic agents to both ends of the thrombus may enhance early recanalization. Collateral imaging may play a role in identifying LVO patients who are most likely to benefit from IVT in the thrombectomy era.

## Supplemental material

**Supplemental Table 1:** Parameters of the dynamic susceptibility-contrast perfusion-weighted imaging sequence in the six participating centres.

| **Parameters** | **Sainte-Anne** | **Lyon** | | **Montpellier** | | **Tours** | **Nancy** | **Orléans** |
|---|---|---|---|---|---|---|---|---|
| Magnetic field strength | 1.5T | 3T | 1.5T | 3T | 1.5T | 3T | 1.5T | 1.5T |
| Echo time (ms) | 60 | 40 | 30-40 | 38 | 38 | 29 | 46 | 30 |
| Repetition time (ms) | 2000 | 1600 | 1550-2260 | 1800 | 1800 | 1750 | 2325 | 1650 |
| Number of phases | 25 | 40 | 40-60 | 100 | 100 | 60 | 30 | 60 |
| Field of view (cm) | 24×24 | 23×23 | 23×23 | 24×24 | 24×24 | 24.5×24.5 | 23×23 | 23×23 |
| Matrix | 64×96 | 112×108 | 212×139 | 100×100 | 108×108 | 128×128 | 96×128 | 128×128 |
| Slice thickness (mm) | 6 | 3.5 | 5 | 5 | 5 | 4 | 5 | 5 |

# Quatrième partie :
# Incidence et facteurs prédictifs de recanalisation précoce dans le cas particulier des accidents ischémiques cérébraux avec déficit neurologique mineur et occlusion proximale

Cette étude a été soumise pour publication dans *Stroke* en septembre 2018 ; le manuscrit soumis est inséré ci-après en totalité.

**Résumé :** Le bénéfice du « bridging therapy », en comparaison à la thrombolyse intraveineuse seule, est incertain en cas d'accident ischémique cérébral avec déficit neurologique mineur et occlusion proximale. L'identification de facteurs prédictifs de l'absence de recanalisation précoce, un marqueur de mauvais pronostic clinique, aiderait à sélectionner les meilleurs candidats à une thrombectomie complémentaire. L'objectif de cette étude était d'étudier les facteurs prédictifs de l'absence de recanalisation précoce dans cette population.

Dans cette étude de sous-groupe de l'étude PREDICT-RECANAL (présentée dans la deuxième partie), seuls les patients avec un score NIHSS ≤5 à l'admission ont été inclus (n=97).

Le score NIHSS médian était de 3 (écart interquartile: 2-4), et l'occlusion était localisée en termino-carotidien, M1 proximal, M1 distal et M2 respectivement chez 4%, 22%, 25% et 50% des patients. Une recanalisation précoce est survenue chez 34% des patients. Après sélection des variables pas-à-pas dans un modèle multivariable, la longueur du thrombus était la seule variable associée de manière significative à l'absence de recanalisation précoce (odds ratio= 1.53 pour chaque mm supplémentaire, IC95% 1.21-1.92, $P$<0.001). La c-statistique de la longueur du thrombus pour prédire l'absence de recanalisation était élevée (0.82; IC95% 0.73-0.92), et le meilleur seuil (index de Youden) pour prédire celle-ci était de 9mm. La sensibilité et spécificité de ce seuil pour l'absence de recanalisation précoce était 67.8% (IC95% 55.9-79.7) et 84.6% (70.7-98.5), respectivement.

*Conclusions:* L'incidence de la recanalisation précoce post-thrombolyse est élevée dans cette population d'accidents ischémiques cérébraux avec déficit neurologique mineur et occlusion proximale, et la longueur du thrombus est un facteur prédictif indépendant puissant de l'absence de recanalisation précoce. Ces données devraient faciliter le dessin d'essais randomisés futurs testant la thrombolyse intraveineuse *vs.* le bridging dans cette population.

**Thrombus length predicts lack of post-thrombolysis early recanalization in minor stroke with large vessel occlusion.** Seners P, Delepierre J, Turc G, Henon H, Piotin M, Arquizan C, Cho TH, Lapergue B, Cottier JP, Richard S, Legrand L, Bricout N, Mazighi M, Dargazanli C, Nighoghossian N, Consoli A, Debiais S, Bracard S, Naggara O, Leclerc X, Obadia M, Costalat V, Berthezène Y, Tisserand M, Narata AP, Gory B, Mas JL, Oppenheim C, Baron JC, on behalf of the PREDICT-RECANAL collaborators. ***Soumis à Stroke le 5/09/2018***


**Abstract**

**Background and purpose:** Whether bridging therapy, *i.e*. intravenous thrombolysis [IVT] followed by mechanical thrombectomy, is beneficial as compared to IVT alone in minor stroke (NIHSS≤5) with large vessel occlusion (LVO) is unknown. Identifying strong predictors of the lack of post-IVT early recanalization (ER), a surrogate marker of poor outcome, may help to select the best candidates for additional thrombectomy.

**Methods:** From a large multicentre French registry of LVO patients referred for thrombectomy immediately after IVT start between 2015 and 2017, we extracted 97 minor strokes with ER evaluated on first angiographic run or non-invasive imaging ≤3hrs from IVT start. Thrombus length was measured using the Susceptibility Vessel Sign (SVS) on T2*-imaging.

**Results:** Median NIHSS was 3 (interquartile range: 2-4), and occlusion sites were intracranial carotid, proximal M1, distal M1 and M2 in 4%, 22%, 25% and 50% of patients, respectively. On pre-IVT MRI, median length of SVS (visible in 90%) was 9.2mm (interquartile range: 7.4-13.3). ER was present in 34% of patients, and SVS length was the only clinical or radiological variable associated with no-ER following stepwise variable selection into a multivariable model (odds ratio= 1.53 per 1-mm increase, 95% confidence interval [95%CI]: 1.21-1.92, $P<0.001$). The c-statistic of SVS length for no-ER prediction was 0.82 (95%CI 0.73-0.92), and the optimal cutoff (Youden) was 9mm. Sensitivity and specificity of this cutoff for no-ER were 67.8% (95%CI 55.9-79.7) and 84.6% (95%CI 70.7-98.5), respectively.

**Conclusions:** ER was frequent in this cohort of IVT-treated minor stroke patients with LVO, and thrombus length was a powerful independent predictor of no-ER. These findings may help design randomized trials aiming to test bridging therapy *vs*. IVT alone in this population.

## Introduction

Intravenous thrombolysis (IVT) is standard-of-care for disabling acute ischemic stroke regardless of severity, and is currently recommended for patients with mild yet disabling symptoms.[27] Although large vessel occlusion (LVO) typically leads to severe stroke, some patients with LVO present with mild symptoms, owing to good collaterals. Despite IVT, these patients are at substantial risk of neurological deterioration and poor 3-month outcome.[144] Although bridging therapy (*i.e*. IVT followed by mechanical thrombectomy) is currently recommended in LVO patients with NIHSS >5 and eligible for IVT,[27] whether it is also beneficial *vs.* IVT alone in less severe strokes with LVO is unknown as very few such patients were enrolled in the pivotal trials.[68] Consequently, according to current guidelines, thrombectomy 'may be reasonable' in minor stroke with LVO.[27] Identifying strong predictors of lack of early post-IVT recanalization (ER), a surrogate marker of poor outcome,[6] may help to select the best candidates for additional thrombectomy in order to optimally design randomized trials.

## Methods

*Study design and data sources*

This is a retrospective analysis of the PREDICT-RECANAL registry that collected data from consecutive stroke patients referred for thrombectomy from 31 stroke centres in France between 2015 and 2017 (see **Supplemental Methods**). Inclusion criteria in this registry were: (1) LVO of the anterior circulation treated with IVT (alteplase); and (2) evaluation of ER before thrombectomy (see below). For the present study, only patients with baseline NIHSS ≤5 were considered.

In accordance with French legislation, each patient was informed of his/her participation in this study, and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an Ethics Committee was not required.

*Clinical and imaging data*

Clinical variables routinely recorded in the acute stroke setting were extracted from the registry (supplemental Methods). A stroke neurologist (PS) blinded to recanalization status reviewed the pre-IVT imaging of all included patients. The following variables were collected (supplemental Methods): (1) occlusion site, divided into 4 categories: intracranial T/L carotid (ICA-T/L), M1 proximal, M1 distal and M2; (2) length of the susceptibility vessel sign (SVS), a specific marker of thrombus on T2*-weighted MRI; and (3) diffusion-weighted imaging lesion extent using the Alberta Stroke Program Early CT score (DWI-ASPECTS).

*ER evaluation*

ER was evaluated ≤3hrs after IVT start on first angiographic run for intended thrombectomy (supplemental Methods). In some patients whose neurological status changed before reaching the angiosuite, ER was evaluated using non-invasive vascular imaging. ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction scale for ICA-T/L or M1 occlusions, and 3 on the Arterial Occlusive Lesion scale for M2 occlusions.

*Statistical analysis*

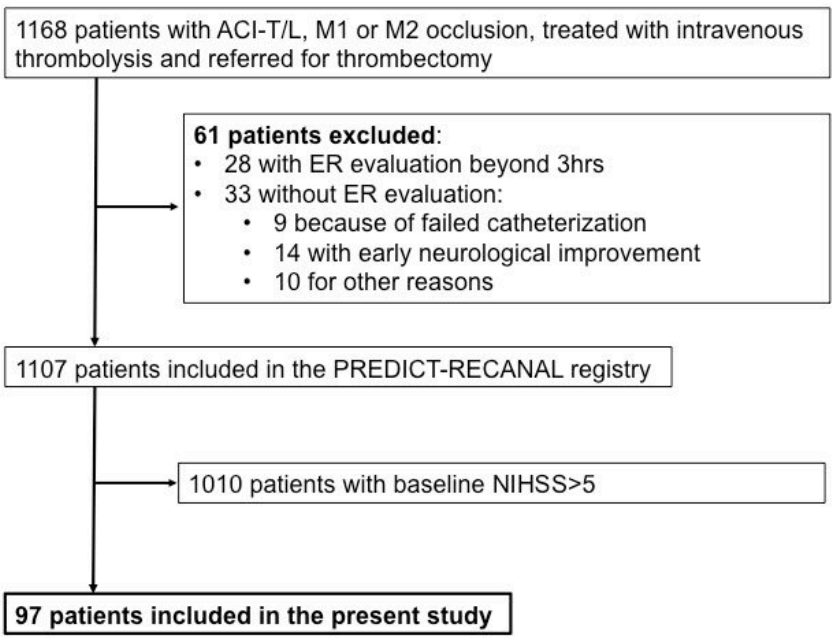
Following univariable comparisons between baseline variables and no-ER, multivariable binary logistic regression was carried out (supplemental Methods). The c-statistic of SVS length for no-ER prediction was determined, and the optimal cutoff was identified using the Youden index.

**Results**

*Study population and incidence of ER*

Ninety-seven patients were included (**Figure 1**). Median age and NIHSS were 67yrs (interquartile range [IQR]: 53-78) and 3 (IQR: 2-4), respectively, and occlusion sites were ICA-T/L, proximal M1, distal M1 and M2 in 4%, 22%, 25% and 50% of patients, respectively. Treatment was *as per* the mothership and drip-and-ship paradigms in 41% and 59%, respectively. On pre-IVT MRI (performed in 98% of patients), median length of SVS (visible in 90%) was 9.2mm (IQR: 7.4-13.3). ER was evaluated on first angiographic run in 75% of patients, and on non-invasive imaging in the remaining. ER occurred in 34% of patients, with rates of 25%, 33%, 38% and 33% in ACI-T/L, proximal M1, distal M1 and M2 occlusions, respectively.

**Figure 1.** Study flowchart.



*Factors associated with no-ER*

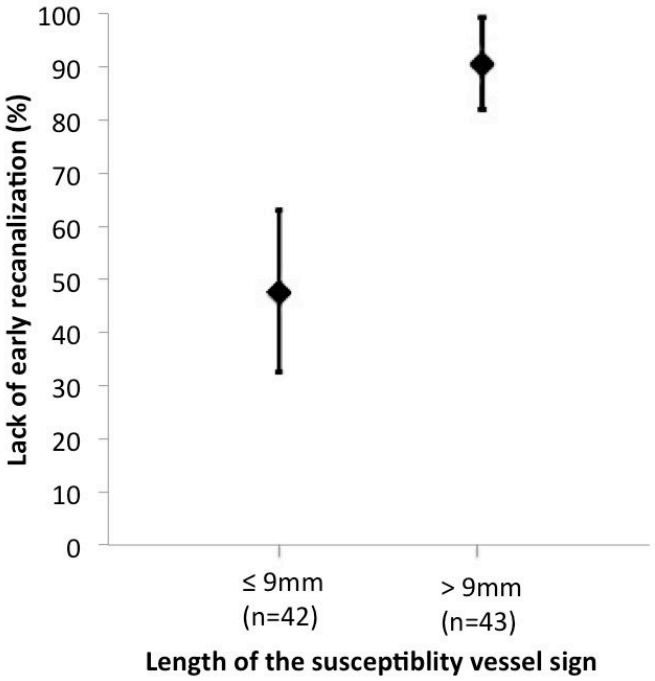
The univariable relationships between no-ER and baseline variables are presented in **Table**. Only lower DWI-ASPECTS (*P*=0.02) and longer SVS (*P*<0.01) were significantly associated with no-ER. Following stepwise variable selection into the multivariable model (including the 85 patients with visible SVS only), SVS length was the sole variable significantly associated with no-ER (odds ratio= 1.53 per 1-mm increase, 95% confidence interval [95%CI]: 1.21-1.92, *P*<0.001). The c-statistic of SVS length for no-ER prediction was 0.82 (95%CI 0.73-0.92), and the optimal cutoff was 9mm. The sensitivity, specificity, negative and positive predictive values of this cutoff for no-ER were 67.8% (95%CI 55.9-79.7), 84.6% (95%CI 70.7-98.5), 57.5% (95%CI 42.6-72.5) and 89.5% (95%CI 80.4-98.7), respectively. **Figure 2** illustrates the no-ER rate according to the dichotomized SVS length.

**Table**. Univariable comparisons of patients with and without ER.[a]

| | **Early recanalization n=33** | **No early recanalization n=64** | ***P*** |
|---|---|---|---|
| Age (years) | 66 (54-81) | 68 (51-77) | 0.82 |
| Mothership paradigm | 10 (30) | 30 (47) | 0.12 |
| NIHSS | 3 (1-4) | 3 (2-5) | 0.07 |
| Onset-to-IVT time (min) | 170 (138-195) | 165 (135-205) | 0.90 |
| Occlusion site | | | 0.98 |
| ICA-T/L | 1 (3) | 3 (5) | |
| Proximal M1 | 7 (21) | 14 (22) | |
| Distal M1 | 9 (27) | 15 (23) | |
| M2 | 16 (49) | 32 (50) | |
| SVS length[b] (mm) | 7.3 (5.7-8.6) | 10.2 (8.6-14.5) | **<0.01** |
| DWI-ASPECTS[c] | 9 (8-10) | 9 (8-9) | **0.02** |
| IVT-to-ER evaluation time (min) | 107 (80-149) | 94 (54-126) | 0.35 |

*Legend:* a: Categorical variables are expressed as numbers (%); continuous variables as median (interquartile range). b: 12 missing values (2 patients with CT and 10 without SVS). c: 2 missing values (patients with CT).

**Figure 2**. Incidence of no-ER according to dichotomized SVS length.




*Legend:* The whiskers indicate the 95% confidence interval.

**Discussion**

This study of minor strokes with LVO treated with IVT disclosed two key findings. First, ER was substantial, occurring in ~1 in 3 patients. Second, thrombus length was a powerful independent predictor of no-ER, with 85% specificity for the 9mm cutoff.

The incidence of ER in our sample was higher than in day-to-day bridging populations (10-20%),[106,107] but is consistent with two previous reports in minor stroke with LVOs.[145,146] This is likely due to more distal occlusions.[107]

This is the first report on no-ER predictors in minor stroke with LVO. The strong association found between thrombus length and no-ER is consistent with findings in unselected thrombectomy populations.[107] The very high specificity for no-ER of the 9mm cutoff is similar to that reported by Riedel *et al*,[57] who did not specifically study minor stroke and evaluated recanalization at 24hrs.

Given current uncertainties regarding optimal treatment of minor stroke with LVO, randomised trials comparing bridging therapy to IVT alone are clearly warranted. However, because of the mild clinical severity and the substantial ER rate following IVT in this population, large samples would be required in such trials in order to show a significant superiority of bridging – a challenge considering how relatively uncommon minor strokes with LVO are. Enrolling only patients at high risk of no-ER, *e.g*. with thrombus length >9mm, would enhance the effect size, and in turn help reduce the sample size required to show a benefit.

Our study has limitations. First, the decision to refer patients for thrombectomy in our study was under the treating physician, which might have induced a selection bias. This would particularly apply to minor stroke given the uncertain benefits from thrombectomy in this population. Second, thrombus length was measured on T2*-weighted MR, which is not widely available in many countries. However, our findings are likely applicable to CT. Third, as our sample was relatively small, other independent predictors might have been overlooked. However, minor stroke with LVO is a relatively uncommon condition.

**Conclusion**

Our study documented a substantial rate of early recanalization in IVT-treated minor stroke with LVO, and showed that thrombus length was the only, and a powerful, predictor of no recanalization. These findings may help to improve the design of randomized trials testing bridging therapy *vs*. IVT alone in this population.

**Supplemental material**

## Supplemental methods

*Study design and data sources*

This is a retrospective analysis of the PREDICT-RECANAL registry that collected data from all stroke patients referred for thrombectomy from 31 stroke centres in France (prospectively collected in 28 and retrospectively in 3) between May 2015 and March 2017. Among these centres, 8 had on-site endovascular capabilities and 23 did not; for the latter, eligible patients were transferred to the nearest thrombectomy capable centre (*i.e.*, drip-and-ship, as opposed to mothership, paradigm).

*Clinical data*

The following variables were extracted from the registry: age, sex, vascular risk factors and past medical history, pre-stroke medication, NIHSS score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time between start of IVT and evaluation of ER (IVT-to-ER evaluation time; see below).

*Imaging data*

In France, MRI is first-line in candidates for reperfusion therapy, and accordingly was implemented in all centers of the present study. CT and CT angiography (CTA) was performed in case of contraindication to MRI. The acute stroke MRI protocol included diffusion-weighted imaging (DWI), T2*-weighted imaging and MR angiography (MRA).

A stroke neurologist reviewed the pre-IVT imaging of all included patients, blinded to recanalization status. The following variables were collected: (1) occlusion site, divided into 4 categories: ICA-T/L, M1 proximal, M1 distal and M2, where the M1 segment was defined as the first portion of the middle cerebral artery up to the main bifurcation, and dichotomized as proximal or distal based on the middle cerebral artery origin-to-clot interface distance (<10mm and ≥10mm, respectively);[110] (2) length of the susceptibility vessel sign (SVS), a specific marker of thrombus on T2*-MRI, based on previously published methodology: the in-plane length (M1 segment) was the distance between the proximal and distal parts of the SVS, and the length in the z-axis (supraclinoid ICA, M2) was the number of slices where the SVS was visible times slice thickness;[111] and (3) DWI lesion extent using the Alberta Stroke Program Early CT score (DWI-ASPECTS). Thrombus length and infarct size were not measured on CT considering first, the small number of patients who underwent CT in our cohort, and second, that merging these CT-based variables with corresponding MR-based variables (namely, SVS and DWI-ASPECTS) in the same statistical analysis was deemed inappropriate.

*ER evaluation*

In all participating centres, patients were referred for thrombectomy as soon as possible after start of IVT. Consequently, ER was evaluated on first angiographic run for intended thrombectomy. However, in some patients with neurological status change occurring before reaching the angiosuite, ER was evaluated using non-invasive vascular imaging (MRA or CTA). Two readers independently evaluated ER, blinded to clinical and imaging data. Discrepancies were resolved by consensus.

*Statistical analysis*

Univariable comparison of ER and no-ER patients was performed using Mann-Whitney *U* tests for continuous variables, and Chi-square or Fisher exact test for categorical variables, as appropriate. Baseline variables associated with no-ER in univariable analysis at $P<0.20$ were candidates for inclusion into a multivariable binary logistic regression model, with no-ER as dependent variable. Variable selection was performed stepwise, whereby candidate variables entered the model at $P<0.20$ and were retained only if they remained associated at $P<0.05$ with the dependent variable. The c-statistic (*i.e.* the area under the receiver operating characteristic curve) of SVS length for no-ER prediction was determined. Statistical analyses were performed using SPSS 16.0 (SPSS Inc). Two-tailed $P<0.05$ was considered statistically significant.

# Cinquième partie :

# Recanalisation précoce après tenecteplase comme agent thrombolytique

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Cette étude est accepté pour publication dans *Journal of Stroke* sous la forme d'une lettre à l'éditeur (actuellement sous presse). Cependant, pour plus de clarté, le manuscrit complet est inséré ci-après (la lettre à l'éditeur est présentée en **Annexe 2**).

**Résumé :** L'essai randomisé EXTEND-IA TNK, publié en 2018, a montré une incidence deux fois plus élevée de recanalisation précoce pré-thrombectomie après thrombolyse intraveineuse par tenecteplase 0.25mg/kg en comparaison à l'alteplase 0.9mg/kg. Cependant, la majorité des patients ont été traités selon le paradigme « mothership », à savoir avec un délai thrombolyse-thrombectomie très court. L'objectif de cette étude était de comparer le taux de recanalisation pré-thrombectomie après thrombolyse intraveineuse par tenecteplase *vs.* alteplase chez des patients traités selon le paradigm « drip-and-ship », la situation actuellement la plus fréquente en routine clinique.

Dans cette étude observationnelle rétrospective, les patients « drip-and-ship » de l'étude PREDICT-RECANAL (traités par alteplase 0.9mg/kg) ont été comparés aux patients « drip-and-ship » traités par tenecteplase 0.25mg/kg dans l'UNV de l'hôpital du Sud Francilien (Essonne). Chaque patient du groupe tenecteplase a été apparié à un patient du groupe alteplase par score de propension, prenant en compte les facteurs confondants potentiels.

Au total, 816 patients ont été inclus dans l'étude (n=160 et 656 traités par tenecteplase et alteplase, respectivement). Dans la cohorte appariée par score de propension (n=131 par groupe), les principaux facteurs de confusion étaient bien équilibrés entre les deux groupes (notamment le site d'occlusion, la longueur du thrombus et le délai thrombolyse-thrombectomie). Une recanalisation précoce était constatée chez 21.4% (IC95%: 14.4-28.4) des patients du groupe tenecteplase *vs.* 18.3% (IC95% 11.7-24.9) dans le groupe alteplase (OR=1.25, IC95%: 0.65-2.41, *P*=0.51).

*Conclusions:* Un taux similaire de recanalisation précoce est constaté après thrombolyse par tenecteplase 0.25mg/kg *vs*. alteplase 0.9mg/kg, chez des patients adressés en thrombectomie mécanique selon le paradigme « drip-and-ship » dans cette population. La mise en perspective de ces données avec les résultats de l'étude EXTEND-IA TNK suggère que même si la recanalisation pré-thrombectomie semble aussi fréquente après alteplase qu'après tenecteplase chez des patients drip-and-ship, cette dernière survient probablement plus précocement. Si cette interprétation est confirmée par des études futures, des conséquences cliniques importantes en découleraient.

**Early recanalization in tenecteplase *vs.* alteplase-treated drip-and-ship patients referred for thrombectomy.** Seners P, Chausson N*, Caroff J*, Turc G, Denier C, Piotin M, Aghasaryan M, Alecu C, Chassin O, Lapergue B, Naggara O, Ferrigno M, Arquizan C, Cho TH, Narata AP, Richard S, Bricout N, Mazighi M, Costalat V, Gory B, Debiais S, Consoli A, Bracard S, Oppenheim C, Mas JL, Smadja D**, Spelle L**, Baron JC**, on behalf of the PREDICT-RECANAL collaborators.
*Equal contribution, **Equal contribution

**Abstract**

**Background and purpose:** The EXTEND-IA TNK trial recently showed 2-fold higher early recanalization (ER) rate before mechanical thrombectomy (MT) following intravenous thrombolysis (IVT) with tenecteplase as compared to alteplase. However, most included patients were directly admitted to MT-capable centres ('mothership' paradigm), *i.e.* with short IVT-to-MT delays. We assessed ER rate before MT following tenecteplase or alteplase in patients transferred for MT from a non MT-capable centre ('drip-and-ship' paradigm), *i.e.* with longer IVT-to-MT delays, currently the most frequent situation.

**Methods:** This was a retrospective multicenter study comparing IVT-induced ER rate with tenecteplase 0.25mg/kg *vs.* alteplase 0.9mg/kg in drip-and-ship large-vessel occlusion patients. ER was identified within 3hrs of IVT start on pre-MT first angiographic run or non-invasive vascular imaging. Propensity-score matching was used to reduce the effects of potential confounders.

**Results:** Eight hundred sixteen patients were included (n=160 and 656 tenecteplase and alteplase-treated, respectively). In the propensity-score matched cohort (n=131 per group), the main confounders for ER were well balanced. ER occurred in 21.4% (95%CI: 14.4-28.4) *vs.* 18.3% (11.7-24.9) patients from the tenecteplase- and alteplase-treated cohorts, respectively (OR=1.25, 95%CI: 0.65-2.41, *P*=0.51).

**Conclusions:** Our study showed similar ER rate following tenecteplase or alteplase in stroke patients intended for MT *as per* the drip-and-ship paradigm. Taken together with the results from EXTEND-IA TNK, these data suggest that, although in drip-and-ship patients recanalization at time of thrombectomy is as frequent with tenecteplase as with alteplase, it may occur earlier with the former, which if confirmed would have clinical relevance.

**Introduction**

In acute stroke patients with large vessel occlusion (LVO), mechanical thrombectomy (MT) added on intravenous thrombolysis (IVT) with alteplase 0.9mg/kg whenever indicated, so-called 'bridging therapy', markedly improves clinical outcome relative to IVT alone,[68] and became standard-of-care in early 2015.[147] These clinical benefits are mainly driven by higher rates of early recanalization (ER), which is strongly associated with improved functional outcome.[10]

Tenecteplase is a modified form of alteplase engineered to improve IVT efficacy,[36] which has been tested in a few trials before the thrombectomy era.[37-39,148] Recently, the EXTEND-IA TNK randomized controlled trial in patients intended for MT showed significantly higher ER rate before MT following tenecteplase at the dose of 0.25mg/kg, as compared to alteplase 0.9mg/kg.[116] However, this study mostly included patients directly admitted to MT-capable centres ('mothership' paradigm) with short IVT to MT delays, while the majority of eligible patients present to stroke centers lacking endovascular facilities and are transferred after initiation of IVT to the nearest MT-capable centre ('drip-and-ship' paradigm). Effectively, even in rich countries <1/3$^{rd}$ of stroke centers are currently MT-capable.[26] It is unknown whether pre-MT ER rates in patients treated according to the drip-and-ship paradigm are also enhanced by tenecteplase, as compared to alteplase.

In the present retrospective study, we compared the ER rate before MT in patients treated with tenecteplase 0.25mg/kg or alteplase 0.9mg/kg, and transferred for MT *as per* the drip-and-ship paradigm.

**Methods**

*Study design, data sources and inclusion criteria*

*Tenecteplase cohort*

Based on the promising results of the Australian tenecteplase trial,[38] the reassuring safety results of the Australian and ATTEST trials,[38,39] and the convenience of tenecteplase over alteplase (bolus administration *vs.* 1-hr continuous infusion, respectively), the physicians of the Sud-Francilien stroke centre – a large stroke centre without endovascular facilities – opted as from May 2015 to use tenecteplase 0.25mg/kg, in place of alteplase, in stroke patients eligible for MT, before transfer to a MT-capable centre. The clinical data of these patients were retrospectively collected for the present study. Inclusion criteria for the present study were acute stroke with LVO of the anterior circulation identified before IVT using MR or CT between May 2015 and October 2017, tenecteplase dose of 0.25mg/kg, and evaluation of ER before MT (see below).

*Alteplase cohort*

The PREDICT-RECANAL registry, collecting data from all stroke patients treated with alteplase 0.9mg/kg and referred for MT between May 2015 and March 2017 in 8 MT-capable stroke centres was used. Inclusion criteria for the present study were as above, except that mothership patients were excluded. Note that the Sud-Francilien center did not participate to the PREDICT-RECANAL study.

In accordance with French legislation, each patient was informed of his/her participation in this study, and was offered the possibility to withdraw. However, as this study only implied retrospective analysis of anonymized data, formal approval by an Ethics Committee was not required.

*Clinical data*

The following variables were extracted from the registries for both cohorts: age, sex, vascular risk factors (hypertension, diabetes mellitus, current smoking), admission and 24-hr NIHSS score, time from symptom onset to start of IVT (onset-to-IVT time), time between IVT start and evaluation of ER (IVT-to-$ER_{eval}$ time; see below) and 3-month modified Rankin scale (mRS).

*Baseline imaging protocol and analysis*

As per the Health Authority guidelines,[133] MRI is the first-line work-up in candidates for reperfusion therapy in France, and was implemented in all centers for both cohorts of the present study. CT and CT angiography (CTA) was performed only in case of contraindication to MRI or restlessness. In France, acute stroke MRI includes diffusion-weighted imaging (DWI), Fluid Attenuated Inversion Recovery, gradient-echo T2* or susceptibility-weighted imaging, and intracranial MR angiography (MRA).

