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Devenir après un infarctus cérébral par occlusion de circulation antérieure traité par thrombectomie mécanique - Influence du traitement thrombolytique par rt-PA intraveineux

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Liste des abréviations

AMM	Autorisation de mise sur le marché
AVC	Accidents vasculaires cérébraux
BT	Bridging therapy
CT	Computed Tomography
ESO	*European Stroke Organisation*
IV	Intraveineuse - Intravenous
MRI	Magnetic Resonance Imaging
mRS	Score de Rankin modifié
mTICI	Modified Thrombolysis In Cerebral Infarction Scale
MT	Mechanical thrombectomy
NIHSS	National institutes of health stroke scale
rt-PA	Recombinant tissue plasminogen activator
TIA	Transient Ischemic Attack

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RESUME

OBJECTIF : Plusieurs études randomisées ont récemment prouvé que l'administration du *recombinant tissue-plasminogen activator* intraveineux (rt-PA IV) suivie par une thrombectomie mécanique (TM) améliore le pronostic fonctionnel des patients ayant présenté un infarctus cérébral causé par l'occlusion artérielle proximale de circulation antérieure. Notre objectif était d'évaluer l'influence du rt-PA IV sur le pronostic, en comparant les caractéristiques et le devenir des patients ayant reçu (groupe thérapie combinée TC) ou non le rt-PA IV (groupe TM seul) avant le traitement endovasculaire.

METHODE : De janvier 2012 à septembre 2015, nous avons inclus dans un registre prospectif tous les patients présentant un infarctus cérébral par occlusion proximale de circulation antérieure, traitée par TM, précédée ou non de rt-PA IV. Nous avons évalué l'influence du rt-PA IV sur le pronostic fonctionnel favorable (défini par un score mRS 0 – 2 ou égal au mRS avant l'AVC) et sur la mortalité à 3 mois.

RESULTATS : 207 patients ont été inclus (médiane âge 63 ans, 44% hommes) : 152 (73%) dans le groupe TC, 55 (27%) dans le groupe TM. Les patients traités par TC présentaient moins souvent d'hypertension artérielle (55% vs 73%, p=0,019), de fibrillation atriale (22% vs 49%, p<0,001) ou d'antécédent d'infarctus du myocarde (3% vs 18%, p=0,001). Ils étaient moins souvent traités par anticoagulant oral avant l'AVC (5% vs 33%, p<0,001) et avaient moins souvent d'AVC d'origine cardio-embolique (34% vs 67%, p<0,001). Ils étaient plus fréquemment transférés à partir d'autres hôpitaux (60% vs 44%, p=0,038). L'analyse bivariée a montré que les patients du groupe TC avaient un taux plus élevé de recanalisation artérielle (74% vs 49%, p=0,001), un meilleur pronostic fonctionnel (57 % vs 33%, p=0,002), un taux de mortalité plus faible (12% vs 29%, p=0,003), sans augmentation du risque d'hémorragie intracérébrale symptomatique (8% vs 11%, p=0,49). L'analyse multivariée a montré que l'administration du rt-PA IV était un facteur prédictif indépendant d'un pronostic fonctionnel favorable (adj OR 2,35, 95%IC 1,01-5,45), et de survie (adj OR 0,30, 95%IC 0,13 – 0,68) à 3 mois.

CONCLUSION : Dans notre population, l'administration au préalable du rt-PA IV améliore le pronostic fonctionnel et vital à 3 mois des patients traités par TM. Ces résultats encouragent l'utilisation du rt-PA IV, en l'absence de contre-indication, avant la procédure endovasculaire pour les occlusions proximales de circulation antérieure.

INTRODUCTION GENERALE

Les accidents vasculaires cérébraux (AVC) : un enjeu de santé publique

Les AVC représentent une pathologie fréquente : en France, ils touchent chaque année près de 150.000 personnes, soit 1 personne toutes les 4 minutes.[1] L'âge moyen de survenue des AVC est de 70 ans, ils constituent la première cause de handicap acquis chez l'adulte. 80% environ des AVC sont de nature ischémique.

Traitements validés à la phase aigue d'une ischémie cérébrale

Ces vingt dernières années, la prise en charge à la phase aigue des infarctus cérébraux s'est fortement modifiée avec quatre axes thérapeutiques actuellement validés ayant prouvé leur efficacité en terme de réduction de la morbi-mortalité :

1- Les anti-agrégants plaquettaires : L'aspirine est depuis les années 1990 le traitement anti-thrombotique de référence, en raison de son efficacité, de sa simplicité d'emploi et de son faible coût. Il permet une réduction du risque de décès (4 pour 1000 patients), de récidive (7 pour 1000 patients) ou de dépendance (12 pour 1000 patients). [2]

[1] Isabelle Benatru et al., « Stable Stroke Incidence Rates but Improved Case-Fatality in Dijon, France, from 1985 to 2004 », *Stroke; a Journal of Cerebral Circulation* 37, n° 7 (juillet 2006): 1674‑79, doi:10.1161/01.STR.0000226979.56456.a8.

[2] Z. M. Chen et al., « Indications for Early Aspirin Use in Acute Ischemic Stroke : A Combined Analysis of 40 000 Randomized Patients from the Chinese Acute Stroke Trial and the

2- Les Unités Neuro-Vasculaires (UNV) : constituées par une équipe pluridisciplinaire médicale et paramédicale spécifiquement formée à la pathologie neuro-vasculaire, elles permettent de réduire à elles seules d'environ 20% le risque de décès ou de dépendance par rapport à une prise en charge en unités conventionnelles. [3]

3- La thrombolyse intraveineuse (IV) par rt-PA : le rt-PA, administré dans les 3 heures suivant l'installation des symptômes chez les patients ayant présenté un infarctus dans le territoire de l'artère cérébrale moyenne (ACM), augmente de 30% les chances de pronostic fonctionnel favorable défini par un score de Rankin 0 ou 1 à 3 mois, ce malgré une augmentation significative du risque hémorragique et sans modification de la mortalité.[4] En 2009, l'étude ECASS III a permis d'étendre la fenêtre thérapeutique à 4H30 avec une efficacité du traitement qui reste cependant étroitement corrélée à la précocité de son administration. [5]

International Stroke Trial. On Behalf of the CAST and IST Collaborative Groups », *Stroke; a Journal of Cerebral Circulation* 31, n° 6 (juin 2000): 1240‑49.

[3] P. Langhorne et al., « Do Stroke Units Save Lives? », *Lancet (London, England)* 342, n° 8868 (14 août 1993): 395‑98.

[4] « Tissue Plasminogen Activator for Acute Ischemic Stroke. The National Institute of Neurological Disorders and Stroke Rt-PA Stroke Study Group », *The New England Journal of Medicine* 333, n° 24 (14 décembre 1995): 1581‑87, doi:10.1056/NEJM199512143332401.

[5] Erich Bluhmki et al., « Stroke Treatment with Alteplase given 3.0-4.5 H after Onset of Acute Ischaemic Stroke (ECASS III): Additional Outcomes and Subgroup Analysis of a Randomised Controlled Trial », *The Lancet. Neurology* 8, n° 12 (décembre 2009): 1095‑1102, doi:10.1016/S1474-4422(09)70264-9.

4- La thrombectomie mécanique : Depuis la parution des résultats de l'essai clinique MR CLEAN [6], la procédure endovasculaire par thrombectomie mécanique réalisée dans les 6 heures du début des signes, est validée dans le traitement d'un AVC ischémique par occlusion d'une artère proximale de la circulation antérieure (occlusion artère cérébrale moyenne ACM portion M1 ou M2, occlusion en T carotidien ou occlusion en tandem). L'étude a montré que la thrombectomie mécanique, réalisée dans les suites de la thrombolyse IV ou en cas de contre-indication au rt-PA, améliore le pronostic fonctionnel des patients à 3 mois.

Principes et modalités pratiques de la thrombectomie mécanique

Il s'agit d'une procédure réalisée par voie endovasculaire par un neuroradiologue interventionnel : elle est débutée immédiatement après l'imagerie cérébrale en cas de contre-indication au rt-PA IV, ou dès la mise en route de la perfusion intraveineuse du rt-PA sans attendre la fin de cette dernière. Elle peut être effectuée sous anesthésie générale ou sédation consciente. Après ponction artérielle fémorale, un cathéter est introduit et placé en amont du thrombus artériel, puis des séquences d'artériographie sont réalisées après injection de produit de contraste iodé, permettant de déterminer la position précise du caillot.

La thrombectomie mécanique est ensuite débutée après introduction d'un microcathéter : soit par aspiration, soit par déploiement d'un stent-retriever, non laissé en place.

[6] Olvert A. Berkhemer et al., « A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke », *The New England Journal of Medicine* 372, n° 1 (1 janvier 2015): 11‑20, doi:10.1056/NEJMoa1411587.

