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Facteurs Prédictifs de Transformation Hémorragique après Thrombectomie Mécanique Des Accidents Ischémiques de Circulation Antérieure

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Martin BRETZNER

JURY

Président :

Monsieur le Professeur Jean-Pierre PRUVO

Assesseurs :

Monsieur le Professeur Xavier LECLERC

Madame le Professeur Charlotte CORDONNIER

Directeur de Thèse :

Monsieur le Docteur Nicolas BRICOUT

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Introduction : La transformation hémorragique après thrombectomie mécanique des AVC ischémiques est une complication majeure menaçant la survie et le pronostic fonctionnel des patients. L'objectif de l'étude était d'évaluer les facteurs prédictifs de transformation hémorragique après thrombectomie mécanique.

Méthodes : Nous avons conduit une étude de cohorte à partir du registre prospectif des patients avec AVC ischémique de circulation antérieure ayant bénéficié d'une thrombectomie mécanique entre 2015 et 2017. Nous avons analysé les données cliniques (antécédents, score NIHSS), biologiques (glycémie, plaquettes, tests de coagulation) et radiologiques (ASPECTS et volume d'infarctus initiaux) de base, les scores de recanalisation angiographiques (mTICI), et la présence d'un remaniement hémorragique sur l'IRM de suivi à J-1 selon la classification ECASS II.

Résultats : Parmi les 643 patients inclus, les facteurs de risque de transformation hémorragique étaient : la thrombolyse intraveineuse, la glycémie, la thrombocytémie à l'admission, le volume lésionnel ischémique initial, le délai de prise en charge ainsi que la recanalisation intracrânienne. Les déterminants d'hémorragie intracrânienne symptomatique (sICH) étaient : le diabète, la thrombolyse intraveineuse, la pression artérielle systolique à l'admission et le volume ischémique. Le délai de prise en charge semblait être un facteur de risque et la recanalisation un facteur protecteur mais ces associations n'étaient pas significatives.

Conclusion : Les facteurs de risque de transformation hémorragique des lésions ischémiques après thrombectomie étaient similaires à ceux après thrombolyse IV à l'exception de l'âge et du NIHSS. La recanalisation était un facteur de risque de transformation hémorragique mais semblait protéger du sICH.

LISTE DES ABREVIATIONS

ADC *: apparent diffusion coefficient*

AIS LVO *: acute ischemic stroke with large intracranial vessel occlusion*

ASPECTS *: Alberta Stroke Program Early CT Score*

AVC *: accidents vasculaires cérébraux*

BBB : *blood-brain barrier*

BHE *: barrière hémato-encéphalique*

DSA *: digital subtraction angiography*

ECASS *: European Cooperative Acute Stroke Study*

HT *: hemorrhagic transformation*

ICA *: internal carotid artery*

IVT *: intravenous thrombolysis*

MCA *: middle cerebral artery*

mRS *: modified Rankin Score*, *: modified Rankin Scale*

MT *: Mechanical thrombectomy*

mTICI *: modified Thrombolysis in Cerebral Infarction scale*

NIHSS *: National Institutes of Health Stroke Scale*

sICH *: symptomatic intracerebral hemorrhage*

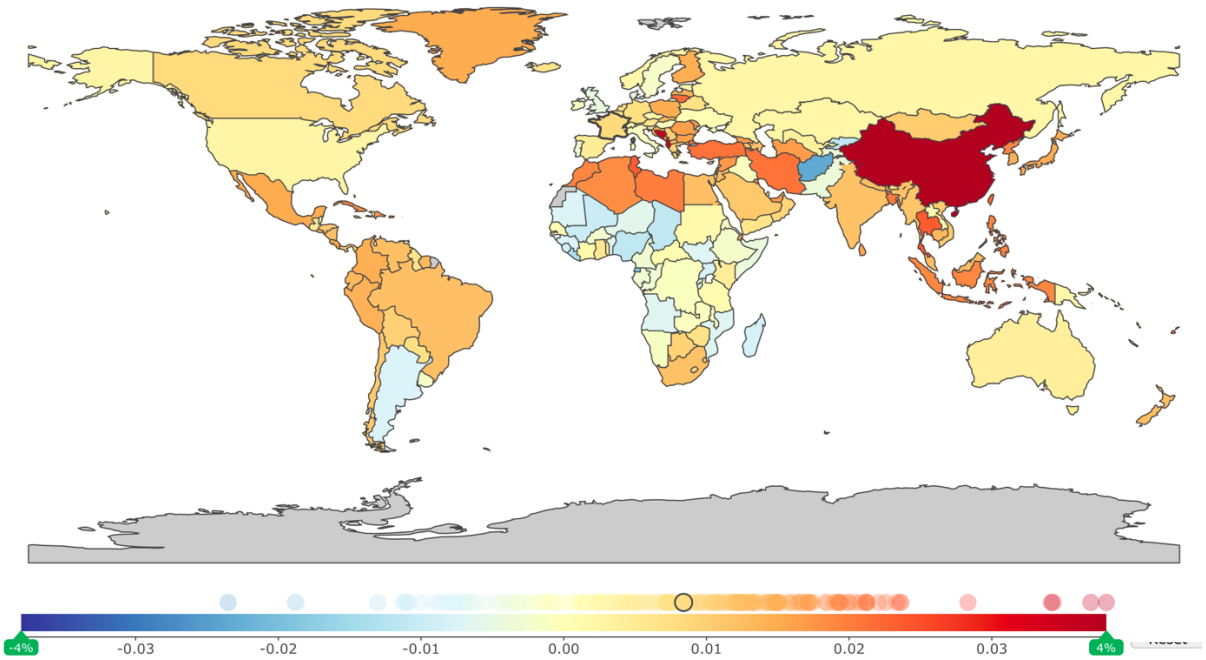
TH *: transformation hémorragique*

INTRODUCTION GENERALE

La pandémie AVC

Les accidents vasculaires cérébraux (AVC) touchent environ 140 000 patients par an en France. Du fait de l'amélioration de la filière de prise en charge, la mortalité a chuté, faisant mécaniquement augmenter le nombre de survivants et donc de handicaps. Les AVC sont la première cause de handicap fonctionnel non traumatique dans le monde et on estime qu'ils ont été responsables de 193 années vécues handicapées en France en 2017[1].

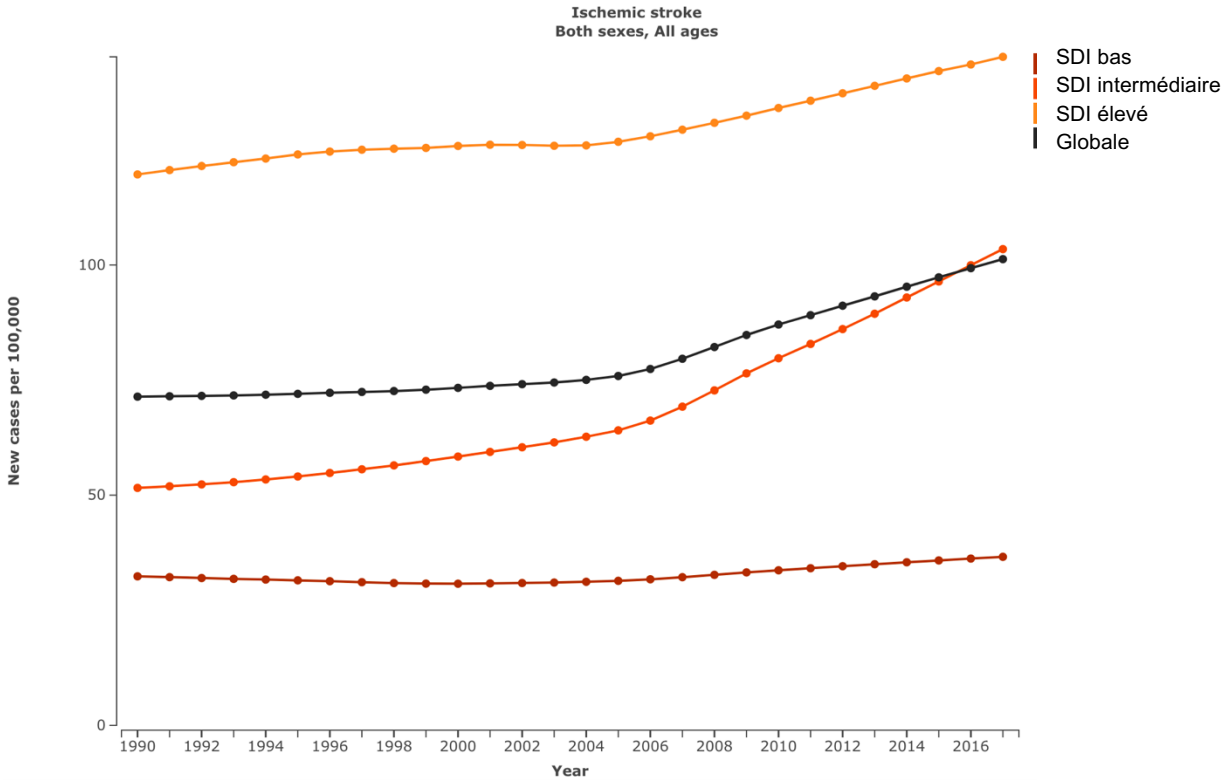
Figure 1 : Évolution de l'incidence des AVC ischémiques dans le monde de 1990 à 2017[1]



On note que les incidences ayant augmenté le plus fortement, représentées en couleurs chaudes, concernent les pays en voie de développement ayant atteint, en 2017, un développement socio-économique intermédiaire. L'incidence des AVC en France entre 1990 et 2017 a augmenté de 0,84%, représentée par un cercle noir sur l'échelle horizontale sous-jacente à la figure.