One stroke neurologist reviewed the pre-IVT MRI and CTA of all included patients from both cohorts, blinded to recanalization status. The following variables were collected: (1) occlusion site, divided into 4 categories: T or L shape internal carotid terminus (ICA-T/L), M1 proximal, M1 distal and M2, where the M1 segment was defined as the first portion of the middle cerebral artery up to the main bifurcation, and dichotomized as proximal or distal based on the middle cerebral artery origin-to-clot interface distance (<10mm and ≥10mm, respectively);[71,110] (2) presence of susceptibility vessel sign (SVS), a specific marker of thrombus on gradient-echo T2* or susceptibility-weighted imaging;[111] (3) SVS length, based on previously published methodology;[111] and (4) DWI lesion extent using the Alberta Stroke Program Early CT score (DWI-ASPECTS). Thrombus length and infarct size were not measured on CT considering first the very small number of patients who underwent CT in both cohorts, and second that merging these CT-based variables with the corresponding MR-based variables (namely, SVS and DWI-ASPECTS) in the same statistical analysis was considered inappropriate as they likely are not equivalent.

*Early recanalization*

All participating primary stroke centres transferred patients eligible for MT as soon as possible after start of IVT. On arrival time at the MT-capable centre, patients immediately underwent conventional angiography for intended MT, and ER was evaluated on the first intracranial run. In a few patients with neurological improvement or deterioration occurring before reaching the angiosuite, ER was evaluated using non-invasive vascular imaging (*i.e.*, MRA or CTA), at the treating physician's discretion. One neurointerventionalist for each centre and one stroke neurologist for the whole dataset independently evaluated ER, blinded to clinical and imaging data save for pre-IVT MRA or CTA. Discrepancies were resolved by consensus. ER was evaluated ≤3hrs after initiation of IVT, a delay that includes typical 'drip-and-ship' situations.[149] ER was defined as 2b-3 on the modified Thrombolysis in Cerebral infarction (mTICI) scale for ACI-T/L or M1 occlusions, and 3 on the Arterial Occlusive Lesion (AOL) scale for M2 occlusions.[110] For sensitivity analysis, mTICI 2c-3 was used as an alternative definition for ER for all occlusion sites, as recent studies suggest this should be the new target of reperfusion therapies.[150-152]

*Secondary outcomes*

The following secondary outcomes were also assessed: i) 3-month functional independence, defined as mRS score 0–2; ii) successful recanalization following MT, defined as mTICI grade 2b-3 at end of endovascular procedure; and iii) symptomatic intracranial haemorrhage, defined as presence of a parenchymal hematoma type-2 on brain CT or T2* MRI, accounting for deterioration with an increase in NIHSS score of ≥4 points within 36hrs of treatment.[153]

*Statistical analysis*

Continuous variables were described as mean±standard deviation or median (interquartile range, IQR), as appropriate, and categorical variables as numbers (%). In order to account for imbalance in potential confounders for the association between thrombolytic agent (tenecteplase *vs*. alteplase) and ER, we *a priori* chose to use propensity score analysis. Based on the available literature,[71,74,76,89,107,154,155] the following variables were considered *a priori* confounders: SVS length, IVT-to-$ER_{eval}$ time, occlusion site, admission NIHSS and onset-to-treatment time. In addition, the choice of imaging method to evaluate ER, which depended on pre-MT clinical events potentially related to ER (see above), was considered another key potential confounder. A propensity score was estimated using a multivariable logistic regression model, with the treatment group as the dependent variable and the above-mentioned potential confounders as covariates. The main analysis for the association between ER and thrombolytic treatment involved a 1:1 matching of patients from the tenecteplase group to patients from the alteplase group. To this aim, we performed a combination of exact matching (for the imaging method to evaluate ER) and propensity score matching (for other potential confounders), using the greedy nearest neighbour algorithm with a fixed caliper width of 0.1.[156] Balance of baseline characteristics between the tenecteplase and alteplase cohorts was assessed before and after propensity-score matching by calculation of absolute standardized differences (ASD). An ASD <20% was interpreted as a small difference.[157] The main analysis of the association between ER and thrombolytic therapy was performed on the propensity score-matched cohorts, using a conditional logistic regression to take into account the matched design.[158] To take into account residual imbalances in spite of matching, this analysis was repeated including in the logistic model those variables with post-matching ASD ≥20%. Heterogeneity in treatment effect size for ER was evaluated within the following subgroups: site of arterial occlusion (ACI-T/L, M1 proximal, M1 distal and M2), SVS length (<10 *vs*. ≥10mm) and NIHSS (<10 *vs*. ≥10). Since matching may reduce power and generalizability because it removes unmatched subjects from the analysis, we subsequently performed a propensity score-weighted logistic regression on the whole cohorts.[158] Finally, because the results of all above-described analyses depend on the validity of the construction of our propensity score, we ensured that we observed similar findings: (1) without using a propensity score, in a multivariable binary logistic regression model adjusted on previously described confounders; (2) using an alternative propensity score constructed with all baseline variables.

The association between the thrombolytic agent and secondary outcomes was studied on the propensity-matched cohorts using logistic regression, adjusting on variables with post-matching ASD ≥20%.

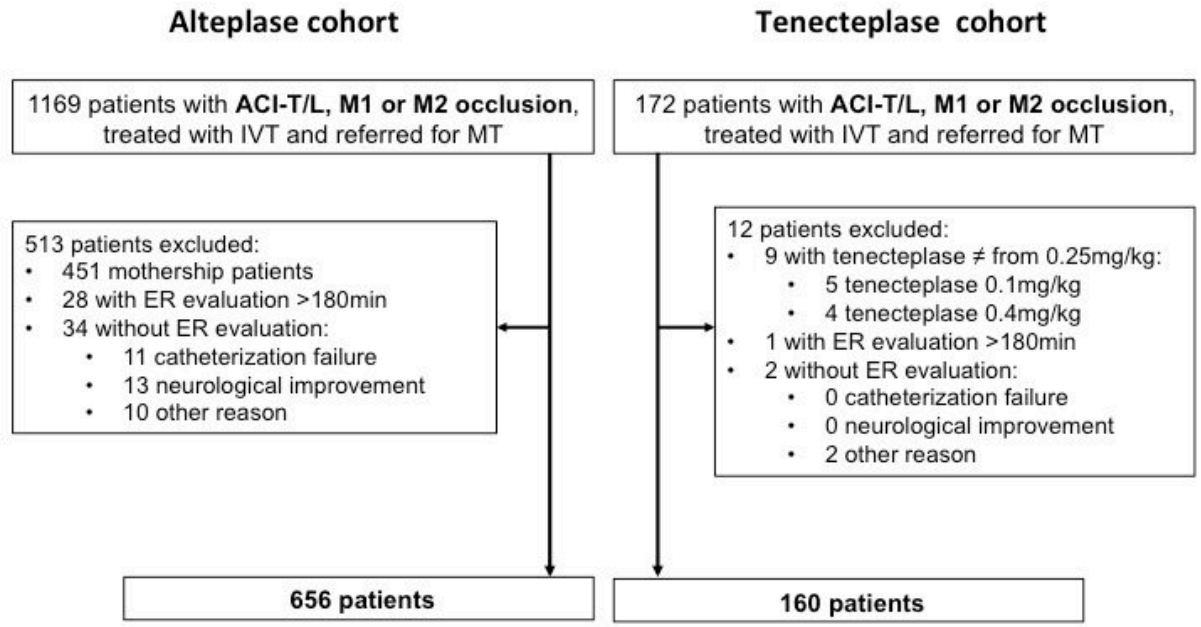
Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc). Two-tailed $P<0.05$ was considered significant.

**Results**

*Study flow chart*

The study flow chart is presented in **Figure 1**. The tenecteplase cohort included 172 patients, 12 of which were excluded (see **Figure 1**), leaving 160 patients for the final analysis. In the alteplase cohort, 1169 patients with LVO received IVT before referral for MT. Of these, 451 mothership patients and 62 patients with ER evaluation >3hrs from IVT start or without ER evaluation were excluded (see **Figure 1**), leaving 656 patients for the final analysis.

**Figure 1 –** Study flow chart.




*Legend:* ER indicates early recanalization; ICA-T/L, T or L shape internal carotid terminus; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

*Characteristics of the two cohorts*

Baseline characteristics of the two study groups before and after propensity score–matching are presented in **Table 1**. Before matching, several meaningful differences (ASD ≥20%) were found: the tenecteplase-treated cohort had longer onset-to-IVT time, more frequent visible SVS, ER status more frequently evaluated on angiography, and shorter IVT-to-$ER_{eval}$ time, than the alteplase-treated cohort. These differences were reduced after propensity score–matching (**Table 1**), with ASDs now <20% for all the pre-specified potential confounders, indicating that the 2 study groups were well-balanced following matching. The only baseline variable for which ASD was ≥20% after matching was diabetes mellitus (**Table 1**).

**Table 1** – Baseline Characteristics According to Thrombolytic Treatment before and after Propensity Score–Matching*

| | Before propensity-score matching | | | After propensity-score matching | | |
|---|---|---|---|---|---|---|
| | **Tenecteplase N=160** | **Alteplase N=656** | ***ASD (%)*** | **Tenecteplase N=131** | **Alteplase N=131** | ***ASD (%)*** |
| **Demographics** | | | | | | |
| Age (years) | 76 (59-83) | 70 (58-80) | 14 | 74 (58-82) | 69 (54-80) | 17 |
| Men | 79 (49.4) | 331 (50.5) | 2 | 67 (51.2) | 66 (50.4) | 8 |
| Hypertension | 103 (65.2) | 369 (57.3) | 16 | 80 (62.0) | 72 (55.0) | 14 |
| Diabetes mellitus | 31 (19.5) | 103 (16.0) | 9 | 24 (18.5) | 12 (9.2) | **27** |
| Current smoking | 20 (12.9) | 122 (18.9) | 17 | 15 (11.8) | 22 (16.8) | 14 |
| **Pre-IVT characteristics** | | | | | | |
| NIHSS | 16 (11-20) | 16 (11-20) | 3 | 16 (11-20) | 15 (9-20) | 8 |
| Onset-to-IVTtime(min) | 152 (123-179) | 145 (120-175) | **20** | 145 (123-175) | 149 (120-180) | 10 |
| **Pre-IVT imaging** | | | | | | |
| MRI and MRA | 151 (94.4) | 611 (93.1) | 5 | 131 (100.0) | 131 (100.0) | 0 |
| Occlusion site | | | 5 | | | 11 |
| ICA-T/L | 34 (21.3) | 148 (22.6) | | 26 (19.9) | 28 (21.4) | |
| Proximal M1 | 69 (43.1) | 277 (42.2) | | 57 (43.5) | 51 (38.9) | |
| Distal M1 | 34 (21.3) | 137 (20.9) | | 30 (22.9) | 33 (25.2) | |
| M2 | 23 (14.4) | 94 (14.3) | | 18 (13.7) | 19 (14.5) | |
| DWI-ASPECTS† | 8 (6-9) | 8 (6-9) | 7 | 8 (6-9) | 7 (6-9) | 17 |
| SVS visible‡ | 135 (90.0) | 505 (83.2) | **20** | 131 (100.0) | 131 (100.0) | 0 |
| SVS length (mm)§ | 11.1 (8.7-17.4) | 11.4 (8.3-17.0) | 4 | 11.1 (8.7-17.4) | 11.3(8.5-16.7) | 1 |
| **ER evaluation** | | | | | | |
| Arteriography | 156 (97.5) | 573 (87.3) | **39** | 127 (97.0) | 127 (97.0) | 0 |
| IVT-to-$ER_{eval}$time(min) | 93 (79-112) | 117 (96-143) | **77** | 94 (79-121) | 92 (79-113) | 3 |

*Legend:* *: Categorical variables are expressed as numbers (%) and continuous variables as median (IQR). †: Missing values: 45 in the alteplase cohort and 9 in the tenecteplase cohort (patients with CTA). ‡: Missing values: 49 in the alteplase cohort (45 with CTA and 4 without T2* imaging) and 10 in the tenecteplase cohort (9 with CTA and 1 without T2* imaging). §: Missing values: 151 in the alteplase cohort (45 with CTA, 4 without T2* imaging and 102 without SVS) and 25 in the tenecteplase cohort (9 with CT, 1 without T2* imaging and 15 without SVS).

Abbreviations: ASD indicates absolute standardized difference; ASPECTS, Alberta Stroke Program Early CT score; DWI, diffusion-weighted imaging; ER, early recanalization; IVT-to-$ER_{eval}$ time, time between intravenous thrombolysis start and evaluation of early recanalization; SVS, susceptibility vessel sign.

*Early recanalization*

In the whole cohorts, raw ER rates were 20.6% (33/160 patients; 95%CI: 14.3-26.9) and 24.2% (159/656 patients; 95%CI: 20.9-27.5) in tenecteplase- and alteplase-treated patients, respectively.

In the propensity score–matched cohorts, ER occurred in 28 out of 131 (21.4%, 95%CI: 14.4-28.4) *vs.* 24 out of 131 (18.3%, 95%CI: 11.7-24.9) in tenecteplase- and alteplase-treated patients, respectively, OR= 1.25 (95%CI: 0.65-2.41, *P*=0.51). These findings were not different after adjustment on diabetes mellitus (**Table 2**). There was no significant heterogeneity in the treatment effect size among predefined subgroups (data not shown) (see Methods).

Similar results to the propensity-matched analysis were found when (1) using the propensity score-weighted analysis on the whole cohorts (OR= 1.23; 95%CI: 0.68-2.21, *P*=0.50), (2) adjusting for the main potential confounding factors without using a propensity score on the whole cohorts (adjusted OR= 1.48 [0.83-2.64, *P*=0.19]); or (3) using an alternative propensity score constructed using all variables described in Table 1 (OR= 0.92; 95%CI 0.52-1.62, *P*=0.77).

As sensitivity analysis, when defined as mTICI 2c/3, ER occurred in 13 out of 131 (9.9%) *vs.* 14 out of 131 (10.7%) in the tenecteplase- and alteplase-treated propensity-matched cohorts, respectively, OR= 0.92 (95%CI: 0.42-2.04, *P*=0.84). Results were similar after adjustment on diabetes mellitus.

*Secondary outcomes*

As shown in **Table 2**, there was no significant association between thrombolytic agent and i) post-thrombectomy successful reperfusion, ii) symptomatic intracranial haemorrhage, and iii) 3-month functional independence in the propensity-matched cohorts.

**Table 2** – Primary and secondary outcomes according to the thrombolytic agent used in the propensity-matched cohort

| | **Tenecteplase N=131** | **Alteplase N=131** | **Adjusted OR* (95% CI)** | ***P*** |
|---|---|---|---|---|
| Early recanalization | 28 (21.4) | 24 (18.3) | 1.11 (0.55-2.23) | 0.78 |
| Post-thrombectomy recanalization | 111 (84.7) | 108 (83.1) | 1.10 (0.57-2.15) | 0.78 |
| Symptomatic intracranial haemorrhage† | 2 (1.6) | 3 (2.4) | 0.61 (0.10-3.77) | 0.59 |
| 3-month functional independence‡ | 70 (56.0) | 71 (56.8) | 1.09 (0.65-1.82) | 0.75 |

*Legend:* *Adjusted on diabetes mellitus; †2 and 6 missing data in the tenecteplase and alteplase groups, respectively; ‡6 and 6 missing data in the tenecteplase and alteplase groups, respectively.

**Discussion**

The present retrospective study on two large cohorts of stroke patients with LVO who received IVT and were then transferred for MT *as per* the drip-and-ship paradigm since bridging therapy entered clinical practice, showed no significant difference in pre-MT ER rates following tenecteplase 0.25mg/kg or alteplase 0.9mg/kg.

Our aim in this study was to test whether tenecteplase was associated with higher recanalization rate over alteplase in the time interval between IVT and MT in drip-and-ship patients. To our knowledge, the EXTEND-IA TNK trial is the only study to date that has reported ER rates, defined as mTICI 2b/3, in tenecteplase-treated patients intended for MT.[116] This study showed two-fold higher ER rate following tenecteplase 0.25mg/kg as compared to alteplase 0.9mg/kg. Comparing ER rates between the two studies, they were similar with tenecteplase (21 *vs.* 22% in our study and EXTEND-IA TNK, respectively), but markedly different with alteplase (18 *vs.* 10%, respectively).

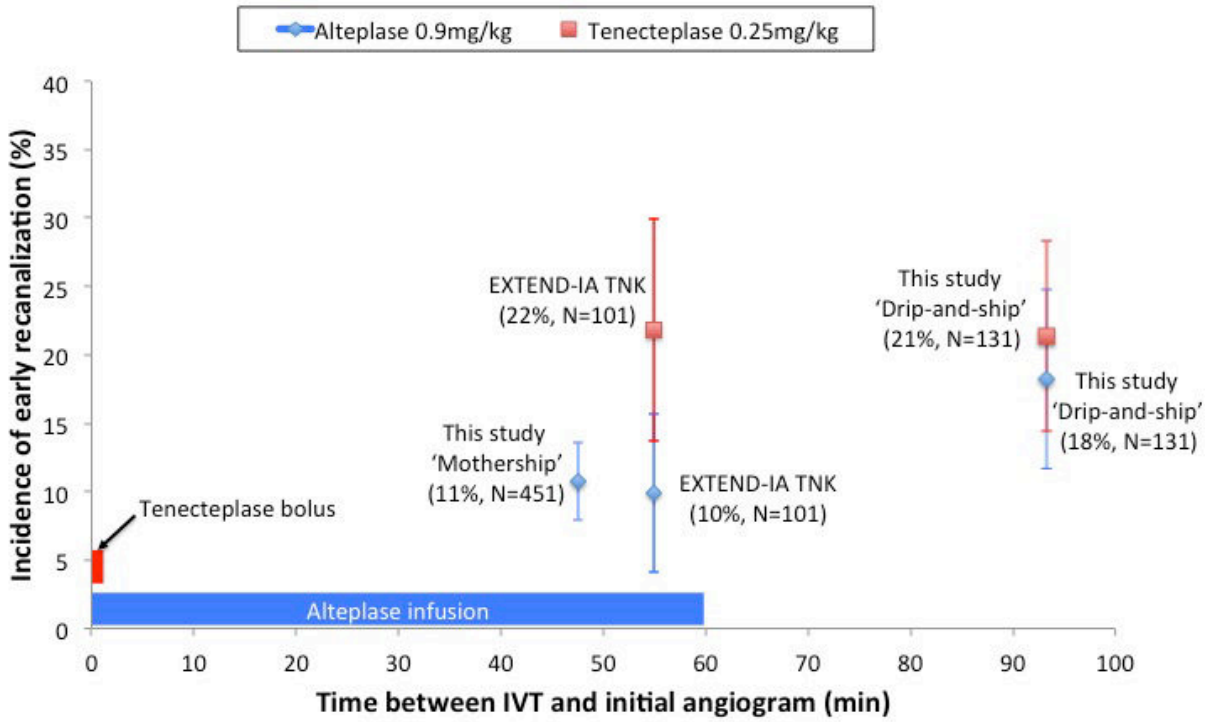
How can this discrepancy be explained? Pre-thrombolysis patients' characteristics, including age, NIHSS score, occlusion site and onset-to-IVT time, were similar in both studies.[116] However, the treatment paradigm differed between the two studies, that is, 100% drip-and-ship *as per* design in our study *vs.* 75% mothership in EXTEND-IA TNK.[116] Accordingly, the median time between IVT start and first intracranial run of angiography was considerably longer in our study than in EXTEND-IA TNK (93min and 56min, respectively).[116] The longer exposure time to alteplase may account for the higher ER rate in our study (18% *vs.* 10%, respectively). Indeed, in a large prospective alteplase-treated cohort, longer IVT-to-$ER_{eval}$ delays were found to be independently associated with higher ER rates.[154] This reflects both the more prolonged exposure to alteplase after full-dose administration, and the fact that some patients, particularly with the mothership paradigm, do not receive the full alteplase dose before MT. Consistent with this, a *post-hoc* analysis of the mothership subset of our alteplase cohort (n=451; excluded *a priori* from the present study which focused on drip-and-ship patients, see Figure 1) showed an ER rate similar to that reported in the alteplase arm of EXTEND-IA TNK (11%), with similar IVT-to-$ER_{eval}$ times as well (data not shown).

To the best of our knowledge, ER rate as a function of time following tenecteplase is unknown. The similar ER rate in our study as compared to EXTEND-IA TNK despite later recanalization assessment suggests that recanalization occurs very early following bolus tenecteplase.

Taken together, therefore, the above data suggest that although in drip-and-ship patients the rate of recanalization at time of thrombectomy is similar with tenecteplase and alteplase, it may occur earlier with the former. This is illustrated in **Figure 2**, which shows the ER rates for alteplase and tenecteplase observed in EXTEND-IA TNK and in our drip-and-ship and mothership cohorts. In

support, Benedict *et al* previously found earlier recanalization with tenecteplase than alteplase in a rabbit carotid thrombosis model.[36] If confirmed, the earlier occurrence of recanalization with tenecteplase in drip-and-ship patients may have clinical relevance given the strong relationship between timing of reperfusion and functional outcome.[10] The lack of significant difference in 3-month mRS between the two thrombolytic agents in our propensity-matched cohorts may be because this putative difference between the two thrombolytic therapies in timing of recanalization – which only concerns ~1 out of 5 patients – is too small to translate into better functional outcomes, and is further compounded by the well-known major effect of MT – performed in ~4 out of 5 patients – on functional outcome. In addition, our propensity-matched cohorts were of moderate size, and were matched on the confounders of ER, not of functional outcome.

**Figure 2** – Association between early recanalization rate and time elapsed between start of intravenous thrombolysis and evaluation of recanalization in the present study and EXTEND-IA TNK trial.




*Legend:* Red and blue squares represent the incidence of early recanalization following tenecteplase 0.25mg/kg and alteplase 0.9mg/kg, respectively. The bars represent the 95% confidence interval.

**Strengths and limitations**

Our study has several strengths. First, it is based on two large cohorts of patients intended for bridging therapy as standard-of-care. Second, ER was assessed by two independent raters, reducing the risk of classification error. Third, and lastly, the propensity score-matching made possible by the large alteplase cohort allowed adjusting for major potential confounders, strengthening the reliability of the results.

Our study has limitations. First, being retrospective, unknown confounding factors may have been overlooked, especially considering that patients from the tenecteplase and alteplase groups were treated in different stroke units. Second, the participating centres, all based in France, mostly used MRI for patient selection for reperfusion therapy before IVT, and the included population might therefore differ from primarily CT-assessed populations. Randomized trials in drip-and-ship cohorts are desirable to confirm our findings.

**Conclusion**

This study found that early recanalization rates following IVT with tenecteplase 0.25mg/kg or alteplase 0.9mg/kg did not differ in stroke patients with LVO intended for MT *as per* the drip-and-ship paradigm. However, taken together with the EXTEND-IA TNK results, the available data suggest that recanalization may occur earlier with tenecteplase than alteplase, which if confirmed in independent studies would have relevance for patient care.

# Sixième partie:
# Synthèse et perspectives

## I. Incidence de la recanalisation précoce après thrombolyse intraveineuse

### I.1 Incidence de la recanalisation précoce

La méta-analyse et la cohorte PREDICT-RECANAL présentées en première et deuxième partie de cette thèse démontrent toutes les deux que l'incidence de la recanalisation précoce après thrombolyse intraveineuse est d'environ 18 à 20% dans une population non sélectionnée d'AIC avec occlusion proximale adressée en thrombectomie. Une méta-analyse publiée par une autre équipe en 2018 a rapporté une incidence nettement inférieure (11%, IC95% 7-16).[106] Néanmoins, celle-ci était très vraisemblablement sous-estimée car l'analyse incluait de nombreuses études dans lesquelles l'imagerie vasculaire initiale était réalisée *après* la thrombolyse intraveineuse (notamment les principaux essais de thrombectomie). En d'autres termes, les patients avec recanalisation précoce post-thrombolyse survenue avant cette imagerie vasculaire étaient exclus *a priori* de ces études, entrainant un important biais de sélection.[109] L'inclusion seule de patients chez lesquels l'imagerie vasculaire initiale est réalisée *avant* le début de la thrombolyse intraveineuse est un point méthodologique crucial pour estimer de manière fiable l'incidence de recanalisation précoce, point que nous avons appliqué pour notre méta-analyse et la cohorte PREDICT-RECANAL.

Le site d'occlusion et le paradigme de traitement étant deux facteurs prédictifs importants de recanalisation précoce post-thrombolyse, facilement et rapidement disponibles dans n'importe quelle UNV, les données d'incidence de recanalisation en fonction de ces deux facteurs dans la cohorte PREDICT-RECANAL totale (cohorte de dérivation + cohorte de validation) sont résumées dans la **Figure 3**. L'incidence de recanalisation précoce varie de manière importante en fonction du site d'occlusion et du paradigme de traitement (mothership *vs.* drip-and-ship): sans distinction sur le site d'occlusion : 11 *vs.* 24% ; artère carotide interne : 1 *vs.* 6% ; M1 proximal : 6 *vs*. 21% ; M1 distal : 17 *vs.* 39% ; et M2 : 25 *vs.* 42% (Figure 3).

Trois nouvelles études de bonne qualité publiées en 2018 présentent également des données sur l'incidence de recanalisation précoce chez des patients avec intention de bridging, sur un effectif néanmoins bien plus faible que le notre (**Table 3)**.[116,130,159] Si les sites d'occlusion et la définition de la recanalisation sont similaires dans ces trois études, les proportions de traitement mothership/drip-and-ship varient de manière importante, ce qui explique les différences d'incidence de recanalisation précoce constatées entre elles, et également avec notre étude.

**Figure 3.** Incidence de la recanalisation précoce selon le site d'occlusion et le paradigme de traitement, dans la cohorte PREDICT-RECANAL (cohorte de dérivation + cohorte de validation).

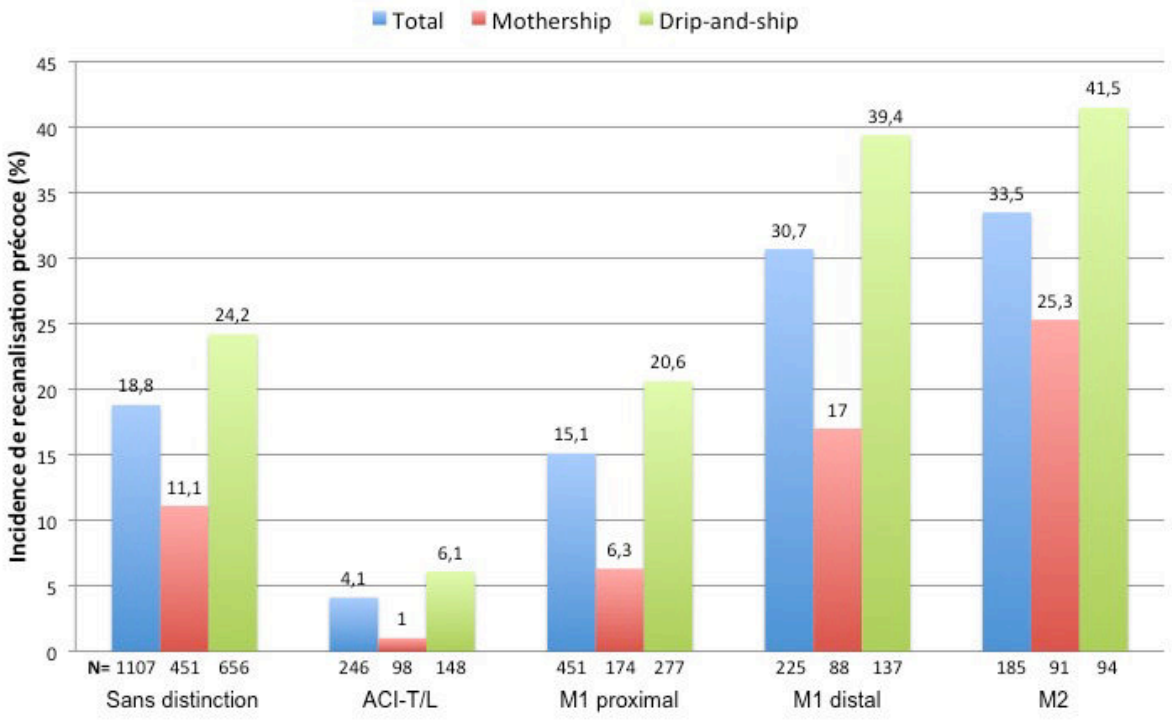



**Table 3.** Principales données récentes (publiées après la publication de la revue systématique présentée en première partie) présentant l'incidence de recanalisation précoce après rtPA intraveineux, chez des patients avec occlusion de la circulation antérieure et candidats à un bridging.

| Article et design | Dates d'inclusion, population | Site d'occlusion | Méthode et délai d'évaluation de la recanalisation* | Incidence de recanalisation précoce |
|---|---|---|---|---|
| **Campbell *et al.*[116] *NEJM* 2018 Prospective** | 2015-2017<br>N=101<br>MS= 77% | ACI 24%<br>M1 58%<br>M2 15% | Artério 100%<br>Délai médian 56min | 10.0% |
| **Kaesmacher *et al.*[130] *Stroke* 2018 Rétrospective** | 2012-2017<br>N=250<br>MS= 100% | ACI 22%<br>M1 49%<br>M2 17% | Artério 100%<br>Délai médian 43min | 6.0% |
| **Yoo *et al.*[159] *Stroke* 2018 Prospective** | 2016-2017<br>N=78<br>MS= ? | ACI 20%<br>M1 61%<br>M2 20% | Artério 90%, autre 10%<br>Délai médian 55 min | 17.9% |

*La recanalisation était définie comme un score mTICI 2b-3 dans les 3 études.