Validation par les essais thérapeutiques

En 2013, 3 essais cliniques randomisés ont été publiés, qui n'ont pas réussi à démontrer l'efficacité du traitement endovasculaire[7] [8] [9]. EN 2015, cinq essais cliniques récents ont publié des résultats positifs sur l'efficacité de la thrombectomie mécanique en comparaison au traitement médical seul. En comparaison des 3 précédents essais négatifs, ces études ont réussi à montrer un bénéfice du traitement endovasculaire grâce à l'utilisation de stents « retrievers », par une confirmation de l'occlusion artérielle sur imagerie dédiée, par une meilleure sélection des patients et un accès au traitement plus rapide.

Les patients étaient inclus jusqu'à 4,5 heures du début des signes dans SWIFT-PRIME[10], jusqu'à 6 heures dans MR CLEAN et EXTEND-IA[11], jusqu'à 8 heures dans REVASCAT[12] et jusqu'à 12 heures dans ESCAPE[13], mais la majorité des patients ont bénéficié de la procédure avant 6 heures.

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[7] Joseph P. Broderick et al., « Endovascular Therapy after Intravenous T-PA versus T-PA Alone for Stroke », *The New England Journal of Medicine* 368, n° 10 (7 mars 2013): 893‑903, doi:10.1056/NEJMoa1214300.

[8] Alfonso Ciccone et al., « Endovascular Treatment for Acute Ischemic Stroke », *The New England Journal of Medicine* 368, n° 10 (7 mars 2013): 904‑13, doi:10.1056/NEJMoa1213701.

[9] Chelsea S. Kidwell et al., « A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke », *The New England Journal of Medicine* 368, n° 10 (7 mars 2013): 914‑23, doi:10.1056/NEJMoa1212793.

[10] Jeffrey L. Saver et al., « Stent-Retriever Thrombectomy after Intravenous T-PA vs. T-PA Alone in Stroke », *The New England Journal of Medicine* 372, n° 24 (11 juin 2015): 2285‑95, doi:10.1056/NEJMoa1415061.

[11] Bruce C.V. Campbell et al., « Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection », *New England Journal of Medicine* 372, n° 11 (12 mars 2015): 1009‑18, doi:10.1056/NEJMoa1414792.

[12] Tudor G. Jovin et al., « Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke », *The New England Journal of Medicine* 372, n° 24 (11 juin 2015): 2296‑2306, doi:10.1056/NEJMoa1503780.

[13] Mayank Goyal et al., « Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke », *New England Journal of Medicine* 372, n° 11 (12 mars 2015): 1019‑30, doi:10.1056/NEJMoa1414905.

Cent pour cents des patients ont reçu un traitement thrombolytique IV par rt-PA avant la procédure dans EXTEND-IA [11] et SWIFT-PRIME [13]. Dans les 3 autres études, il était possible d'inclure des patients ayant une contre-indication au rt-PA IV, avec une proportion de patients traités par thrombectomie mécanique seule qui est restée faible. Le traitement par thrombectomie mécanique permettait d'obtenir un succès de recanalisation artérielle, définie comme un score mTICI 2b-3, de 59 à 88%. Le pronostic fonctionnel à 3 mois, défini dans les 5 études par un score de Rankin inférieur ou égale à 2, variait de 33 à 71%. Le risque de saignement n'était pas augmenté. Une tendance à la diminution de la mortalité était observée.

Recommandations européennes par l'ESO (European Stroke Organisation)

Ces recommandations ont été validées et mises à jour en mai 2015 après la publication des données positives des grands essais cliniques sur la thrombectomie mécanique [14] :

1- La thrombectomie mécanique, associée au traitement thrombolytique intraveineux par rt-PA dans les 4H30 du début des symptômes, est recommandée pour traiter les AVC ischémiques avec occlusion proximale de circulation antérieure dans les 6 heures après le début des symptômes.

2- Elle ne doit pas empêcher l'initiation du rt-PA IV si celui est indiqué, mais l'administration du rt-PA IV ne doit pas retarder la thrombectomie mécanique.

3- Elle doit être réalisée le plus rapidement possible, si possible en utilisant les stent-retrievers (validés par les autorités de santé locales). Les autres

[14] Nils Wahlgren et al., « Mechanical Thrombectomy in Acute Ischemic Stroke: Consensus Statement by ESO-Karolinska Stroke Update 2014/2015, Supported by ESO, ESMINT, ESNR and EAN », *International Journal of Stroke: Official Journal of the International Stroke Society* 11, n° 1 (janvier 2016): 134‑47, doi:10.1177/1747493015609778.

techniques interventionnelles sont autorisées, à la discrétion du neuroradiologue interventionnel, à condition que ces techniques soient rapides, sécurisées et permettent une revascularisation complète.

4- En cas de contre-indication au rt-PA intraveineux, la thrombectomie mécanique est indiquée en première intention.

Problématique

Dans 3 des 5 grands essais cliniques décrits plus hauts, certains patients n'ont pas reçu de traitement thromboytique intraveineux par rt-PA avant la procédure endovasculaire : l'effet de la thrombectomie mécanique sr le pronostic fonctionnel ne semblait pas différent entre les patients ayant bénéficié d'une thérapie combinée (intraveineuse et endovasculaire) et les patients traités par thrombectomie mécanique seule.

Débuter le traitement endovasculaire en première intention sans rt-PA intraveineux au préalable pourrait permettre de réduire le délai d'accès au traitement intra-artériel, et par conséquent, réduire le délai entre le début des symptômes et la recanalisation artérielle. De nombreuses données ont montré que ce délai est un facteur prédicteur important du devenir fonctionnel favorable.[15] [16] Cela pourrait également réduire le

[15] Joung-Ho Rha et Jeffrey L. Saver, « The Impact of Recanalization on Ischemic Stroke Outcome: A Meta-Analysis », *Stroke; a Journal of Cerebral Circulation* 38, n° 3 (mars 2007): 967‑73, doi:10.1161/01.STR.0000258112.14918.24.

[16] Mazighi.M et al, « Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. -. Circulation. 2013 May 14;127(19):1980-5. doi: 10.1161/CIRCULATIONAHA.112.000311

risque hémorragique, à la fois intra et extra cérébral. [17]

Cependant, des données récentes suggèrent que l'administration du traitement thrombolytique intraveineux pourrait faciliter la procédure endovasculaire, notamment lors de l'extraction du thrombus, avec un meilleur taux de recanalisation [18], et une durée de procédure plus courte [19]. Par ailleurs, le traitement par rt-PA IV permettrait de dissoudre les thrombus distaux, non accessibles par thrombectomie mécanique, ce qui pourrait améliorer le pronostic. [20]

Aucun essai thérapeutique randomisé n'a encore comparé la thrombectomie mécanique seule au traitement combiné dans les AVC ischémique par occlusion de la circulation antérieure. Les données de la littérature sont issues d'études rétrospectives : certaines données suggèrent un taux de recanalisation et un pronostic fonctionnel similaire entre thrombectomie mécanique seule et traitement combiné [21] [22] [23] [24]. A l'inverse, trois études plaident en faveur du traitement combiné

[17] Anne Broeg-Morvay et al., « Direct Mechanical Intervention Versus Combined Intravenous and Mechanical Intervention in Large Artery Anterior Circulation Stroke: A Matched-Pairs Analysis », *Stroke*, 23 février 2016, STROKEAHA.115.011134, doi:10.1161/STROKEAHA.115.011134.

[18] C. A. Lewandowski et al., « Combined Intravenous and Intra-Arterial R-TPA versus Intra-Arterial Therapy of Acute Ischemic Stroke: Emergency Management of Stroke (EMS) Bridging Trial », *Stroke; a Journal of Cerebral Circulation* 30, n° 12 (décembre 1999): 2598‑2605.

[19] Thomas Pfefferkorn et al., « Preceding Intravenous Thrombolysis Facilitates Endovascular Mechanical Recanalization in Large Intracranial Artery Occlusion », *International Journal of Stroke: Official Journal of the International Stroke Society* 7, n° 1 (janvier 2012): 14‑18, doi:10.1111/j.1747-4949.2011.00639.x.

[20] Jean-Philippe Desilles et al., « Alteplase Reduces Downstream Microvascular Thrombosis and Improves the Benefit of Large Artery Recanalization in Stroke », *Stroke; a Journal of Cerebral Circulation* 46, n° 11 (novembre 2015): 3241‑48, doi:10.1161/STROKEAHA.115.010721.

[21] Tareq Kass-Hout et al., « Is Bridging with Intravenous Thrombolysis of Any Benefit in Endovascular Therapy for Acute Ischemic Stroke? », *World Neurosurgery* 82, n° 3‑4 (octobre 2014): e453-458, doi:10.1016/j.wneu.2013.01.097.

avec des taux de recanalisation plus élevés [25] [26] et un meilleur pronostic fonctionnel à 3 mois [27].

Objectif

L'objectif de notre étude était d'évaluer l'apport du rt-PA IV chez des patients traités par procédure endovasculaire pour un AVC ischémique par une occlusion artérielle proximale de circulation antérieure, en comparant les caractéristiques cliniques et radiologiques, et le devenir à 3 mois, entre les patients ayant bénéficié d'un traitement combiné (rt-PA IV et thrombectomie mécanique) et les patients traités par thrombectomie mécanique seule.