[1] Institute for Health Metrics and Evaluation (IHME). GBD Compare. Disponible sur : http://vizhub.healthdata.org/gbd-compare (Accédé le 20/11/2018).

Figure 2 : Évolution de l'incidence annuelle d'AVC ischémique par 100 000 habitants par région homogène de SDI[1].



Le SDI (Index de Développement Sociodémographique) est un indicateur de santé mixte prenant en compte le revenu par habitant, le niveau d'éducation et un indice synthétique de fécondité.

Le coût économique est considérable : on estime en Europe que les AVC ont engendré 45 milliards d'euros de dépenses en 2016 dont 20 milliards directement imputés aux systèmes de santé nationaux[2].

A l'échelle mondiale, on assiste à une augmentation rapide de l'incidence des AVC accompagnant l'occidentalisation des pays en voie de développement, ce phénomène est illustré sur les **figures 1 et 2**.

[2] Wilckins et al., "European Cardiovascular Disease Statistics 2017 Edition."

Les traitements disponibles

Pour les besoins de ce travail nous nous focaliserons sur les AVC ischémiques par occlusion artérielle.

Le premier traitement des AVC demeure l'unité de soins intensifs neurovasculaire, diminuant de 29% le risque de mortalité ou de dépendance fonctionnelle[3].

En 1995, l'étude NINDS introduit le traitement fibrinolytique intraveineux dans les 3 heures suivant le début des symptômes permettant à 1 patient sur 7 pris en charge précocement d'augmenter ses chances de conserver une indépendance fonctionnelle à 3 mois[4]. En 2008, l'étude ECASS III étend cette fenêtre thérapeutique à 4h30 faisant augmenter le nombre de patients éligibles[5].

Vingt ans après NINDS, le traitement de l'AVC est révolutionné par la publication rapprochée de plusieurs études randomisées contrôlées retrouvant un très large bénéfice d'une thérapie combinée associant la thrombectomie mécanique au traitement fibrinolytique[6,7,8,9,10,11]. Le bénéfice est considérable ramenant le nombre de patients à traiter à 3 pour 1 patient fonctionnellement indépendant. On assiste alors à une redistribution des cartes dans les filières de soins de l'AVC. Le nombre de thrombectomies réalisées augmente de manière exponentielle sur le territoire français passant de 1222 en 2014 à 5591 en 2017. La thrombectomie est alors proposée dans les 6 à 8 heures suivant le début des symptômes. En 2018, deux études, DAWN et DEFUSE3, proposent d'étendre la fenêtre thérapeutique jusqu'à

[3] "Collaborative Systematic Review of the Randomised Trials of Organised Inpatient (Stroke Unit) Care after Stroke."
[4] Disorders and Group, "Tissue Plasminogen Activator for Acute Ischemic Stroke."
[5] Hacke et al., "Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke."
[6] Berkhemer et al., "A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke."
[7] Goyal et al., "Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke."
[8] Saver et al., "Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke."
[9] Campbell et al., "Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection."
[10] Jovin et al., "Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke."
[11] Bracard et al., "Mechanical Thrombectomy after Intravenous Alteplase versus Alteplase Alone after Stroke."

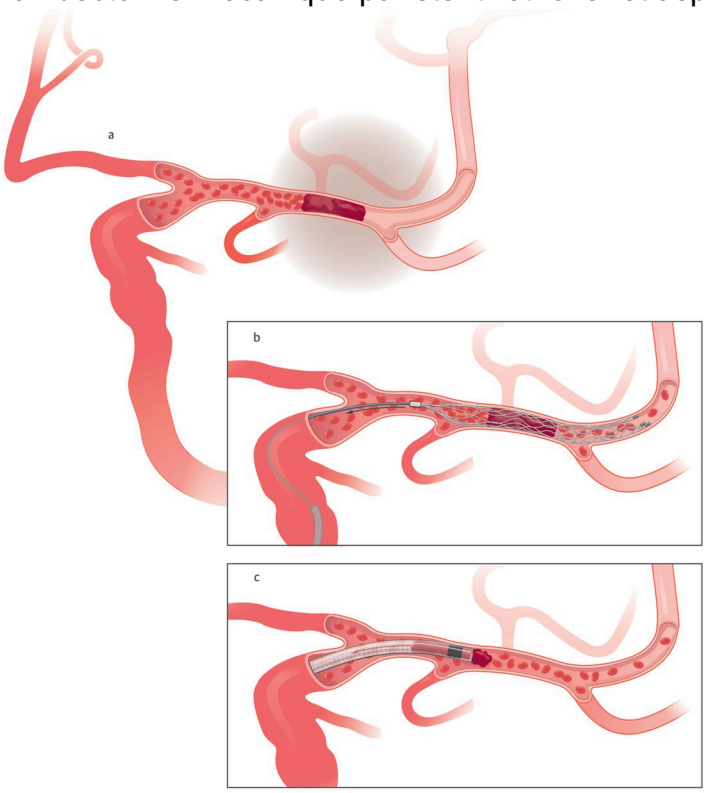
24 heures après sélection par imagerie avancée, notamment de perfusion, augmentant encore le nombre de patients éligibles[12,13]. De manière analogue, l'étude WAKE-UP[14], et bientôt l'étude ECASS IV[15], valident l'utilisation de la thrombolyse IV dans les AVC de début inconnus après sélection IRM.

Qu'est-ce que la thrombectomie mécanique ?

Lors de l'AVC ischémique, une artère intracrânienne est occluse par un caillot. La thrombectomie mécanique peut être proposée pour lever cet obstacle à la circulation cérébrale. C'est une technique de recanalisation endovasculaire pouvant se dérouler sous anesthésie générale ou sédation consciente. L'opérateur place par voie fémorale un cathéter dans l'artère cervicale cible, et procède au retrait du thrombus intracrânien par aspiration de contact et/ou stent-retriever. Ces deux techniques sont illustrées sur la **figure 3**.

[12] Nogueira et al., "Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct."
[13] Albers et al., "Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging."
[14] Thomalla et al., "MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset."
[15] Amiri et al., "European Cooperative Acute Stroke Study-4."

Figure 3 : La thrombectomie mécanique par stent-retriever et aspiration distale[16]



a : occlusion par un caillot sanguin du segment M1 de l'artère cérébrale moyenne ; b : stent-retriever déployé au sein du caillot ; c : cathéter d'aspiration distal positionné au contact du caillot.

La transformation hémorragique : la complication majeure

La complication majeure de l'AVC ischémique est la transformation hémorragique (TH). Il s'agit d'un saignement survenant au sein de la zone infarcie grevant le pronostic fonctionnel et la survie du patient[17]. Son incidence au décours d'un AVC ischémique est largement variable selon les études, avec des taux rapportés s'élevant jusqu'à 85%[18]. La sévérité de l'hémorragie étant dépendante de son extension, elle est divisée radiologiquement en 4 catégories, comme figurées en **table 1**[19].

[16] Papanagiotou and White, "Endovascular Reperfusion Strategies for Acute Stroke."
[17] van Kranendonk et al., "Hemorrhagic Transformation Is Associated with Poor Functional Outcome in Patients with Acute Ischemic Stroke Due to a Large Vessel Occlusion."
[18] Lindley et al., "Frequency and Risk Factors for Spontaneous Hemorrhagic Transformation of Cerebral Infarction."
[19] Hacke et al., "Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke."

Table 1 : Classification radiologique des transformations hémorragiques

Transformation hémorragique		**Critères radiologiques**
HI1	Infarctus hémorragique de type 1	Hémorragie pétéchiale
HI2	Infarctus hémorragique de type 2	Hémorragie pétéchiale confluente
PH1	Hématome parenchymateux de type 1	Hématome occupant <30% de l'infarctus, pas d'effet de masse
PH2	Hématome parenchymateux de type 2	Hématome occupant >30% de l'infarctus, effet de masse

La TH est également fréquemment classée selon qu'elle apparaît symptomatique, si elle entraîne une perte concomitante de 4 points du score National Institutes of Health Stroke Scale (NIHSS), ou non. Ce caractère symptomatique est la traduction clinique d'un hématome généralement étendu de type PH2, et vient grever le pronostic fonctionnel ainsi que la survie du malade. Cependant même en l'absence du caractère symptomatique, il semble que la TH vienne dégrader la récupération fonctionnelle et cognitive à long terme[20]. La prévention des TH qu'elles soient symptomatiques et étendues ou bien limitées et infracliniques est donc un enjeu important de la prise en charge.

Principaux mécanismes physiopathologiques de la transformation hémorragique.

Au cours de l'ischémie, des lésions de la barrière hémato-encéphalique (BHE) et de la membrane basale apparaissent. Ces lésions sont médiées par la production de radicaux libres oxygénés et de métalloprotéases venant altérer l'ensemble des

[20] Park et al., "Is Asymptomatic Hemorrhagic Transformation Really Innocuous ?"

constituants de l'unité neurovasculaire : les cellules endothéliales, les péricytes, les cellules musculaires lisses et les astrocytes. Il en résulte une augmentation de la perméabilité de la BHE et de la membrane basale favorisant la diapédèse immunitaire et le démarrage d'un processus thromboinflammatoire complexe à l'origine d'un cercle vicieux de lésion cellulaire cérébrale. Il apparaît également que ces processus sont catalysés par la reperfusion, c'est le concept d'ischémie-reperfusion. La traduction de ces lésions de la BHE et de l'unité neurovasculaire est l'apparition plus fréquence et plus sévère de transformation hémorragique et d'œdème cérébral[21,22].