*Abréviations* : MS : mothership.

## I.2 Limites et perspectives

### I.2.1 Recanalisation spontanée

Dans cette thèse nous nous sommes focalisés sur les patients avec intention de bridging, et de ce fait les patients adressés en thrombectomie sans thrombolyse préalable n'ont pas été inclus. Ainsi, il n'est pas certain que l'incidence de recanalisation précoce rapportée soit exclusivement liée à la thrombolyse intraveineuse, des recanalisations spontanées étant parfois constatées. Très peu d'études ont comparé la recanalisation précoce spontanée *vs.* après rtPA intraveineux, et aucune d'entres elles n'était randomisée (**Table 4**).[130,160,161] Ces études montrent cependant qu'il existe une forte association entre la thrombolyse intraveineuse et la survenue d'une recanalisation précoce, suggérant un fort lien de causalité. La supériorité de la thrombolyse *vs.* placebo en termes de pronostic fonctionnel constatée dans les essais randomisés pivots, y compris en cas de déficit neurologique très sévère – suggérant la présence d'une occlusion proximale –, renforce encore cette hypothèse.[16] Compte-tenu de l'incidence très faible de recanalisation précoce spontanée (Table 4), il ne nous a pas paru pertinent d'en étudier les facteurs prédictifs.

**Table 4.** Etudes observationnelles rapportant l'incidence de recanalisation précoce spontanée *vs.* post-thrombolyse intraveineuse, en cas d'AIC avec occlusion artérielle proximale.

| Article et design | Dates d'inclusion, population | Méthode, définition et délai d'évaluation de la recanalisation | Incidence de recanalisation précoce |
|---|---|---|---|
| **Molina *et al.*[160] *Stroke* 2001 Rétrospective** | 2000-2001<br>Population 100% non bridging<br>Occl: M1 74%, M2 26%. | Méthode : doppler transcrânien<br>Définition : TIBI 4-5<br>Délai médian environ 180min | Spontanée: 4.1% (2/48)<br>rtPA: 33.3% (8/24) |
| **Kaesmacher *et al.*[130] *Stroke* 2018 Rétrospective** | 2012-2017<br>Population bridging (mothership 100%)<br>Occl: ACI 22%, M1 49%, M2 17%. | Méthode : angiographie 100%<br>Définition : mTICI 2b-3<br>Délai médian 43min (IQR 33-66) | Spontanée: 0.8% (3/377)<br>rtPA: 6.0% (15/250) |
| **Menon *et al.*[161] *JAMA* 2018 Prospective, non randomisée** | 2010-2016<br>Population bridging ou non (42/58%)<br>Occl: ACI 20%, M1 42%, M2 30%. | Méthode : CTA 59% ; angio 41%<br>Définition : rAOL 2b-3<br>Délai médian 133min (IQR 62-238) | Spontanée: 13.3% (14/105)<br>rtPA: 30.4% (143/470) |

### I.2.2 Occlusion basilaire

Seuls les patients avec occlusion de la circulation antérieure ont été inclus dans cette thèse, car ces patients représentent l'immense majorité de la population adressée en thrombectomie.[30] Les occlusions basilaires représentent moins de 5% des patients avec occlusion proximale admis à la phase aigüe de l'AIC,[24] et il existe très peu de données sur la recanalisation précoce après thrombolyse intraveineuse chez ces patients. Dans notre méta-analyse, seuls 49 patients avaient une occlusion basilaire, et l'incidence de recanalisation complète post-thrombolyse était de 4% (IC95% très large : 0-22). Depuis notre méta-analyse, une étude incluant 51 patients avec occlusion basilaire et intention de bridging (mothership et drip-and-ship) a été publiée, montrant une recanalisation de 13% sur le premier jet de l'artériographie ou sur angioscanner (délai médian d'évaluation : 114min).[162] Cependant, compte tenu des faibles effectifs, l'incidence précise de recanalisation précoce post-thrombolyse intraveineuse est incertaine dans cette population, et de plus larges études sont nécessaires pour déterminer les patients qui pourraient bénéficier le plus de la thrombolyse avant transfert en thrombectomie.

### I.4 Conséquence des résultats de l'incidence de recanalisation précoce post-thrombolyse

Documenter une incidence significative de recanalisation précoce post-thrombolyse intraveineuse est importante dans le débat actuel où certains experts envisagent de sursoir à la thrombolyse chez les patients candidats à un bridging selon les recommandations actuelles. En effet, un taux de recanalisation précoce proche de zéro serait un argument fort en faveur d'un transfert direct en thrombectomie, sans thrombolyse préalable, même si d'autres bénéfices potentiels de la thrombolyse sont évoqués comme l'amélioration de la micro-vascularisation après recanalisation de l'artère occluse,[114] la facilitation du geste de thrombectomie[163] et la réduction du risque d'emboles dans de nouveaux territoires liés à la procédure de thrombectomie.[32,115]

Les patients avec intention de bridging mais présentant une recanalisation post-thrombolyse avant la thrombectomie étaient exclus de l'immense majorité des études observationnelles comparant le pronostic fonctionnel de patients traités par bridging *vs*. thrombectomie seule,[164-168] ce qui est un biais important compte-tenu de l'incidence de recanalisation précoce post-rtPA rapportée ici. Nous avons rédigé une lettre à l'éditeur mentionnant ce point pour l'un de ces articles,[164] qui est présentée en **Annexe 3**.[109] Seuls des essais randomisés comparant bridging *vs*. thrombectomie seule permettront de trancher sur l'utilité de la thrombolyse avant la thrombectomie. Cependant, compte-tenu des 20% de recanalisation précoce post-thrombolyse dans une population tout-venant de bridging, il nous paraît déraisonnable d'inclure une population non sélectionnée dans ces essais. Le développement d'outils prédictifs de recanalisation précoce post-thrombolyse serait donc important pour sélectionner les patients résistants au rtPA en vue de ce type d'essai, et à l'inverse pour sélectionner les patients rtPA-sensibles en vue d'un essai comparant thrombolyse *vs*. bridging visant à limiter les « transferts futiles ». La détermination des facteurs prédictifs indépendants de recanalisation précoce, étape indispensable à l'élaboration de ces outils et à la compréhension des mécanismes physiopathologiques sous-jacents, constituait le deuxième objectif de cette thèse, présenté dans ce qui suit.

## II. Facteurs prédictifs et mécanismes sous-tendant la recanalisation précoce post-thrombolyse

Les caractéristiques du thrombus, le délai entre la thrombolyse intraveineuse et l'évaluation de la recanalisation, et la qualité du réseau artériel collatéral (ou la sévérité de l'hypoperfusion cérébrale) sont les facteurs prédictifs indépendants de recanalisation précoce post-thrombolyse mis en évidence dans cette thèse.

### II.1. Caractéristiques du thrombus

#### II.1.1 Synthèse des résultats

La localisation du thrombus dans l'arbre artériel et sa longueur sont deux facteurs indépendamment associés à la recanalisation précoce dans notre cohorte, celle-ci étant plus fréquente en cas de thrombus distal (M1 distal ou M2 *vs.* M1 proximal ou terminaison carotide) et de thrombus plus court. Ces données sont concordantes avec celles des autres cohortes ayant étudié ces associations, malgré des méthodes d'évaluation variées de la taille du thrombus : longueur mesurée par angioscanner, par scanner sans injection [hyperdensité spontanée intra-artérielle], ou par IRM sur la séquence T2* [susceptibility vessel sign, SVS]; ou « clot burden score » sur angioscanner.[71,72,130,159,161,162] Cette concordance malgré des techniques d'imagerie différentes renforce la validité de cette association.

L'explication physiopathologique la plus plausible pour rendre compte de l'association entre la taille du thrombus et la recanalisation précoce est que la quantité de rtPA administrée serait insuffisante pour lyser la totalité de la fibrine présente dans le thrombus. Trois éléments soutiennent cette hypothèse. Premièrement, une étude préclinique sur un modèle d'occlusion carotide chez le lapin a montré un taux plus élevé de recanalisation avec l'augmentation des doses de rtPA intraveineux.[36] Deuxièmement, une étude chez l'homme a montré une résolution plus importante du volume de thrombus – mesuré par scanner sans injection en coupes fines avant thrombolyse puis une heure après –, et de recanalisation complète, avec des doses plus élevées de rtPA intraveineux.[169] Le troisième argument est l'existence dans notre cohorte d'une association indépendante entre un délai thrombolyse-évaluation de la recanalisation plus long et la fréquence de recanalisation. En effet, le rtPA étant administré par perfusion continue d'une heure, les patients chez lesquels la recanalisation est évaluée très précocement (<1h) n'ont pas reçu la dose totale de rtPA, pouvant expliquer la moindre recanalisation. A noter cependant que l'incidence de recanalisation précoce dans notre méta-analyse était similaire entre les études utilisant la dose de 0.9mg/kg de rtPA et celles utilisant 0.6mg/kg.[107] Ce résultat est néanmoins à prendre avec précaution car de nombreux biais n'ont pas été pris en compte dans cette analyse (site d'occlusion, délai thrombolyse-évaluation de recanalisation, *etc*...). L'adaptation de la dose de rtPA administrée en fonction de la taille du thrombus, et non pas uniquement en fonction du poids comme actuellement recommandé (0.9mg/kg), mériterait d'être étudiée à l'avenir. Il n'en demeure pas moins que l'augmentation de dose de rtPA expose à un risque plus élevé de complications hémorragiques.

Bien que dans notre cohorte la longueur du thrombus soit corrélée – à un certain degré – à sa localisation dans l'arbre artériel (*cf.* supplemental Figure 7 de la deuxième partie, page 74), l'inclusion de ces deux variables dans le modèle multivariable n'a pas induit de multi-colinéarité, ce qui confirme que ces deux variables sont associées de manière indépendante à la recanalisation précoce. Ceci suggère que le volume du thrombus (qui est le produit de sa longueur et du diamètre de l'artère occluse, donc sa localisation) est un facteur prédictif clé de recanalisation précoce. Une étude très récemment publiée mesurant le volume du thrombus par scanner sans injection à l'aide d'un logiciel semi-automatisé a confirmé cette hypothèse, et a montré que le volume du thrombus était plus performant que sa longueur pour prédire la recanalisation précoce.[159]

### II.1.2 Limites et perspectives

#### *II.1.2.1 Limites de la séquence T2**

Dans cette thèse, la longueur du thrombus était évaluée par une mesure manuelle de la longueur du SVS, qui correspond à l'artefact de susceptibilité magnétique causé par le thrombus sur la séquence T2*. Cette méthode, qui reproduit celle décrite en 2013 par Naggara *et al,* a pour avantages d'être simple (réalisable en routine clinique par des lecteurs entrainés, quelle que soit la console utilisée), reproductible pour des lecteurs entrainés, et fortement corrélée à la longueur du thrombus mesurée par l'artériographie.[111] Néanmoins, plusieurs limites de cette approche se doivent d'être mentionnées :

- Premièrement, un SVS n'est pas toujours visible en cas d'occlusion artérielle, le taux de visibilité variant selon les études de 35% à 100% en cas d'occlusion proximale,[55,59,170-178] bien qu'il s'établisse plutôt autour de 80% dans les études les plus récentes (84% dans la notre).[171,172,177,178] De fait, les analyses sur la longueur du SVS réalisées dans cette thèse ont inclut uniquement les patients avec SVS, ce qui pourrait avoir biaisé les résultats. Plusieurs facteurs peuvent expliquer l'absence de SVS, comme la composition ou l'étiologie du thrombus,[174,179-181] sa taille[111] ou sa localisation,[172,180] mais également le type (écho de gradient *vs.* séquence de susceptibilité magnétique)[170] et les paramètres de la séquence T2* utilisée (épaisseur de coupe, temps de répétition et temps d'écho, *etc*...).[182] Dans notre étude, le type de séquence T2* et ses paramètres variaient d'un centre à l'autre, occasionnant un taux de SVS allant de 54% à 99% selon les centres (un taux de SVS >80% était présent chez 71% des centres). Le taux de SVS était plus élevé dans les centres utilisant une séquence de susceptibilité magnétique *vs.* écho-de-gradient (respectivement 96% et 82%). Compte-tenu de l'importance de la longueur du SVS pour la recanalisation précoce, l'utilisation en routine de séquences très sensibles (comme la séquence de susceptibilité magnétique) paraîtrait tout-à-fait légitime. Le temps d'acquisition de ces séquences est néanmoins actuellement plus long que celui des séquences écho-de-gradient, ce qui rend leur utilisation à la phase aigüe de l'AIC sujet à débat. Des progrès visant à réduire la durée d'acquisition de ces séquences sont donc fortement souhaitables, par exemple en les couplant avec l'ARM temps de vol.[183]

- Deuxièmement, bien que ces deux mesures soient fortement corrélées, la longueur du SVS surestime la longueur réelle du thrombus.[111,184] Ce point ne remet cependant en rien en question l'association observée entre longueur du SVS et recanalisation précoce, car comme on l'a vu l'association thrombus-recanalisation est retrouvée indépendamment de la modalité d'imagerie, mais il suggère que les seuils de longueur de thrombus décrits dans cette thèse ne sont pas nécessairement transposables à d'autres méthodes d'imagerie non invasives comme le scanner. Aucune étude n'a à ce jour comparé la longueur du thrombus mesurée sur la séquence T2* *vs.* par scanner ou angioscanner chez les mêmes sujets. Cependant, Yan *et al.* ont montré que la longueur du SVS est supérieure à celle du thrombus mesurée chez les mêmes patients par séquence IRM T1 acquise à un temps tardif après injection de gadolinium – une méthode proche de celle utilisée en angioscanner dynamique (*cf.* **Table 5**) –,[184] en accord avec la surestimation probable de la longueur du thrombus mesurée par SVS en comparaison aux autres modalités d'imagerie.[111] L'effet du type et des paramètres de la séquence T2* sur la longueur du SVS est actuellement inconnue, aucune étude ne l'ayant étudié chez les mêmes patients. Dans la cohorte PREDICT-RECANAL, la longueur du SVS mesurée par imagerie de susceptibilité magnétique *vs.* écho de gradient n'était pas significativement différente (cohorte de dérivation : respectivement 13.2 *vs.* 11.8mm, $P$=0.14 ; cohorte de validation : 11.9 *vs.* 11.5mm, $P$=0.25), mais il nous est impossible de conclure formellement, les imageries n'ayant pas été réalisées chez les mêmes patients.

- Troisièmement, en raison des artéfacts osseux au niveau de la base du crâne, la détection du SVS et sa mesure sont difficiles pour les thrombi carotidiens. Ainsi, la longueur du SVS décrite dans nos travaux pour les occlusions carotide est probablement sous-estimée. Cependant, ces derniers étant déjà très longs (*cf.* supplemental Figure 7 dans la deuxième partie, page 74), il est peu probable que cette limite ait impacté nos résultats de manière significative.

- Enfin, bien qu'excellente entre lecteurs expérimentés,[111] la reproductibilité inter-observateurs de la méthode de mesure du SVS utilisée dans notre thèse n'est pas connue pour des lecteurs peu ou pas entrainés. Il serait utile de développer des méthodes automatisées de mesure de longueur ou de volume du SVS pour s'affranchir de cette limite en routine clinique.[159]

La description et les avantages et inconvénients des principales méthodes d'imagerie utilisées dans la littérature pour évaluer la taille du thrombus sont présentés dans la **Table 5** et les **Figures 4-9**.[55,56,58,71,184-187]

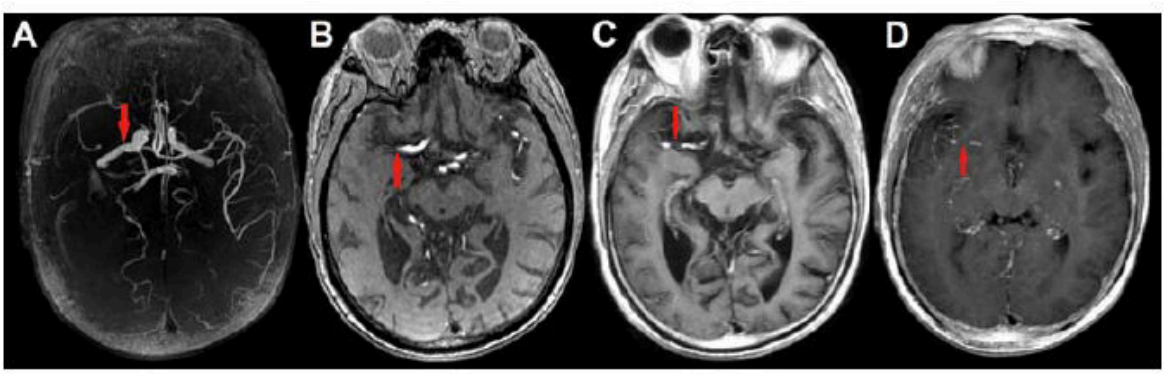
**Table 5.** Avantages et inconvénients des principales méthodes de mesure de la taille du thrombus

| Type de mesure | Outil d'imagerie | Brève description | Avantages | Inconvénients |
|---|---|---|---|---|
| Longueur | IRM T2*[111]<br>*Cf.* supplemental Figure 2 dans la deuxième partie, page 69 | Mesure manuelle du SVS | Simple et rapide<br>Pas de traitement d'image nécessaire après acquisition<br>Reproductible<br>Validée en comparaison à la mesure du thrombus sur artério | Surestimation de la longueur<br>Difficile pour les thrombi termino-carotidiens<br>Nécessite une IRM<br>SVS parfois non visible |
| Longueur | IRM T1 avec acquisition tardive après injection[184]<br>*Cf.* Figure 4, ci-après | Mesure manuelle de la zone intra-artérielle non opacifiée, après recalage et fusion des images natives de l'ARM TOF et du T1 injecté à temps tardif | Reproductible | Nécessite un traitement d'image après acquisition<br>Nécessite une acquisition tardive (inadapté au contexte d'urgence)<br>Nécessite une IRM |
| Longueur | Angioscanner[56]<br>*Cf.* Figure 5, ci-après | Mesure manuelle de la zone intra-artérielle non opacifiée après reconstruction MIP dans plusieurs plans. | Disponibilité de l'angioscanner<br>Reproductible | Nécessite un angioscanner dynamique,[188] peu usité en pratique<br>Nécessite un traitement d'image après acquisition<br>Surestime la longueur si mauvaises collatérales (sauf si angioscanner dynamique) |

**Table 5 (suite).**

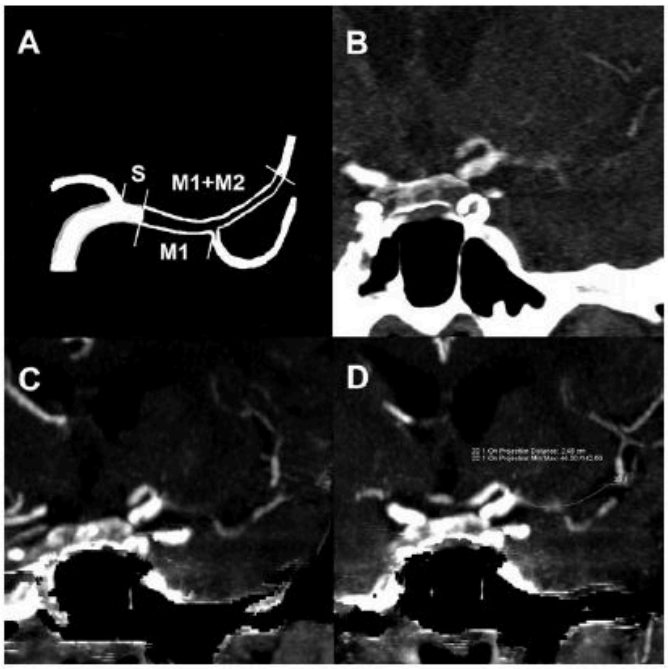
| Type de mesure | Outil d'imagerie | Brève description | Avantages | Inconvénients |
|---|---|---|---|---|
| Longueur | Scanner sans injection[185]<br>*Cf.* Figure 6, ci-après | Mesure de l'hyperdensité spontanée intra-artérielle après reconstruction MIP. Mesure manuelle ou semi-automatisée à l'aide d'un logiciel basé sur la densité du thrombus. | Disponibilité du scanner<br>Traitement d'image simple et rapide post-acquisition<br>Reproductible | Hyperdensité spontanée intra-artérielle parfois non visible[189] (importance de l'épaisseur de coupe)<br>Difficile pour les thrombi termino-carotidiens |
| Clot burden score | IRM T2*[55]<br>*Cf.* Figure 7, ci-après | Score visuel semi-quantitatif comptabilisant la présence du SVS dans des zones prédéfinies. | Evaluation visuelle simple et rapide<br>Pas de traitement d'image nécessaire<br>Reproductible | Difficile pour les thrombi termino-carotidiens<br>Estimation approximative<br>SVS parfois non visible<br>Nécessite une IRM |
| Clot burden score | Angioscanner[187]<br>*Cf.* Figure 8, ci-après | Score visuel semi-quantitatif comptabilisant l'absence d'opacification intra-artérielle dans des zones prédéfinies après reconstruction selon plusieurs plans. | Evaluation visuelle simple et rapide<br>Traitement d'image simple et rapide post-acquisition<br>Disponibilité de l'angioscanner | Nécessite un angioscanner dynamique,[188] peu usité en routine<br>Estimation approximative<br>Surestime la longueur si mauvaises collatérales (sauf si angioscanner dynamique) |
| Volume | Scanner sans injection[159,186]<br>*Cf.* Figure 9, ci-après | Méthode semi-automatisée mesurant le volume de l'hyperdensité intra-artérielle spontanée à l'aide d'un logiciel basé sur la densité. | Le volume du thrombus est probablement le paramètre le plus pertinent<br>Reproductible par méthode semi-automatisée | Hyperdensité spontanée intra-artérielle parfois non visible[189] (importance de l'épaisseur de coupe)<br>Nécessite un traitement d'image après acquisition |

**Figure 4.** Illustration de la mesure de longueur du thrombus sur la séquence T1 acquise à un temps tardif après injection chez un patient avec occlusion M1 proximale, d'après Yan *et al.*[184]




*Légende :* A : Reconstruction de l'ARM TOF, montrant le site d'occlusion (M1 proximal droit). B : Image d'acquisition de l'ARM TOF montrant l'occlusion M1. C : séquence T1 injectée, au temps tardif, recalée sur l'ARM TOF. D : fusion des images B et C, permettant la mesure du thrombus.

**Figure 5.** Illustration de la mesure de longueur du thrombus par angioscanner dynamique chez un patient avec occlusion M1 proximale, d'après Rohan *et al*.[56]




*Légende :* A : schéma montrant la localisation de l'absence d'opacification sur l'angioscanner. B : reconstruction avec 'maximum intensity projection' (MIP) classique de l'angioscanner, en coupe coronale, montrant une mauvaise opacification des branches en aval du thrombus, rendant difficile l'évaluation de l'extrémité distale de ce dernier. C : même angioscanner après reconstruction avec MIP temporel : l'extrémité distale est nettement plus facilement visualisable. D : mesure de la longueur du thrombus.

**Figure 6.** Illustration de la mesure de longueur de l'hyperdensité intra-artérielle spontanée par scanner sans injection en coupes fines, après reconstruction MIP chez un patient avec occlusion M1, d'après Riedel *et al.*[185] L'hyperdensité intra-artérielle spontanée peut-être mesurée manuellement ou à l'aide d'un logiciel semi-automatisé basé sur la densité du thrombus.

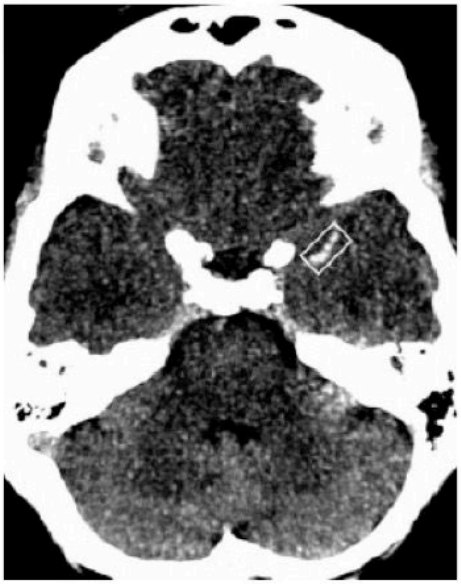
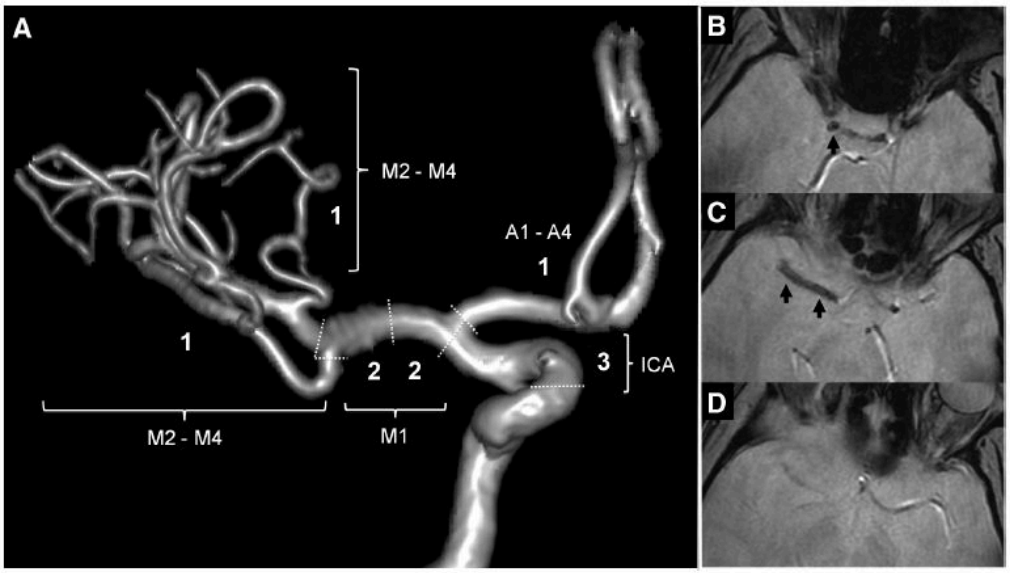
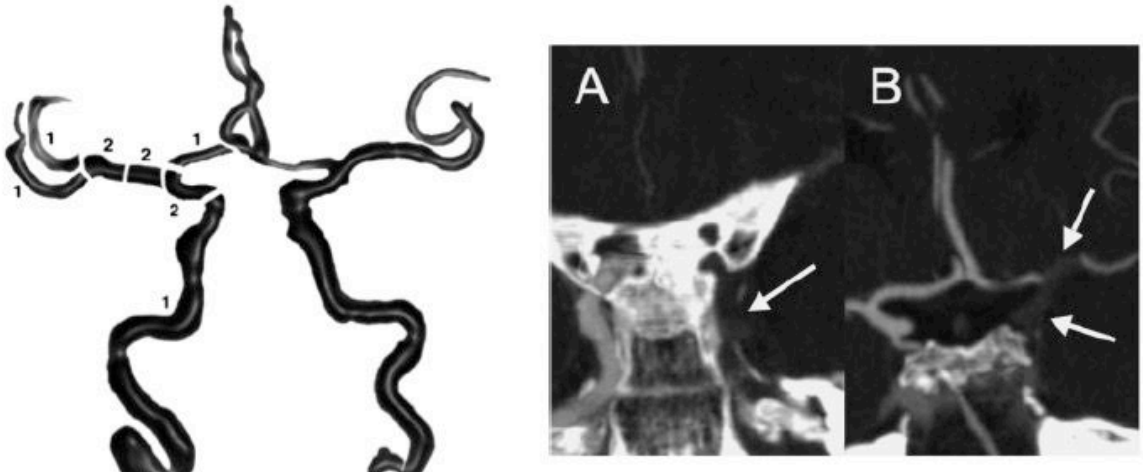


**Figure 7.** Méthode de calcul clot burden score sur la séquence T2* en IRM (susceptibility vessel sign), et illustration chez un patient avec occlusion carotide et M1, d'après Legrand *et al.*[55]



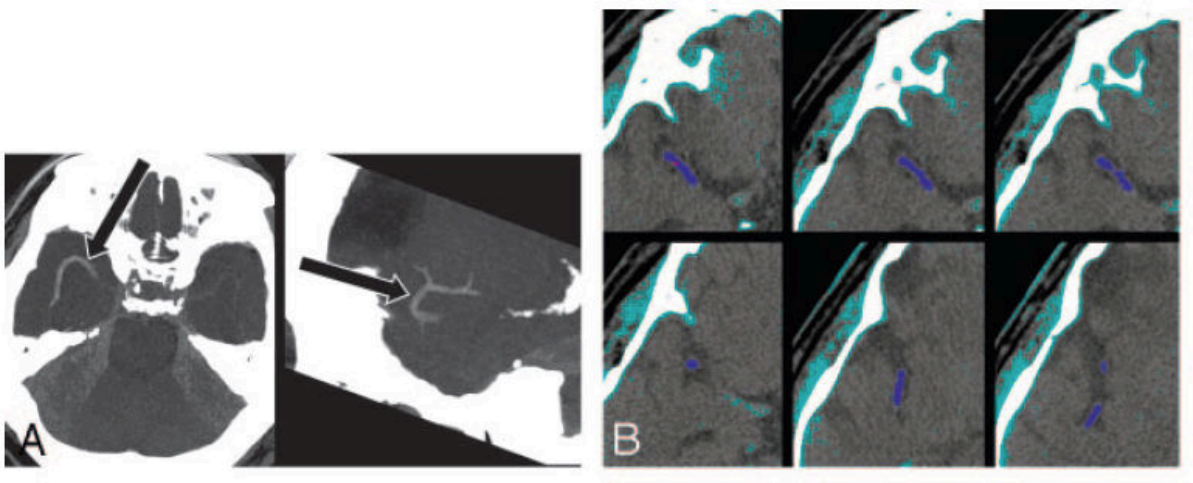

*Légende :* A : Un clot bruden score de 10 correspond à l'absence de SVS visible. 3 points sont à retirer en cas de SVS visible dans la partie supra-clinoïdienne de la carotide, 2 points pour chaque partie de M1 (proximale et distale), 1 point en cas de SVS entre A1 et A4, et 1 point pour chaque SVS entre M2 et M4 (2 maximum). B à D : illustration chez un patient avec occlusion termino-carotide et M1 : clot burden score à 3 (SVS présent en termino-carotide, M1 proximal et M1 distal).