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[22] Rohit Bhatia et al., « Combined Full-Dose IV and Endovascular Thrombolysis in Acute Ischaemic Stroke », *International Journal of Stroke* 9, n° 8 (décembre 2014): 974‑79, doi:10.1111/j.1747-4949.2012.00890.x.

[23] Ronen R. Leker et al., « Is Bridging Necessary? A Pilot Study of Bridging versus Primary Stentriever-Based Endovascular Reperfusion in Large Anterior Circulation Strokes », *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association* 24, n° 6 (juin 2015): 1163‑67, doi:10.1016/j.jstrokecerebrovasdis.2015.01.008.

[24] Ralph Weber et al., « Comparison of Outcome and Interventional Complication Rate in Patients with Acute Stroke Treated with Mechanical Thrombectomy with and without Bridging Thrombolysis », *Journal of NeuroInterventional Surgery*, 22 février 2016, neurintsurg-2015-012236, doi:10.1136/neurintsurg-2015-012236.

[25] Pierre Guedin et al., « Prior IV Thrombolysis Facilitates Mechanical Thrombectomy in Acute Ischemic Stroke », *Journal of Stroke and Cerebrovascular Diseases* 24, n° 5 (mai 2015): 952‑57, doi:10.1016/j.jstrokecerebrovasdis.2014.12.015.

[26] Daniel Behme et al., « Intravenous Thrombolysis Facilitates Successful Recanalization with Stent-Retriever Mechanical Thrombectomy in Middle Cerebral Artery Occlusions », *Journal of Stroke and Cerebrovascular Diseases* 25, n° 4 (avril 2016): 954‑59, doi:10.1016/j.jstrokecerebrovasdis.2016.01.007.

[27] Pfefferkorn et al., « Preceding Intravenous Thrombolysis Facilitates Endovascular Mechanical Recanalization in Large Intracranial Artery Occlusion ».

ARTICLE

Outcome after large artery anterior circulation stroke treated by mechanical thrombectomy – Influence of intravenous recombinant tissue plasminogen activator (IV rt-PA).

Projet de publication

INTRODUCTION

Beside intravenous (IV) thrombolysis, mechanical thrombectomy (MT) has now proven its efficacy to improve functional outcome in patients with stroke related to proximal vessel occlusion in anterior circulation, with the publication in 2015 of 5 positive trials (1)(2)(3)(4)(5). In 2 of these large trials (4)(5), MT was proposed as an adjunctive therapy to IV thrombolysis. In the 3 remaining trials where it was possible to include patients not having received IV recombinant tissue plasminogen activator (rt-PA), the therapeutic effect of MT did not significantly differ between patients having or not received prior treatment with IV rt-PA, suggesting that it could be possible to avoid IV thrombolysis and to propose MT alone in patients with stroke secondary to an occlusion of a large artery in the anterior circulation. Avoiding prior IV thrombolysis could reduce the delay between stroke onset and initiation of intra-arterial therapy, and therefore reduce the time to recanalization which has been shown to be an important predictor of outcome (6)(7). It could also reduce the risk of hemorrhage, both intra and extra-cerebral (8). However, it has also been suggested that previous administration of IV rt-PA could facilitate MT, with a higher rate of successful recanalization (9), a shorter procedure duration (10) and a shorter time to recanalization (11). Moreover, it could help to dissolve distal thrombi not accessible with MT (12), which could lead to a better patient's functional outcome. No randomized trial has yet compared MT to bridging therapy (BT) in stroke related to large artery occlusion in the anterior circulation. Some studies have focused on the safety and efficacy of endovascular treatment alone compared to BT, however with contradictory results (8)(9)(10)(11)(13)(14)(15)(16)(17)(18).

The aim of our study was to evaluate the contribution of IV rt-PA in patients treated

with endovascular procedure in case of acute ischemic stroke related to an occlusion of a proximal artery in the anterior circulation, by comparing clinical and radiological characteristics and outcomes between patients treated by BT (IV rt-PA + MT) and patients treated by MT alone.

PATIENTS AND METHODS

After January 2012, we prospectively collected a hospital-based registry of stroke patients with large artery occlusion admitted in the stroke unit of the Lille University hospital in order to receive an endovascular revascularization treatment. The organization of this stroke unit has previously been reported (19) (20). For the purpose of this study, we have included patients with stroke related to a proximal occlusion in the anterior circulation and treated by MT between January 2012 and September 2015. We have excluded patients with basilar artery occlusion and patients with stroke related to an anterior circulation occlusion who did not undergo MT because of recanalization, either spontaneously, either after IV rt-PA.

Eligibility criteria

Eligibility criteria for IV thrombolysis were those of ECASS 2 study with a time window extended to 4,5 hours (21). Age over 80 years was not an exclusion criteria (21)(22)(23). Patients with unknown time of stroke onset were treated if they had a DWI/FLAIR mismatch on MRI (Magnetic Resonance Imaging) performed at admission.

Eligibility criteria for endovascular treatment were: age beyond 18 years, NIHSS score ≥ 2 (National Institute of Health Stroke Scale), presence of large vessel

occlusion in anterior circulation on non-invasive vascular imaging performed as an emergency, possibility to start endovascular treatment within 8 hours after stroke onset. As for IV thrombolysis, patients with unknown time of onset were treated if they had a DWI/FLAIR mismatch on MRI performed at admission. Endovascular treatment was proposed after IV rt-PA in patients eligible for IV thrombolysis (BT) and as a first-line treatment only in patients with contra-indication to IV thrombolysis (MT alone).

Treatments

All eligible patients received a full dose of IV rt-PA according to the recommendations of ESO (22) (0.9 mg/kg, maximum 90 mg; 10% bolus followed by a 60-min infusion). Treatment with IV rt-PA was administered as soon as possible: in Lille Hospital in case of patients directly admitted in our institution, or before transfer in case of patients referred from remote hospitals.

The endovascular procedure was initiated as soon as possible and consisted of MT with thromboaspiration and/or stent-retrievers, depending on occlusion type and neurointerventionalists preference. The choice of the device was left to the discretion of the operator. The procedure was performed by one of the trained neurointerventionalists of the Lille University Hospital, under conscious sedation, by femoral access.

Imaging

At admission, the first-line imaging was MRI with FLAIR, gradient echo T2*, diffusion b1000 with ADC mapping and TOF sequences. In case of contra-indication for MRI, patients underwent CT (Computed-Tomography) and CTA (Computed-Tomography

Angiography). All patients underwent another MRI or CT scan 24 hours after treatment, or earlier in case of clinical worsening.

Data collection

Clinical data

We prospectively collected the following data: demographic characteristics (age, gender), main vascular risk factors (hypertension, diabetes, high cholesterol, active or history of tobacco use, excessive alcohol consumption), vascular history (previous myocardial infarction, previous or current atrial fibrillation, previous history of transient ischemic attack (TIA) in the preceding seven days, previous cerebral infarction or TIA having occurred more than seven days before the qualifying event), antithrombotic drugs received prior to stroke. Blood pressure and serum level glucose prior to MT were recorded.

Clinical severity was assessed using the NIHSS score (24) at admission, immediately before endovascular treatment, 2 hours and 24 hours after treatment, and at day 7 or at discharge for patients discharged before day 7. Early neurological improvement was defined by an improvement of more than 8 points of the NIHSS score or by NIHSS score equal 0 at 24 hours.

We recorded the time of symptom onset, needle time (start of IV rt-PA infusion) and time of groin puncture (conventional angiography). For patients with unknown stroke onset time, we recorded the time where the patient was last seen normal. When the time of onset was unknown, the onset-to-endovascular treatment time was considered as the delay between the last time the patient was seen normal and time of groin puncture, if it was 8 hours or less. When the delay was potentially of more than 8 hours and the decision of treatment given on the basis of a diffusion/Flair

mismatch, we considered the delay as being of 8 hours. The duration of the procedure was considered, measured by the time elapsed between the first and last contrast injection images of the conventional angiography. Etiology of stroke was determined at discharge according to TOAST criteria (25). We collected complications, including major hemorrhage, occurring during the first 7 days after stroke or before discharge, if discharge occurred before day 7. The occurrence of symptomatic intracerebral hemorrhage (sICH) was relieved, according to ECASS-2 trial (21), if the patient had clinical deterioration with an increase in the NIHSS score ≥ 4 points and if the hemorrhage was likely to be the cause of the clinical deterioration.