Problématique

De nombreux études décrivant les facteurs de risque de transformation hémorragique après thrombolyse intraveineuse sont disponibles[23,24,25,26,27,28,29,30], cependant les données précisant ces déterminants après thrombectomie mécanique restent limitées. L'avènement de la thrombectomie mécanique moderne datant de 2015, la vaste majorité des études publiées évaluent des dispositifs médicaux et des techniques réformées comme la thrombolyse intra-artérielle, le dispositif MERCI ou

[21] De Meyer Simon F. et al., "Thromboinflammation in Stroke Brain Damage."
[22] Jickling et al., "Hemorrhagic Transformation after Ischemic Stroke in Animals and Humans."
[23] Larrue et al., "Risk Factors for Severe Hemorrhagic Transformation in Ischemic Stroke Patients Treated with Recombinant Tissue Plasminogen Activator."
[24] Flint et al., "The THRIVE Score Predicts Symptomatic Intracerebral Hemorrhage after Intravenous TPA Administration in SITS-MOST."
[25] Strbian et al., "Symptomatic Intracranial Hemorrhage after Stroke Thrombolysis."
[26] Menon et al., "Risk Score for Intracranial Hemorrhage in Patients With Acute Ischemic Stroke Treated With Intravenous Tissue-Type Plasminogen Activator."
[27] Cucchiara et al., "A Risk Score to Predict Intracranial Hemorrhage After Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke."
[28] Mazya et al., "Predicting the Risk of Symptomatic Intracerebral Hemorrhage in Ischemic Stroke Treated with Intravenous Alteplase."
[29] Lou et al., "The HAT Score."
[30] Asuzu et al., "Validation of TURN, a Simple Predictor of Symptomatic Intracerebral Hemorrhage after IV Thrombolysis."

encore la fragmentation de caillot. En 2015, *Nogueira et al*. ont publié la plus grande analyse rétrospective étudiant ces déterminant sur 1122 patients, cependant seuls 218 d'entre eux avaient bénéficié de thrombectomie mécanique[31]. Parmi le peu d'études incluant la reperméabilisation de l'occlusion dans les analyses, les données apparaissent contradictoires. Certaines études retrouvent la recanalisation comme facteur protecteur de TH [32 , 33] tandis que d'autres ne rapportent aucune association[34,35,36]. Au total, les données disponibles sont inhomogènes et différentes de la prise en charge moderne de l'AVC ischémique.

De plus, le traitement étiologique de l'AVC comporte fréquemment des thérapeutiques antithrombotiques et/ou une revascularisation de carotide qui sont d'indication délicate chez des patients à risque ou présentant une transformation hémorragique. Des données récentes permettant de mieux identifier les patients à risque de TH sont donc nécessaires afin de guider ces choix thérapeutiques.

Objectif

Notre objectif est de déterminer, dans notre cohorte monocentrique, les facteurs de risque de transformation hémorragique chez les patients traités par thrombectomie

[31] Nogueira et al., "Predictors and Clinical Relevance of Hemorrhagic Transformation after Endovascular Therapy for Anterior Circulation Large Vessel Occlusion Strokes."
[32] Kaesmacher et al., "Hemorrhagic Transformations after Thrombectomy."
[33] Wang et al., "Successful Recanalization Post Endovascular Therapy Is Associated with a Decreased Risk of Intracranial Haemorrhage."
[34] Raychev et al., "Determinants of Intracranial Hemorrhage Occurrence and Outcome after Neurothrombectomy Therapy."
[35] van Kranendonk et al., "Hemorrhagic Transformation Is Associated with Poor Functional Outcome in Patients with Acute Ischemic Stroke Due to a Large Vessel Occlusion."
[36] Desilles et al., "Successful Reperfusion With Mechanical Thrombectomy Is Associated With Reduced Disability and Mortality in Patients With Pretreatment Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Score ≤6."

mécanique pour un accident vasculaire cérébral ischémique par occlusion d'une artère intracrânienne de circulation antérieure.

INTRODUCTION

Mechanical thrombectomy (MT) is now the standard of care for revascularization of acute ischemic stroke with large intracranial vessel occlusion (AIS LVO) (1–6). Hemorrhagic transformation of the ischemic lesion is a dreaded complication as it darkens the patient's prognosis (7,8) whether symptomatic or not (9,10). Identifying the patients at risk is crucial to guide etiological treatment and secondary prevention like antithrombotics or carotid revascularization.

Exhaustive literature studying hemorrhagic transformation (HT) risk factors after intravenous thrombolysis (IVT) is already available (11–21) but limited data are published following mechanical thrombectomy (7,22–25) especially in the era of stent-retriever. Indeed, most of the studies included intra-arterial tpa and other -- decommissioned devices and technique such as MERCI, balloon or guidewire fragmentation (26–29), and more data using up-to-date devices are needed. In 2015, *Nogueira et al*. published the largest retrospective analysis of pooled data from 13 centers, but only 218 of the 1122 patients included underwent mechanical thrombectomy and 102 aspiration procedures (26).

On the few analyses available that include recanalization as a risk factor, conflicting data exist between recanalization and HT. Some authors report recanalization as a protecting factor for HT (30,31) while other studies retrieve no association (32–34).

Stroke prevention and etiological treatment frequently includes antithrombotics and/or carotid revascularization which might be unsafe in case of HT (35–38). Recent data concerning HT risk factors after MT is needed to graduate therapeutic action accordingly.

We aimed to study the determinants of hemorrhagic transformation in patients treated by MT for an AIS LVO in our comprehensive stroke center cohort and to provide more homogeneous data from the modern era of stroke treatment.

METHODS

Ethics

The ethical committee (*Comité de Protection des Personnes Nord Ouest IV, France)* approved the study on March 9th, 2010 (registration number 10.677). Patients gave informed consent themselves or via a close relative for the follow-up.

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

Study design

We conducted this observational study from a prospective registry of patients consecutively admitted to our comprehensive stroke center for an acute ischemic stroke, who underwent MT. For the purpose of this study we considered only patients recruited between January 2015 and December 2017.

Population

We included all consecutive stroke patients treated by MT in our hospital. Patients with basilar artery occlusion or extracranial carotid artery occlusion were excluded. Eligibility for IVT and MT has been previously published (39) . Briefly, IVT was administrated on the basis of modified ECASS-2 (European Cooperative Acute Stroke Study) criteria without any upper age limit (40) and MT procedure was performed within 8 hours from onset.

Wake-up strokes were treated on the basis of the diffusion-weighted imaging (DWI) - fluid-attenuated inversion recovery (FLAIR) mismatch profile (41–43). Our inclusions criteria evolved as DAWN and DEFUSE 3 trials were published (44,45), especially the DEFUSE 3 perfusion criteria were added.

Clinical data

We prospectively collected common demographic characteristics, vascular risk factors, vascular history, and antithrombotic medication received prior to stroke. We recorded the pre-stroke scores on the modified Rankin Scale (mRS). Blood pressure, glycemia, platelet count, and coagulation tests (PT, ACT, INR) before treatment were collected. The clinical severity was assessed by a senior vascular neurologist using the National Institutes of Health Stroke Scale (NIHSS) before procedure.

We recorded the times of symptom onset, first cerebral imaging (MRI or CT), and time of groin puncture (estimated by the time of pretreatment cerebral angiography). For patients with unknown stroke onset time, we recorded the time when the patient was last seen normal.

The occurrence of symptomatic intracerebral hemorrhage (sICH) was defined according to the ECASS-2 trial as a 4 NIHSS points loss concomitant to any intracranial hemorrhage (40).

Image analysis

Brain MRI (or CTA if contraindicated) was performed before and 24-36 hours after endovascular procedure. Ischemic lesions were evaluated using the Alberta Stroke Program Early CT Score (ASPECTS) or DWI-ASPECTS on the last brain imaging available before MT (46,47). Volumes of the ischemic cores were estimated using a semi-automated software (Olea Sphere, Olea Medical SAS, La Ciotat, France) based on a thresholding method of the initial apparent diffusion coefficient maps (ADC) with an upper level of 0,6 .10-3 mm2/s.

The occlusion site was assessed on initial digital subtraction angiography (DSA): middle cerebral artery occlusion (MCA- M1 or M2), terminus internal carotid artery ICA occlusion, or tandem occlusion. The degree of recanalization after MT was evaluated using the modified Thrombolysis in Cerebral Infarction scale (mTICI) on final angiogram (48,49). Radiological images (MRI, CT, DSA) were analyzed by a senior neuroradiologist blinded to clinical data.

Hemorrhagic transformations were assessed on day-1 brain MRI, or CT if contraindicated, using the ECASS 2 criteria (40) described in **Table 1**.

Table 1: Radiological classification of hemorrhagic transformation.

Hemorrhagic transformation		**Radiological features**
HI1	Hemorrhage infarction type 1	Petechial hemorrhage
HI2	Hemorrhage infarction type 2	Confluent petechial hemorrhage
PH1	Parenchymal hematoma type 1	Hematoma occupying <30% of the infarct zone, no significant mass effect
PH2	Parenchymal hematoma type 2	Hematoma occupying >30% of the infarct zone, significant mass effect

Endovascular procedure and intravenous therapy

All patients were treated endovascularly using a transfemoral or brachial access under conscious sedation or general anesthesia, using up-to-date stent-retriever and/or aspiration catheter.

All eligible patients received a full dose of intravenous tpa as soon as possible according to the recommendations of the European Stroke Organization (50) (0.9 mg/kg, maximum 90 mg; 10% bolus followed by a 60-minute infusion).