***Figure 8.*** Méthode de calcul du clot burden score sur angioscanner, et illustration chez un patient avec occlusion carotide et M1, d'après Puetz *et al.*[187]




*Légende :* Panel de gauche : un clot bruden score de 10 correspond à l'absence d'occlusion artérielle sur l'angioscanner. 1 point est à retirer en cas d'absence d'opacification dans la partie infra-clinoïdienne de la carotide, 2 points pour la partie supra-clinoïdienne de la carotide, 2 points pour chaque partie de M1 (proximale et distale), 1 point pour A1, et 1 point pour chaque branche M2 (2 maximum). Panel de droite (A et B) : exemple chez un patient avec occlusion carotide et M1 : absence d'opacification de la partie infra-clinoïdienne (A), de la partie supra-clinoïdienne et de M1 proximal (B) : le clot burden score est de 5.

***Figure 9.*** Illustration de la mesure du volume de l'hyperdensité spontanée intra-artérielle en scanner sans injection en coupes fines, chez un patient avec occlusion M1 proximale, d'après Kim *et al.*[186]



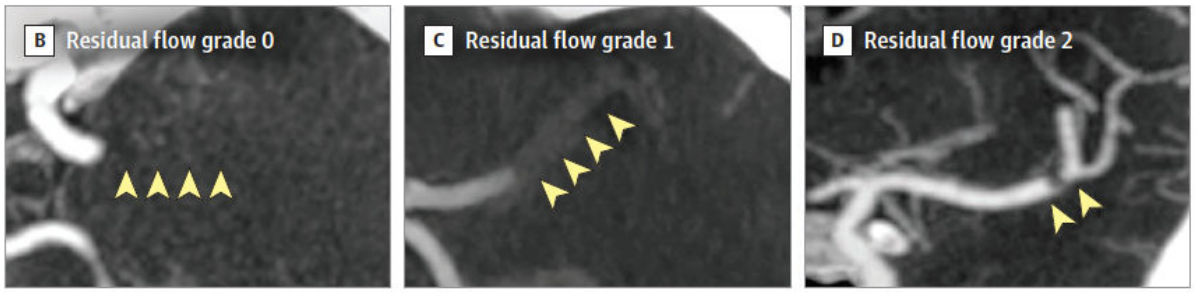

*Légende :* A : scanner sans injection avec reconstruction MIP, montrant l'hyperdensité spontanée intra-artérielle en M1 et M2. B : Segmentation semi-automatique de l'hyperdensité spontanée : application d'un seuil d'unité Hounsfield entre 50 et 100 dans la région d'intérêt sélectionnée manuellement. Le volume est ensuite automatiquement mesuré par le logiciel.

### *II.1.2.2 Perméabilité du thrombus*

La perméabilité du thrombus semble être un facteur prédictif important de recanalisation précoce après thrombolyse intraveineuse, selon les résultats de quatre études ayant évalué ce signe radiologique par angioscanner « classique » (**Figure 10**),[71,161] angioscanner dynamique,[131] ou scanner de perfusion.[77] L'hypothèse physiopathologique invoquée est une meilleure pénétration du rtPA au sein du thrombus, facilitant sa dissolution. Dans une étude récente sur un échantillon large, l'effet de la perméabilité du thrombus sur la recanalisation précoce était par ailleurs indépendant du clot burden score.[161]

En l'absence d'ARM injectée dans l'immense majorité des patients inclus, il n'a pas été possible d'évaluer la perméabilité du thrombus dans cette thèse. Il sera néanmoins envisageable d'étudier ce paramètre à terme dans notre cohorte, en utilisant la méthodologie décrite par Ahn *et al*. sur scanner de perfusion,[77] qui pourrait être reproduite sur IRM de perfusion.

**Figure 10.** Images illustrant la perméabilité du thrombus évaluée par angioscanner chez trois patients différents avec occlusion M1, d'après Menon *et al*.[161]



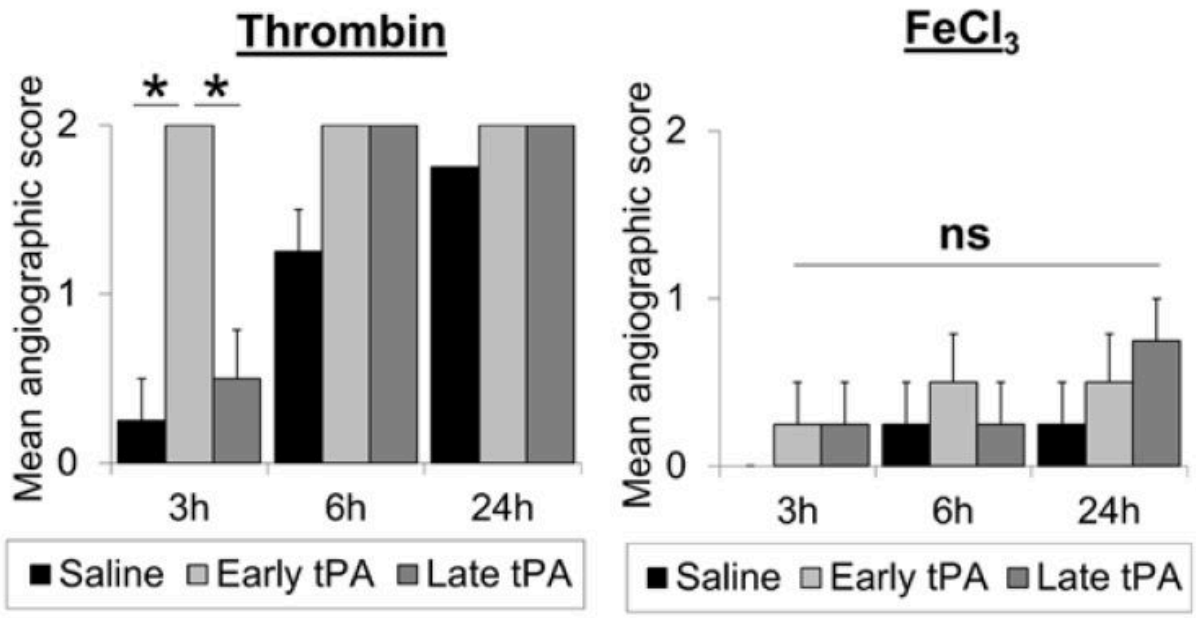

*Légende :* B : thrombus totalement occlusif (absence de flux résiduel au site du thrombus, coupe axiale). C : thrombus partiellement occlusif (minime flux résiduel au sein du thrombus, coupe axiale). D : thrombus non occlusif (flux résiduel au sein du thrombus, coupe coronale).

### *II.1.2.3 Composition du thrombus*

Les thrombi intracrâniens contiennent des proportions très variables en fibrine, plaquettes, globules rouges et globules blancs, et autres constituants (vWF et NETs).[46,47] Comme le rtPA n'est actif que sur la lyse de fibrine, il est hautement probable que la composition du thrombus soit associée à la probabilité de recanalisation post-thrombolyse.[50] La thrombectomie permet désormais d'accéder facilement aux thrombi, permettant leur analyse histologique et biochimique, et ouvre de ce fait un champ d'étude vaste et important.[46] Cependant, seuls les thrombi résistants au rtPA peuvent être récupérés et analysés, ce qui explique qu'il n'existe aucune donnée chez l'homme sur l'effet de la composition du thrombus sur la recanalisation précoce post-thrombolyse.[46] Une étude récente apporte néanmoins des informations intéressantes en analysant, chez des patients traités par rtPA intraveineux et transférés en thrombectomie, la composition des thrombi partiellement sensibles au rtPA (à savoir, avec réduction de leur taille entre l'imagerie pré-rtPA et l'artériographie) *vs*. ceux résistants au rtPA (à savoir, sans modification de la taille).[190] Elle montre que les thrombi sensibles au rtPA ont une proportion plus grande en globules rouges et plus faible en fibrine et plaquettes,[190] concordant avec des données précliniques (*cf.* exemple montré dans la

**Figure 11**).[50,191] Des études *in vitro* ou chez l'animal apportent d'autres informations intéressantes, montrant que la proportion de NETs,[47,48] ou la structure des polymères de fibrine modifiant les propriétés physiques du thrombus,[192,193] sont associés à la réponse fibrinolytique. Les études ayant analysé les thrombi intracrâniens humains (récupérés par thrombectomie) sont néanmoins très rares, ce qui mérite d'être approfondi à l'avenir avant d'envisager de tester de nouvelles thérapies intraveineuses.[47,48,190]

**Figure 11.** Effet de la composition du thrombus sur la recanalisation post-rtPA intraveineux dans un modèle murin d'accident ischémique cérébral, d'après Martinez de Lizzarondo *et al*.[50]




*Légende :* A gauche : Modèle murin d'AIC après injection *in situ* de thrombine, occasionnant des thrombi mixtes (fibrine et plaquettes). L'administration précoce ou tardive de rtPA (n=5 par groupe) entraine une recanalisation artérielle ('mean angiographic score' =2). A droite : Modèle murin d'AIC après application de FeCl3, occasionnant des thrombi purement plaquettaires. L'administration précoce ou tardive de rtPA (n=5 par groupe) n'entraine pas de recanalisation artérielle.

L'extrapolation de la composition du thrombus par ses caractéristiques sur l'imagerie pourrait permettre d'étudier indirectement le lien entre la composition du thrombus et la recanalisation post-thrombolyse. Les liens entre les caractéristiques des thrombi à l'imagerie et leur composition sont encore mal connus et semblent dépendre des paramètres d'imagerie, et nécessiteront d'être approfondis à l'avenir. Ces connaissances peuvent être résumées comme suit:

- Susceptibility vessel sign (SVS) : seules deux études ont étudié le lien entre la présence du SVS en T2* et la composition histologique de thrombi récupérés en thrombectomie, montrant une proportion plus importante en globules rouges et plus faible en plaquettes et fibrine en cas de SVS.[174,175] Cependant, une étude *in vitro* a récemment montré que les paramètres de séquence T2* influençaient significativement la

présence d'un SVS, indépendamment de la composition du thrombus,[182] remettant en question la pertinence de l'estimation de l'histologie du thrombus par cette séquence. Les résultats discordants des travaux ayant étudié l'effet de la présence du SVS sur la recanalisation post-thrombolyse (certains décrivant une association,[74,194] d'autres pas[55,174,180]) sont en ligne avec cette observation. Des études prospectives futures étudiant le lien entre la composition du thrombus extrapolée par les caractéristiques du SVS (visibilité, ou autres paramètres[178,195]) et la recanalisation précoce après thrombolyse intraveineuse sont néanmoins envisageables mais nécessiteront au préalable i) l'homogénéisation des paramètres T2* pour tous les patients inclus dans l'étude, et ii) l'étude de la corrélation entre la composition du SVS et sa visibilité avec les paramètres de T2* utilisés.

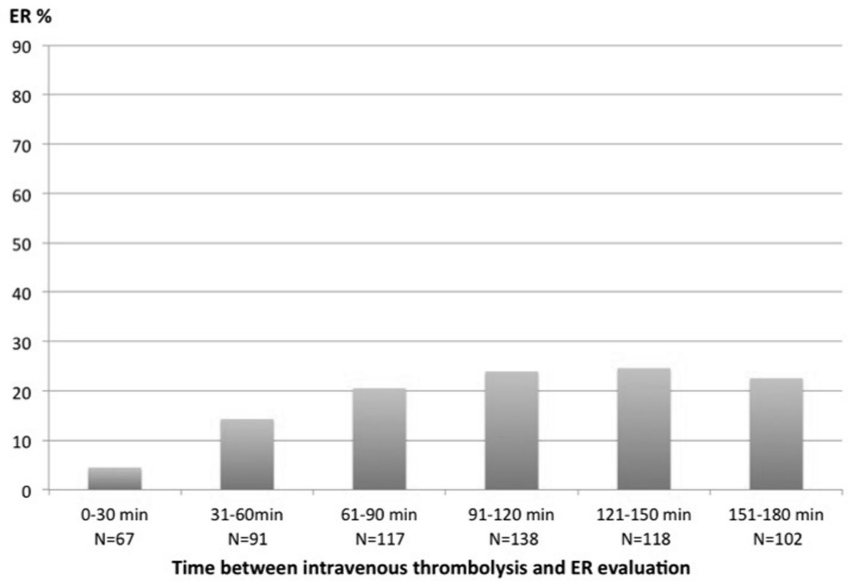
- Hyperdensité spontanée intra-artérielle au scanner: la présence d'une hyperdensité spontanée intra-artérielle est associée à une proportion plus importante de globules rouges,[46,196,197] mais pas de fibrine ni de plaquettes.[198,199] Une étude récente a rapporté une association entre la densité (en unités Hounsfield) de l'hyperdensité spontanée intra-artérielle et la proportion de fibrine et de globules rouges des thrombi récupérés par thrombectomie (plus la densité est élevée, plus la proportion de globules rouges est importante, et celle de fibrine faible),[197] mais ceci nécessite d'être confirmé dans d'autres cohortes. Une étude récente comprenant deux cohortes d'AIC avec occlusion proximale traités par thrombolyse intraveineuse, une prospective et l'autre rétrospective, a montré des résultats divergents sur l'effet de la densité de l'hyperdensité spontanée intra-artérielle sur la recanalisation précoce : une densité plus élevée (qui correspondrait d'après les données présentées ci-dessus à une proportion moindre de fibrine et plus grande de globules rouges) était associée à une moindre recanalisation dans la cohorte rétrospective, mais cette association n'était pas confirmée dans la cohorte prospective.[159] D'autres études prospectives sont donc nécessaires concernant cette problématique.

## II.2. Délai thrombolyse – thrombectomie

### II.2.1 Synthèse des résultats

Le délai entre le début de la thrombolyse intraveineuse et l'évaluation de la recanalisation est indépendamment associé à la survenue d'une recanalisation précoce dans la cohorte PREDICT-RECANAL, la probabilité de survenue de la recanalisation augmentant avec le temps. Cette association a été décrite très récemment dans deux autres études,[108,161] bien que dans Mueller *et al.* l'association disparaissait après ajustement sur les autres variables.[108] L'incidence de recanalisation ne semble pas linéaire : elle augmente rapidement au cours des 90 premières minutes suivant la thrombolyse intraveineuse, puis beaucoup plus lentement ensuite (*cf.* **Figure 12** ci-dessous, déjà présentée dans la partie 2). Cette observation s'explique par la demi-vie très courte du rtPA (6-7 min), celui ci-étant complètement éliminé au bout de 30-35min (5 demi-vies, soit ~90min après le début de la perfusion de rtPA qui dure 1 heure).

**Figure 12.** Incidence de la recanalisation précoce, en fonction du délai d'évaluation de celle-ci après le début de la thrombolyse intraveineuse, dans la cohorte PREDICT-RECANAL.



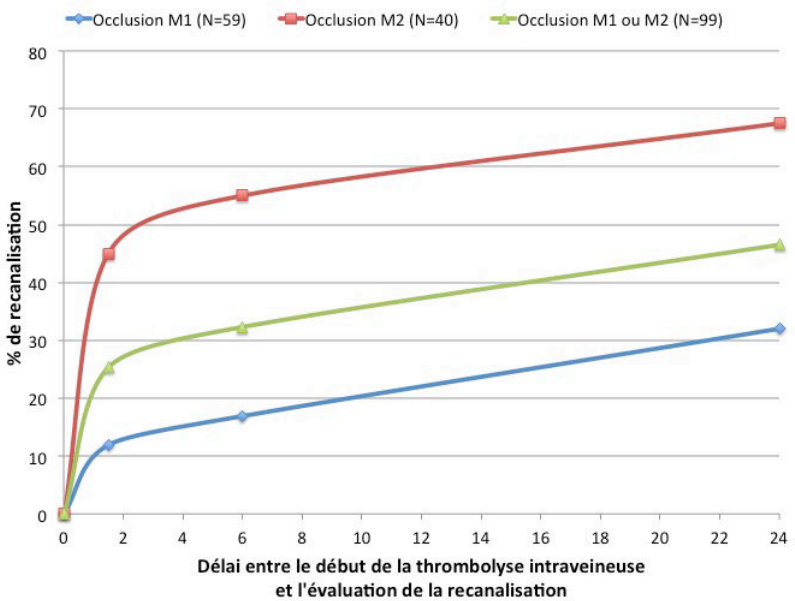

La lente augmentation du taux de recanalisation au delà des 90 premières minutes s'explique vraisemblablement par les recanalisations spontanées, liées à la fibrinolyse physiologique par le tPA endogène. En effet, comme indiqué dans le paragraphe I.2.1 page 129, quelques études ont montré que des recanalisations précoces surviennent en l'absence de traitement thrombolytique (Table 4, page 129).[130,160,161] Par ailleurs, Kim *et al.* ont récemment montré que, bien que la thrombolyse intraveineuse entrainait une recanalisation précoce chez une minorité de patients de leur cohorte (9,4% à 1h), le volume du thrombus (évalué par scanner sans injection en coupes fines avant et une heure après la thrombolyse) était réduit chez la majorité d'entre eux (80%).[200] La réduction du volume de thrombus par la thrombolyse intraveineuse pourrait faciliter la fibrinolyse naturelle par le tPA endogène.

### II.2.2 Limites

Les données issues de notre cohorte (ainsi que des deux articles récents mentionnés plus haut) concernant l'association entre délai d'évaluation post-thrombolyse et recanalisation sont limitées par le fait qu'elles ont été recueillies chez des patients différents. Il est en effet possible que certains facteurs aient pu influencer cette association : par exemple, l'incidence plus élevée de recanalisation chez les patients évalués tardivement pourrait être en partie liée au fait que les patients les moins sévères sont évalués moins rapidement après la thrombolyse. Seule l'évaluation séquentielle de la recanalisation post-thrombolyse selon un protocole longitudinal permet d'évaluer ce biais potentiel. Une étude présente ce type de données dans cohorte avec occlusion proximale, avec évaluation séquentielle de la recanalisation post-thrombolyse par echo-Doppler transcrânien (à 1h30, 6h et 24h après le début du rtPA)[90]: en accord avec nos données, elle montre que l'incidence de recanalisation augmente rapidement au cours des premières 90min suivant la thrombolyse, puis beaucoup plus lentement au cours des 22h qui suivent, quel que soit le site d'occlusion (**Figure 13**).

Tous les patients inclus dans la cohorte PREDICT-RECANAL étaient évalués pour la recanalisation dans les 3 heures suivant la thrombolyse, une évaluation plus tardive étant exceptionnelle dans les centres participant à l'étude (28 patients ont été exclus pour cette raison, soit 2.5% du total). Cette situation est cependant probablement moins exceptionnelle dans certaines régions du monde, et l'effet du délai thrombolyse-thrombectomie sur la recanalisation pourrait-être encore plus important si des patients avec évaluation plus tardive avaient été inclus. Cependant, l'odds-ratio ajusté de l'effet du rtPA sur la recanalisation précoce dans notre cohorte évaluant la recanalisation jusqu'à 3h est similaire à celui décrit dans l'étude de Menon et *al.*[161] qui évalue la recanalisation jusqu'à 6h après la thrombolyse (1.43 [IC95% 1.11-1.67] *vs.* 1.28 [1.18-1.38] pour chaque 30min supplémentaires, respectivement). Ceci semble logique compte-tenu de la très lente évolution du taux de recanalisation présente après 90minutes (Figure 13).

**Figure 13.** Incidence de recanalisation après thrombolyse intraveineuse en fonction du délai entre le début de la thrombolyse et l'évaluation de la recanalisation, dans la seule étude avec évaluation séquentielle de celle-ci par écho-Doppler transcrânien.[90]



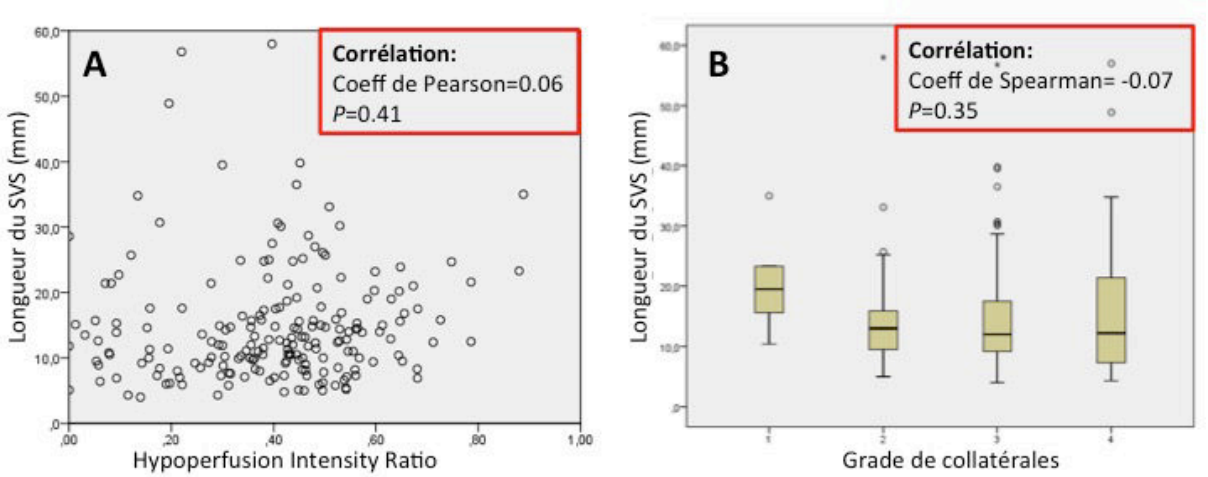
## II.3 Collatérales et perfusion

### II.3.1 Synthèse des résultats

La présence d'un bon réseau artériel collatéral ou d'une hypoperfusion cérébrale peu sévère – évaluée par l'*Hypoperfusion Intensity Ratio* (HIR) – sont associés de manière indépendante à la survenue d'une recanalisation précoce dans la sous-population de la cohorte PREDICT-RECANAL avec IRM de perfusion pré-thrombolyse. Cette observation est concordante avec les données d'études antérieures ayant montré une association entre bon réseau artériel collatéral et recanalisation précoce[70] ou à 24h,[139,140] ou entre la sévérité de l'hypoperfusion cérébrale et la recanalisation à 24h.[61,62] Cependant, aucune de ces études n'avait ajusté les analyses statistiques sur les caractéristiques du thrombus, ce qui en limite fortement les conclusions. Confortant nos résultats, Yoo *et al.* ont récemment montré une forte tendance à la significativité (*P*=0.056) entre la présence d'un bon réseau artériel collatéral évalué sur angioscanner et la recanalisation précoce dans une petite cohorte coréenne (n=78), après ajustement sur le volume du thrombus.[159]

Point important, nous n'avons pas constaté de corrélation entre la qualité du réseau artériel collatéral ou la sévérité de l'hypoperfusion cérébrale d'une part, et la longueur du thrombus d'autre part (**Figure 14**). Trois études ont étudié la corrélation entre la longueur du thrombus ou le clot burden score (mesurés en angioscanner non dynamique) et le grade de collatérales, montrant toutes une corrélation inverse (c'est-à-dire, de mauvaises collatérales sont associées à un thrombus plus long).[58,142,201] Cependant, l'utilisation de l'angioscanner non-dynamique pour mesurer le thrombus (ou le clot burden score) dans ces articles constitue en soi une limite majeure, car elle conduit à surestimer celle-ci en cas de mauvaises collatérales (*cf.* exemple sur la Figure 5, page 136).[56,155]

**Figure 14.** Etude de l'association entre sévérité de l'hypoperfusion (A) ou grade de collatérales (B) et longueur du SVS dans notre cohorte.

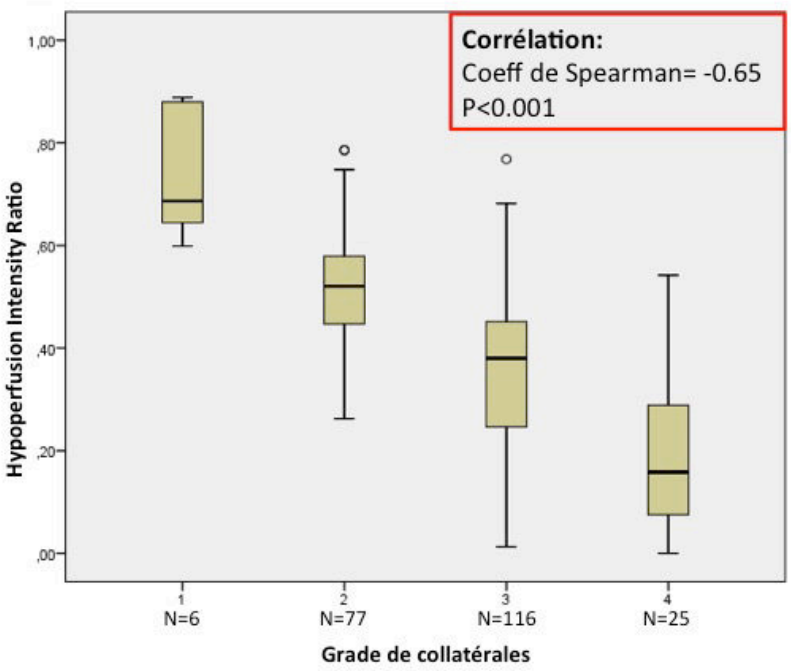



*Légende :* A : chaque point représente un patient. B: les boites indiquent l'écart interquartile; les lignes horizontales la médiane; les moustaches les 5è et 95è percentiles; et les points les valeurs extrêmes.

Deux hypothèses physiopathologiques principales sont invoquées pour expliquer l'association entre un bon réseau artériel collatéral et la recanalisation précoce après thrombolyse, bien qu'il n'existe que très peu d'arguments pour les étayer. Premièrement, la présence de bonnes collatérales pourrait permettre d'augmenter l'accessibilité du thrombolytique aux deux extrémités du thrombus. Deuxièmement, de bonnes collatérales pourraient majorer les contraintes de cisaillement à l'extrémité distale du thrombus, et favoriser ainsi sa dissolution.[139] En faveur de cette hypothèse, Zhang *et al.* ont montré que la rapidité (et non l'étendue) des collatérales était associée avec la recanalisation à 24h post-thrombolyse.[139] De fait, la recanalisation précoce était 2,5 fois plus fréquente en cas de collatérales de grade 4 en comparaison aux collatérales de grade 3 dans notre cohorte, également en faveur de ce mécanisme. En effet, les collatérales prennent en charge la totalité du territoire sylvien dans ces deux grades, mais elles sont plus rapides dans le grade 4 que dans le grade 3 (*cf.* Figure 3 et 4 du chapitre 2 de la partie 3, pages 97-98).

Deux hypothèses sont avancées pour expliquer l'association entre hypoperfusion moins sévère et recanalisation précoce. Premièrement, de par la présence d'un bon réseau artériel collatéral, via les mécanismes proposés ci-dessus. Il existe en effet une forte corrélation entre la collatéralité et le HIR,[136-138] comme confirmé dans notre cohorte (**Figure 15**). Deuxièmement, via la présence d'un thrombus partiellement perméable (*cf.* paragraphe II.1.2.2, page 139), car il est plausible en effet que la perméabilité du thrombus soit associée à la sévérité de l'hypoperfusion, bien qu'aucune étude n'ait à ce jour étudié cette association.

**Figure 15.** Corrélation entre grade de collatéralité et sévérité de l'hypoperfusion cérébrale dans notre cohorte.




*Légende :* B: les boites indiquent l'écart interquartile; les lignes horizontales la médiane; les moustaches les 5è et 95è percentiles; et les points les valeurs extrêmes.

### II.3.2 Limites et perspectives

Nos travaux sur la sévérité de l'hypoperfusion et la collatéralité présentent certaines limites. Premièrement, environ 40% des patients inclus dans les six centres participant à l'étude ont été exclus en raison de l'absence d'IRM de perfusion, ou d'une imagerie de qualité insuffisante, pouvant occasionner un biais de sélection. Nous n'avons cependant pas constaté de différence significative concernant les principales caractéristiques cliniques et radiologiques des patients inclus et exclus de l'étude. Il serait néanmoins idéal de confirmer ces résultats dans une population moins sélectionnée, par exemple en étudiant l'étendue des hypersignaux vasculaires visibles sur la séquence FLAIR (séquence disponible pour l'immense majorité des patients de l'étude). En effet, une étude récente de notre équipe a montré que l'étendue de ces hypersignaux vasculaires est fortement corrélée au HIR, et est donc un bon marqueur de la collatéralité.[202]

Deuxièmement, l'imagerie de la collatéralité et la sévérité de l'hypoperfusion ont été évalués à partir de la séquence de perfusion en IRM, méthode d'imagerie nettement moins répandue que le scanner. Il serait ainsi important de confirmer nos résultats sur des cohortes chez lesquelles la collatéralité a été évaluée par angioscanner dynamique (plus fiable que l'angioscanner standard),[203,204] et le HIR par scanner de perfusion.[205]

Enfin, notre cohorte était de taille relativement limitée, notamment l'effectif de patients avec recanalisation précoce était faible, et nos observations demandent à être confirmées dans de plus larges cohortes.