Radiological data

The ischemic volume was estimated using the ASPECT score (26) determined on the last imaging (MRI or CT-scan) performed before the endovascular procedure, corresponding either to the first imaging performed in an emergency, and for some patients (especially those referred from other hospitals) to a second imaging performed just before MT. The volume of ischemic lesion was calculated for patients with MRI on diffusion-weighted imaging (DWI) sequence ADC by an automatic segmentation system (Multi-modality Tumor Tracking Application, Phillips). The proportion of patients with a volume superior to 70 ml was calculated, based on previous studies (27)(28). Intracerebral hemorrhage was classified radiologically on imaging performed at 24 hours using ECASS trials criteria (21)(29)(30) as hemorrhagic infarction HI-1 or HI-2, parenchymal hematoma PH-1, PH-2. Site of occlusion was determined on angiographic images: middle cerebral artery (M1 or M2), terminus ICA occlusion, Tandem occlusion (ICA + MCA), isolated ICA occlusion. Recanalization in the territory of the treated artery was evaluated using modified

Thrombolysis in Cerebral Infarction scale (m-TICI) (31). Successful recanalization was defined as m-TICI score 2b or 3. Radiological images (MRI, CT-Scan, conventional angiography) were analyzed by a neuroradiologist blinded to clinical data (NB). The volume of the ischemic lesion on ADC sequences was measured by a neurologist (MF). The type of stent-retrievers used was noticed as the number of passes during the procedure.

Outcome measures

The mRS score (mRS) (32) was assessed at month-3 by a senior vascular neurologist during face to face interviews. For patients who did not undergo the 3-month visit, the mRS score was obtained by telephone contact (with the patient, his family or general practitioner). The endpoints were the proportion of survivors without dependency (mRS score 0-2 or similar to the pre stroke mRS) and the mortality rate at 3 months.

Statistical Analysis

The statistical analysis was performed on SPSS 22.0 package for windows, using median values, extremes, and percentages. The first step consisted of a bivariate analysis comparing demographics and clinical variables between (i) patients treated by BT and patients treated with MT alone; (ii) patients who were independent at 3 months (defined as having an mRS score 0-2 or similar to the pre-stroke mRS) and those who were not; (iii) patients who were dead at 3 months and those who were not. We used the Khi-2 test, corrected with Fisher's exact test when appropriate, to compare qualitative factors between groups, and we used Mann and Whitney's U test to compare quantitative variables. The last step of statistical analysis consisted of two regression analysis evaluating factors predicting functional independence at 3 months and factors predicting death at 3 months. The independent variables included

in the analysis were selected for the bivariate analysis with a 0.10 level as a screening criterion for the selection of candidate variables.

Ethics

The stroke database was declared at the institutional data protection board of Lille University hospital. The study was considered as observational by the internal review board.

RESULTS

POPULATION

- ***General features***

Between 1 January 2012 and 30 September 2015, 207 patients were enrolled in our study *(flow-chart figure 1).* Fifty-five patients (27%) were treated by MT alone because of contraindications to the use of IV rt-PA, listed in ***Table 1***. Among them, 11 patients had more that one type of contraindication. One hundred and fifty-two patients (73%) received IV rt-PA before the endovascular procedure (BT group).

In 9 patients (4%), the intracranial occlusion could not be accessed and the procedure was aborted. Thromboaspiration alone was sufficient for 30 patients (15%), the deployment of stent-retrievers alone concerned 68 patients (33%) and both types of procedure were used in 100 patients (48%). Regarding the stent-retrievers, in most cases, only one device was used (74%): Solitaire© (33) for 67 patients, Trevo© (34) for 27 patients, Revive© for 26 patients (study Re-ACT), Erik© for 4 patients and Catch© for 2 patients. In 28 patients (17%), a combination of different devices was used. Data were not available for 15 patients (9%).

➔ ***Main characteristics of the patients***

Table 2 presents demographic and baseline characteristics for the whole population and by treatment group. Among the 207 patients, 92 (44%) were males, the median age was 63 years (range: 18-95). The median NIHSS before the endovascular procedure was 18 (0 - 27). Forty-five patients (22%) were treated with unknown onset symptoms time, 115 patients (56%) were referred from other hospitals, 15 (7%) suffered their index stroke while they were already admitted in our institution (either in the stroke unit, either in another unit of the hospital). Two hundred and two patients (98%) underwent MRI before the endovascular procedure: the median volume on diffusion-weight sequence was 18 ml (0 - 275). One hundred and ninety-five patients (94%) underwent MRI at H24. The most frequent site of arterial occlusion was the middle cerebral artery (55%) portion M1.

Patients treated by BT were less likely to have arterial hypertension (55% vs 73%, p=0,019), previous or current atrial fibrillation (22% vs 49%, p<0,001), history of myocardial infarction (3% vs 18%, p=0,001). They were less often treated with anticoagulant prior to stroke (5% vs 33%, p<0,001) and less likely to have a cardio-embolic stroke (34% vs 67%, p<0,001). They were more likely to have been referred from remote hospitals (60% vs 44%, p=0,038), less likely to have presented their stroke when already hospitalized in our institution (1% vs 24%, p<0,001).

The delay between stroke onset and groin puncture did not differ significantly between groups (259 min for BT, 243 min for MT alone, p=0,387). In the group of patients with known stroke onset time, the delay from stroke onset to groin puncture tended to be shorter in patients treated by MT alone (216 min for MT alone, 229 min for BT, p=0,054).

Procedure duration and number of passes were similar in both groups of patients.

When considering only patients with successful recanalization, procedure duration was longer in the BT group (48 min vs 30 min, p=0,005): there was no difference for the number of passes between the groups (median 1.5 vs 1, p=0.263).

CLINICAL OUTCOMES

Data on clinical outcomes are presented in *Table 3*. Patients receiving BT had an overall better outcome: At month-3, the proportion of patients with favorable functional outcome was 57% in the BT group compared to 33% in the MT group (p=0,002). The 90-day mortality rate was 12% in the BT group versus 29% in the MT group (p=0,003). There was no difference in sICH between the two groups: 8% in the BT group vs 11% in the MT alone group (p=0,49). The rate of successful revascularization (mTICI 2b or 3) was higher in the BT group than in the MT group (74% vs 49%, p=0,001). The number of passes of stent retrievers did not differ between groups of patients (median 2 vs 2, p=0,163). The median of procedure duration was 54 min in the BT group and 45 min in the MT alone group (p=0,86). After excluding patients with no successful recanalization the duration of the procedure was longer when patients received IV rt-PA before MT (48 min vs 30 min, p=0,005).

➔ ***Functional outcome at 3 months***

The results of the bivariate analysis are given in *table 4.* Patients with a good functional outcome at 3 months (cmRS 0 - 2) were younger (61 vs 66 years, p=0,006), with a lower NIHSS score at baseline (15 vs 18, p<0,001). They were more often treated by BT (83% vs 64%, p=0,002), had a higher recanalization rate (88% vs 46%, p<0,001), and less sICH (2% vs 16%, p<0,001). They were less likely to have

ischemic lesion > 70 ml on initial MRI (12% vs 24%, p=0,023), and intracranial hemorrhage type PH-1 or 2 on H24 imaging (15 vs 28%, p=0,032). They were more likely to have MCA occlusion (71% vs 55%), and less likely to have Terminus ICA occlusion (5% vs 11%, p=0,034). The delay between stroke onset and groin puncture was shorter in patients with favorable functional outcome (234 vs 262 min, p=0,045). The difference did not remain significant after exclusion of patients with unknown stroke onset time (211 mn vs 240 mn, p=0,107).

The results of the multivariate analysis are given in *table 6.* The logistic regression analysis was performed on 199 patients because of missing data for 8 patients. The following variables were entered in the model: age, transfer from remote hospitals, NIHSS pre-MT, site of occlusion on arteriography, ADC volume > 70 mL, bridging therapy, successful recanalization, sICH, delay between stroke onset - groin puncture, and procedure duration. IV rt-PA before MT was an independent predictor of favorable functional outcome (adj OR 2,35, 95%IC 1,01-5,45) with a higher rate of favorable outcome in the group of patients treated by bridging therapy.

➔ ***Mortality at 3 months***

The results of the bivariate analysis are given in *table 5.* At month-3, the proportion of patients treated by BT among the group dead was 53% whereas it was 78% among those who survived (p=0,003). The risk of death at month-3 was associated with a higher age (67 vs 63 years, p=0,016), stroke with unknown onset symptoms time (38% vs 18%, p=0,011), cardioembolic stroke (65% vs 39%, p=0,037) and higher NIHSS pre-MT (21 vs 17, p=0,005). Patients have died before month-3 presented more often ischemic lesion volume > 70 mL on ADC sequences (78% vs 53%,

p<0,001), less frequently successful recanalization (47% vs 71%, p=0,006) and more often sICH (29% vs 5%, p<0,001).

The results of the Multivariate analysis are given in *table 6.*

The logistic regression analysis with death at 3 months was performed on 207 patients. The following variables were entered in the model: age, stroke with unknown stroke onset time, NIHSS score before MT, TOAST category, bridging therapy, successful recanalization, sICH and the delay from stroke onset to groin puncture. Bridging therapy was an independent predictor of mortality (adj OR 0,30, 95%IC 0,13 – 0,68) with a lower rate of death in the group of patients treated by bridging therapy.

DISCUSSION

In our cohort of 207 patients with ischemic stroke related to a proximal occlusion in the anterior circulation, BT compared to MT alone was associated to a better functional outcome and a lower mortality rate, with a higher rate of recanalization, without influence on the risk of sICH.