Statistical analysis

Continuous variables are expressed as means (standard deviation) or medians (interquartile range, IQR) and categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and Shapiro-Wilk test. Patients were divided in three groups according to occurrence or not of hemorrhagic infarction (HI) and parenchymal hematoma (PH) within 24 hours after endovascular treatment. We firstly compared the baseline characteristics between the study groups using univariable multinomial logistic regression models. To assess the independent predictors of HI and PH separately, baseline characteristics that differed between the study groups with a $P<0.20$ in univariate analysis were included into a multivariable multinomial logistic regression model with a backward-stepwise approach using a removal criterion of $P>0.05$ and “no hemorrhagic transformation” as reference category. Odds ratio (ORs) of HI versus “no hemorrhage”, and ORs of PH versus “no hemorrhage” were derived from multinomial logistic regression model as effect sizes. To prevent expected collinearity between initial infarct volume and

ASPECTS (r=-0.81), only initial volume was considered as a candidate predictor into the multivariate analysis. We further investigated independent predictors of symptomatic intracranial hemorrhage. Bivariate analyses were done using Chi-square tests (or Fisher's exact tests when expected cell frequency was <5) for categorical characteristics and the Student t-test (or Mann-Whitney U test for non-Gaussian distribution) for continuous characteristics. A multivariable binary logistic regression model was performed by including all baseline characteristics with $p<0.20$ in univariate analysis.

Multivariate analysis was repeated after inclusion of recanalization grade (mTICI 0, 1, 2a vs. 2b vs. 3) as covariate to determine whether consideration of this interim outcome modifies the estimated effect of the baseline characteristics as predictors of hemorrhagic events. To avoid case deletion in both univariate and multivariate analyses due to missing data on baseline characteristics, missing data were imputed by simple imputation (0 to 3% of missing data by parameters). Imputation procedure was performed under the missing at random assumption using study groups and all baseline characteristics with a predictive mean matching method for continuous variables and logistic regression model (binary or multinomial) for categorical variables. Statistical testing was done with a two-tailed α risk level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

RESULTS

On the 667 consecutive patients treated by mechanical thrombectomy between January 2015 and December 2017, 24 patients were excluded from analysis for the following reasons: extracranial ICA occlusion (n=17), or missing data on occurrence of symptomatic intracranial hemorrhage (n=7) (deceased before day-1 imaging). Baseline clinical and imaging characteristics are represented on **Table 2**, uncommon features included: 142 (22.1%) patients with a pre-stroke modified Rankin Score (mRS) $\geq$ 2, 156 (24.3%) wake-up strokes, 338 (52.6%) M1 middle cerebral artery (MCA) occlusions. On the 643 included patients, there were 211 (32.8%) HI (n=99 HI1, and n=112 HI2) and 150 (23.3%) PH (n=97 PH1, and n=53 PH2). 57 patients (8.9%) presented a symptomatic intracranial hemorrhage (sICH). 588 patients (91.4%) were screened using MRI and 55 (8.6%) using CT.

Table 2: Baseline characteristics N=643

	N	Values
Age, years	643	69.5 (15.3)
Men	643	290 (45.1)
Hypertension	643	421 (65.5)
Diabetes	643	116 (18.0)
Hypercholesterolemia	643	274 (42.6)
Current smoking	643	232 (36.1)
Current alcohol consumption	643	78 (12.1)
Previous ischemic heart disease	642	74 (11.5)
Previous or current AF	643	250 (38.9)
Previous stroke or TIA <7 days	643	34 (5.3)
pre-AVC mRs ≥2	643	142 (22.1)
Anticoagulation treatment	643	116 (18.0)
Anti-platelet treatment	643	200 (31.1)
Combined IV rtPA and thrombectomy	643	451 (70.1)
Wake up stroke	643	156 (24.3)
Site of occlusion on initial angiogram		
MCA-M2	643	88 (13.7)
MCA-M1	643	338 (52.6)
Intracranial ICA	643	116 (18.0)
MCA/ICA Tandem	643	101 (15.7)
Admission systolic BP, mmHg	643	145.3 (24.9)
Admission glycemia, mg/dL, median (IQR)	641	123 (105 to 150)
Infarct volume, cm3, median (IQR)	606	12.0 (5.0 to 32.0)
Admission NIHSS, median (IQR)	643	18 (13 to 22)
ASPECTS, median (IQR)	641	8 (5 to 9)
Time from onset to groin puncture, minutes, median (IQR)	640	261 (201 to 349)
Symptom onset to imaging	640	131 (89 to 244)
Imaging to groin puncture	643	114 (55 to 146)
Prothrombin time	624	94 (83 to 100)
aPTT	639	1.0 (0.9 to 1.0)
Platelets counts	641	236 (195 to 288)

Abbreviations: aPTT= activated partial thromboplastin time, AF=atrial fibrillation, ASPECTS=Alberta Stroke Program Early CT Score; BP=blood pressure; HI=hemorrhagic infarction; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=Middle cerebral artery; mRs=modified rankin score; NIHSS=National Institutes of Health Stroke Scale; PH=Parenchymal Hematoma; rtPA=recombinant tissue plasminogen activator; SD=standard deviation.

Determinants of Main Hemorrhagic Transformation Subtypes

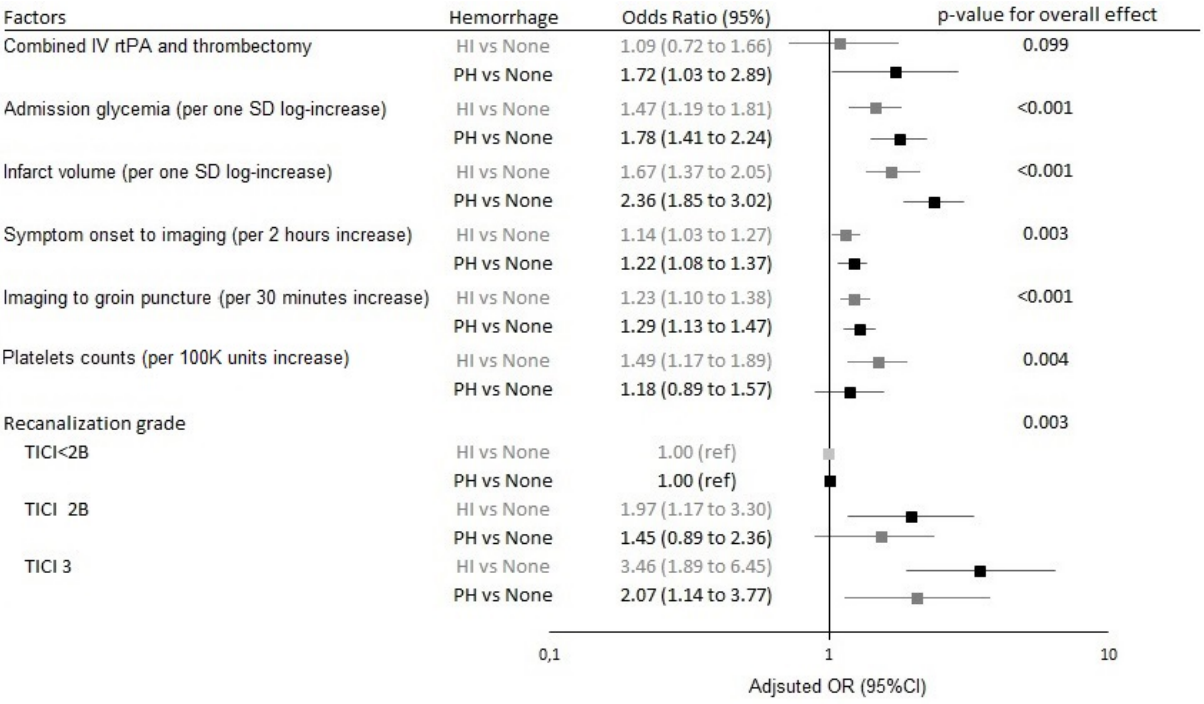
After handling missing data by simple imputation, age, diabetes, hypercholesterolemia, smoking, pre-stroke mRs≥2, antithrombotic drugs prior to stroke onset, wake-up stroke, site of occlusion on initial angiogram, admission NIHSS, admission glycaemia, initial infarct volume, initial ASPECT score, symptoms onset to imaging time, imaging to groin puncture time, intravenous thrombolysis (IVT), and platelet count differed between the study groups (P<0.20) and were included in multivariable multinomial logistic regression analysis (**Table 3**). As shown in **Supplemental Figure 1**, using the group of patients without hemorrhagic transformation as a reference, admission glycaemia, initial infarct volume, platelet counts, symptom onset to imaging time and imaging to groin puncture time were independent predictors of HI. Concerning PH, similar predictors were found (although the association with platelet rates did not reach statistical significance) with addition of IVT. The previous multivariable model was not modified when recanalization grade was added except for HI which was not significantly associated with IV tpa anymore (**Figure 1**). Reperfusion grade appeared also as an independent predictor of both HI and PH.