## II.4 Biomarqueurs de recanalisation

Dans cette thèse, nous nous sommes focalisés sur les facteurs vasculaires (caractéristiques morphologiques du thrombus, collatérales) et tissulaires (perfusion) associés à la recanalisation précoce. L'étude de l'association de biomarqueurs d'hémostase spécifiques à la recanalisation précoce pourrait aider à améliorer la compréhension des mécanismes physiopathologiques sous-tendant cette dernière, et de là à promouvoir le développement de nouvelles approches thérapeutiques.

### II.4.1 Inhibiteurs de la fibrinolyse

La mise en évidence d'un lien entre recanalisation précoce et les inhibiteurs de la fibrinolyse que sont alpha-2-antiplasmine, PAI-1 et TAFI serait un argument fort pour promouvoir la recherche sur l'administration de thérapies adjuvantes au rtPA visant à diminuer l'activité de ces inhibiteurs, et ainsi améliorer la recanalisation. Plusieurs études issues de deux cohortes espagnoles ont montré une association entre les inhibiteurs de la fibrinolyse et la survenue d'une recanalisation précoce après thrombolyse, mais cette dernière était associée à la sonothrombolyse, ce qui pourrait avoir affecté les résultats.[65-67] Par ailleurs, des facteurs confondants majeurs comme les caractéristiques du thrombus n'étaient pas prises en compte dans ces études.

### II.4.2 Autres biomarqueurs

Les NETs et le vWF (*cf.* Introduction) pourraient également jouer un rôle dans la physiopathologie de la recanalisation précoce post-thrombolyse, des données précliniques ayant montré que l'administration de DNAse (permettant la lyse des NETs) associée au rtPA, de N-Acetyl-cystéine[50] ou de protéase ADAMTS-13[49] (permettant de cliver le vWF) améliore la lyse du thrombus. Aucune étude chez l'homme n'a à ce jour étudié l'association entre le dosage biologique de ces marqueurs, avant l'administration du rtPA, et la fréquence de la recanalisation précoce.

Des travaux récents ont mis en évidence le rôle important des microvésicules dans la physiopathologie de l'hémostase et des accidents vasculaires cérébraux.[206,207] Les microvésicules sont des vésicules membranaires émises par les cellules activées, dont la détection en périphérie serait la signature d'un processus de souffrance ou d'apoptose cellulaire. De nombreuses études ont montré que toutes les cellules sont capables de produire des microvésicules, qui peuvent exercer un large spectre d'activités biologiques, la plus étudiée étant leur activité procoagulante.[206] Cependant, une activité fibrinolytique des microvésicules endothéliales a récemment été mise en évidence : ces microvésicules fibrinolytiques possèdent la capacité d'activer le plasminogène à leur surface, ce qui a été démontré *in vitro* et *in vivo* à la fois chez le témoin sain et dans différents contextes pathologiques.[208,209] Des données récentes ont permis de proposer un nouveau mécanisme de génération de plasmine nommé *cross-talk* fibrinolytique selon lequel le plasminogène porté par une surface (plaquettes, fibrine...) est spécifiquement activé par la pro-urokinase portée par les microvésicules fibrinolytiques.[210] Ainsi, dans certains microenvironnements, ces dernières pourraient compenser l'activité procoagulante des microvésicules circulantes totales. Ceci ouvre de nouvelles perspectives sur l'étude des microvésicules comme biomarqueurs spécifiques d'activation cellulaire et comme vecteurs d'agents fibrinolytiques. Il n'existe aucune donnée dans la littérature sur l'association entre microvésicules (totales ou fibrinolytiques) et la recanalisation après thrombolyse intraveineuse d'un AIC, mais cette piste semble intéressante à explorer car elle pourrait ouvrir de nouvelles perspectives thérapeutiques.

### II.4.3 Perspectives

Une étude multicentrique prospective collectant, en plus des données cliniques et radiologiques étudiées dans cette thèse, les biomarqueurs mentionnés ci-dessus est actuellement envisagée. Les données sur l'incidence et les facteurs prédictifs de recanalisation présentées plus haut permettent d'estimer de manière fiable le nombre de sujets nécessaires à inclure dans cette étude.

## III. Prédiction de la recanalisation précoce post-thrombolyse

Le dernier objectif de cette thèse était de créer et valider des scores de prédiction de recanalisation précoce après thrombolyse par rtPA, qui seraient utilisables en routine clinique et aideraient à la sélection des patients pour des essais randomisés. Aucune étude n'apporte actuellement ce type d'information.

### III.1 Scores FIRE-6 et FIRE-4

#### III.1.1 Synthèse des résultats

A partir des résultats des facteurs prédictifs associés de manière indépendante à la recanalisation précoce après thrombolyse dans la cohorte de dérivation de l'étude PREDICT-RECANAL, nous avons créé le score FIRE-6, comportant 3 items : 1) longueur du SVS : ≤7.0mm = 0pt, >7.0 et ≤10.0mm = 1pt, >10.0mm et ≤14.0mm = 3pts, >14.0mm = 4pts; 2) site d'occlusion: M1 distal ou M2 = 0pt, terminaison carotide ou M1 proximal = 1pt ; 3) paradigme de traitement: drip-and-ship = 0pt, mothership = 1pt. Il est important de préciser ici que le paradigme de traitement (mothership *vs.* drip-and-ship) étant très fortement corrélé au délai thrombolyse-évaluation de la recanalisation (délai significativement plus long pour les patients drip-and-ship *vs.* mothership), il était nécessaire de faire un choix entre ces deux variables pour figurer dans le score. Nous avons opté pour la première car elle est plus facilement utilisable en routine clinique. Il est en effet difficile en pratique de connaître à l'avance le délai entre la thrombolyse intraveineuse et l'artériographie, surtout en situation de drip-and-ship, plusieurs facteurs pouvant impacter celui-ci : délai d'arrivée du SAMU pour transport vers l'UNV de recours et temps de transport variant selon le trafic routier, notamment. Par ailleurs, la c-statistique du modèle multivariable incluant le paradigme de traitement est similaire à celle du modèle incluant le délai thrombolyse-artériographie, suggérant qu'il n'y a pas de perte d'information. Le score FIRE-6 permettait une prédiction précise de l'absence de recanalisation précoce dans la cohorte de dérivation, et présentait une excellente validité externe dans celle de validation (c-statistique= 0.854 et 0.888).

Le SVS étant parfois absent, et la valeur de longueur du thrombus mesuré en T2* pas nécessairement transposable au scanner (*cf.* paragraphe II.1.2.1, page 132), nous avons également créé un score prédictif excluant la longueur du SVS, à partir de l'analyse multivariable *ad-hoc*. Ce score est sur 4 points (FIRE-4) et comporte 3 items : 1) score NIHSS : ≤12 = 0pt, >12 = 1pt ; 2) site d'occlusion: M1 distal ou M2 = 0pt, M1 proximal = 1pt, terminaison carotide = 2pts; 3) paradigme de traitement: drip-and-ship = 0pt, mothership = 1pt. FIRE-4 permettait une prédiction moins précise de l'absence de recanalisation précoce que FIRE-6 dans les deux cohortes, mais celle-ci restait néanmoins très satisfaisante (c-statistique= 0.746 et 0.752, respectivement).

L'objectif des scores FIRE-4 et FIRE-6 était de déterminer de manière fiable i) les patients à très haute probabilité de recanalisation précoce post-thrombolyse, représentant les « transferts futiles » en thrombectomie, chez qui un essai thérapeutique comparant thrombolyse seule *vs.* bridging doit être envisagé; et ii) les patients à très haute probabilité de non-recanalisation précoce post-thrombolyse, chez qui un essai

testant bridging *vs.* thrombectomie seule doit être envisagé. En effet, dans l'optique d'une médecine personnalisée permettant de réduire les complications iatrogènes et les coûts matériels, humains et financiers, il serait utile de proposer un seul des deux traitements à chaque patient, en fonction des caractéristiques cliniques, biologiques et radiologiques individuelles.

Malheureusement, même le grade le plus bas (grade 0) de chacun des deux scores ne permet pas de prédire de manière suffisamment fiable la survenue d'une recanalisation : environ 20% des patients avec un FIRE-6 à 0 (à savoir, SVS≤7.0mm, occlusion M1 distale ou M2 et paradigme drip-and-ship) et 50% des patients avec un FIRE-4 à 0 (score NIHSS≤12, occlusion M1 distale ou M2 et paradigme drip-and-ship) ne présentent pas de recanalisation précoce, et peuvent en conséquence bénéficier d'une thrombectomie complémentaire. Ces scores ne semblent donc pas utiles pour réfuter un transfert en thrombectomie en routine clinique. Le taux néanmoins très élevé de recanalisation précoce en cas de FIRE-6 à 0 est concordant avec les résultats d'une analyse *post-hoc* de l'essai de thrombectomie THERAPY, montrant que plus le thrombus est court plus bénéfice du bridging (*vs.* thrombolyse intraveineuse seule) est faible; le bénéfice du bridging semblant même absent en cas de thrombus<10mm.[113] Il parait légitime d'après ces données d'envisager un essai randomisé comparant thrombolyse seule *vs.* bridging chez les patients avec un score FIRE-6 bas. Celui-ci semble cependant extrêmement difficile à mener, compte-tenu de la faible proportion de la population présentant un score FIRE-6 à 0 (~5% dans notre cohorte).

A l'inverse, les grades élevés de chacun des deux scores FIRE permettent de prédire de manière quasi-parfaite l'absence de recanalisation précoce après thrombolyse : un grade FIRE-6 ≥4 ou FIRE-4 ≥3, correspondant à une proportion importante de notre cohorte (~60% et ~30%, respectivement), ont une spécificité >90% pour prédire l'absence de recanalisation précoce. Ainsi, ces scores peuvent être utiles pour la sélection des patients dans des essais randomisés comparant thrombectomie seule *vs.* bridging. En effet, inclure une population non sélectionnée dans ce type d'essai semblerait trop radical – voire non éthique –, compte-tenu de l'incidence relativement importante de recanalisations précoces dans notre cohorte globale. Deux essais de ce type sont actuellement en cours, incluant uniquement des patients mothership avec occlusion M1 ou de la terminaison-carotide dans la première (SWIFT DIRECT : NCT03192332), population dans laquelle l'incidence de recanalisation précoce est de 7% (27/361) dans notre cohorte ; et des patients mothership avec occlusion M2, M1 ou de la terminaison-carotide dans la seconde (MR CLEAN NO-IV), population dans laquelle l'incidence de recanalisation précoce est de 11% (50/451) dans notre cohorte. Il est important de préciser que, compte-tenu des bénéfices potentiels de la thrombolyse intraveineuse en dehors de la recanalisation artérielle (amélioration de la microcirculation après thrombectomie, diminution du risque d'embolie dans un nouveau territoire ou facilitation du geste de thrombectomie),[32,114,115,163] sursoir à la thrombolyse intraveineuse pourrait être délétère y compris chez des patients avec score FIRE élevé, et ne doit pas être envisagé en routine clinique sur la base de nos données.

### III.1.2 Limites et perspectives

Comme mentionné dans le paragraphe II.1.2.1 de la Discussion (page 132), en raison de la surestimation de la longueur du thrombus par le SVS, les seuils décrits dans nos travaux ne sont pas nécessairement transposables à d'autres méthodes d'imagerie non invasives, comme le scanner. Ceci limite la généralisation du score FIRE-6 aux patients avec scanner, qui est la méthode d'imagerie la plus répandue dans de nombreux pays. Il serait ainsi important à l'avenir de tester ce score sur une population bénéficiant du scanner et de l'angioscanner.

Nos scores n'incluent pas le grade de collatérales ou la sévérité de l'hypoperfusion, deux marqueurs indépendant de la survenue d'une recanalisation précoce (*cf.* paragraphe II.3, page 145). L'inclusion de ces variables pourrait améliorer encore la prédiction de la recanalisation, et éventuellement aider à réfuter un transfert en thrombectomie si le profil du patient rend très probable la survenue d'une recanalisation. Ceci est désormais envisageable grâce à la commercialisation de logiciels de post-traitements de données de perfusion semi-automatisés, rapides et fiables,[135,137,143] dont l'utilisation dans un contexte d'urgence est possible et compatible avec une prise de décision en temps réel. Dans notre cohorte, l'IRM de perfusion n'a été réalisée que chez une minorité de patients, rendant irréaliste l'intégration de ces variables dans nos scores et leur validation externe. Compte tenu des données récentes sur l'utilité en routine clinique de l'imagerie de perfusion pour la prise de décision de thrombectomie[127,128] ou la sélection des patients tirant le plus grand bénéfice du traitement endovasculaire,[124,125,205] il est probable que l'imagerie de perfusion cérébrale sera plus largement utilisée à l'avenir, ce qui permet d'envisager à moyen terme la création d'un score intégrant les collatérales et/ou la sévérité de l'hypoperfusion.

## III.2 Déficit neurologique mineur

### III.2.1 Synthèse des résultats

Dans cette sous-étude de la cohorte PREDICT-RECANAL incluant uniquement les patients avec un score NIHSS <6, nous avons montré que la longueur du SVS est la seule variable associée de manière indépendante à la recanalisation précoce. Le seuil de 9mm a une sensibilité et une spécificité élevées pour prédire l'absence de recanalisation, respectivement de 67.8% et 84.6%. Cette donnée est importante car compte-tenu des incertitudes sur le traitement optimal des patients avec déficit mineur et occlusion proximale,[27] des études randomisées comparant bridging *vs.* thrombolyse seule sont aujourd'hui nécessaires. Cependant, compte-tenu du déficit mineur et du taux important de recanalisation précoce post-thrombolyse dans cette population (34% dans notre cohorte), ces études devront inclure un nombre considérable de patients pour espérer mettre en évidence une éventuelle supériorité du bridging, ce qui représente un véritable défi compte-tenu de la rareté de cette situation clinique. Inclure uniquement les patients à haut risque de non recanalisation – et par conséquent présentant un plus fort risque d'aggravation clinique précoce et de mauvais pronostic fonctionnel[211,212] –, par exemple ceux avec SVS>9mm (représentant 50% de notre population), augmenterait l'importance du bénéfice clinique attendu, et réduirait ainsi le nombre de patients à inclure pour montrer une différence significative.

### III.2.1 Limites et perspectives

Cette étude a inclut uniquement les patients adressés en thrombectomie. Ce traitement n'étant actuellement pas formellement recommandé dans ce cas de figure, il est probable qu'une proportion significative de ces patients qui se sont présentés initialement dans les centres participants n'a pas été incluse dans l'étude. Ainsi, l'extrapolation de nos résultats se doit d'être prudente. Par ailleurs, bien que notre effectif de patients représentant cette population relativement rare soit l'un des plus grands de la littérature, il reste de taille modeste en termes absolus. Il est ainsi possible que certaines associations n'aient pas été détectées en raison du manque de puissance, notamment le site d'occlusion artérielle ou le paradigme de traitement.

Enfin, comme pour le score FIRE-6, en raison de la surestimation de la longueur du thrombus par le SVS le seuil de 9mm n'est pas nécessairement transposable aux thrombi évalués par scanner ou angioscanner, limitant sa généralisation. Il serait ainsi important à l'avenir de confirmer cette donnée sur une population étudiée au moyen du scanner ou de l'angioscanner.

## IV. Tenecteplase : nouveau thrombolytique avant transfert en thrombectomie ?

### IV.1 Synthèse des résultats

L'essai randomisé de phase IIb EXTEND-IA TNK, publié début 2018, a montré une incidence deux fois plus élevé de recanalisation précoce pré-thrombectomie après thrombolyse intraveineuse par tenecteplase 0.25mg/kg en comparaison à l'alteplase 0.9mg/kg.[116] Cependant, la majorité des patients de cette étude était traitée selon le paradigme mothership, à savoir avec un délai thrombolyse-thrombectomie très court. Dans la dernière partie de cette thèse, l'incidence de recanalisation précoce pré-thrombectomie après thrombolyse par tenecteplase 0.25mg/kg dans une UNV française sans possibilité de thrombectomie a été comparée à celle obtenue après alteplase 0.9mg/kg (cohorte PREDICT-RECANAL) dans le sous-groupe de patients traités en drip-and-ship (à savoir, avec un délai thrombolyse thrombectomie nettement plus long que dans EXTEND-IA TNK), la situation actuellement la plus fréquente en routine clinique. Contrairement à EXTEND-IA TNK, le taux de recanalisation précoce était similaire dans le groupe tenecteplase : 21.4% *vs.* alteplase : 18.3%.

En fait, le taux de recanalisation après tenecteplase dans notre cohorte était similaire à celui observé dans l'étude EXTEND-IA TNK (21 *vs.* 22%, respectivement), mais celui après alteplase était nettement plus élevé (18 *vs.* 10%, respectivement).[116] Comme mentionné plus haut (paragraphe I.1 page 127 et Figure 3 page 128), la différence importante de paradigme de traitement entre les deux études – 75% mothership dans EXTEND-IA TNK *vs.* 100% drip-and-ship dans notre cohorte, occasionnant un délai thrombolyse-artériographie nettement plus long dans notre cohorte (56min *vs*. 93min) –, rend compte de cette différence de taux de recanalisation après alteplase entre les deux études. L'évolution temporelle de la recanalisation après tenecteplase est inconnue mais il est probable que, compte-tenu de son administration en bolus, celle-ci survienne très précocement suite à son administration. Nos résultats, associés à ceux d'EXTEND-IA TNK, suggèrent ainsi que bien que le taux de recanalisation pré-thrombectomie soit similaire avec les deux thrombolytiques chez des patients drip-and-ship, celle-ci surviendrait plus précocement après tenecteplase. Une étude pré-clinique sur un modèle de thrombose carotide chez le lapin a montré que la recanalisation après tenecteplase survenait plus précocement qu'après alteplase, renforçant notre hypothèse.[36] Si cette hypothèse se confirme dans d'autres études, les conséquences cliniques en seraient importantes compte-tenu de la relation forte entre le délai de reperfusion et le pronostic fonctionnel.[10] Dans notre étude, il n'existait cependant pas de différence significative entre les deux groupes pour le handicap à 3 mois. Ceci pourrait s'expliquer par le fait que la différence supposée de délai de survenue de la recanalisation entre les deux thrombolytiques (survenant chez seulement 1 patient sur 5 en moyenne) soit trop faible pour entrainer une différence sur le score de Rankin à l'échelle du groupe entier. Dans EXTEND-IA TNK, il existait cependant une différence significative de handicap fonctionnel entre les deux groupes, en faveur de la tenecteplase.[116]

**IV.2 Limites et perspectives**

Bien que nous nous soyons efforcés, à l'aide d'un score de propension, de limiter au mieux les principaux facteurs de confusion connus, il reste envisageable que des facteurs de confusion inconnus, notamment liés au fait que les patients étaient pris en charge dans des centres différents, aient biaisé nos résultats.

Les résultats d'EXTEND-IA TNK sont très encourageants et doivent conduire à la réalisation de nouveaux essais de phase III comparant la tenecteplase à l'alteplase avant thrombectomie, utilisant cette fois un critère de jugement principal clinique (score de Rankin modifié à 3 mois). Des essais de phase III sont actuellement en cours chez des patients sans occlusion proximale (TEMPO-2 : NCT02398656 et ATTEST-2 : NCT02814409), tandis qu'un essai de phase II compare l'effet de deux doses différentes de tenecteplase (0.25 *vs.* 0.4mg/kg) en cas d'occlusion proximale, sur l'incidence de recanalisation avant thrombectomie (EXTEND-IA TNK part 2 : NCT03340493).

# Conclusions

Malgré les limites discutées en détail ci-dessus, ce travail de thèse a montré que l'incidence de recanalisation précoce post-thrombolyse intraveineuse dans une population d'accidents ischémiques cérébraux avec occlusion proximale adressée pour thrombectomie est relativement importante, survenant en moyenne chez environ 1 patient sur 5. De plus, nous avons montré que la localisation du thrombus dans l'arbre artériel, sa longueur, le délai entre la thrombolyse et l'évaluation de la recanalisation (équivalent au paradigme de traitement mothership *vs.* drip-and-ship) et la qualité du réseau artériel collatéral ou la sévérité de l'hypoperfusion cérébrale, sont associés de manière indépendante à la survenue d'une recanalisation précoce. Ces données nouvelles permettent d'améliorer notre compréhension des mécanismes physiopathologiques de la recanalisation post-rtPA. Nous avons également montré qu'un score prédictif combinant les trois premières variables permet de prédire l'absence de recanalisation avec une très grande spécificité, mais non la survenue d'une recanalisation. Ce score devrait aider à la sélection des patients dans des essais randomisés comparant bridging *vs.* thrombectomie seule. Par ailleurs, nous avons observé que la longueur du thrombus est le seul facteur associé à la recanalisation dans notre population d'AIC avec déficit mineur, et le seuil de 9mm permet de prédire l'absence de recanalisation avec un bon rapport sensibilité/spécificité, ce qui pourrait aider au dessin d'essais randomisés testant thrombolyse intraveineuse seule *vs.* bridging dans cette population pour laquelle le traitement optimal est incertain. Enfin, contrairement aux résultats de l'essai de phase II EXTEND-IA TNK montrant une incidence deux fois plus élevée de recanalisation précoce pré-thrombectomie après thrombolyse par tenecteplase 0.25mg/kg *vs.* alteplase 0.9mg/kg dans une population majoritairement mothership, l'incidence de recanalisation était dans notre étude similaire dans une population drip-and-ship, suggérant que celle-ci survient plus précocement après tenecteplase, ce qui pourrait avoir des conséquences cliniques importantes.

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# Annexes

**Annexe 1.** Version publiée du manuscrit « Incidence and predictors of early recanalization following IV thrombolysis. A systematic review and Meta-Analysis. » **Seners P**, Turc G, Maïer B, Oppenheim C, Mas JL, Baron JC. Stroke 2016 Sep;47(9):2409-12.

**Annexe 2.** Version « lettre à l'éditeur » de l'étude sur la tenecteplase présentée en partie 5, telle que acceptée dans le *Journal of Stroke*.

**Annexe 3.** Version publiée de la lettre à l'éditeur « Mechanical Thrombectomy After Intravenous Thrombolysis vs Mechanical Thrombectomy Alone in Acute Stroke. » **Seners P**, Oppenheim C, Baron JC. *JAMA Neurol*. 2017;74:1014-1015

Annexe 1

# Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis

## A Systematic Review and Meta-Analysis

Pierre Seners, MD*; Guillaume Turc, PhD*; Benjamin Maïer, MD; Jean-Louis Mas, MD; Catherine Oppenheim, PhD; Jean-Claude Baron, ScD

***Background and Purpose***—After the demonstration of efficacy of bridging therapy, reliably predicting early recanalization (ER; ≤3 hours after start of intravenous thrombolysis) would be essential to limit futile, resource-consuming, interhospital transfers. We present the first systematic review on the incidence and predictors of ER after intravenous thrombolysis alone.

***Methods***—We systematically searched for studies including patients solely treated by intravenous thrombolysis that reported incidence of ER and its association with baseline variables. Using meta-analyses, we estimated pooled incidence of ER, including according to occlusion site, and summarized the available evidence regarding predictors of no-ER.

***Results***—We identified 26 studies that together included 2063 patients. The overall incidence of partial or complete ER was 33% (95% confidence interval, 27–40). It varied according to occlusion site: 52% (39–64) for distal middle cerebral artery, 35% (28–42) for proximal middle cerebral artery, 13% (6–22) for intracranial carotid artery, and 13% (0–35) for basilar occlusion. Corresponding rates for complete ER were 38% (22–54), 21% (15–29), 4% (1–8), and 4% (0–22), respectively. Proximal occlusion and higher National Institute of Health Stroke Scale were the most consistent no-ER predictors. Other factors, such as long or totally occlusive thrombus and poor collateral circulation, emerged as potential predictors but will need confirmation.

***Conclusion***—The overall incidence of ER after intravenous thrombolysis is substantial, highlighting the importance of reliably predicting ER to limit futile, interhospital transfers. Incidence of no-ER is particularly high for proximal occlusion and severe strokes. Given the scarcity of published data, further studies are needed to improve no-ER prediction accuracy. **(*Stroke*. 2016;47:2409-2412. DOI: 10.1161/STROKEAHA.116.014181.)**

**Key Words:** endovascular procedures ■ fibrinolysis ■ incidence ■ meta-analysis ■ stroke ■ thrombectomy



Recent randomized trials demonstrated the superiority of bridging therapy (mechanical thrombectomy [MT] added on intravenous thrombolysis [IVT]) compared with IVT alone for the treatment of acute stroke because of large artery occlusion.[1] However, endovascular procedures can currently be provided in comprehensive stroke centers only. Therefore, candidates for MT admitted to primary stroke centers or general hospitals should urgently be transferred after initiation of IVT, and futile, interhospital transfers (ie, patients who ultimately do not undergo MT) because of early recanalization (ER) are as high as 30%.[2] Consequently, it is essential to improve no-ER prediction based on admission data to limit futile, resource-consuming, interhospital transfers. To date, 2 published meta-analyses have provided partial data on recanalization rates after IVT, but the first merged early- and later-assessed recanalization,[3] whereas the second included only sonothrombolysis trials.[4] Moreover, neither provided information on incidence of ER according to site of occlusion, nor on ER predictors.

We therefore performed a systematic review and meta-analysis of the incidence and predictors of ER after IVT.

## Methods

The article was prepared in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines. Studies published between January 1,1990 and January 27, 2016 were eligible for review if they: (1) enrolled ≥15 IVT-treated stroke patients; (2) confirmed the presence of arterial occlusion before IVT; and (3) reported data on incidence or predictors of ER. ER was defined as occurring ≤3 hours after initiation of IVT, regardless of the imaging method used. Details on search strategy, study exclusion criteria, data extraction, assessment of study quality, and definition of complete and partial ER are provided in the Methods section and Tables I through III in the online-only Data Supplement.

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*Drs Seners and Turc contributed equally.

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### Statistical Analysis

Estimates of proportions (incidence) of ER were pooled after Freeman–Tukey double arcsine method and then back-transformed onto the original scale. Given the heterogeneity regarding modalities and timing of recanalization assessment across studies, we computed random-effects pooled ER incidences. The methods used to summarize available data on no-ER predictors are described in the Methods section in the online-only Data Supplement. A meta-analysis was performed only for variables assessed in ≥4 studies.

## Results

Twenty-six studies were included in this review (Figure I in the online-only Data Supplement). The list and characteristics of the included studies (including imaging method and scale used) are summarized in Table IV in the online-only Data Supplement.

### Incidence of ER

The overall incidence of partial or complete ER was 33% (95% confidence interval, 27–40) and that of complete ER was 20% (15–26; Figure 1). The incidence of partial or complete ER was 52% (39–64) for distal middle cerebral artery (M2–M3) occlusion, 35% (28–42) for proximal middle cerebral artery (M1) occlusion, 13% (6–22) for intracranial carotid artery occlusion, and 13% (0–35) for basilar artery occlusion. Corresponding incidence for complete ER were 38% (22–54), 21% (15–29), 4% (1–8), and 4% (0–22), respectively (Figure 1). The details of each meta-analysis are presented in Figures II though XI in the online-only Data Supplement. Incidence of partial or complete ER was significantly lower in studies using digital subtraction angiography compared with other methods, but complete ER rate was similar across imaging modalities (Results section in the online-only Data Supplement). Funnel plots did not suggest publication bias (Figure XII in the online-only Data Supplement).

### No-ER Predictors

For anterior circulation strokes, proximal occlusion (M1 or intracranial carotid artery) was a strong predictor of no-ER (OR=2.09; 95% confidence interval, 1.50–2.94; Figure 2). Higher admission National Institute of Health Stroke Scale (NIHSS) score was the only clinical variable associated with no-ER (standardized mean difference=0.20; 95% confidence interval, 0.01–0.39; Figure 2).

The results of the systematic review regarding no-ER predictors assessed in <4 studies are presented in Table and Table VI in the online-only Data Supplement. Variables associated with no-ER were poor arterial collaterals on arteriography, M1 susceptibility vessel sign on T2* magnetic resonance, clot located <10 mm from middle cerebral artery origin, long thrombus, no residual flow within the clot on computed tomography angiography (CTA); no anterograde flow beyond the clot on 4-dimensional CTA; and low HDL-cholesterol.

## Discussion

Here we focused on the incidence of ER after IVT and its predictors, with the objective to assist patient triaging for MT.

### Incidence of ER

Overall, partial or complete ER occurred in 33%, and complete ER in 20% of patients. We found lower ER rates in intracranial carotid artery than M1, and even more so than M2–M3 occlusions. The overall rate of ER after IVT is consistent with the reported rate of futile, interhospital transfers for MT,[2] with the majority of the latter representing ER.