Many previous studies found prognosis to be similar in patients treated by BT compared to MT alone (8)(11)(14)(16)(17). However, some have included small numbers of patients (8)(11)(15) or have included not only patients with anterior circulation but also patients with basilar occlusion (11)(14)(16)(18), for whom the response to the different treatments (intravenous as endovascular) might differ from patients with stroke related to anterior circulation occlusion. In some of these studies, not all patients had received a full dose of IV rt-PA prior to endovascular treatment (8)(11)(18), which could have decreased the efficacy of the IV treatment. However,

other data suggest that IV rt-PA prior to MT might improve outcome. Guedin and colleagues (15), in a population of 68 patients with MCA occlusion, reported an increased rate of patients with early neurologic improvement when patients were treated by BT compared to MT alone. In that study, the rate of patients with favorable outcome at month 3 was higher in patients treated by BT (68% vs 52%), but the difference was not significant, which might be explained by the small number of patients (15). Pfefferkorn and colleagues reported that patients treated by BT were more likely to be functionally independent at month-3 (10). Kass-Hout and colleagues reported a lower rate of death at 3 months when patients were treated by IV rt-PA before the endovascular procedure (19% vs 29%), but the difference was not significant (11). Our study is, to our knowledge, the first to have found both functional and vital outcomes to be improved in patients treated by BT compared to MT alone.

This better outcome is probably mainly explained by the higher rate of successful recanalization obtained with the association of IV rt-PA to MT. Previous data have suggested that administration of IV rt-PA could facilitate MT with a higher rate of recanalization (9)(13)(15), which is in accordance with our results. Regarding the procedure, previous studies showed a shorter procedure duration (10)(13)(15) and a lower number of passes during procedure necessary to obtain recanalization (15). In our population, procedure duration and number of passes of stent retrievers did not differ between groups of patients. After excluding patients with no successful recanalization, the duration of the procedure was even longer in patients having received IV rt-PA before MT. This discrepancy is probably partly explained by difference in occlusion site in the different populations, with, in our study a higher proportion of tandem occlusion (22% vs 8%) in the BT group, which could explain the longer procedure duration, already reported in patients with tandem occlusion (35).

In our population, the time from stroke onset to groin puncture did not differ significantly between patients treated by BT and patients treated with MT alone, suggesting that, in centers well trained to IV thrombolysis, avoiding IV rt-PA will not necessarily lead to reduce the delay to initiation of endovascular treatment. However, it is important to notice, that in our population, the most frequent contra-indication for IV thrombolysis was the use of oral anticoagulant, which has led us to wait for biological results, before to decide if the patient could receive IV rt-PA. Our data do not allow any conclusion for patients without contra-indication to IV rt-PA. Time to initiation of MT was, however, in our population, not found to be a strong predictor of outcome, even after exclusion of patients with unknown onset time. The selection of patients on MRI criteria may partly explain this result, allowing to select patients who can still benefit of revascularization treatments, even when the delay from stroke onset increases. Another explanation is the major influence on prognosis of successful recanalization.

Our study has included quite a large number of patients, with data prospectively collected, with very few missing data and no patient lost to follow up. The characteristics of our patients and the outcome at 3 months are similar to those reported in the recent trials on MT (1)(2)(3)(4)(5), suggesting a good external validity of our findings. The main limitation is the monocentric nature of our study, whose results require to be confirmed by data from other centers with different procedures. In our institution, MT alone is reserved to patients with contra-indication to IV rt-PA, and we cannot extend our results to patients without contra-indication to IV thrombolysis. However, our findings encourage not to avoid IV thrombolysis prior to MT, when it is possible, before therapeutic trials prove that MT alone is as effective as BT in stroke related to large artery occlusion in the anterior circulation.

Figure 1: Flow-chart of inclusions

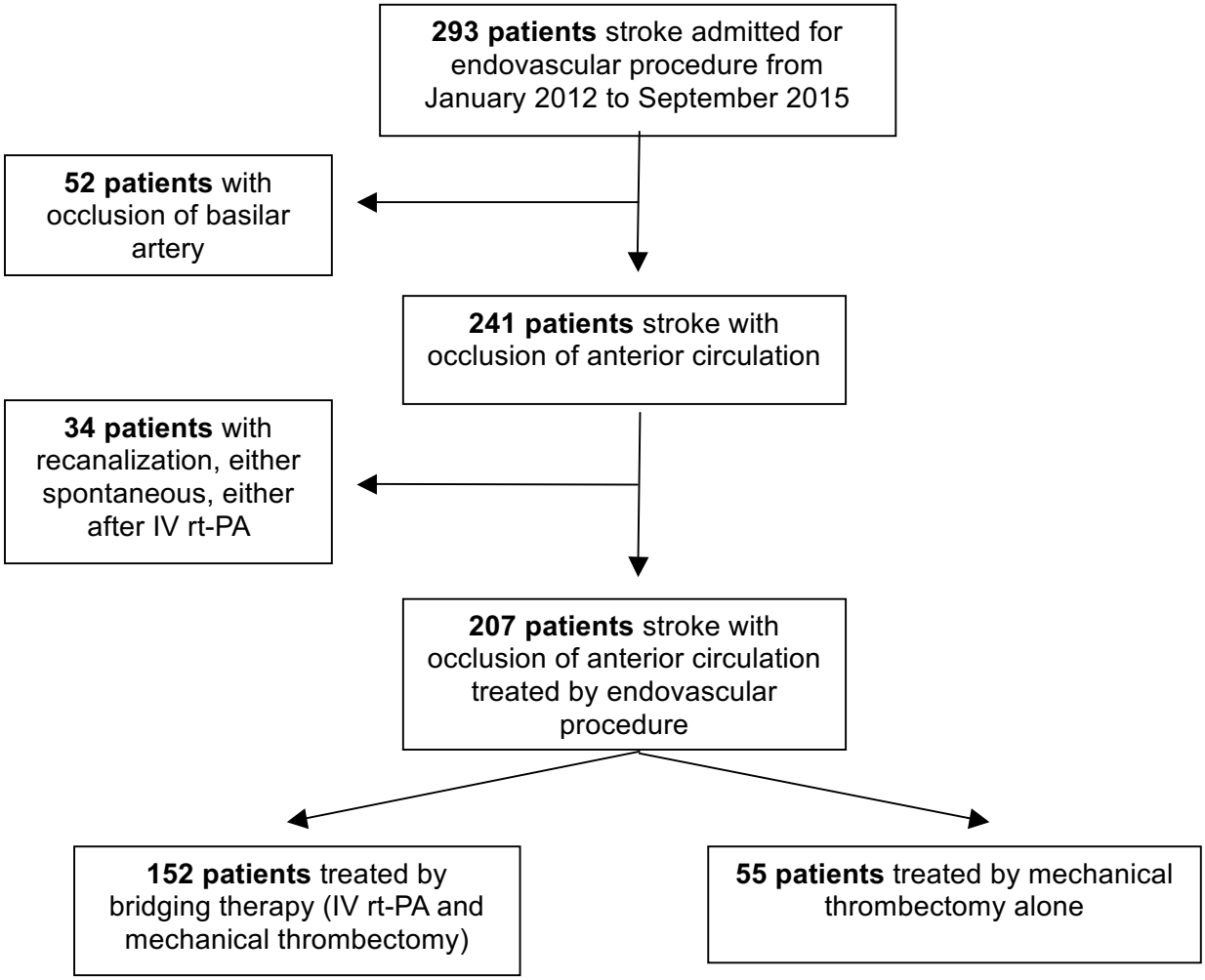

Table 1: Contraindications for administration of intravenous rt-PA

Type of contraindication	Number of patients = 55
Anticoagulation treatment (INR > 1,7)	25 (38%)
Recent surgery	12 (18%)
Acute ischemic stroke > 4,5 hours	10 (15%)
Significant volume of ischemic lesion *	8 (12%)
Recent major hemorrhage	7 (11%)
Unknown onset stroke **	2 (3%)
Brain tumor	1 (1%)
Endocarditis	1 (1%)

*Volume estimated on ASPECT score or diffusion-weighted imaging MRI (in milliliter), decision taken individually
** No DWI/FLAIR mismatch in MRI at admission

Table 2: Baseline characteristics of all patients, patients treated by bridging therapy and patients treated with mechanical thrombectomy alone