Table 3. Univariate association of HI and PH with baseline characteristics

	Hemorrhagic transformation			
	None (n=282)	HI (n=211)	PH (n=150)	P Value
Age, years	72.0 (15.5)	67.2 (14.9)	67.9 (14.9)	0.001
Men	126 (44.7)	95 (45.0)	69 (46.0)	0.97
Hypertension	191 (67.7)	138 (65.4)	92 (61.3)	0.41
Diabetes	39 (13.8)	45 (21.3)	32 (21.3)	0.051
Hypercholesterolemia	135 (47.9)	81 (38.4)	58 (38.7)	0.059
Current smoking	94 (33.3)	74 (35.1)	64 (42.7)	0.15
Current alcohol consumption	32 (11.3)	26 (12.3)	20 (13.3)	0.83
Previous ischemic heart disease	36 (12.8)	25 (11.8)	13 (8.7)	0.44
Previous or current AF	116 (41.1)	82 (38.9)	52 (34.7)	0.43
Previous stroke or TIA <7 days	14 (5.0)	13 (6.2)	7 (4.7)	0.78
pre-AVC mRs ≥2	76 (27.0)	39 (18.5)	27 (18.0)	0.032
Anticoagulation treatment	61 (21.6)	39 (18.5)	16 (10.7)	0.021
Anti-platelet treatment	94 (33.3)	61 (28.9)	45 (30.0)	0.55
Combined IV rtPA and thrombectomy	187 (66.3)	147 (69.7)	117 (78.0)	0.042
Wake up stroke	55 (19.5)	56 (26.5)	45 (30.0)	0.035
Site of occlusion on initial angiogram				
MCA-M2	40 (14.2)	29 (13.7)	19 (12.7)	0.034
MCA-M1	163 (57.8)	105 (49.8)	70 (46.7)	
Intracranial ICA	41 (14.5)	39 (18.5)	36 (24.0)	
MCA/ICA Tandem	38 (13.5)	38 (18.0)	25 (16.7)	
Admission systolic BP, mmHg	144.8 (25.9)	143.7 (22.2)	148.2 (26.6)	0.22
Admission glycemia, mg/dL, median(IQR)	117 (103 to 138)	126 (106 to 160)	132 (110 to 171)	<0.001*
Infarct volume, cm3, median (IQR)	7.5 (3.0 to 17.0)	15.0 (6.0 to 38.0)	22.0 (10.0 to 40.0)	<0.001*
Volume>70ml	13 (4.6)	18 (8.5)	13 (8.7)	0.14
Admission NIHSS, median (IQR)	8 (3 to 18)	13 (6 to 20)	18 (11 to 23)	<0.001
ASPECTS, median (IQR)	8 (7 to 9)	7 (5 to 9)	6 (4 to 8)	<0.001
ASPECT <6	41 (14.5)	68 (32.2)	67 (44.7)	<0.001
Symptom onset to groin puncture, minutes, median (IQR)	240 (177 to 318)	266 (213 to 368)	284 (226 to 386)	0.002
Symptom onset to imaging	*129 (85 to 218)*	*129 (93 to 271)*	*146 (92 to 293)*	*0.050*
Imaging to groin puncture	*87.5 (47 to 134)*	*122 (69 to 145)*	*130 (73 to 156)*	*<0.001*
Prothrombin time	93 (80 to 100)	95 (81 to 100)	95 (84 to 100)	0.41
aPTT	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)	0.42
Platelets counts	225 (189 to 273)	247 (211 to 300)	244 (196 to 284)	<0.001
Recanalization grade				
TICI<2B	80 (28.4)	48 (22.7)	24 (16.0)	0.011
TICI 2B	78 (27.7)	75 (35.5)	63 (42.0)	
TICI 3	124 (43.9)	88 (41.8)	63 (42.0)	

Values are n (%) or mean (SD). Descriptive parameters and p-values were calculated after handling missing values by simple imputation. Abbreviations: AF=atrial fibrillation, aPTT= activated partial thromboplastin time, ASPECTS=Alberta Stroke Program Early CT Score; BP=blood pressure; HI=hemorrhagic infarction; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=Middle cerebral artery; mRs=modified rankin score; NIHSS=National Institutes of Health Stroke Scale; PH=Parenchymal Hematoma; rtPA=recombinant tissue plasminogen activator; SD=standard deviation.

Figure 1: Results of multivariate analysis assessing independent predictors of HI and PH



Odds ratios and P values were calculated after handling missing data by simple imputation using a backward-stepwise multinomial logistic regression model including all univariate predictors at P<0.20 excepted recanalization grade. Abbreviations: HI= hemorrhagic infarction; IV= intravenous; OR= Odds ratio; PH=parenchymal hematoma; rtPA= recombinant tissue plasminogen activator; SD=standard deviation.

Determinants of Symptomatic Intracranial Hemorrhage

After handling missing data, diabetes, previous ischemic heart disease, current or history of atrial fibrillation, anticoagulant drugs prior to stroke onset, IVT, wake-up stroke, site of occlusion on initial angiogram, admission systolic blood pressure, glycaemia, initial infarct volume, admission NIHSS, initial ASPECT score and imaging to groin puncture time were considered as candidate predictors in multivariable binary logistic regression analysis. In addition to baseline characteristics, reperfusion grade was associated with lower symptomatic intracranial hemorrhage (**Table 3**). As shown in **supplemental table 1**, in multivariate analysis, diabetes, IVT, admission systolic blood pressure, initial infarct volume and imaging to groin puncture time remained significantly associated with an increased risk of symptomatic intracranial.

When the recanalization grade was added in previous multivariable model, imaging to groin puncture time and recanalization grade did not remain significantly associated with symptomatic intracranial hemorrhage but remained close to significance (p=0.053 and p=0.092 respectively). All other results were similar (**Table 4**).

Table 3: Univariate association with symptomatic intracranial hemorrhage

	Symptomatic intracranial hemorrhage		
	No (N=586)	**Yes (N=57)**	**P value**
Age, years	69.3 (15.4)	71.0 (14.0)	0.44
Men	263 (44.9)	27 (47.4)	0.72
Hypertension	381 (65.0)	40 (70.2)	0.43
Diabetes	99 (16.9)	17 (29.8)	0.015
Hypercholesterolemia	251 (42.8)	23 (40.4)	0.72
Current smoking	213 (36.3)	19 (33.3)	0.65
Current alcohol consumption	72 (12.3)	6 (10.5)	0.70
Previous ischemic heart disease	64 (10.9)	10 (17.5)	0.13
Previous or current AF	236 (40.3)	14 (24.6)	0.020
Previous stroke or TIA <7 days	33 (5.6)	1 (1.8)	0.35
pre-AVC mRS ≥2	132 (22.5)	10 (17.5)	0.39
Anticoagulation treatment	111 (18.9)	5 (8.8)	0.057
Anti-platelet treatment	180 (30.7)	20 (35.1)	0.50
Combined IV rtPA and thrombectomy	404 (68.9)	47 (82.5)	0.033
Wake up stroke	449 (76.6)	38 (66.7)	0.094
Site of occlusion on initial angiogram			
MCA-M2	81 (13.8)	7 (12.3)	0.079
MCA-M1	316 (53.9)	22 (38.6)	
Intracranial ICA	101 (17.2)	15 (26.3)	
MCA/ICA Tandem	88 (15.0)	13 (22.8)	
Admission systolic BP, mmHg	144.3 (24.6)	155.3 (26.0)	0.001
Admission glycemia, mg/dL, median (IQR)	122 (104 to 148)	130 (110 to 182)	0.023*
Infarct volume, cm3, median (IQR)	12 (5 to 29)	23 (8 to 50)	0.002*
Admission NIHSS, median (IQR)	18 (13 to 22)	19 (16 to 22)	0.15
ASPECTS, median (IQR)	8 (5 to 9)	6 (4 to 9)	0.028
Time from onset to groin puncture, minutes, median (IQR)	261 (199 to 345)	273 (228 to 450)	0.061
Symptom onset to imaging	130 (90 to 244)	138 (92 to 315)	0.46
Imaging to groin puncture	111 (54 to 145)	135 (99 to 156)	0.010
Prothrombin time	94 (81 to 100)	94 (86 to 100)	0.88
aPTT	1.0 (0.9 to 1.0)	1.0 (0.9 to 1.0)	0.84
Platelets counts	235 (195 to 287)	239 (182 to 290)	0.88
Recanalization grade			
TICI<2B	132 (22.5)	20 (35.1)	0.10
TICI 2B	199 (34.0)	17 (29.8)	
TICI 3	255 (43.5)	20(35.1)	

Values are n (%) or mean (SD). Descriptive parameters and p-values were calculated after handling missing values by simple imputation* P-values obtained after log transformation.

Abbreviations: aPTT= activated partial thromboplastin time, AF=atrial fibrillation, ASPECTS=Alberta Stroke Program Early CT Score; BP=blood pressure; HI=hemorrhagic infarction; ICA=internal carotid artery; IQR=interquartile range; IV=intravenous; MCA=Middle cerebral artery; mRS=modified rankin score ; NIHSS=National Institutes of Health Stroke Scale; PH=Parenchymal Hematoma; rtPA=recombinant tissue plasminogen activator; SD=standard deviation.

Table 4: Multivariable regression analysis of predictors of symptomatic intracranial hemorrhage.

Predictors	OR (95% CI) *	*P* Value*
Diabetes	2.30 (1.21 to 4.37)	0.011
Combined IV r-tPA and thrombectomy	2.63 (1.23 to 5.60)	0.012
Admission systolic BP (per 10 mmHg increase)	1.21 (1.08 to 1.35)	<0.001
Infarct volume (per one SD log-increase)	1.80 (1.32 to 2.47)	<0.001
Imaging to groin puncture (per 30 min increase)	1.18 (0.99 to 1.39)	0.053
Recanalization grade		
TICI <2B	1.00 (ref)	0.092
TICI 2B	0.49 (0.24 to 1.01)	
TICI 3	0.52 (0.26 to 1.04)	

*OR calculated after handling missing data by simple imputation using a backward-stepwise logistic model including all univariate predictors at P<0.20 and recanalization grade. Abbreviations: BP=blood pressure; CI=confidence interval; IV=intravenous; OR=odds ratio; rtPA= recombinant tissue plasminogen activator; SD= Standard deviation.