### Predictors of No-ER

Proximal occlusion site was the strongest no-ER predictor. Moreover, thrombus location within 10 mm from middle cerebral artery origin predicted higher no-ER rate.[6]

Several other potential radiological predictors of no-ER emerge from this systematic review but have been assessed in few studies. First, poor collaterals was predictive of no-ER in one angiography study,[5] consistent with another study reporting that magnetic resonance perfusion–based collaterals influenced recanalization rate 24 hours after IVT.[12] Good collaterals would facilitate retrograde access of the thrombolytic agent to the thrombus. Second, long thrombi, intuitively more resistant to IVT, seem predictive of no-ER.[6–8] Last, completely

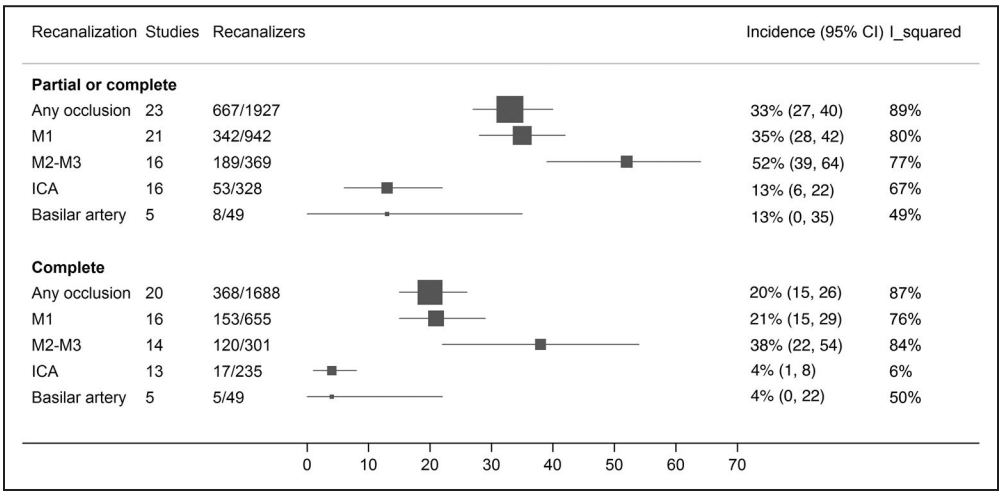


**Figure 1.** Incidence of early recanalization (ER) according to occlusion site and degree of recanalization. Studies: number of studies included; recanalizers: number of patients with ER/total number. CI indicates confidence interval; and ICA, intracranial carotid artery.

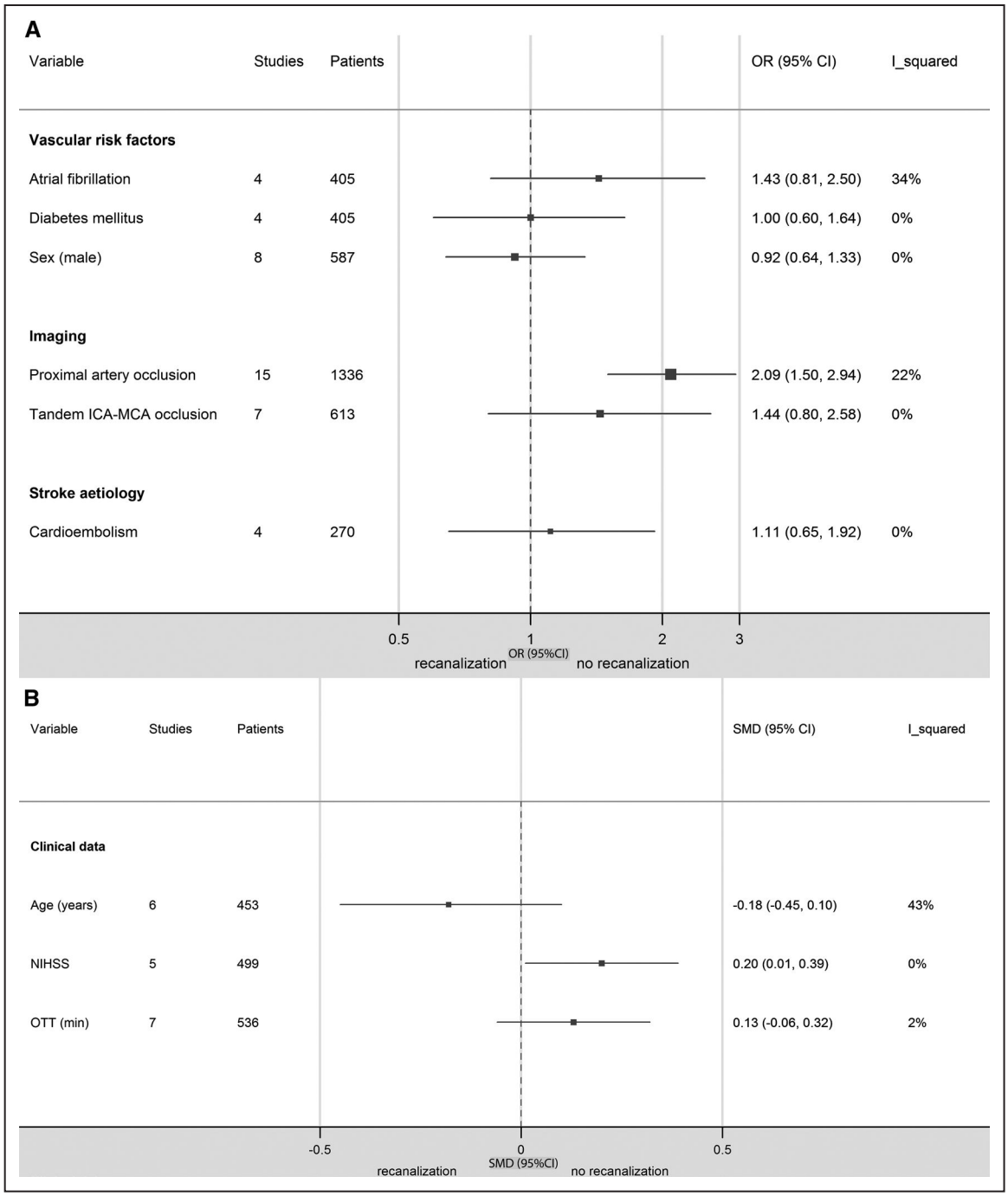


**Figure 2.** Summary of odds ratios and standardized mean differences for the associations between no-ER and (**A**) categorical and (**B**) continuous baseline variables measured in intravenous thrombolysis (IVT)–treated patients in ≥4 studies. CI indicates confidence interval; ER, early recanalization; ICA, intracranial carotid artery; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; and SMD, standardized mean difference.

occlusive thrombi seem strongly associated with no ER,[6,10] as studied using standard CTA[6] or 4-dimensional CTA.[10] This association was also reported using a novel computed tomography perfusion–based evaluation of thrombus permeability, although ER was assessed at slightly later time points.[13] All the above points to the crucial role advanced imaging may hold in predicting no-ER after IVT. For instance, collaterals can now be evaluated using multiphase CTA, computed tomography perfusion, perfusion magnetic resonance imaging, or conventional magnetic resonance imaging.[14] Among clinical factors, higher NIHSS was the only no-ER predictor. However, this may reflect the strong association between NIHSS and occlusion site.

The present meta-analysis has several limitations. First, a substantial heterogeneity between studies regarding ER incidence was observed. This can be explained by selection bias in digital subtraction angiography studies and variable recanalization scales, time of baseline, and post-IVT imaging among

**Table. Predictors of No-ER Assessed in <4 Studies**

| Predictor | Number of Patients | OR (CI 95%) or *P* Value |
|---|---|---|
| Poor collaterals[5] | 32 | 5.33 (1.07–26.61)* |
| Long thrombus[6–8] | 228[6] | *P*<0.001 |
| | 96[7] | *P*=0.01 |
| | 41[8] | *P*=0.15 |
| Thrombus location <10 mm from MCA origin[6] | 117 | 3.06 (1.22–7.69)* |
| M1 susceptibility vessel sign on T2*-MR[9] | 132 | 7.16 (1.76–29.17)† |
| No anterograde blood flow beyond the thrombus on 4D-CTA[10] | 67 | 13.25 (2.08–84.52)* |
| No residual blood flow in thrombus on CTA[6] | 228 | 6.25 (3.03–14.29)* |
| Low HDL cholesterol[11] | 70 | *P*=0.004† |

CI indicates confidence interval; CTA, computed tomography angiography; ER, early recanalization; HDL, high-density lipoprotein; MCA, middle cerebral artery; MR, magnetic resonance; and OR, odds ratio.

*Calculated from raw data.

†Multivariable analysis.

studies. Moreover, the accuracy of recanalization assessment may vary among imaging methods. Second, because the majority of patients included in this systematic review had M1 occlusion, our findings regarding ER prediction mainly apply to this stroke subtype. Last, this systematic review was limited by the scarce data available for the majority of admission variables, preventing strong conclusions.

In conclusion, the incidence of ER after IVT is substantial, pointing to the importance of reliably predicting it to avoid futile interhospital transfers. Although proximal occlusion site was confirmed as the strongest no-ER predictor, this systematic review identified additional potential predictors from advanced imaging that may in the future improve ER prediction. Further studies are needed to confirm the latter and identify novel markers, aiming toward improved patient triaging for bridging procedures.

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## Disclosures

None.

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# Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis: A Systematic Review and Meta-Analysis

Pierre Seners, Guillaume Turc, Benjamin Maïer, Jean-Louis Mas, Catherine Oppenheim and Jean-Claude Baron

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**SUPPLEMENTAL MATERIAL**

## Supplemental Methods

The manuscript was prepared in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines.[1]

*Selection Criteria and Definition of ER*

We did not include studies that combined intravenous thrombolysis (IVT) with other therapeutic interventions, such as sonothrombolysis, considering their potential effects on recanalization rate.[2] Studies on bridging therapy were included only if the vascular status before the endovascular procedure was available, which ensured that early recanalization (ER) was solely due to IVT.

ER was defined as occurring ≤3hrs after initiation of IVT, which seems a reasonable upper limit to start endovascular procedures following IVT. ER was considered as *complete* if reaching grade 4-5 on the Thrombolysis in Brain Infarction (TIBI) scale, 3 on the Arterial Occlusive Lesion (AOL) and Thrombolysis in Myocardial Infarction (TIMI) scales, 2b-3 on the Thrombolysis in Cerebral Infarction (TICI) or modified-TICI (mTICI) scales, or 3-4 on the Mori scale (**Supplemental Table I**).[3] We also considered a second category combining *partial or complete* recanalization, defined as grade ≥2 on AOL, TIMI, TICI, mTICI, or Mori's scales, or as improvement in flow signal by ≥1 TIBI grade.

*Search Strategy*

We searched Medline and Embase for articles published between 1/01/1990 and 27/01/2016, using the terms detailed in **Supplemental Table II**. We also hand-searched the reference lists of all included articles, any relevant review articles, and books of abstracts from recent international stroke conferences. A first reviewer was responsible for the entire selection process. From a random sample (10%) of all articles, a second reviewer assessed the reproducibility of the process. When two or more articles from the same group used an expanded cohort, we included only the article reporting the largest sample.

*Data Extraction and Evaluation of Study Quality*

Using a standardized form (**Supplemental table III**), two readers independently extracted data from selected articles. All discrepancies were resolved by consensus. Whenever appropriate, authors were contacted to obtain further information. For the three studies that assessed the incidence of ER at two different timepoints after IVT in the same cohort, only the data pertaining to 3hrs were used.

The quality of included studies was scored using items derived from the STROBE checklist (**Supplemental Table IV**).[4]

*Statistical Analysis*

Incidence of ER

Estimates of proportions (incidences) of ER were pooled after Freeman–Tukey double arcsine method and then back transformed onto the original scale.[5] 95% confidence intervals (CIs) around these estimates were calculated using the Wilson method. Heterogeneity across studies was assessed using Cochran's Q (reported as a P-value) and the $I^2$ statistics. Given the heterogeneity regarding the modalities and timing of recanalization assessment across studies, we decided *a priori* to compute random-effects rather than fixed-effect pooled incidences of ER. Potential sources of heterogeneity were investigated by stratifying studies according to potentially relevant variables, such as the dose of alteplase or the imaging method used for recanalization assessment, and by meta-regression. Publication bias was investigated using funnel plots.

Associations between baseline variables and no-ER

Given the heterogeneity regarding the modalities of recanalization assessment across studies, we decided to compute random-effects rather than fixed-effect meta-analysis of potential predictors of no-ER. However, because the between-study heterogeneity may only be accurately estimated in a random-effects model including more than 3 studies[6], we performed a meta-analysis for potential predictors assessed only in case at least 4 studies were available. For each binary predictor assessed in at least 4 studies, crude Odds Ratios (OR) and 95%CI were recorded or calculated in each study, and pooled as a global OR (95%CI) in a random-effects meta-analysis. For each continuous predictor assessed in at least 4 studies, mean, standard deviation and sample size were recorded in each study, and summarized as pooled standardized mean difference (SMD) and its 95%CI in a random-effects meta-analysis. Statistical analysis and plots were done using STATA 11.0 (Statacorp) and SAS 9.4 (SAS Inc).

## Supplemental Results

*Incidence of ER according to imaging modality*

Analysis of ER incidence according to imaging modality (DSA *vs* others) was only performed for M1 occlusions because the other subgroups were too small. Incidence of *partial or complete* ER was significantly lower in studies using DSA compared with other methods (27%, 95%CI 20-35, $I^2$=69% *vs* 46%, 95%CI 35-57, $I^2$=75%, respectively; P=0.01). However, *complete* ER rate was similar (18%, 95%CI 10-28 and 25%, 95%CI 14-37, respectively; P=0.46).

*Incidence of ER according to alteplase dose*

Most studies used alteplase at the dose of 0.9 mg/kg, except 6 using the 0.6 mg/kg dose, and one using a fixed dose of 100 mg. Analysis of ER incidence according to alteplase dose was feasible for M1 occlusions only. Incidence of *partial or complete* ER was similar for the two doses, namely 34% (95%CI 22-47, $I^2$=86%) and 38% (95%CI 25-51, $I^2$=73%) for 0.9mg/kg and 0.6mg/kg, respectively (P=0.65). The results were similar for *complete* ER: 22% (95%CI 12-33) and 23% (95%CI 13-35), respectively (P=0.88).

**Supplemental Table I:** Recanalization scales used in the included studies.

| Scale | Details |
|---|---|
| **TIMI**[7] | **0:** No perfusion<br>**1:** Perfusion past the initial occlusion, but no distal branch filling<br>**2:** Perfusion with incomplete or slow distal branch filling<br>**3:** Full perfusion with filling of all distal branches, including M3-4 |
| **TICI**[8] | **0:** No Perfusion (No antegrade flow beyond the point of occlusion)<br>**1:** Penetration With Minimal Perfusion (The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run)<br>**2:** Partial Perfusion (The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, eg, the opposite cerebral artery or the arterial bed proximal to the obstruction).<br>**2a:** Only partial filling (<2⁄3) of the entire vascular territory is visualized.<br>**2b:** Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.<br>**3:** Complete Perfusion. Anterograde flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery. |
| **mTICI**[9] | **0:** No perfusion<br>**1:** Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion<br>**2a:** Perfusion of less than half of the vascular distribution of the occluded artery (eg, filling and perfusion through 1 M2 division)<br>**2b:** Perfusion of half or greater of the vascular distribution of the occluded artery (eg, filling and perfusion through 2 or more M2 divisions)<br>**3:** Full perfusion with filling of all distal branches |
| **TIBI**[10] | **0:** Absent (Absent flow signals)<br>**1:** Minimal (Systolic spikes of variable velocity and duration. Absent diastolic flow during all cardiac cycles)<br>**2:** Blunted (Flattened systolic flow acceleration of variables duration compared to control. Positive end diastolic velocity and pulsatility index<1.2)<br>**3:** Dampened (Normal systolic flow acceleration. Positive end diastolic velocity. Decreased mean flow velocities (MFV) by>30% compared to control)<br>**4:** Stenotic (MFV of >80cm/s and velocity difference of >30% compared to the control side)<br>**5:** Normal (<30% mean velocity difference compared to control. Similar waveform shapes compared to control) |
| **AOL**[11] | **0:** No recanalization of the occlusion<br>**1:** Incomplete or partial recanalization of the occlusion, with no distal flow<br>**2:** Incomplete or partial recanalization of the occlusion, with any distal flow<br>**3:** Complete recanalization of the occlusion with any distal flow |
| **Mori**[12] | **0:** Unchanged<br>**1:** Movement of thrombus not associated with any improvement of perfusion<br>**2:** Partial (branch) recanalization with reperfusion in less than 50% of ischemia-related area<br>**3:** Partial (branch) recanalization with reperfusion in more than 50% of ischemia-related area<br>**4:** Complete or near-complete recanalization with full return of perfusion |

AOL: Arterial occlusive lesion ; TIBI: Thrombolysis in Brain Ischemia ; TICI: Thrombolysis in Cerebral Infarction ; mTCI: modified TICI ; TIMI: Thrombolysis in Myocardial Infarction.

**Supplemental Table II:** Search terms in MEDLINE and EMBASE

| | |
|---|---|
| MEDLINE search | ("Recanalization" [All Fields] OR "Reperfusion" [Mesh]) AND ("Thrombolysis" [All Fields] OR "Fibrinolysis" [All Fields] OR "Thrombolytic therapy" [Mesh]) AND ("Stroke" [Mesh] OR "Cerebrovascular disorders" [Mesh] OR "Ischemic stroke" [All Fields]) AND ("1990/01/01" [PDAT] : "2016/01/27" [PDAT]) AND "humans" [MeSH Terms] AND English [lang] |
| EMBASE search | 'recanalization'/exp OR 'reperfusion'/exp AND ('thrombolysis'/exp OR 'thrombolytic therapy'/exp) AND ('ischemic stroke'/exp OR 'stroke'/exp OR 'cerebrovascular disorders'/exp) AND [english]/lim AND [humans]/lim AND [embase]/lim AND [1-1-1990]/sd NOT [27-01-2016]/sd |

**Supplemental Table III:** Standardized form used for data extraction

| | |
|---|---|
| General information | Publication year |
| | Journal of publication |
| | Abstract only (Yes/No) |
| | First author name |
| Study location, relevant dates | Study location |
| | Mono/Multicentric |
| | Dates of patients inclusion |
| Methods of patients selection | Onset-to-IVT inclusion time |
| | Type of cerebral admission imaging |
| | Type of vascular admission imaging |
| | Dose of Alteplase used |
| Information on ER evaluation | Type of ER imaging |
| | Timing of ER evaluation |
| | Scale used for ER evaluation |
| | Definition used for partial ER |
| | Definition used for complete ER |
| Characteristics of included patients | Total number of patients |
| | Number of patients with ICA occlusion |
| | Number of patients with proximal MCA occlusion (M1) |
| | Number of patients with distal MCA occlusion (M2-M3) |
| | Number of patients with tandem occlusion |
| | Number of patients with anterior cerebral artery occlusion |
| | Number of patients with basilar artery occlusion (BA) |
| | Number of patients with vertebral artery occlusion |
| | Number of patients with posterior cerebral artery occlusion |
| | Number of patients with other site of arterial occlusion |
| Data on ER incidence | Total number of patients with *partial or complete* ER |
| | Total number of patients with *complete* ER |
| | Number of *partial or complete* ER in patients with ICA occlusion |
| | Number of *complete* ER in patients with ICA occlusion |
| | Number of *partial or complete* ER in patients with M1 occlusion |
| | Number of *complete* ER in patients with M1 occlusion |
| | Number of *partial or complete* ER in patients with M2-M3 occlusion |
| | Number of *complete* ER in patients with M2-M3 occlusion |
| | Number of *partial or complete* ER in patients with tandem occlusion |
| | Number of *complete* ER in patients with tandem occlusion |
| | Number of *partial or complete* ER in patients with BA occlusion |
| | Number of *complete* ER in patients with BA occlusion |
| General information on study of ER prediction | Study of ER prediction (Yes/No) |
| | Number of predictors studied |
| | Name of predictor (repeated for each predictor) |
| | Number of patients studied for this predictor (repeated for each predictor) |
| Data on ER prediction, for categorical variables | Number of patient with presence of predictor and ER |
| | Number of patient with presence of predictor and no-ER |
| | Number of patient with absence of predictor and ER |
| | Number of patient with absence of predictor and no-ER |
| Data on ER prediction, for continuous variables | Predictor mean (or median), in patients with ER |
| | Predictor standardized deviation (or interquartile range), in patients with ER |
| | Predictor mean (or median), in patients with no-ER |
| | Predictor standardized deviation (or interquartile range), in patients with no-ER |

IVT: intravenous thrombolysis; ER: early recanalization; ICA: intracranial internal carotid artery; MCA: middle cerebral artery; BA: basilar artery

**Supplemental Table IV:** Characteristics of the 26 studies included in the Systematic Review

| Study | Onset to IVT time | Arterial imaging on admission | Occlusion sites | ER imaging method | Timing of ER evaluation† | ER scale used‡ | N |
|---|---|---|---|---|---|---|---|
| **Von Kummer 1992**[13] | ≤6h | DSA | ICA,MCA | DSA | 90min | TIMI | 32 |
| **Alexandrov 2004**[14] | ≤3h | TCD | MCA | TCD | 60 and 120min | TIBI | 63 |
| **Wunderlich 2005**[15] | ≤6h | TCDD | ICA | TCDD | 90min | TIBI | 15 |
| **Lee 2007**[16] | ≤3h | CTA | ICA,MCA,BA | DSA | M=120min | TICI | 31 |
| **Wunderlich 2007**[17] | ≤6h | TCDD | MCA | TCDD | 90min | TIBI | 99 |
| **Eggers 2008**[18] | ≤3h | TCDD | MCA | TCDD | 60min | TIBI | 18 |
| **Jeong 2009**[19] | ≤3h | CTA | ICA,MCA,VA,BA,PCA | DSA | M≈90min | TIMI | 32 |
| **Mazighi 2009**[20] | ≤3h | CTA/MRA/TCD | ICA,MCA,BA,PCA | DSA | NP | TIMI | 53 |
| **Kawakami 2010**[21] | ≤3h | MRA | ICA,MCA,BA | DSA | 60min | TIMI | 18 |
| **Smadja 2011**[22] | ≤4.5h | MRA | MCA | MRA | 90min | TIMI | 40 |
| **Ernst 2011**[23]* | NP | CTA | MCA | DSA | M=142min | TIMI | 27 |
| **Kimura 2011**[24] | ≤3h | MRA | ICA,MCA | MRA | 120min | S.-M. | 132 |
| **Garcia-Bermejo 2012**[25] | ≤6h | TCDD/TCD | MCA | TCDD/TCD | 60 and 120min | TIBI | 122 |
| **Sanak 2012**[26] | ≤4.5h | CTA/MRA | MCA | TCD/DSA | <180min | TIBI/TICI | 146 |
| **Frölich 2013**[27]* | M≈150min | CTA | ICA,MCA | DSA | M≈85min | TICI | 67 |
| **Koga 2013**[28] | ≤3h | MRA | ICA,MCA | MRA | M≈65min | Mori | 70 |
| **Uzuner 2013**[29] | ≤4.5h | TCD | MCA | TCD | 60min | TIBI | 90 |
| **Behrens 2014**[30] | M=119min | CTA/MRA | ICA,MCA,BA,PCA | DSA | M=98min | TICI | 96 |
| **Yoshimura 2014**[31] | ≤3h | CTA/MRA | ICA,MCA,BA | DSA | 60-180min | mTICI | 194 |
| **Kim 2014**[32]* | NP | CTA/MRA | ICA,MCA | DSA | M=75min | AOL | 118 |
| **Luby 2014**[33] | ≤3h | MRA | ICA,MCA,ACA, BA,VA,PCA | MRA | 180min | S.-M. | 45 |
| **Mishra 2014**[34] | M=120min | CTA | ICA,MCA | DSA | M=70min | TICI | 228 |
| **Von Kummer 2014**[35]* | ≤3h | CTA | ICA,MCA,BA,VA | DSA | NP | NP | 189 |
| **Fjetland 2015**[36] | ≤4.5h | CTA | ICA,MCA,BA | DSA | M=75min | mTICI | 57 |
| **Campbell 2015**[37] | ≤4.5h | CTA | ICA,MCA | DSA | M=74min | mTICI | 35 |
| **Ritzenthaler 2015**[38] | ≤4.5h | MRA | ICA,MCA | MRA | <180min | AOL | 41 |

*Abstract only. †: Timing between initiation of IVT and evaluation of ER. ‡: Details of each scale a presented in supplemental Table 1.

ER: early recanalization. IVT: Intravenous thrombolysis. N: Number of patients. M: mean. NP: Non-precised. TCDD: transcranial duplex Doppler. TCD: transcranial Doppler. CTA: computed tomography angiography. MRA: magnetic resonance angiography. DSA: digital subtracted angiography. ICA: internal carotid artery. MCA: middle cerebral artery. ACA: anterior cerebral artery. PCA: posterior cerebral artery. BA: Basilar artery. VA: vertebral artery. TICI: Thrombolysis in cerebral infarction. mTICI: modified TICI. TIMI: Thrombolysis in myocardial infarction. AOL: Arterial occlusive lesion. TIBI: Thrombolysis in brain ischemia. S-.M: self-made scale.

**Supplemental Table V:** Quality assessment of included studies

| | Methods | | | | Results | | | |
|---|---|---|---|---|---|---|---|---|
| | Location, relevant dates | Sources and methods of selection of participants | Specified criteria of ER | Specified timing of ER evaluation | Characteristics of patients† | Data on arterial occlusion sites | Incidence of ER | Uni or multivariate analysis of ER predictors |
| **Von Kummer 1992**[13] | Yes | yes | yes | yes | no | yes | yes | yes |
| **Alexandrov 2004**[14] | No | yes | yes | yes | no | yes | yes | yes |
| **Wunderlich 2005**[15] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Lee 2007**[16] | No | yes | yes | yes | no | yes | yes | yes |
| **Wunderlich 2007**[17] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Eggers 2008**[18] | No | yes | yes | yes | no | yes | yes | yes |
| **Jeong 2009**[19] | No | yes | yes | yes | yes | yes | yes | yes |
| **Mazighi 2009**[20] | Yes | yes | yes | no | yes | no | yes | no |
| **Kawakami 2010**[21] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Smadja 2011**[22] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Ernst 2011**[23]* | Yes | no | yes | yes | yes | yes | yes | yes |
| **Kimura 2011**[24] | Yes | yes | no | yes | yes | yes | yes | yes |
| **Garcia-Bermejo 2012**[25] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Sanak 2012**[26] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Frölich 2013**[27]* | No | yes | no | yes | no | no | yes | yes |
| **Koga 2013**[28] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Uzuner 2013**[29] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Behrens 2014**[30] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Yoshimura 2014**[31] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Kim 2014**[32]* | No | no | yes | yes | no | yes | yes | yes |
| **Luby 2014**[33] | Yes | yes | yes | yes | yes | yes | yes | no |
| **Mishra 2014**[34] | Yes | yes | yes | yes | no | yes | yes | yes |
| **Von Kummer 2014**[35]* | Yes | yes | no | no | yes | yes | yes | yes |
| **Fjetland 2015**[36] | Yes | yes | yes | yes | yes | yes | yes | yes |
| **Campbell 2015**[37] | Yes | yes | no | yes | yes | yes | yes | no |
| **Ritzenthaler 2015**[38] | Yes | yes | yes | yes | yes | yes | yes | yes |
| Number of « yes » answers | 20/26 (77%) | 24/26 (92%) | 22/26 (88%) | 24/26 (92%) | 19/26 (73%) | 24/26 (92%) | 26/26 (100%) | 21/26 (81%) |

For each study, one reader (PS) scored each item as "Yes" or "No" according to the definition of the quality item. We considered items separately and calculated a global score for each item (corresponding to the proportion of "Yes" answers).

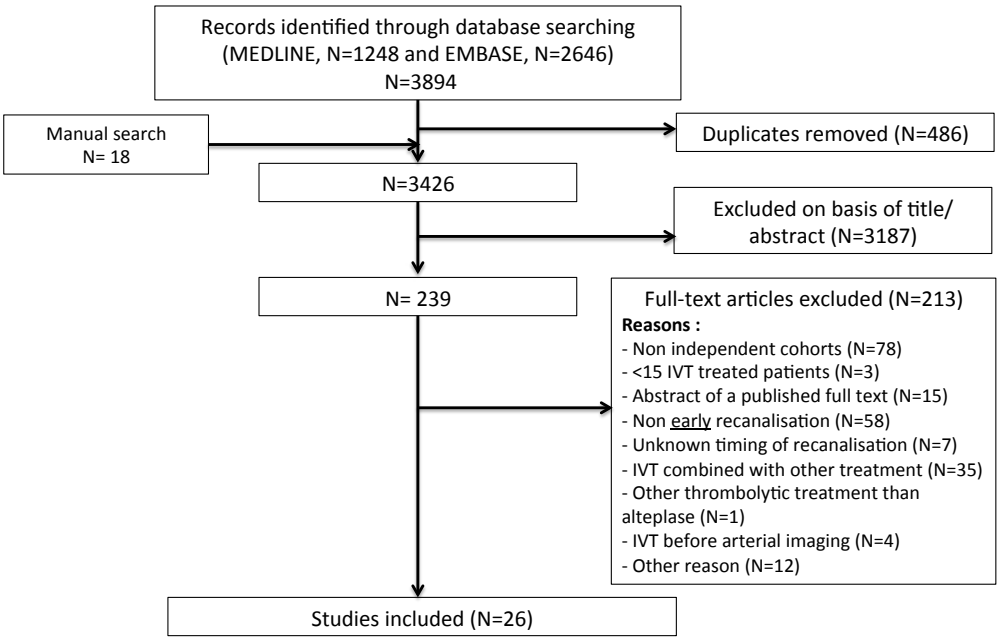
*Abstract only. ER: Early recanalisation. † Characteristics of study patients: number of eligible, included and analysed patients.