	All patient n = 207	Missing data	Bridging treatment n = 152	Mechanical thrombectomy n = 55	P
Demographic					
Male gender	92 (44%)	0	66 (43%)	26 (47%)	0,622
Age *	63 (18 - 95)	0	63 (18 - 95)	65 (28 - 89)	0,745
Age > 80 years	23 (11%)	0	16 (11%)	7 (13%)	0,656
Medical history					
Arterial hypertension	123 (59%)	0	83 (55%)	40 (73%)	**0,019**
Diabetes mellitus	23 (11%)	0	17 (11%)	6 (11%)	0,956
Hypercholesterolemia	77 (37%)	0	55 (36%)	22 (40%)	0,616
Previous or current tobacco use	95 (46%)	0	71 (47%)	24 (44%)	0,695
Excessive alcohol consumption	30 (13%)	0	18 (12%)	12 (22%)	0,394
Past vascular					
Previous myocardial infarction	15 (7%)	0	5 (3%)	10 (18%)	**0,001**
Previous or current fibrillation atrial	60 (29%)	0	33 (22%)	27 (49%)	**<0,001**
Previous TIA < 7 days	14 (7%)	0	9 (6%)	5 (9%)	0,53
Previous TIA or stroke > 7 days	30 (14%)	0	18 (12%)	12 (22%)	0,072
Antithrombotic before stroke					
Oral anticoagulation	26 (13%)	0	8 (5%)	18 (33%)	**<0,001**
Antiaggregation platelet	52 (25%)	0	37 (24%)	15 (27%)	0,668
Functional status prior to stroke					
mRS before stroke > 2	15 (7%)	0	8 (5%)	7 (13%)	0,067
Stroke characteristics					
Unknown onset stroke	45 (22%)	0	30 (20%)	15 (27%)	0,246
Patients referred from other hospital	115 (56%)	0	91 (60%)	24 (44%)	**0,038**
In-hospital stroke	15 (7%)	0	2 (1%)	13 (24%)	**<0,001**
NIHSS at admission *	17 (3 - 27)	0	17 (3 - 27)	18 (3 - 27)	0,186
NIHSS before thrombectomy *	18 (0 - 27)	0	17 (0 - 26)	19 (6 - 27)	0,158
Delay stroke onset - admission hospital (minutes) *	201 (0 - 480)	0	205 (0 - 480)	153 (0 - 480)	**0,011**
Delay stroke onset - needle (minutes) *		0	144 (30 - 480)		
Clinical and biological characteristics					
Arterial blood pressure systolic (mmHg) *	143 (95 - 220)	2	144 (95 - 210)	140 (95 - 220)	0,408
Arterial blood pressure diastolic (mmHg) *	80 (50 - 120)	2	80 (50 - 120)	80 (55 - 120)	0,815
Serum blood glucose (g/L) *	1,1 (0,7 - 3,1)	3	1,1 (0,7 - 3,1)	1,1 (0,7 - 2,5)	0,848
Imaging characteristics					
Volume ADC (mL) *	18 (0 - 275)	6	19 (0 - 194)	14 (0 - 275)	0,521
Volume ADC > 70 mL	35 (17%)	6	26 (17%)	9 (17%)	0,981
ASPECT score *	8 (2 - 10)	5	8 (2 - 10)	8 (3 - 10)	0,797
Characteristics of the procedure					
Delay stroke onset - start arteriography (minutes) *	256 (72 - 480)	0	259 (93 - 480)	243 (72 - 480)	0,387
Procedure duration (minutes) *	54 (4 - 253)	0	54 (4 - 211)	45 (5 - 253)	0,86
Site of occlusion on arteriography :		1			0,26
MCA - M2	*16 (8%)*		12 (8%)	4 (7%)	
MCA - M1	*113 (55%)*		81 (53%)	32 (59%)	
T occlusion	*36 (17%)*		23 (16%)	13 (24%)	
ICA	*3 (2%)*		2 (1%)	1 (2%)	
Tandem occlusion	*38 (18%)*		34 (22%)	4 (8%)	
Stroke Mechanism (TOAST)		0			**<0,001**
Atherothrombotic	33 (16%)		30 (20%)	3 (5%)	
Cardioembolic	89 (43%)		52 (34%)	37 (67%)	
Other know cause	17 (8%)		15 (10%)	2 (4%)	
Unknown cause	68 (33%)		55 (36%)	13 (24%)	

* Median values (extremes)
TIA < 7 days: transient ischemic attack occurred less 7 days
TIA or stroke > 7 days: transient ischemic attack or stroke occurred more than 7 days
mRS: modified Rankin Score
NIHSS at admission or before thrombectomy: National Institute of Health Stroke Scale
Volume ADC: volume diffusion-weighted imaging MRI (in milliliter) / ASPECT score: on MRI or CT

Table 3: Outcomes of all patients, patients treated by bridging therapy and patients treated with mechanical thrombectomy alone

	All patient n = 207	Missing data	Bridging treatment n = 152	Mechanical thrombectomy n = 55	P
Clinical data					
NIHSS H24	12 (0 - 38)	0	10 (0 - 38)	17 (0 - 38)	**0,001**
NIHSS H24 - H0	- 6 (- 24 - 21)	0	- 6 (- 21 - 21)	- 1 (- 24 - 19)	**0,002**
Early neurological outcome	70 (34%)	0	58 (38%)	12 (22%)	**0,028**
Pneumopathy day 7	44 (21%)	0	24 (16%)	20 (36%)	**0,001**
Urinary infection day 7	18 (9%)	0	10 (7%)	8 (15%)	0,072
Pulmonary embolism day 7	5 (2%)	0	4 (3%)	1 (2%)	1
Major hemorrhage day 7	6 (3%)	0	5 (3%)	1 (2%)	1
Angioedema day 7	1 (0,5%)	0	1 (1%)	0 (0%)	1
Malignant infarction day 7	21 (10%)	0	14 (9%)	7 (13%)	0,459
Hemicraniectomy	16 (8%)	0	12 (8%)	4 (7%)	1
Other complications	38 (18%)	0	29 (19%)	9 (16%)	0,656
NIHSS day 7	7 (0 - 35)	0	5 (0 - 35)	12 (0 - 35)	0,056
cMRS 0-1 3 months	66 (32%)	0	55 (36%)	11 (20%)	**0,027**
cMRS 0-2 3 months	105 (51%)	0	87 (57%)	18 (33%)	**0,002**
Symptomatic ICH (ECASS-2)	18 (9%)	0	12 (8%)	6 (11%)	0,49
Mortality 3 months	34 (16%)	0	18 (12%)	16 (29%)	**0,003**
Imaging H24 data					
Any hemorrhage	112 (54%)	0	86 (57%)	26 (47%)	0,235
HI 1 or 2	68 (33%)	0	49 (32%)	19 (35%)	0,755
PH 1 or 2	44 (21%)	0	37 (24%)	7 (13%)	0,071
Arteriography data					
Recanalization :		0			**0,032**
TICI 0	*43 (21%)*		25 (16%)	18 (33%)	
TICI 1	*5 (2%)*		3 (2%)	2 (4%)	
TICI 2A	*21 (10%)*		13 (9%)	8 (14%)	
TICI 2B	*68 (33%)*		55 (36%)	13 (24%)	
TICI 3	*70 (34%)*		56 (37%)	14 (25%)	
Recanalization TICI 2B or 3	138 (67%)	0	111 (74%)	27 (49%)	**0,001**
Number of pass	2 (0 - 6)	12	2 (0 - 6)	2 (1 - 6)	0,163

* Median values (extremes)
mRS: modified Rankin Score. cMRS: modified Rankin Score or similar to pre-stroke mRS
NIHSS before thrombectomy: National Institute of Health Stroke Scale
NIHSS H24 – H0: difference between NIHSS at 24 hours and NIHSS before thrombectomy
Other complications: seizure, recurrence of stroke, acute pulmonary oedema, phlebitis, myocardial infarction
ICH: intracranial hemorrhage
PH-1 or PH-2: parenchymal hematoma type 1 or 2 (ECASS-2) /HI 1 or 2: hemorrhagic infarction type 1 or 2 (ECASS-2)

Table 4: Bivariate analysis of factors predictive good functional outcome at 3 months (mRS ≤ 2 or similar pre-stroke mRS)