DISCUSSION

Major findings

This is, to our knowledge, the largest well phenotyped cohort of patients on which determinants of hemorrhagic transformation were assessed after up-to-date mechanical thrombectomy.

Risk factors for any hemorrhagic transformation included: IV tpa, admission glycemia, initial infarct volume, times from symptom onset to imaging and from picture to puncture, elevation of the platelet count and successful recanalization.

Risk factors for sICH included: IV tpa, diabetes, admission systolic blood pressure and infarct volume. There was a strong trend toward association with time from imaging to groin puncture as a risk factor for sICH and successful recanalization as a protecting factor.

Successful recanalization (mTICI 2b-3) was associated with an increased risk of hemorrhagic transformation but seemed to be associated with a decreased risk of sICH. As far as we know, this is the first study reporting successful recanalisation after mechanical thrombectomy as a risk factor for both HI and PH. Moreover, it seems that the higher the recanalization grade, the higher the risk of HT, and especially of HI.

Patients treated with bridging therapy presented more hemorrhagic transformation than patients treated with endovascular therapy only (OR = 1.90 for PH, *ns* for HI). This provide conflicting data concerning HI as *Kaesmacher et al.* reported IV tpa as a protecting factor for HI (aOR=0.512) (30), but is consistent with the cohort studied by *Nogueira et al* (aOR = 1.43) (51).

Hemorrhagic transformation risk factors following mechanical thrombectomy seemed similar to those published evaluating patient treated with IVT except for age and NIHSS (11,52) which were not retrieved in our cohort.

Risk factors for hemorrhagic transformation

Successful recanalization (mTICI 2b-3) was associated with an increased risk of HI and PH. This finding is coherent with the concept of brain ischemia-reperfusion injury. In animal stroke models, some degree of evidence exists that mechanical or chemical reperfusion of brain ischemic lesions leads to more HT than permanent occlusion (53–56). In human, *Bang et al*. have published a study retrieving recanalization as a risk factor for HT in the case of poor cerebral collaterals on patients treated using multimodal therapy (MERCI and/or IA tpa) (57). Poor collaterals in the context of AIS LVO can result in deeper and rapidly progressing ischemic injury, thus reducing the time window for an effective and safe recanalization.

Time from onset to imaging, time from picture to puncture and initial ischemic lesion volume were associated with higher risk of HT. This is consistent with previous findings concerning IV tpa (11,52,58,59). In fact, in the case of a proximal intracranial LVO, time and ischemic lesion volume are similar parameters, indeed, time is brain but collaterals set the pace (60).

Additionally, time from picture to puncture was a stronger risk factor for HT than time from onset to imaging. This could be explained by an exponential relationship of HT

over time. This is in accordance with a previous study reporting timing of spontaneous recanalization >6 hours as a risk factor of HT (61).

One unexpected hemorrhagic risk factor retrieved was the initial platelet count increase. One explanation could be distal infra-radiologic small vessels reocclusions that lead to ineffective cerebral blood flow restoration causing deeper ischemia, vessel ischemic injury and blood-brain barrier (BBB) disruption and then more HT (62). Several studies have found platelet count and mean platelet volume as risk factors for ischemic stroke (63–69) and *Mosiman et al.* in a recent study retrieved platelet count as the most determinant risk factor for early vessel reocclusion after successful mechanical thrombectomy (70). In a less intuitive manner, during the early stages of ischemia, a complex thromboinflammatory process partially mediated by platelets occurs. Interactions between platelets and inflammatory cells via the contact-kinin and the Van Willebrand factor pathways worsen the cerebrovascular unit damages and could aggravate the risk of HT (71,72). Platelet count is systematically checked upon admission to settle IV tpa eligibility, it could also help identifying patients at risk of HT.

Initial hyperglycemia is a well-known risk factor for HT and worse outcome in AIS patients treated with IV tpa (73,74). In animal stroke model, hyperglycemia has been described as a risk factor for infarct growth and HT (75) as it seems to alter mitochondrial function in the ischemic cortical penumbra speeding its decay (76). Hyperglycemia appears as a risk factor for bad outcome and HT regardless of the revascularization therapy used (71,74).

Intravenous tpa was retrieved as a risk factor for PH, and not HI, as in ECASS II (11), but when recanalization was added to the model it did not remain significatively

associated. Further studies are needed to analyze whether it increases the risk differently depending on the recanalization grade and/or the timing of recanalization.

Determinants of Symptomatic Intracranial Hemorrhage

Diabetes mellitus was retrieved as a risk factor for sICH, this could be explained by the chronic damages to the BBB exacerbating ischemic related inflammatory process, cerebral edema, risk and severity of bleedings (76).

Infarct volume and time were associated with an increased risk of sICH similarly to studies assessing HT risk factors after IV tpa (11,58).

Analogously admission systolic blood pressure appears to be a shared sICH determinant of thrombolysis and MT (77–80).

Despite remaining non-significant, we observed a strong trend toward association between successful recanalization and a reduction in the incidence of sICH. Symptomatic ICH is defined as a 4 points loss of NIHSS concomitant to any HT. Early neurological improvement following MT could conceal its detection. Moreover, sICH scoring seems inadequate for large volume and severe stroke patients whom high NIHSS score cannot grow 4 supplemental points. This could partially explain the lack of significance regarding recanalization as a protecting factor for sICH, in the present study or in previously published ones.

Limits

We acknowledge several limitations, first the inherent bias impeding monocentric and retrospective studies, even though the data collection remained prospective.

Secondly this study was not randomized and is subject to selection bias that could explain why age and NIHSS were not associated with HT likewise following IV tpa. The determinants of HT from the present study concern only early hemorrhage since their incidence was assessed on day-1 imaging, delayed HT may not share common risk factors and interpretation concerning their occurrence should remain cautious. Finally, several other suspected risk factors for HT following IV tpa and/or MT have been published and were not studied in our cohort such as: cerebral leukopathy (81,82), intracranial arterial tortuosity (83), location of infarct (84), severity of lesion ADC value (85) and of hypoperfusion (86) or more recently BBB permeability (87,88).

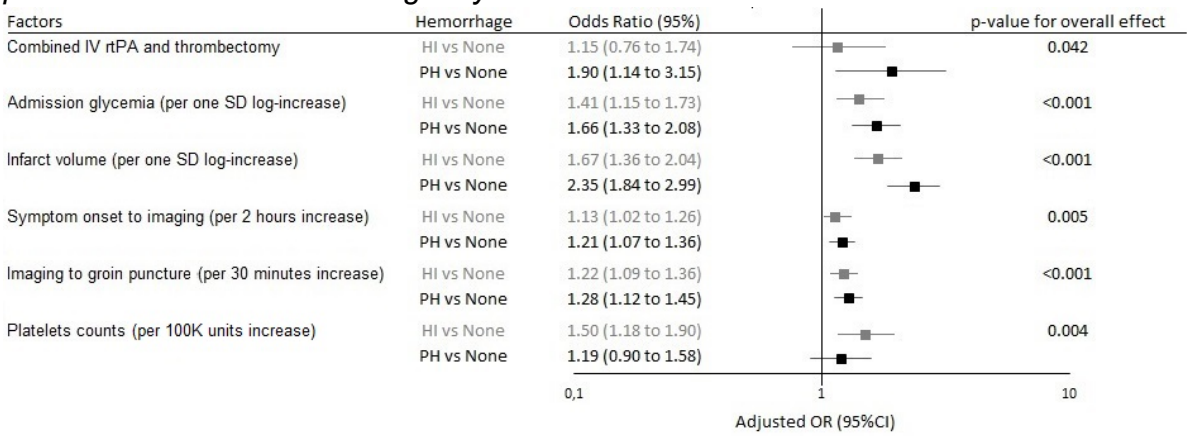
CONCLUSION

In our modern thrombectomy well phenotyped cohort of 643 patients: risk factors of hemorrhagic transformation after mechanical thrombectomy for acute ischemic stroke included intravenous thrombolysis, glycemia, infarct volume, time from onset to imaging, time from picture to puncture, platelet count and mTICI 2b and 3 recanalization.

Risk factors for symptomatic intracranial hemorrhage included intravenous thrombolysis, diabetes mellitus, infarct volume, admission systolic blood pressure. Successful recanalization seemed to be associated with a decrease risk of sICH.

ANNEXES

Supplemental Figure 1: Results of multivariate analysis assessing independent predictors of HI and PH using only baseline characteristics.



Odds ratios and P values were calculated after handling missing data by simple imputation using a backward-stepwise multinomial logistic regression model including all univariate predictors at P<0.20 excepted recanalization grade. Abbreviations: HI= hemorrhagic infarction; IV= intravenous; OR= Odds ratio; PH=parenchymal hematoma; rtPA= recombinant tissue plasminogen activator; SD=standard deviation.

Supplemental table 1: Multivariable regression analysis of predictors of symptomatic intracranial hemorrhage using only baseline characteristics.

Predictors	**OR (95%CI)***	***P* Value***
Diabetes	2.15 (1.14 to 4.08)	0.018
Combined IV rtPA and thrombectomy	2.41 (1.15 to 5.09)	0.020
Admission systolic BP (per 10 mmHg increase)	1.23 (1.10 to 1.37)	<0.001
Infarct volume (per one SD log-increase)	1.77 (1.29 to 2.42)	<0.001
Imaging to groin puncture (per 30 min increase)	1.19 (1.01 to 1.40)	0.043

*OR calculated after handling missing data by simple imputation using a backward-stepwise logistic model including all univariate predictors at P<0.20 excepted recanalization grade. Abbreviations: BP=blood pressure; CI=confidence interval; IV=intravenous; OR=odds ratio; rtPA= recombinant tissue plasminogen activator; SD= Standard deviation.