**Supplemental Table VI:** Variables without consistent association with no-ER, assessed in less than 4 studies.

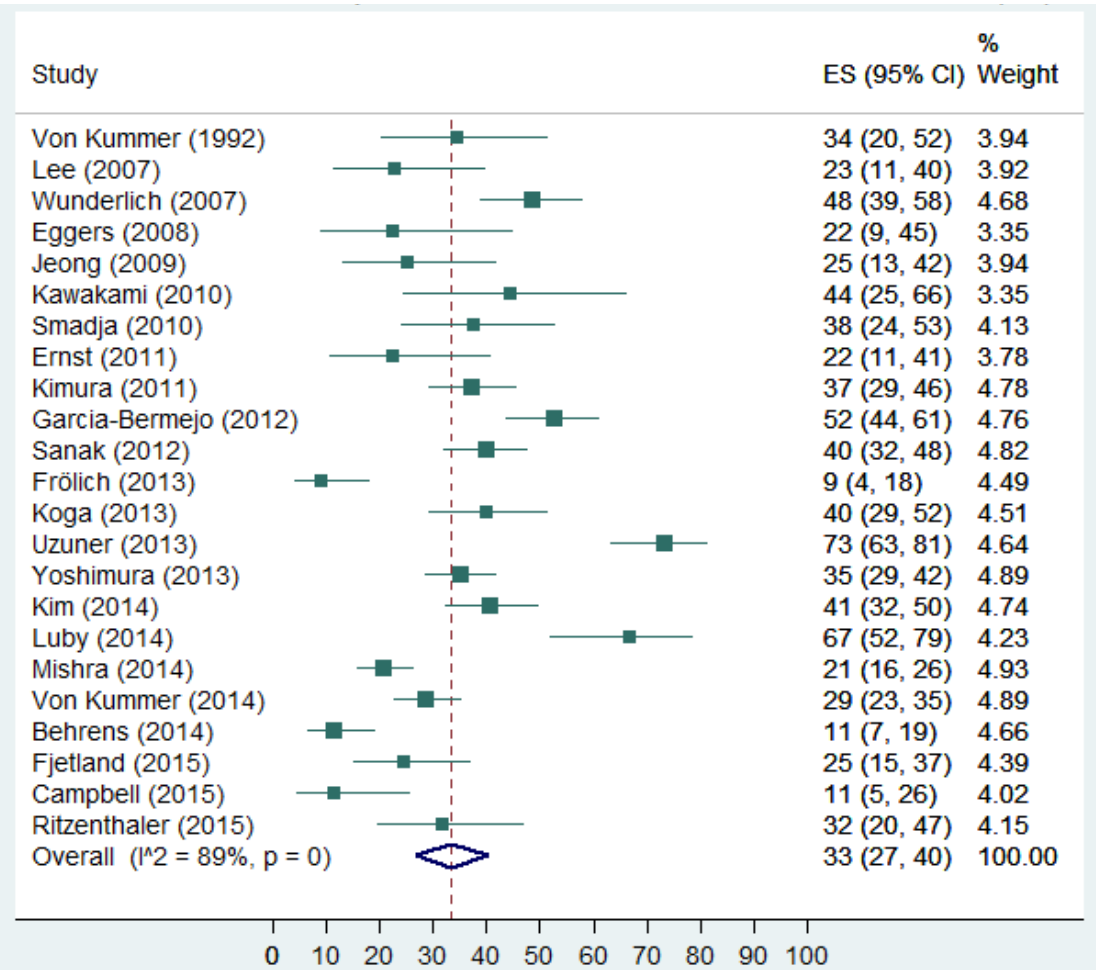
| Variable | Number of studies (number of patients) |
|---|---|
| **Vascular risk factors** | |
| Hyperlipidemia | 2 (202) |
| Hypertension | 3 (259) |
| Current smoking | 2 (202) |
| **Past medical history** | |
| Coronary heart disease | 2 (127) |
| Congestive heart failure | 1 (70) |
| Previous stroke | 1 (57) |
| **Previous treatment** | |
| Antiplatelets* | 2 (278) |
| Anticoagulant | 1 (132) |
| Statin | 1 (146) |
| **Clinical data on admission** | |
| Systolic blood pressure | 3 (348) |
| Diastolic blood pressure | 2 (278) |
| Heart rate | 1 (70) |
| **Imaging** | |
| Susceptibility Vessel Sign (any artery) | 1 (41) |
| Hyperdense MCA sign | 1 (27) |
| DWI-ASPECTS | 1 (70) |
| DWI volume | 1 (132) |
| **Biological parameters** | |
| Leucocyte count | 2 (202) |
| Erythrocyte count | 1 (132) |
| Hemoglobin | 1 (70) |
| Platelets count | 2 (202) |
| INR | 2 (202) |
| Fibrinogen | 1 (70) |
| Antithrombin III | 1 (70) |
| D-dimers | 2 (202) |
| Fibrin degradation product | 1 (70) |
| Total cholesterol level | 1 (70) |
| LDL cholesterol level | 1 (70) |
| Triglyceride level | 1 (70) |
| Glucose level | 3 (348) |
| HbA1c | 2 (202) |
| C-reactive protein* | 2 (202) |
| Creatinine | 2 (202) |
| Brain natriuretic peptide | 1 (70) |
| **Stroke aetiology** | 1 (132) |
| Large artery atherosclerosis | 2 (168) |

* Discordant results between the two studies.

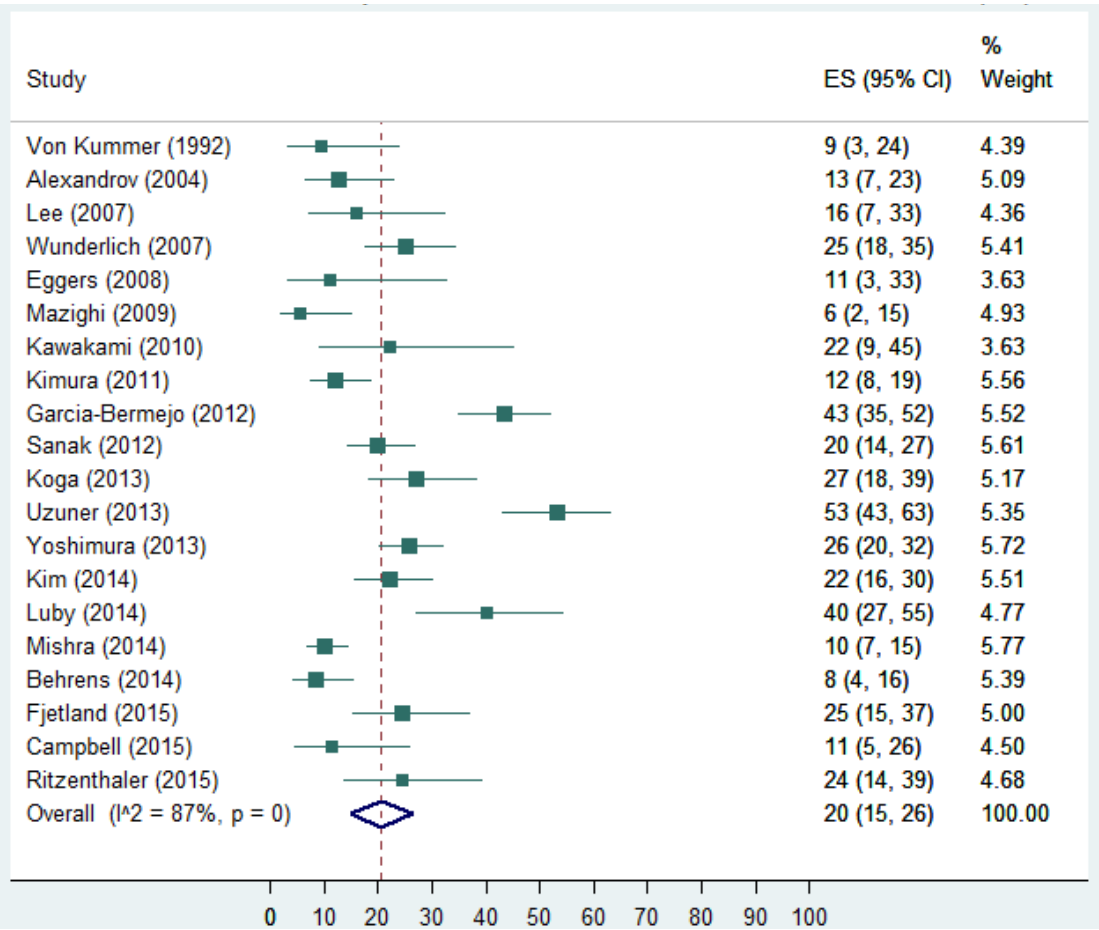
**Supplemental Figure I:** Flow chart of the selection process.



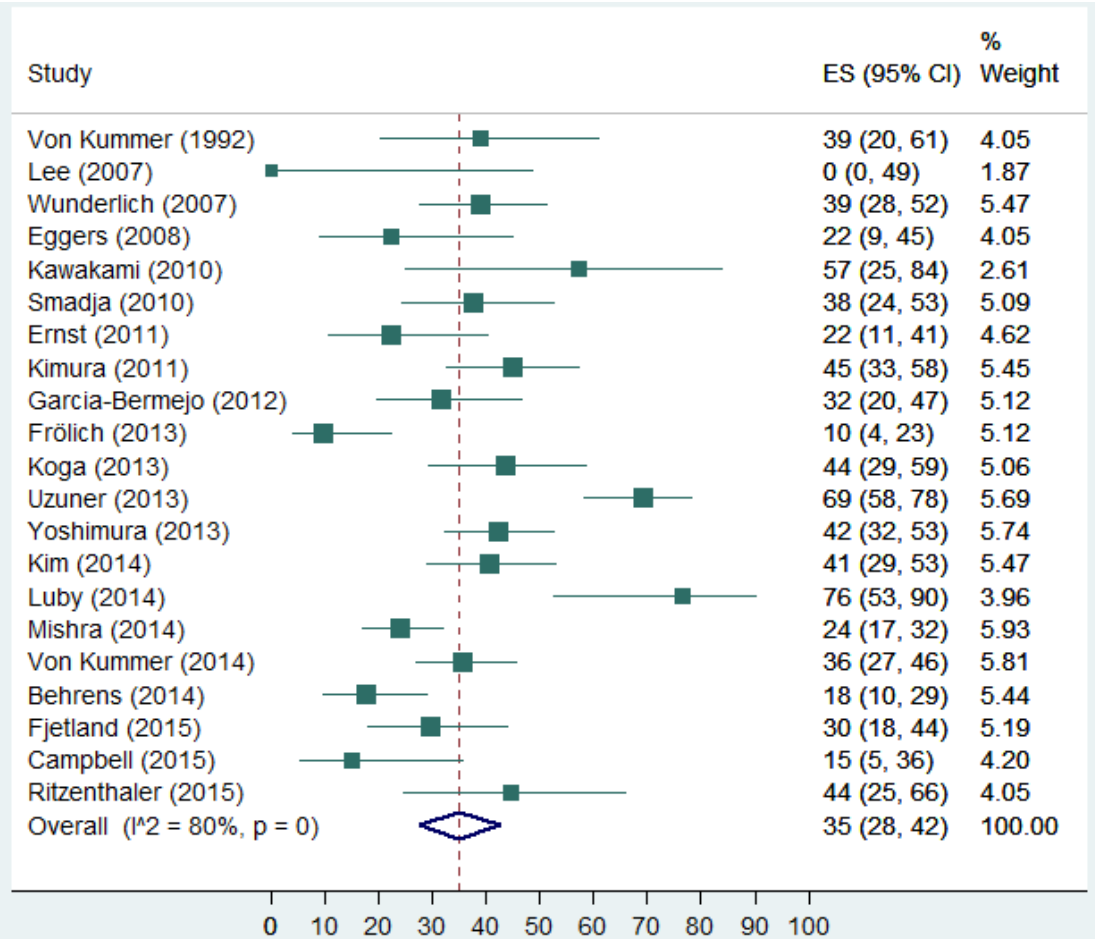
**Supplemental Figure II:** Meta-analysis of incidence of early *partial or complete* recanalization regardless of occlusion site.[13,16,17,19,21,24-38]



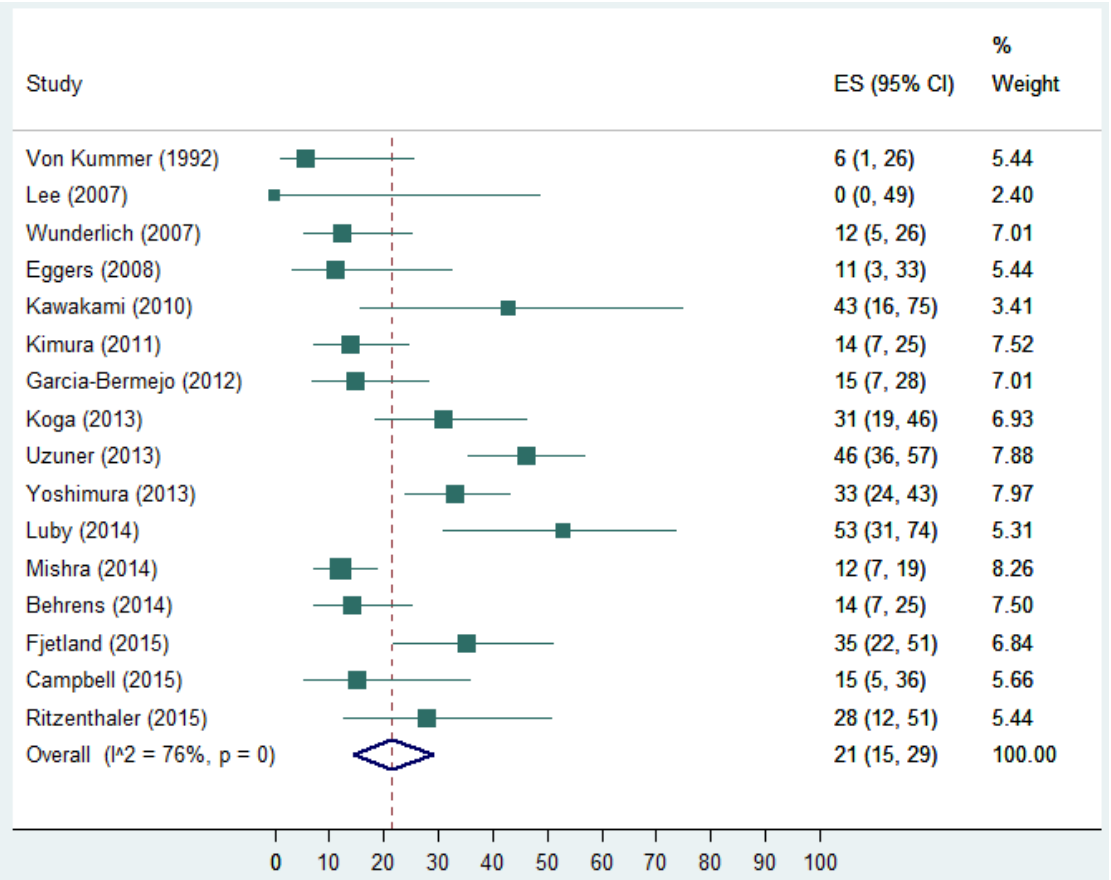
**Supplemental Figure III:** Meta-analysis of incidence of early *complete* recanalization regardless of occlusion site. [13,14,16,17,20,21,24-26,28-34,36-38]



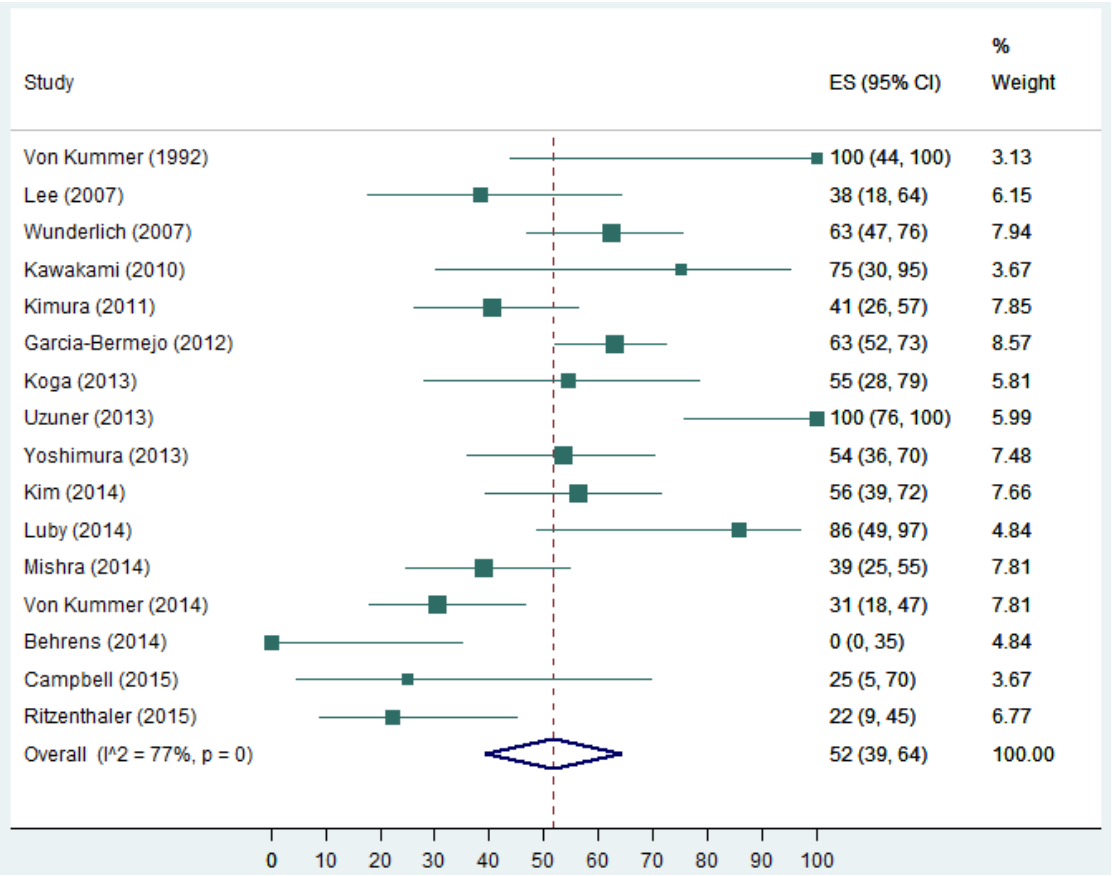
**Supplemental Figure IV:** Meta-analysis of incidence of early *partial or complete* recanalization in M1 occlusion.[13,16-18,21-25,27-38]



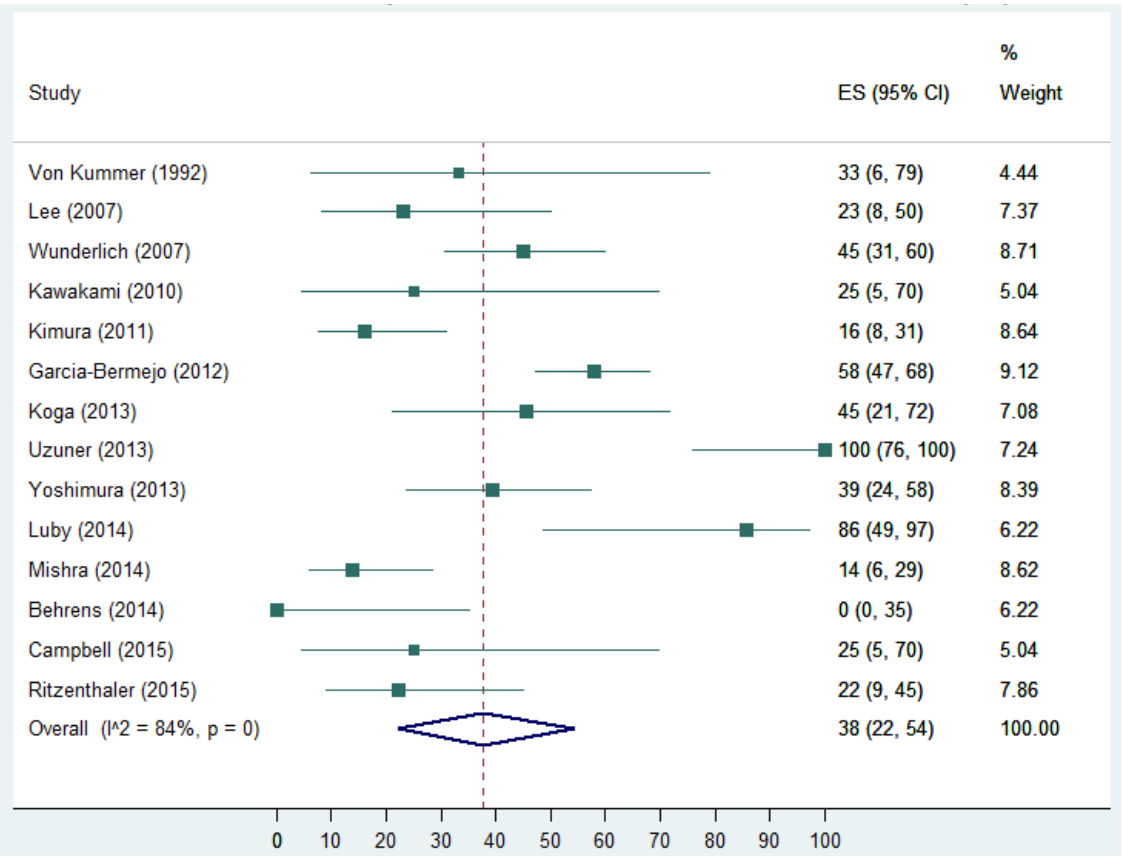
**Supplemental Figure V:** Meta-analysis of incidence of early *complete* recanalization in M1 occlusion.[13,16-18,21,24,25,28-31,33,34,36-38]



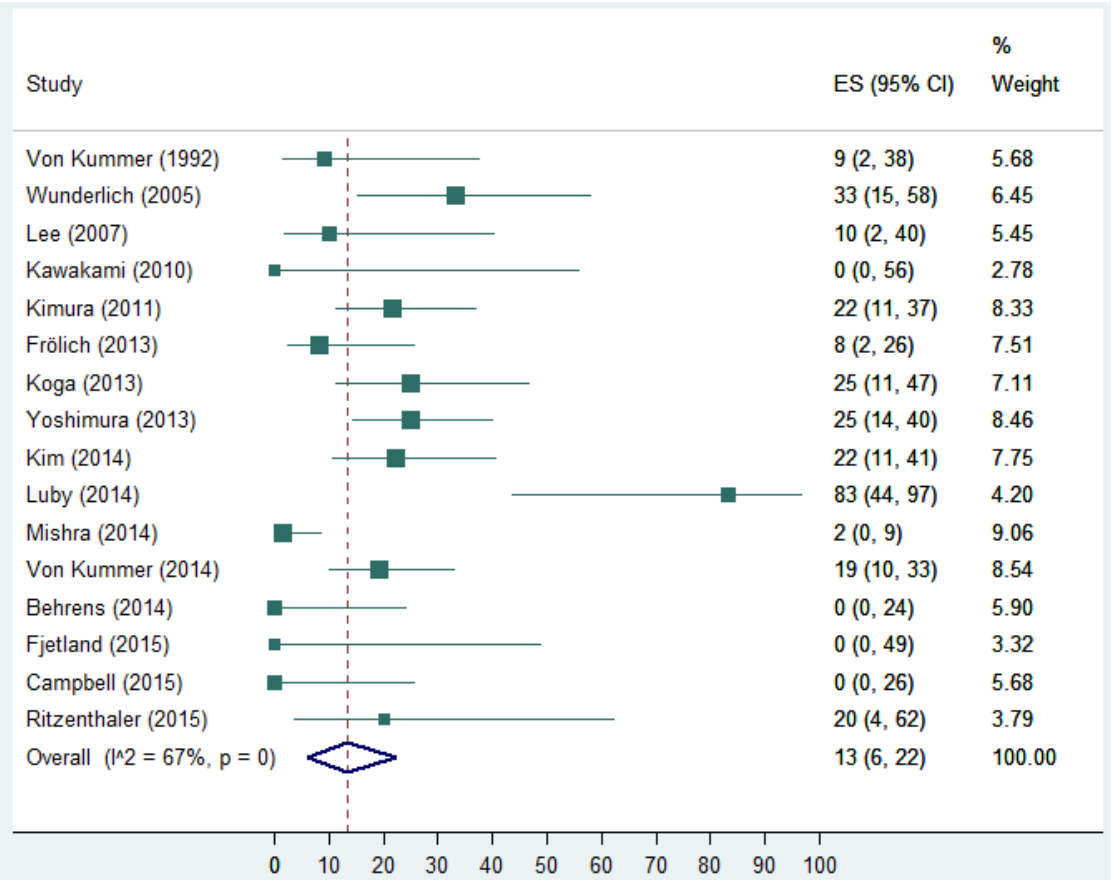
**Supplemental Figure VI:** Meta-analysis of incidence of early *partial or complete* recanalization in M2-M3 occlusion.[13,16,17,21,24,25,28-34,37,38]



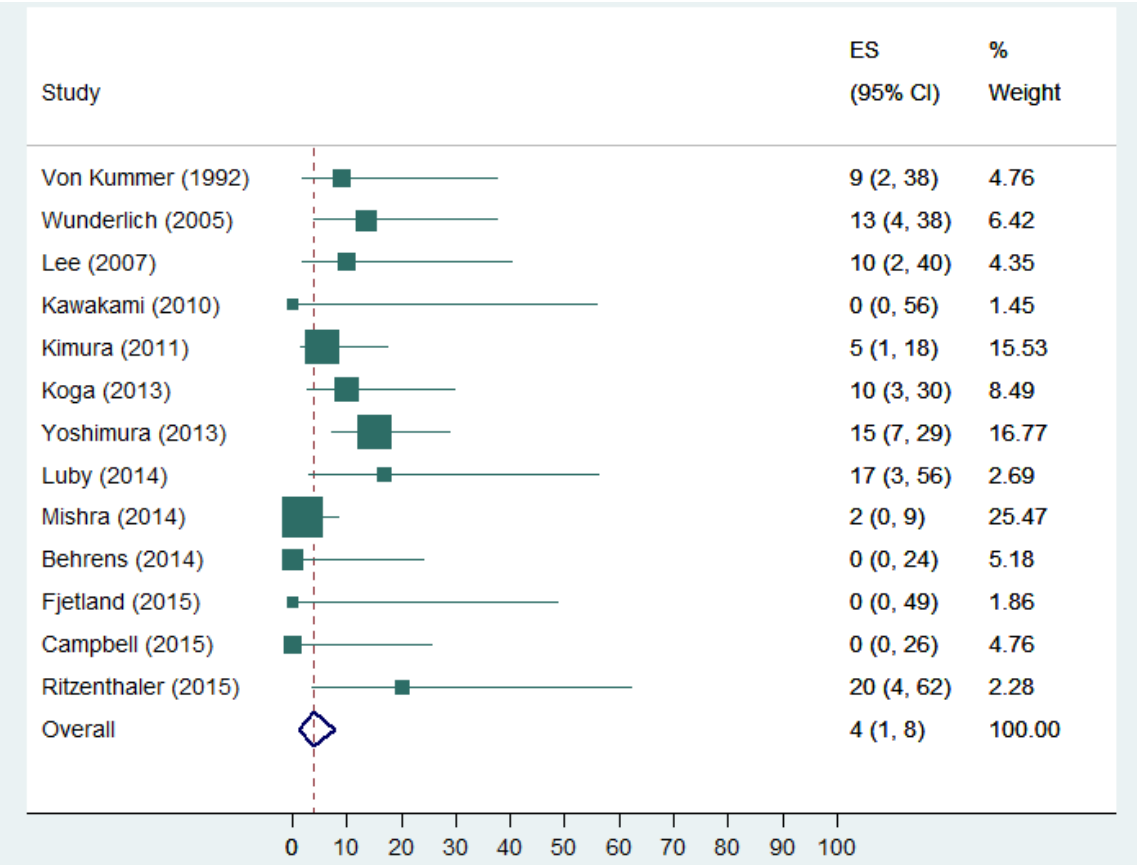
**Supplemental Figure VII:** Meta-analysis of incidence of early *complete* recanalization in M2-M3 occlusion.[13,16,17,21,24,25,28-31,33,34,37,38]