	cmRS ≤ 2 n = 105	cmRS > 2 n = 102	P
Demographic			
Age *	61 (18 - 88)	66 (33 - 95)	**0,006**
Stroke characteristics			
Unknown onset stroke	19 (18%)	26 (26%)	0,197
Patients referred from other hospital	52 (50%)	63 (62%)	0,076
In-hospital stroke	6 (6%)	9 (9%)	0,388
NIHSS at admission *	15 (3 - 24)	18 (3 - 27)	**< 0,001**
NIHSS before thrombectomy *	16 (0 - 24)	20 (6 - 27)	**< 0,001**
Delay stroke onset - admission hospital (minutes) *	186 (0 - 480)	221 (0 - 480)	**0,047**
Delay stroke onset - needle (minutes) *	135 (30 - 480)	165 (45 - 480)	**0,03**
rt-PA before thrombectomy (Bridging)	87 (83%)	65 (64%)	**0,002**
Imaging characteristics			
Volume ADC (mL) *	16 (0 - 194)	22 (0 - 275)	0,22
ASPECT score	8 (2 - 10)	7 (3 - 10)	0,162
Volume ADC > 70 (mL) *	12 (12%)	23 (24%)	**0,023**
Characteristics of the procedure			
Delay stroke onset - start arteriography (minutes) *	234 (87 - 480)	262 (72 - 480)	**0,045**
Procedure duration (minutes) *	47 (14 - 211)	60 (4 - 253)	**0,017**
Site of occlusion on arteriography :			**0,034**
MCA - M2	11 (11%)	5 (5%)	
MCA - M1	63 (60%)	50 (50%)	
T occlusion	11 (11%)	25 (25%)	
ICA	1 (1%)	2 (2%)	
Tandem occlusion	19 (18%)	19 (19%)	
Stroke Mechanism (TOAST)			0,423
Atherothrombotic	22 (21%)	11 (11%)	
Cardioembolic	40 (38%)	49 (48%)	
Other know cause	9 (9%)	8 (8%)	
Unknown cause	34 (32%)	34 (33%)	
Clinical data			
NIHSS H24 *	5 (0 - 25)	19 (0 - 38)	**< 0,001**
NIHSS H24 - H0 *	- 8 (- 21 - 21)	0 (- 24 - 19)	**< 0,001**
Early neurological outcome	61 (58%)	9 (9%)	**< 0,001**
NIHSS day 7	3 (0 - 23)	16 (0 - 35)	**< 0,001**
Pneumopathy day 7	5 (5%)	39 (38%)	**< 0,001**
Urinary infection day 7	9 (9%)	9 (9%)	0,949
Pulmonary embolism day 7	1 (1%)	4 (4%)	0,208
Major hemorrhage day 7	2 (2%)	4 (4%)	0,441
Malignant infarction day 7	2 (2%)	19 (19%)	**< 0,001**
Hemicraniectomy	2 (2%)	14 (14%)	**0,001**
Other complications	14 (13%)	24 (24%)	0,058
Symptomatic HIC (ECASS-2)	2 (2%)	16 (16%)	**< 0,001**
Imaging H24 data			
Any hemorrhage	52 (49%)	60 (59%)	0,139
HI-1 or 2	36 (34%)	32 (31%)	0,655
PH 1 or 2	16 (15%)	28 (28%)	**0,032**
Arteriography data			
Recanalization TICI 2B or 3	92 (88%)	47 (46%)	**< 0,001**

* Median values (extremes)
NIHSS before thrombectomy: National Institute of Health Stroke Scale
NIHSS H24 – H0: difference between NIHSS at 24 hours and NIHSS before thrombectomy
Other complications: seizure, recurrence of stroke, acute pulmonary oedema, phlebitis, myocardial infarction
ICH: intracranial hemorrhage
PH-1 or PH-2: parenchymal hematoma type 1 or 2 (ECASS-2) / HI 1 or 2: hemorrhagic infarction type 1 or 2 (ECASS-2)

Table 5: Bivariate analysis of factors predictive mortality at 3 months

	DEATH n = 34	ALIVE n = 173	p
Demographic			
Age *	67 (42 - 95)	63 (18 - 93)	**0,016**
Stroke characteristics			
Unknown onset stroke	13 (38%)	32 (18%)	**0,011**
Patients referred from other hospital	21 (62%)	94 (54%)	0,425
In-hospital stroke	4 (12%)	11 (6%)	0,278
NIHSS at admission *	20 (9 -25)	16 (3 - 27)	**0,017**
NIHSS before thrombectomy *	21 (9 - 25)	17 (0 - 27)	**0,005**
Delay stroke onset - admission hospital (minutes) *	213 (0 - 480)	199 (0 - 480)	0,276
Delay stroke onset - needle (minutes) *	202 (56 - 480)	140 (30 - 480)	**0,022**
rt-PA before thrombectomy (Bridging)	18 (53%)	134 (78%)	**0,003**
Imaging characteristics			
Volume ADC (mL) *	22 (0 - 275)	18 (0 - 194)	0,933
ASPECT score *	8 (3 - 10)	8 (2 - 10)	0,952
Volume ADC > 70 (mL)	18 (53%)	134 (78%)	**< 0,001**
Characteristics of the procedure			
Delay stroke onset - start arteriography (minutes) *	250 (72 - 480)	258 (76 - 480)	0,403
Site of occlusion on arteriography :			0,858
MCA - M2	1 (3%)	15 (9%)	
MCA - M1	18 (55%)	95 (55%)	
T occlusion	11 (33%)	25 (15%)	
ICA	2 (6%)	1 (1%)	
Tandem occlusion	1 (3%)	37 (21%)	
Stroke Mechanism (TOAST)			**0,037**
Atherothrombotic	0	33 (19%)	
Cardioembolic	22 (65%)	67 (39%)	
Other know cause	1 (3%)	16 (9%)	
Unknown cause	11 (32%)	57 (33%)	
Clinical data			
NIHSS H24 *	25 (0 - 38)	10 (0 - 38)	**< 0,001**
NIHSS H24 - H0 *	- 8 (- 21 - 21)	0 - 24 - 19)	**< 0,001**
Early neurological outcome	1 (3%)	69 (40%)	**< 0,001**
NIHSS day 7 *	13 (0 - 35)	6 (0 - 25)	0,755
Pneumopathy day 7	12 (35%)	32 (18%)	**0,029**
Urinary infection day 7	3 (9%)	15 (9%)	1
Pulmonary embolism day 7	0	5 (3%)	0,594
Major hemorrhage day 7	1 (3%)	5 (3%)	1
Malignant infarction day 7	8 (24%)	13 (8%)	**0,005**
Hemicraniectomy	4 (12%)	12 (7%)	0,307
Other complications	9 (27%)	29 (17%)	0,181
Symptomatic HIC (ECASS-2)	10 (29%)	8 (5%)	**< 0,001**
Imaging H24 data			
Any hemorrhage	19 (56%)	93 (54%)	0,773
HI-1 or 2	8 (24%)	60 (35%)	0,206
PH 1 or 2	11 (32%)	33 (19%)	0,084
Arteriography data			
Recanalization TICI 2B or 3	16 (47%)	123 (71%)	**0,006**

* Median values (extremes)
mRS: modified Rankin Score. cMRS: modified Rankin Score or similar to pre-stroke mRS
NIHSS before thrombectomy: National Institute of Health Stroke Scale
NIHSS H24 – H0: difference between NIHSS at 24 hours and NIHSS before thrombectomy
Other complications: seizure, recurrence of stroke, acute pulmonary oedema, phlebitis, myocardial infarction
ICH: intracranial hemorrhage
PH-1 or PH-2: parenchymal hematoma type 1 or 2 (ECASS-2) /HI 1 or 2: hemorrhagic infarction type 1 or 2 (ECASS-2)

Table 6: Results of the logistic regression analysis (See text for other variables not selected by the model)

Dependent variables	Logistic regression	Independent variable	adjOR	95% CI.OR	p values
mRS 0 - 2 at month 3 or similar to the pre-stroke mRS	Overall *p* value < 0,001	Successful recanalization	9,03	3,979 - 20,493	< 0,001
	R2 = 0,453	Bridging therapy	2,354	1,017 - 5,448	0,046
	Well classified = 77,9%	NIHSS score pre-MT	0,881	0,815 - 0,952	0,001
		Transfer from remote hospital	0,374	0,176 - 0,794	0,01
		ADC volume > 70 mL	0,368	0,143 - 0,947	0,038
		sICH	0,123	0,024 - 0,622	0,011
Death at month 3	Overall *p* value < 0,001	sICH	9,15	3,038 - 27,561	< 0,001
	R2 = 0,236	Age (years)	1,039	1,009 - 1,071	0,011
	Well classified = 85,5%	Bridging therapy	0,296	0,129 - 0,681	0,004

mRS: modified Rankin Score.
NIHSS score pre-MT: National Institute of Health Stroke Scale before mechanical thrombectomy
sICH: symptomatic intracranial hemorrhage (ECASS-2)
Successful recanalization: score TICI 2b or 3
OR: odds ratio / adjOR: adjusted odds ratio / 95% CI: 95% confidence interval

REFERENCES

1. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 1 janv 2015;372(1):11‑20.

2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. N Engl J Med. 12 mars 2015;372(11):1019‑30.

3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 11 juin 2015;372(24):2296‑306.

4. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. N Engl J Med. 12 mars 2015;372(11):1009‑18.

5. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 11 juin 2015;372(24):2285‑95.

6. Rha J-H, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke J Cereb Circ. mars 2007;38(3):967‑73.

7. Mazighi M, Chaudhry SA, Ribo M, Khatri P, Skoloudik D, Mokin M, et al. Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. Circulation. 14 mai 2013;127(19):1980‑5.

8. Broeg-Morvay A, Mordasini P, Bernasconi C, Bühlmann M, Pult F, Arnold M, et al. Direct Mechanical Intervention Versus Combined Intravenous and Mechanical Intervention in Large Artery Anterior Circulation Stroke: A Matched-Pairs Analysis. Stroke. 23 févr 2016;STROKEAHA.115.011134.

9. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. Stroke J Cereb Circ. déc 1999;30(12):2598‑605.

10. Pfefferkorn T, Holtmannspötter M, Patzig M, Brückmann H, Ottomeyer C, Opherk C, et al. Preceding intravenous thrombolysis facilitates endovascular mechanical recanalization in large intracranial artery occlusion. Int J Stroke Off J Int Stroke Soc. janv 2012;7(1):14‑8.