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. 2015 Jan 1;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. 2015 Mar 12;372(11):1019–30.

3. 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. 2015 Mar 12;372(11):1009–18.

4. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, et al. Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. Int J Stroke Off J Int Stroke Soc. 2015 Apr;10(3):439–48.

5. 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. 2015 Jun 11;372(24):2296–306.

6. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016 Oct 1;15(11):1138–47.

7. van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, van den Berg LA, Chalos V, et al. Hemorrhagic transformation is associated with poor functional outcome in

patients with acute ischemic stroke due to a large vessel occlusion. J Neurointerventional Surg. 2018 Oct 8;

8. Berger C, Fiorelli M, Steiner T, Schäbitz WR, Bozzao L, Bluhmki E, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? Stroke. 2001 Jun;32(6):1330–5.

9. Park JH, Ko Y, Kim W-J, Jang MS, Yang MH, Han M-K, et al. Is asymptomatic hemorrhagic transformation really innocuous? Neurology. 2012 Feb 7;78(6):421–6.

10. Dzialowski I, Pexman JHW, Barber PA, Demchuk AM, Buchan AM, Hill MD, et al. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. Stroke. 2007 Jan;38(1):75–9.

11. Larrue V, von Kummer R R, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke. 2001 Feb;32(2):438–41.

12. Asuzu D, Nystrom K, Amin H, Schindler J, Wira C, Greer D, et al. Comparison of 8 scores for predicting symptomatic intracerebral hemorrhage after IV thrombolysis. Neurocrit Care. 2015 Apr;22(2):229–33.

13. Cucchiara B, Tanne D, Levine SR, Demchuk AM, Kasner S. A Risk Score to Predict Intracranial Hemorrhage After Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2008 Nov 1;17(6):331–3.

14. Sung S-F, Chen SC-C, Lin H-J, Chen Y-W, Tseng M-C, Chen C-H. Comparison of risk-scoring systems in predicting symptomatic intracerebral hemorrhage after intravenous thrombolysis. Stroke. 2013 Jun;44(6):1561–6.

15. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke. 2012 Jun;43(6):1524–31.

16. Liu M, Pan Y, Zhou L, Wang Y. Predictors of post-thrombolysis symptomatic intracranial hemorrhage in Chinese patients with acute ischemic stroke. PloS One. 2017;12(9):e0184646.

17. Menon BK, Saver JL, Prabhakaran S, Reeves M, Liang L, Olson DM, et al. Risk Score for Intracranial Hemorrhage in Patients With Acute Ischemic Stroke Treated With Intravenous Tissue-Type Plasminogen Activator. Stroke. 2012 Sep 1;43(9):2293–9.

18. Strbian D, Engelter S, Michel P, Meretoja A, Sekoranja L, Ahlhelm FJ, et al. Symptomatic intracranial hemorrhage after stroke thrombolysis: The SEDAN Score. Ann Neurol. 2012 May 1;71(5):634–41.

19. Lou M, Safdar A, Mehdiratta M, Kumar S, Schlaug G, Caplan L, et al. The HAT Score. Neurology. 2008 Oct 28;71(18):1417–23.

20. Flint AC, Gupta R, Smith WS, Kamel H, Faigeles BS, Cullen SP, et al. The THRIVE Score Predicts Symptomatic Intracerebral Hemorrhage after Intravenous tPA Administration in SITS-MOST. Int J Stroke. 2014 Aug 1;9(6):705–10.

21. Asuzu D, Nyström K, Amin H, Schindler J, Wira C, Greer D, et al. Validation of TURN, a simple predictor of symptomatic intracerebral hemorrhage after IV thrombolysis. Clin Neurol Neurosurg. 2016 Jul 1;146:71–5.

22. Nogueira RG, Gupta R, Jovin TG, Levy EI, Liebeskind DS, Zaidat OO, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointerventional Surg. 2015 Jan;7(1):16–21.

23. Kaesmacher J, Kaesmacher M, Maegerlein C, Zimmer C, Gersing AS, Wunderlich S, et al. Hemorrhagic Transformations after Thrombectomy: Risk Factors and Clinical Relevance. Cerebrovasc Dis Basel Switz. 2017;43(5–6):294–304.

24. Wang DT, Churilov L, Dowling R, Mitchell P, Yan B. Successful recanalization post endovascular therapy is associated with a decreased risk of intracranial haemorrhage: a retrospective study. BMC Neurol. 2015 Oct 7;15:185.

25. Jiang S, Fei A, Peng Y, Zhang J, Lu Y-R, Wang H-R, et al. Predictors of Outcome and Hemorrhage in Patients Undergoing Endovascular Therapy with Solitaire Stent for Acute Ischemic Stroke. PloS One. 2015;10(12):e0144452.

26. Sussman ES, Connolly ES. Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke. Front Neurol. 2013;4:69.

27. Vora NA, Gupta R, Thomas AJ, Horowitz MB, Tayal AH, Hammer MD, et al. Factors Predicting Hemorrhagic Complications after Multimodal Reperfusion Therapy for Acute Ischemic Stroke. Am J Neuroradiol. 2007 Aug 1;28(7):1391–4.

28. Shi Z-S, Liebeskind DS, Loh Y, Saver JL, Starkman S, Vespa PM, et al. Predictors of subarachnoid hemorrhage in acute ischemic stroke with endovascular therapy. Stroke. 2010 Dec;41(12):2775–81.

29. Raychev R, Jahan R, Liebeskind D, Clark W, Nogueira RG, Saver J. Determinants of Intracranial Hemorrhage Occurrence and Outcome after Neurothrombectomy Therapy: Insights from the Solitaire FR With Intention For Thrombectomy Randomized Trial. Am J Neuroradiol. 2015 Dec 1;36(12):2303–7.

30. Kaesmacher J, Kaesmacher M, Maegerlein C, Zimmer C, Gersing AS, Wunderlich S, et al. Hemorrhagic Transformations after Thrombectomy: Risk Factors and Clinical Relevance. Cerebrovasc Dis. 2017;43(5–6):294–304.

31. Wang DT, Churilov L, Dowling R, Mitchell P, Yan B. Successful recanalization post endovascular therapy is associated with a decreased risk of intracranial haemorrhage: a retrospective study. BMC Neurol [Internet]. 2015 Oct 7 [cited 2018 Sep 4];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4597389/

32. van Kranendonk KR, Treurniet KM, Boers AMM, Berkhemer OA, van den Berg LA, Chalos V, et al. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. J NeuroInterventional Surg. 2018 Oct 8;neurintsurg-2018-014141.

33. Raychev R, Jahan R, Liebeskind D, Clark W, Nogueira RG, Saver J, et al. Determinants of Intracranial Hemorrhage Occurrence and Outcome after Neurothrombectomy Therapy: Insights from the Solitaire FR With Intention For Thrombectomy Randomized Trial. AJNR Am J Neuroradiol. 2015 Dec;36(12):2303–7.

34. Desilles J-P, Consoli A, Redjem H, Coskun O, Ciccio G, Smajda S, et al. Successful Reperfusion With Mechanical Thrombectomy Is Associated With Reduced Disability and Mortality in Patients With Pretreatment Diffusion-Weighted Imaging–Alberta Stroke Program Early Computed Tomography Score ≤6. Stroke. 2017 Apr;48(4):963–9.

35. Furie KL, Jayaraman MV. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke. Stroke. 2018 Mar;49(3):509–10.

36. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke. 2007 Feb;38(2):423–30.

37. Stone JA, Willey JZ, Keyrouz S, Butera J, McTaggart RA, Cutting S, et al. Therapies for Hemorrhagic Transformation in Acute Ischemic Stroke. Curr Treat Options Neurol. 2017 Jan;19(1):1.

38. Naylor AR, Ricco J-B, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2018 Jan;55(1):3–81.

39. Ferrigno M, Bricout N, Leys D, Estrade L, Cordonnier C, Personnic T, et al. Intravenous Recombinant Tissue-Type Plasminogen Activator: Influence on Outcome in Anterior Circulation Ischemic Stroke Treated by Mechanical Thrombectomy. Stroke. 2018 Jun;49(6):1377–85.

40. 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). The Lancet. 1998 Oct;352(9136):1245–51.

41. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med. 2018 Aug 16;379(7):611–22.

42. Lansberg MG, Cereda CW, Mlynash M, Mishra NK, Inoue M, Kemp S, et al. Response to endovascular reperfusion is not time-dependent in patients with salvageable tissue. Neurology. 2015 Aug 25;85(8):708–14.

43. Jovin TG, Liebeskind DS, Gupta R, Rymer M, Rai A, Zaidat OO, et al. Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients. Stroke. 2011 Aug;42(8):2206–11.

44. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2017 Nov 11;

45. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018 Feb 22;378(8):708–18.

46. 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. The Lancet. 2000 May 13;355(9216):1670–4.

47. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JHW, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. J Neurol Neurosurg Psychiatry. 2005 Nov;76(11):1528–33.

48. Higashida RT, Furlan AJ, Roberts H, Tomsick T, Connors B, Barr J, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003 Aug;34(8):e109-137.

49. Fugate JE, Klunder AM, Kallmes DF. What is meant by "TICI"? AJNR Am J Neuroradiol. 2013 Sep;34(9):1792–7.

50. 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.

51. Nogueira RG, Gupta R, Jovin TG, Levy EI, Liebeskind DS, Zaidat OO, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointerventional Surg. 2015 Jan;7(1):16–21.

52. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. Stroke. 1997 May;28(5):957–60.