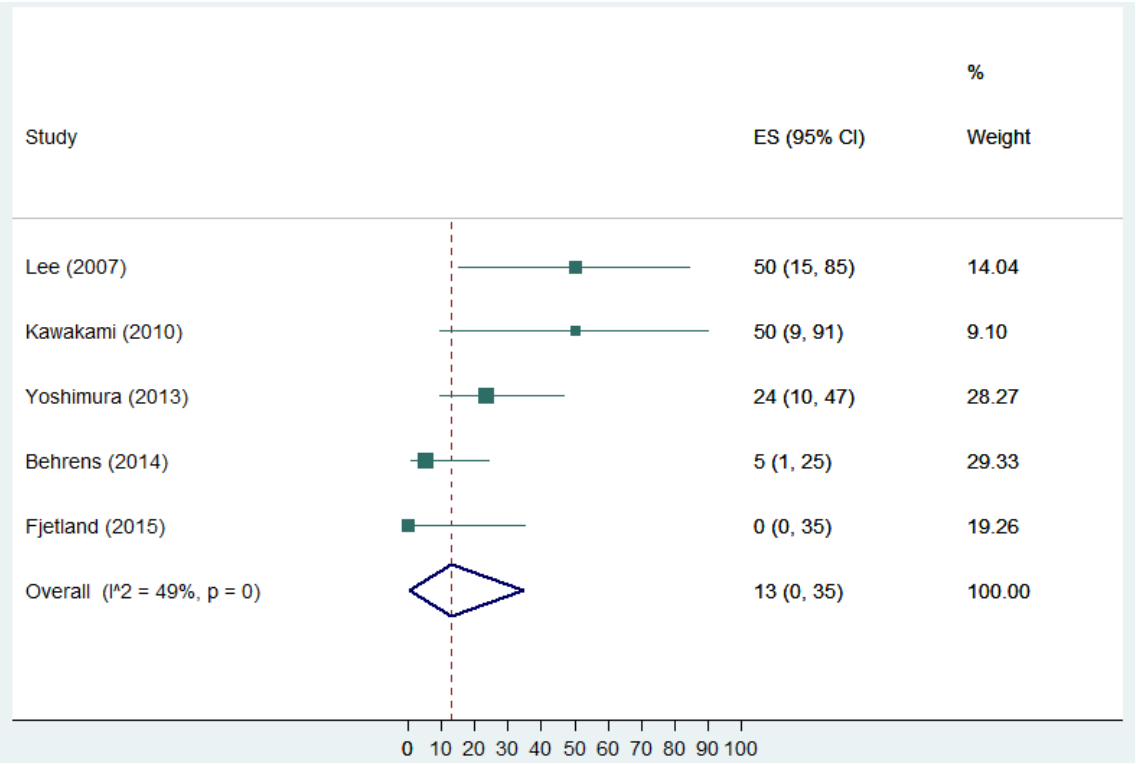
**Supplemental Figure VIII:** Meta-analysis of incidence of early *partial or complete* recanalization in intracranial carotid artery occlusion.[13,15,16,21,24,27,28,30-38]



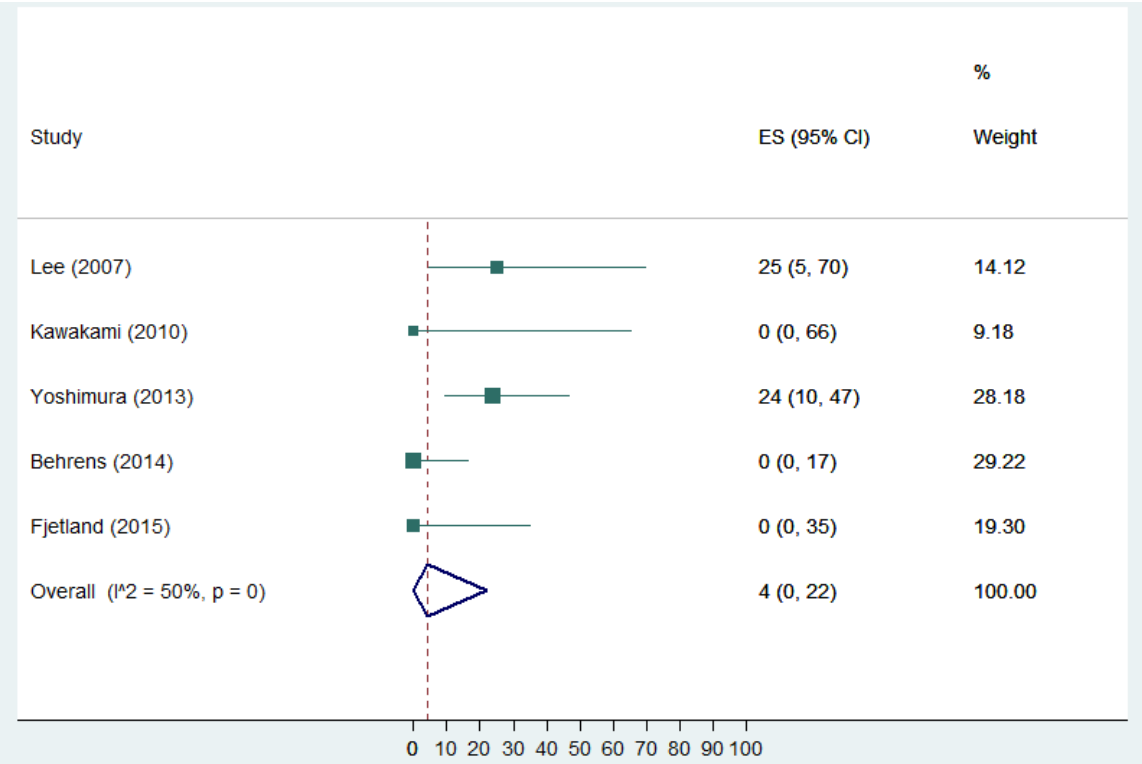
**Supplemental Figure IX:** Meta-analysis of incidence of early *complete* recanalization in intracranial carotid artery occlusion.[13,15,16,21,24,28,30,31,33,34,36-38]



**Supplemental Figure X:** Meta-analysis of incidence of early *partial or complete* recanalization in basilar artery occlusion.[16,21,30,31,36]

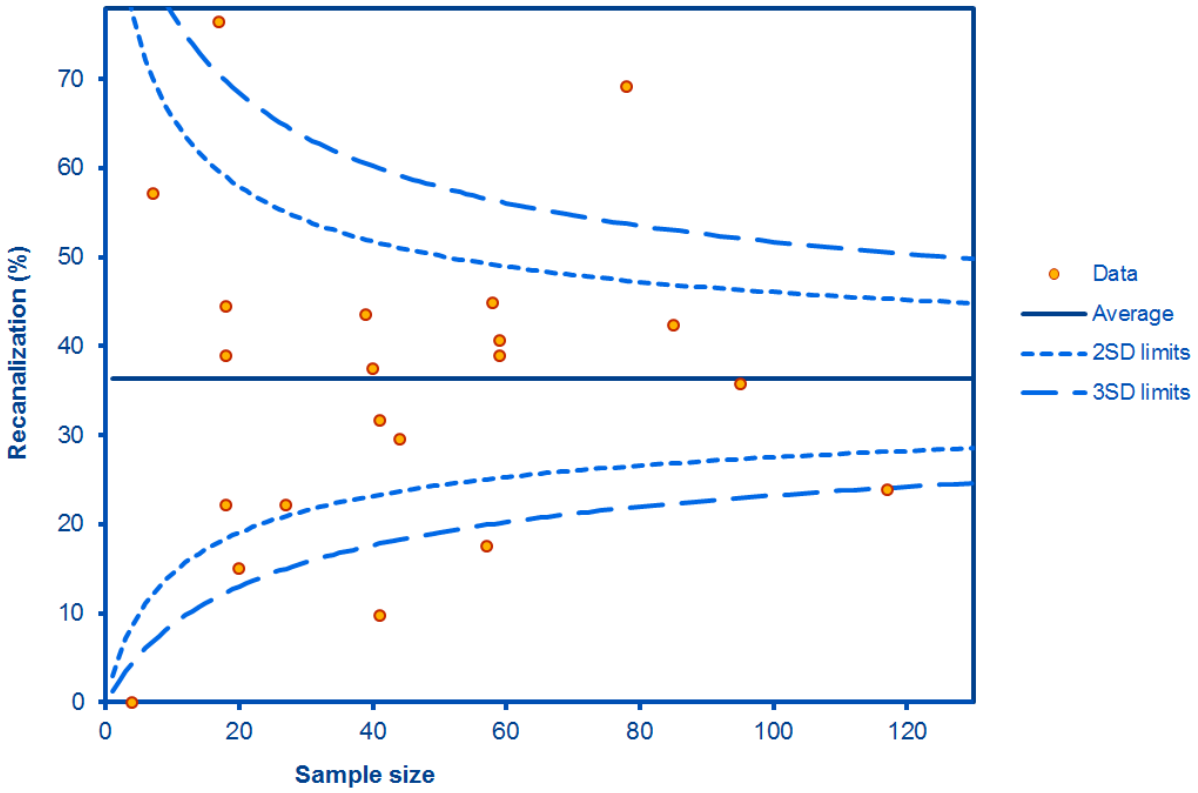


**Supplemental Figure XI:** Meta-analysis of incidence of early *complete* recanalization in basilar artery occlusion.[16,21,30,31,36]

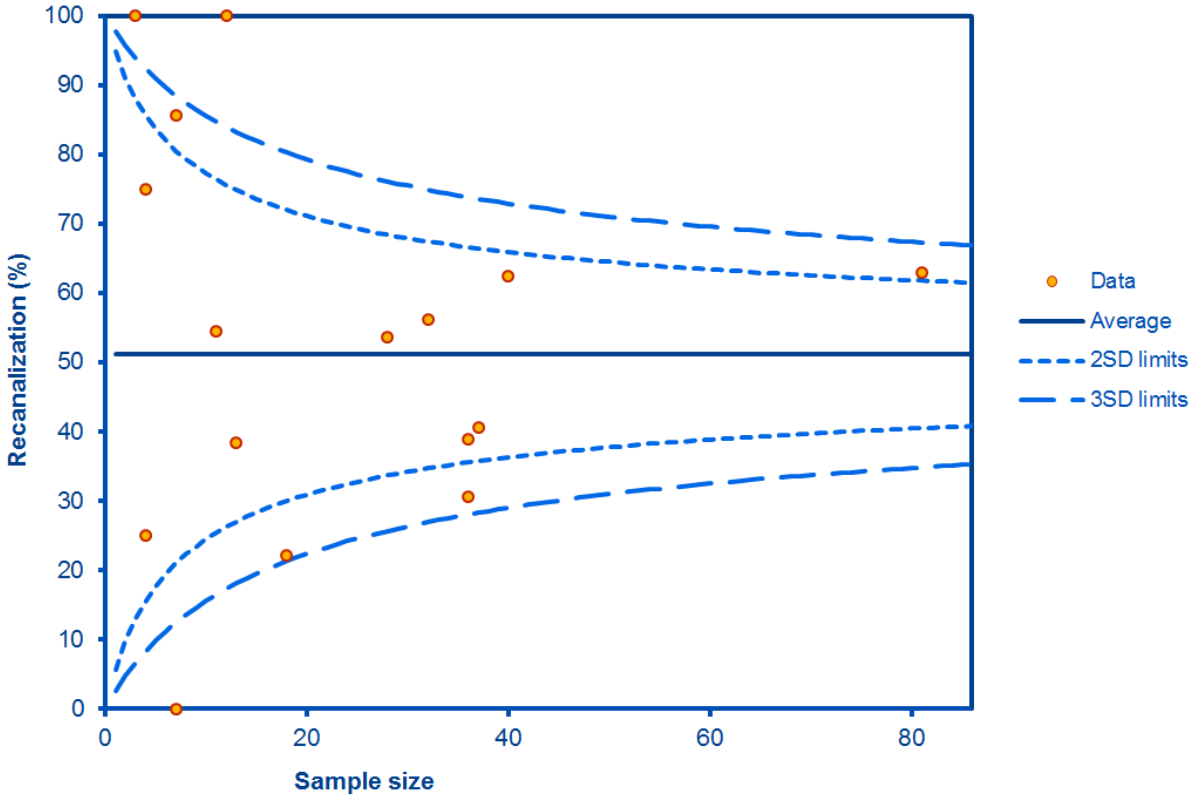


**Supplemental Figure XII:** Funnel plots assessing potential publication bias for assessment of incidence of early recanalisation.

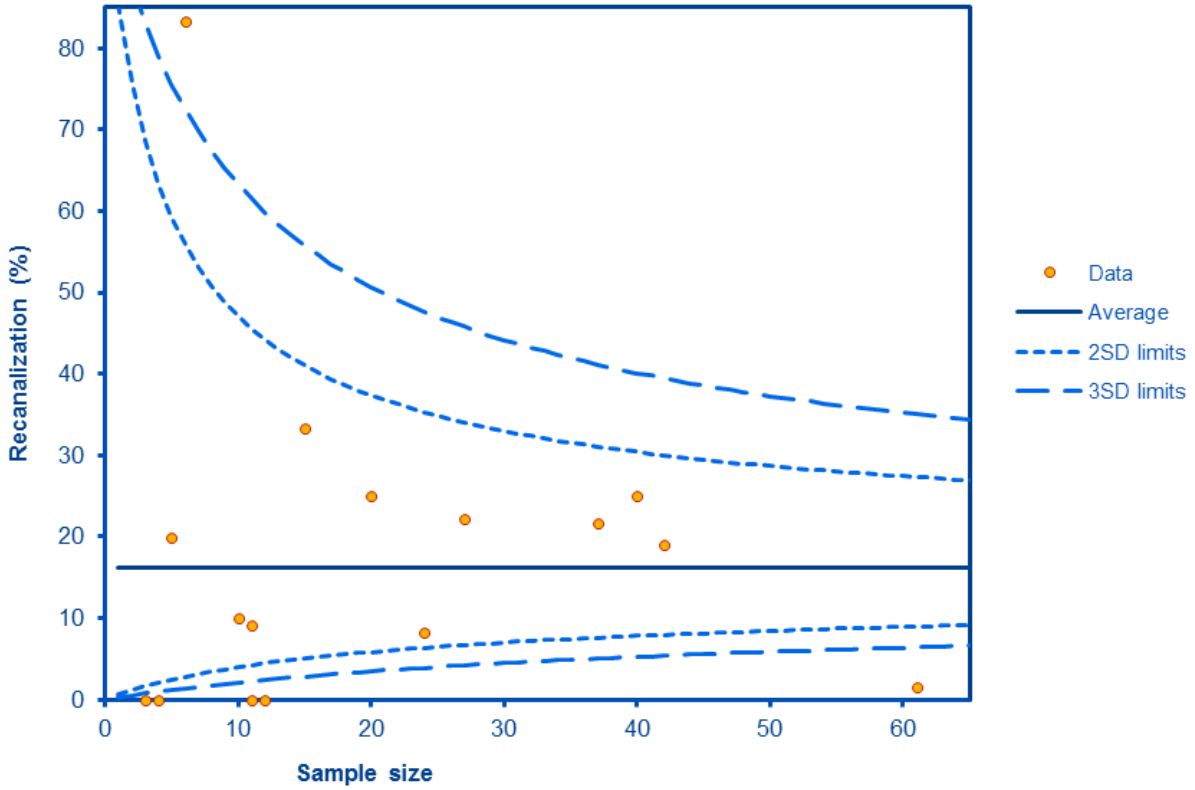
**A :** Proximal MCA occlusions (M1)




**B :** Distal MCA occlusions (M2-M3)



**C :** Intracranial ICA occlusions




Funnel plots are based on raw proportions. 2 SD and 3 SD limits are calculated using Wilson's method.

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# Annexe 2

**Letter to the editor (Journal of Stroke)**

**Recanalization before thrombectomy in tenecteplase *vs.* alteplase-treated drip-and-ship patients**

**Running title:** Alteplase *vs* tenecteplase before thrombectomy

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The EXTEND-IA TNK trial recently showed 2-fold higher early recanalization (ER) rate before mechanical thrombectomy (MT) following intravenous thrombolysis (IVT) with tenecteplase 0.25mg/kg, as compared to alteplase 0.9mg/kg.[1] However, most included patients were directly admitted to MT-capable centres ('mothership' paradigm), implying short IVT-to-MT delays. Tenecteplase may therefore be preferred in the mothership setting. Here, we assessed ER rate before MT following tenecteplase or alteplase in patients transferred for MT from a non MT-capable centre ('drip-and-ship' paradigm), *i.e.* implying longer IVT-to-MT delays, currently the most frequent situation.[2]

Inclusion criteria for the present retrospective study were (1) acute stroke with large vessel occlusion treated with IVT with tenecteplase 0.25mg/kg or alteplase 0.9mg/kg; and (2) ER evaluation ≤3hrs from IVT start on pre-MT first angiographic run or non-invasive vascular imaging. Tenecteplase patients were all treated in one large French non MT-capable centre, which based on previous trials[3,4] and for practical convenience opted to use tenecteplase off-label before transfer for MT. Alteplase patients were from 23 other French non MT-capable centres. ER was defined as modified Thrombolysis-in-cerebral-infarction scale ≥2b score. In accordance with French legislation, patients were informed of their participation in this study, and offered the possibility to withdraw. As per current French law, approval by an Ethics Committee was not required as this study implied retrospective analysis of anonymized data. To reduce the effects of potential confounders, a 1:1 propensity-score matching of patients from the tenecteplase group to patients from the alteplase group was performed, using confounders based on available literature.[5]

From May 2015 to October 2017, 816 patients were identified (n=160 and 656 tenecteplase- and alteplase-treated, respectively). In the propensity-score matched cohorts (n=131 per group), the main confounders for ER were well balanced (**Table**). ER occurred in 21.4% (95%CI: 14.4-28.4) *vs.* 18.3% (11.7-24.9) patients from the tenecteplase- and alteplase-treated cohorts, respectively

(OR=1.25, 95%CI: 0.65-2.41, *P*=0.51). There was no significant association between thrombolytic agent used and 3-month functional independence (modified Rankin score 0-2: 56% *vs*. 56% in the tenecteplase- and alteplase-treated cohorts, *P*=0.75).

Comparing our study to EXTEND-IA TNK, ER rates following tenecteplase were similar (21 *vs.* 22%, respectively), but were markedly higher following alteplase (18 *vs.* 10%, respectively).[1] The radically different care paradigm between the two studies, namely 100% drip-and-ship in our study *vs.* 75% mothership in EXTEND-IA TNK,[1] which translates into longer IVT-to-angiography delays, may account for the higher ER rate with alteplase in our study. Indeed, short IVT-to-angiography time implies that some patients, particularly with the mothership paradigm, do not receive the full alteplase dose before MT. Taken together with EXTEND-IA TNK, therefore, our data suggest that although in drip-and-ship patients the recanalization rate before thrombectomy may be similar with both thrombolytics, recanalization may occur earlier with tenecteplase (**Figure**). In support, one study reported earlier recanalization with tenecteplase than with alteplase in a rabbit carotid thrombosis model.[6] If this hypothesis is confirmed, it may have clinical relevance given the strong relationship between reperfusion timing and functional outcome. The lack of difference in 3-month mRS between the two thrombolytic agents in our study may be because any difference in recanalization timing would only concern ~1 in 5 patients, which may not translate into better functional outcomes across the whole sample.

Our study has limitations. First, uncovered confounding factors cannot be ruled out, especially since the tenecteplase and alteplase groups were treated in different centers. Second, as the participating centers mostly used MR for patient workup, the population studied might differ from primarily CT-assessed populations.

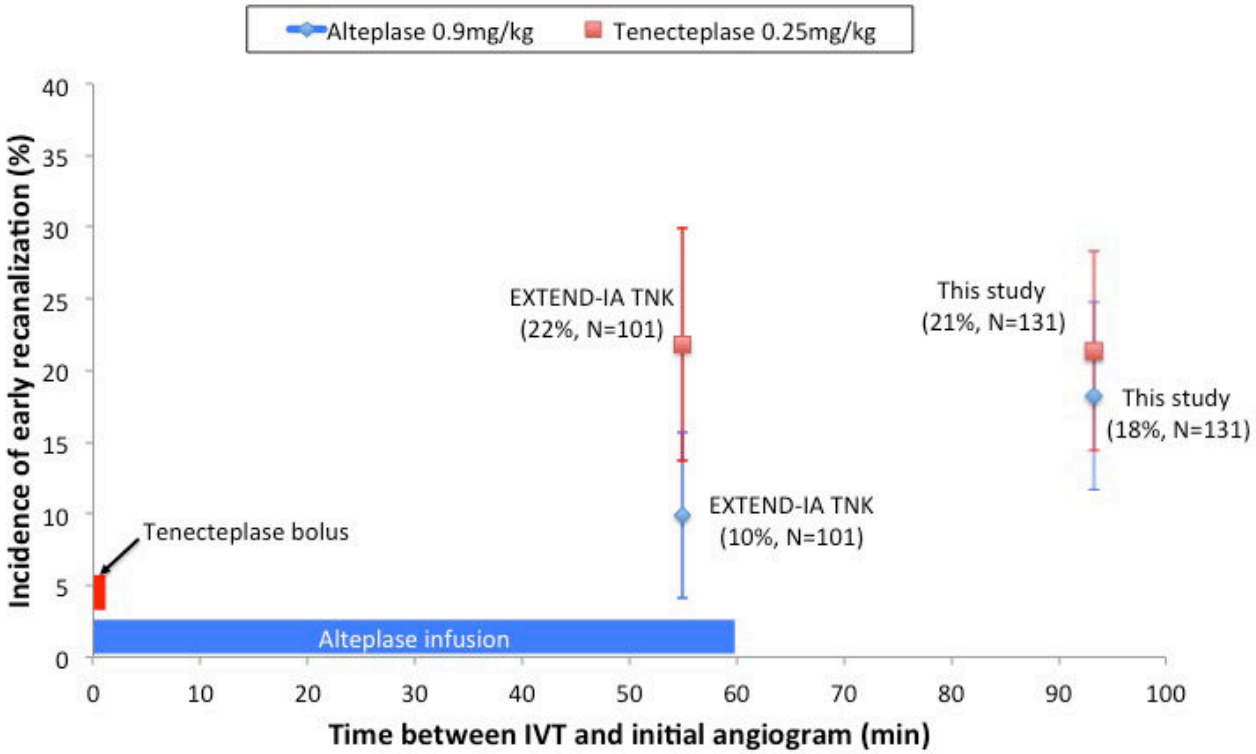
**Table** – Baseline characteristics according to thrombolytic treatment in the propensity matched cohorts*

| | **Tenecteplase N=131** | **Alteplase N=131** | ***ASD (%)*** |
|---|---|---|---|
| **Clinical** | | | |
| Age (years) | 74 (58-82) | 69 (54-80) | 17 |
| NIHSS | 16 (11-20) | 15 (9-20) | 8 |
| Onset-to-IVT time (min) | 145 (123-175) | 149 (120-180) | 10 |
| **Pre-IVT imaging** | | | |
| Occlusion site | | | 11 |
| Intracranial carotid | 26 (19.9) | 28 (21.4) | |
| M1 | 87 (66.4) | 84 (64.1) | |
| M2 | 18 (13.7) | 19 (14.5) | |
| Thrombus length# (mm) | 11.1 (8.7-17.4) | 11.3 (8.5-16.7) | 1 |
| **ER evaluation** | | | |
| Angiography | 127 (97.0) | 127 (97.0) | 0 |
| IVT-to-ER evaluation time (min) | 94 (79-121) | 92 (79-113) | 3 |

*: Categorical variables are expressed as numbers (%) and continuous variables as median (interquartile range). #: manually measured using the susceptibility vessel sign on T2*-MRI.

ASD indicates absolute standardized difference. An ASD<20% is interpreted as a small difference.

**Figure –** Association between ER rate and time elapsed between IVT start and ER assessment in the present study and EXTEND-IA TNK trial.




The red and blue bars in the lower left corner represent the duration of tenecteplase or alteplase intravenous administration. Red and blue squares represent ER incidence following tenecteplase and alteplase, respectively. The bars represent the 95% confidence interval.

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# Annexe 3

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1. Liebeskind DS, Malhotra K, Hinman JD. Imaging as the nidus of precision cerebrovascular health: a Million Brains Initiative. *JAMA Neurol*. 2017;74(3):257-258.

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**In Reply** The enthusiasm expressed for the Million Brains Initiative[1] and the thoughtful consideration of ethical facets by Byram and Illes are much appreciated. The authors underscore a few of the inevitable ramifications that will undoubtedly parallel the realization of precision stroke medicine and the transformation from blissful ignorance to big data in stroke medicine.[2] The current paradigm for cerebrovascular disorders from stroke to dementia is founded on individual clinical symptoms that prompt the acquisition, routine interpretation, and archiving of neuroimaging results. Impressions are readily generated and documented in the electronic health record of every individual. Such imaging data are unnecessarily isolated, antithetically preventing the use of the big data approaches that are required to define the incidentaloma, or 1-in-a-million concept.[3] Similarly, normative changes in the brain across the age span and the construct of cerebrovascular health are only achievable by disrupting this archaic and disconnected health care framework.[4] Crowdsourcing such data will likely unfold like the methods enveloping all aspects of life in the postdigital age, with empowered patients rapidly gaining and reclaiming access as the owners of their health care data.

The nidus for the formative concept and definition of cerebrovascular health resides with using imaging through the Million Brains Initiative as an initial step along the research trajectory required to directly address the ethical challenges raised by Byram and Illes. Crowdsourcing the Million Brains Initiative does not replace the existing clinical paradigm and chain of responsibility in routine clinical care. Moreover, these big data and related research findings on potential incidentalomas are required to define any imaging finding as incidental. Potential crowdsources for gathering imaging results for a million brains include patients not providing new scans, but rather those that have already been interpreted and billed; thus, any responsibility for incidental findings belongs to the interpreting physician. A second crowdsource is the vast number of already completed clinical research studies, of both small and large sample size, that pooled represent a substantial data set on which to make large and important observations.[5] Again, this source of imaging has already been obtained and reviewed for any incidental findings by the study principal investigators. Thus, the "discovery" of anomalies in the Million Brains Initiative would be very close to zero and should not be viewed as an impediment to putting such a powerful initiative to work.

The argument of the authors regarding distributive justice is a major concern in all areas of biomedical research while the observations about cerebrovascular health that the Million Brains Initiative might generate—the true incidence of silent stroke, an improved understanding of age-related cerebral atrophy, or the anticipation of a tailored therapy for a specific group—are more likely to be tangibly accessed by many rather than a few. Contributions from either government-funded research or voluntary submissions would require publicly disclosing the findings. This would arguably make the Million Brains Initiative the most equitable distribution of medical discoveries and promote the public's active participation to advance cerebrovascular health.

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## Mechanical Thrombectomy After Intravenous Thrombolysis vs Mechanical Thrombectomy Alone in Acute Stroke

**To the Editor** In their recent article, Coutinho et al[1] address whether patients who have had an acute stroke with proximal occlusion should undergo intravenous thrombolysis (IVT) before a mechanical thrombectomy (MT). In this analysis of pooled data from the SWIFT and STAR trials, MT after IVT did not appear to provide clinical benefits over MT alone. The authors concluded that randomized clinical trials should confirm their observation.[1]

The main reason for withholding IVT would be that the occurrence of early recanalization (ER) after IVT is too low to justify the additional hemorrhagic risk, cost, and time lost. However, the SWIFT and STAR trials were not designed to compare these 2 paradigms, as in both trials persistent proximal occlusion on the first angiographic run was an inclusion criterion.[2,3] To address this shortcoming, Coutinho et al[1] argue that ER following IVT is rare in proximal occlusions. Based on the ESCAPE, SWIFT PRIME, REVASCAT, and MR CLEAN trial data, they quote post-IVT recanalization rates of 3% to 7% on the first angiographic run. However, this is an underestimation,

because in these trials, patient selection was based on vascular imaging that was mostly conducted after the start of IVT. Thus, an unknown fraction of patients with post-IVT ER before selection imaging were excluded a priori. In our meta-analysis reviewing all 26 studies implementing vascular imaging before starting IVT —which therefore excluded the previously mentioned trials but included EXTEND-IA—[4] complete ER within 3 hours of undergoing IVT was indeed very low (4%) in intracranial carotid occlusion, but substantial in M1 and M2 occlusions (21% and 38%, respectively).[4] These figures were recently confirmed in a large prospective study, even when recanalization was evaluated 60 minutes after IVT.[5]

Early recanalization rates depend on the amount of time that has elapsed since IVT.[5] Thus, ER rates are expected to be lower in the case of direct admissions to comprehensive stroke centers (the "mothership" paradigm) but substantial with the "drip and ship" paradigm, in which IVT-to-angiography times are often less than 60 minutes vs up to 3 hours, respectively. Consequently, the results of Coutinho et al[1] may approximate the former, but they cannot be translated to the latter paradigm, which is the most frequent day-to-day situation currently and will likely remain so in most countries.

We concur with Coutinho et al[1] that randomized clinical trials comparing MT after IVT with MT alone are needed. However, given the substantial ER rates among unselected populations, such trials should only include patients with a very low probability of developing IVT-related ER.

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**In Reply** We read with interest the letter by Seners and colleagues regarding our recent publication.[1] The possibility of early recanalization among patients with acute ischemic stroke and a proximal intracranial occlusion was underestimated in the recent trials on mechanical thrombectomy (MT) because vascular imaging was in part done after starting intravenous thrombolysis (IVT), particularly in the MR CLEAN trial.[2] However, Seners et al[3] observed higher recanalization rates for M1 and M2 occlusions at an early stage, but this was not the case for carotid occlusions.[3] Additionally, they defined early recanalization as happening within 3 hours of the start of IVT. Currently, MT has become standard of care and centers are trying to reduce treatment delays; one may wonder if recanalization 3 hours after starting IVT can still be considered "early." Another limitation of their meta-analysis is that they included a very heterogeneous set of studies. Baseline methods, follow-up imaging, the timing of follow-up imaging, and the scores for recanalization had all differed considerably between these studies.[3] This heterogeneity is also exemplified by the observed rates of early recanalization that varied between 6% and 53%. These limitations make it difficult to translate the results of this meta-analysis to current clinical practice.

Regarding their second point, we fully agree that the results of future randomized clinical trials that evaluate MT with IVT compared with MT alone cannot be directly translated to represent all patients who have had an acute stroke. These trials will probably only include mothership patients, and even if such trials would show that direct MT is superior to MT after IVT, it would need to be determined whether the result also applies to patients who are initially admitted to a primary stroke center. The possibility of commencing IVT much earlier than MT in these patients could negate any positive effects of omitting IVT. However, despite these limitations, we strongly feel that randomized clinical trials are warranted to determine if IVT is valuable for patients who undergo MT.

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