11. Kass-Hout T, Kass-Hout O, Mokin M, Thesier DM, Yashar P, Orion D, et al. Is bridging with intravenous thrombolysis of any benefit in endovascular therapy for acute ischemic stroke? World Neurosurg. oct 2014;82(3‑4):e453-458.

12. Desilles J-P, Loyau S, Syvannarath V, Gonzalez-Valcarcel J, Cantier M, Louedec L, et al. Alteplase Reduces Downstream Microvascular Thrombosis and Improves the Benefit of Large Artery Recanalization in Stroke. Stroke J Cereb Circ. nov 2015;46(11):3241‑8.

13. Behme D, Kabbasch C, Kowoll A, Dorn F, Liebig T, Weber W, et al. Intravenous Thrombolysis Facilitates Successful Recanalization with Stent-Retriever Mechanical Thrombectomy in Middle Cerebral Artery Occlusions. J Stroke Cerebrovasc Dis. avr 2016;25(4):954‑9.

14. Bhatia R, Shobha N, Menon BK, Bal SP, Kochar P, Palumbo V, et al. Combined full-dose IV and endovascular thrombolysis in acute ischaemic stroke. Int J Stroke. déc 2014;9(8):974‑9.

15. Guedin P, Larcher A, Decroix J-P, Labreuche J, Dreyfus J-F, Evrard S, et al. Prior IV Thrombolysis Facilitates Mechanical Thrombectomy in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. mai 2015;24(5):952‑7.

16. Leker RR, Pikis S, Gomori JM, Cohen JE. Is Bridging Necessary? A Pilot Study of Bridging versus Primary Stentriever-Based Endovascular Reperfusion in Large Anterior Circulation Strokes. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. juin 2015;24(6):1163‑7.

17. Weber R, Nordmeyer H, Hadisurya J, Heddier M, Stauder M, Stracke P, et al. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. J NeuroInterventional Surg. 22 févr 2016;neurintsurg-2015-012236.

18. Wolfe T, Suarez JI, Tarr RW, Welter E, Landis D, Sunshine JL, et al. Comparison of Combined Venous and Arterial Thrombolysis with Primary Arterial Therapy Using Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. mai 2008;17(3):121‑8.

19. Bodenant M, Leys D, Debette S, Cordonnier C, Dumont F, Hénon H, et al. Intravenous thrombolysis for acute cerebral ischaemia: comparison of outcomes between patients treated at working versus nonworking hours. Cerebrovasc Dis Basel Switz. 2010;30(2):148‑56.

20. Litke R, Moulin S, Cordonnier C, Fontaine P, Leys D. Influence of glycaemic control on the outcomes of patients treated by intravenous thrombolysis for cerebral ischaemia. J Neurol. nov 2015;262(11):2504‑12.

21. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet Lond Engl. 17 oct 1998;352(9136):1245‑51.

22. European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis Basel Switz. 2008;25(5):457‑507.

23. IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet Lond Engl. 23 juin 2012;379(9834):2352‑63.

24. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke J Cereb Circ. nov 1994;25(11):2220‑6.

25. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke J Cereb Circ. janv 1993;24(1):35‑41.

26. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet Lond Engl. 13 mai 2000;355(9216):1670‑4.

27. Mlynash M, Lansberg MG, De Silva DA, Lee J, Christensen S, Straka M, et al. Refining the definition of the malignant profile: insights from the DEFUSE-EPITHET pooled data set. Stroke J Cereb Circ. mai 2011;42(5):1270‑5.

28. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol. oct 2012;11(10):860‑7.

29. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 4 oct 1995;274(13):1017‑25.

30. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, et al. Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. Lancet Neurol. déc 2009;8(12):1095‑102.

31. Tomsick T, Broderick J, Carrozella J, Khatri P, Hill M, Palesch Y, et al. Revascularization results in the Interventional Management of Stroke II trial. AJNR Am J Neuroradiol. mars 2008;29(3):582‑7.

32. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke J Cereb Circ. mai 1988;19(5):604‑7.

33. Dávalos A, Pereira VM, Chapot R, Bonafé A, Andersson T, Gralla J, et al. Retrospective multicenter study of Solitaire FR for revascularization in the treatment of acute ischemic stroke. Stroke J Cereb Circ. oct 2012;43(10):2699‑705.

34. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet Lond Engl. 6 oct 2012;380(9849):1231‑40.

35. Marnat G, Mourand I, Eker O, Machi P, Arquizan C, Riquelme C, et al. Endovascular Management of Tandem Occlusion Stroke Related to Internal Carotid Artery Dissection Using a Distal to Proximal Approach: Insight from the RECOST Study. AJNR Am J Neuroradiol. 10 mars 2016;

CONCLUSION GENERALE

Notre travail a montré qu'en cas d'infarctus cérébral par occlusion proximale de circulation antérieure, l'administration de rt-PA IV avant la procédure endovasculaire (thérapie combinée), comparée à la thrombectomie mécanique seule, est associée à un meilleur pronostic fonctionnel et un taux de mortalité plus faible à 3 mois, avec un meilleur taux de recanalisation, et ce, sans augmenter le risque hémorragique.

Nos résultats encouragent donc l'administration de rt-PA IV avant la procédure endovasculaire, en l'absence de contre-indications, en attendant que des études thérapeutiques randomisées prouvent que la thrombectomie mécanique est aussi efficace que la thérapie combinée dans les infarctus cérébraux par occlusion artérielle de circulation antérieure.

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Date de Soutenance : 19 MAI 2016

Titre de la Thèse : Devenir après un infarctus cérébral par occlusion de circulation antérieure traité par thrombectomie mécanique – Influence du traitement thrombolytique par rt-PA intraveineux

Thèse - Médecine - Lille 2016

Cadre de classement : *Neurologie*

DES + spécialité : *Neurologie*

Mots-clés : Infarctus cérébral. Ischémie cérébrale. Thrombolyse. Thrombectomie mécanique. Thérapie combinée. Devenir.

Résumé :

Objectif : Plusieurs études randomisées ont récemment prouvé que l'administration du *recombinant tissue-plasminogen activator* intraveineux (rt-PA IV) suivie par une thrombectomie mécanique (TM) améliore le pronostic fonctionnel des patients ayant présenté un infarctus cérébral causé par l'occlusion artérielle proximale de circulation antérieure. Notre objectif était d'évaluer l'influence du rt-PA IV sur le pronostic, en comparant les caractéristiques et le devenir des patients ayant reçu (groupe thérapie combinée TC) ou non le rt-PA IV (groupe TM seul) avant le traitement endovasculaire.

Méthode : De janvier 2012 à septembre 2015, nous avons inclus dans un registre prospectif tous les patients présentant un infarctus cérébral par occlusion proximale de circulation antérieure, traitée par TM, précédée ou non de rt-PA IV. Nous avons évalué l'influence du rt-PA IV sur le pronostic fonctionnel favorable (défini par un score mRS 0 – 2 ou égal au mRS avant l'AVC) et sur la mortalité à 3 mois.

Résultats : 207 patients ont été inclus (médiane âge 63 ans, 44% hommes) : 152 (73%) dans le groupe TC, 55 (27%) dans le groupe TM. Les patients traités par TC présentaient moins souvent d'hypertension artérielle (55% vs 73%, p=0,019), de fibrillation atriale (22% vs 49%, p<0,001) ou d'antécédent d'infarctus du myocarde (3% vs 18%, p=0,001). Ils étaient moins souvent traités par anticoagulant oral avant l'AVC (5% vs 33%, p<0,001) et avaient moins souvent d'AVC d'origine cardio-embolique (34% vs 67%, p<0,001). Ils étaient plus fréquemment transférés à partir d'autres hôpitaux (60% vs 44%, p=0,038). L'analyse bivariée a montré que les patients du groupe TC avaient un taux plus élevé de recanalisation artérielle (74% vs 49%, p=0,001), un meilleur pronostic fonctionnel (57 % vs 33%, p=0,002), un taux de mortalité plus faible (12% vs 29%, p=0,003), sans augmentation du risque d'hémorragie intracérébrale symptomatique (8% vs 11%, p=0,49). L'analyse multivariée a montré que l'administration du rt-PA IV était un facteur prédictif indépendant d'un pronostic fonctionnel favorable (adj OR 2,35, 95%IC 1,01-5,45), et de survie (adj OR 0,30, 95%IC 0,13 – 0,68) à 3 mois.

Conclusion : Dans notre population, l'administration au préalable du rt-PA IV améliore le pronostic fonctionnel et vital à 3 mois des patients traités par TM. Ces résultats encouragent l'utilisation du rt-PA IV, en l'absence de contre-indication, avant la procédure endovasculaire pour les occlusions proximales de circulation antérieure.

Composition du Jury :

Président : Pr Jean-Pierre PRUVO

Assesseurs : Pr Xavier LECLERC, Pr Mikael MAZIGHI, Pr Charlotte CORDONNIER, Dr Hilde HENON