53. Lu A, Clark JF, Broderick JP, Pyne-Geithman GJ, Wagner KR, Khatri P, et al. Mechanical reperfusion is associated with post-ischemic hemorrhage in rat brain. Exp Neurol. 2009 Apr;216(2):407–12.

54. Yang GY, Betz AL. Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. Stroke. 1994 Aug;25(8):1658–64; discussion 1664-1665.

55. Copin J-C, Gasche Y. Effect of the duration of middle cerebral artery occlusion on the risk of hemorrhagic transformation after tissue plasminogen activator injection in rats. Brain Res. 2008 Dec 3;1243:161–6.

56. García-Yébenes I, Sobrado M, Zarruk JG, Castellanos M, Pérez de la Ossa N, Dávalos A, et al. A mouse model of hemorrhagic transformation by delayed tissue plasminogen activator administration after in situ thromboembolic stroke. Stroke. 2011 Jan;42(1):196–203.

57. Bang Oh Young, Saver Jeffrey L., Kim Suk Jae, Kim Gyeong-Moon, Chung Chin-Sang, Ovbiagele Bruce, et al. Collateral Flow Averts Hemorrhagic Transformation After Endovascular Therapy for Acute Ischemic Stroke. Stroke. 2011 Aug 1;42(8):2235–9.

58. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet. 2014 Nov 29;384(9958):1929–35.

59. Thomalla Götz, Sobesky Jan, Köhrmann Martin, Fiebach Jochen B., Fiehler Jens, Zaro Weber Olivier, et al. Two Tales: Hemorrhagic Transformation but Not Parenchymal Hemorrhage After Thrombolysis Is Related to Severity and Duration of Ischemia. Stroke. 2007 Feb 1;38(2):313–8.

60. Rocha Marcelo, Jovin Tudor G. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke. Stroke. 2017 Sep 1;48(9):2621–7.

61. Molina CA, Montaner J, Abilleira S, Ibarra B, Romero F, Arenillas JF, et al. Timing of spontaneous recanalization and risk of hemorrhagic transformation in acute cardioembolic stroke. Stroke. 2001 May;32(5):1079–84.

62. Mizuma A, You JS, Yenari MA. Targeting Reperfusion Injury in the Age of Mechanical Thrombectomy. Stroke. 2018 Jul;49(7):1796–802.

63. Du J, Wang Q, He B, Liu P, Chen J-Y, Quan H, et al. Association of mean platelet volume and platelet count with the development and prognosis of ischemic and hemorrhagic stroke. Int J Lab Hematol. 2016 Jun;38(3):233–9.

64. Bath P, Algert C, Chapman N, Neal B, PROGRESS Collaborative Group. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke. 2004 Mar;35(3):622–6.

65. Vasudeva K, Munshi A. Genetics of platelet traits in ischaemic stroke: Focus on mean platelet volume and platelet count. Int J Neurosci. 2018 Oct 29;0(ja):1–26.

66. Elsayed AM, Mohamed GA. Mean platelet volume and mean platelet volume/platelet count ratio as a risk stratification tool in the assessment of severity of acute ischemic stroke. Alex J Med. 2017 Mar;53(1):67–70.

67. Quan W, Chen Z, Yang X, Li J, Li X, Weng Y, et al. Mean platelet volume/platelet count ratio as a predictor of 90-day outcome in large artery atherosclerosis stroke patients. Int J Neurosci. 2017 Nov;127(11):1019–27.

68. van der Bom JG, Heckbert SR, Lumley T, Holmes CE, Cushman M, Folsom AR, et al. Platelet count and the risk for thrombosis and death in the elderly. J Thromb Haemost JTH. 2009 Mar;7(3):399–405.

69. del Zoppo GJ. The role of platelets in ischemic stroke. Neurology. 1998 Sep;51(3 Suppl 3):S9-14.

70. Mosimann PJ, Kaesmacher J, Gautschi D, Bellwald S, Panos L, Piechowiak E, et al. Predictors of Unexpected Early Reocclusion After Successful Mechanical Thrombectomy in Acute Ischemic Stroke Patients. Stroke. 2018 Nov;49(11):2643–51.

71. Kerenyi L, Kardos L, Szász J, Szatmári S, Bereczki D, Hegedüs K, et al. Factors influencing hemorrhagic transformation in ischemic stroke: a clinicopathological comparison. Eur J Neurol. 2006 Nov;13(11):1251–5.

72. Venkat P, Chopp M, Chen J. Blood-Brain Barrier Disruption, Vascular Impairment, and Ischemia/Reperfusion Damage in Diabetic Stroke. J Am Heart Assoc. 2017 Jun 1;6(6).

73. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med. 1983 Apr 1;74(4):540–4.

74. Paciaroni M, Agnelli G, Caso V, Corea F, Ageno W, Alberti A, et al. Acute Hyperglycemia and Early Hemorrhagic Transformation in Ischemic Stroke. Cerebrovasc Dis. 2009;28(2):119–23.

75. Desilles J-P, Syvannarath V, Ollivier V, Journé C, Delbosc S, Ducroux C, et al. Exacerbation of Thromboinflammation by Hyperglycemia Precipitates Cerebral Infarct Growth and Hemorrhagic Transformation. Stroke. 2017;48(7):1932–40.

76. Venkat P, Chopp M, Chen J. Blood–Brain Barrier Disruption, Vascular Impairment, and Ischemia/Reperfusion Damage in Diabetic Stroke. J Am Heart Assoc Cardiovasc Cerebrovasc Dis [Internet]. 2017 Jun 1 [cited 2018 Nov 11];6(6). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5669184/

77. Butcher K, Christensen S, Parsons M, De Silva DA, Ebinger M, Levi C, et al. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. Stroke. 2010 Jan;41(1):72–7.

78. Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke. 2012 Jun;43(6):1524–31.

79. Perini F, De Boni A, Marcon M, Bolgan I, Pellizzari M, Dionisio LD. Systolic blood pressure contributes to intracerebral haemorrhage after thrombolysis for ischemic stroke. J Neurol Sci. 2010 Oct 15;297(1–2):52–4.

80. Waltimo T, Haapaniemi E, Surakka IL, Melkas S, Sairanen T, Sibolt G, et al. Post-thrombolytic blood pressure and symptomatic intracerebral hemorrhage. Eur J Neurol. 2016;23(12):1757–62.

81. Yang C-M, Hung C-L, Su H-C, Lin H-J, Chen C-H, Lin C-C, et al. Leukoaraiosis and risk of intracranial hemorrhage and outcome after stroke thrombolysis. PLOS ONE. 2018 May 1;13(5):e0196505.

82. Shi Z-S, Loh Y, Liebeskind DS, Saver JL, Gonzalez NR, Tateshima S, et al. Leukoaraiosis Predicts Parenchymal Hematoma After Mechanical Thrombectomy in Acute Ischemic Stroke. Stroke J Cereb Circ. 2012 Jul;43(7):1806–11.

83. Shirakawa M, Yoshimura S, Uchida K, Shindo S, Yamada K, Kuroda J, et al. Relationship between Hemorrhagic Complications and Target Vessels in Acute Thrombectomy. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2017 Aug;26(8):1732–8.

84. Loh Y, Towfighi A, Liebeskind DS, MacArthur DL, Vespa P, Gonzalez NR, et al. Basal ganglionic infarction before mechanical thrombectomy predicts poor outcome. Stroke. 2009 Oct;40(10):3315–20.

85. Tong DC, Adami A, Moseley ME, Marks MP. Relationship between apparent diffusion coefficient and subsequent hemorrhagic transformation following acute ischemic stroke. Stroke. 2000 Oct;31(10):2378–84.

86. Campbell BCV, Christensen S, Parsons MW, Churilov L, Desmond PM, Barber PA, et al. Advanced imaging improves prediction of hemorrhage after stroke thrombolysis. Ann Neurol. 2013 Apr;73(4):510–9.

87. Kim T, Koo J, Kim S-H, Song I-U, Chung S-W, Lee K-S. Blood-brain barrier permeability assessed by perfusion computed tomography predicts hemorrhagic transformation in acute reperfusion therapy. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2018 Jun 16;

88. Li Q, Gao X, Yao Z, Feng X, He H, Xue J, et al. Permeability Surface of Deep Middle Cerebral Artery Territory on Computed Tomographic Perfusion Predicts Hemorrhagic Transformation After Stroke. Stroke. 2017;48(9):2412–8.

CONCLUSION GENERALE

Notre étude apporte une mise à jour des connaissances disponibles sur les facteurs de risque de transformation hémorragique après thrombectomie mécanique moderne. Dans notre cohorte de 643 patients, les déterminants de la transformation hémorragique étaient : la thrombolyse intraveineuse, la glycémie, le volume d'infarctus, les délais séparant l'apparition des symptômes de l'imagerie et l'imagerie de la thrombectomie, la thrombocytémie et la recanalisation mTICI 2b et mTICI 3.

Les facteurs de risque de l'hémorragie intracrânienne symptomatique incluaient : la thrombolyse intraveineuse, le diabète, le volume d'infarctus, et la pression systolique à l'admission. La recanalisation mTICI 2b/3 semblait être un facteur protecteur.

Cette analyse retrouve une majorité de déterminants communs avec la thrombolyse intraveineuse mais rapporte un risque accru chez les patients bénéficiant d'une recanalisation efficace.

Bretzner Martin

AUTEUR : Nom : BRETZNER Prénom : MARTIN

Date de Soutenance : Jeudi 20 décembre 2018

Titre de la Thèse : Facteurs Prédictifs de Transformation Hémorragique après Thrombectomie Mécanique Des Accidents Ischémiques de Circulation Antérieure

Thèse - Médecine - Lille 2018

Cadre de classement : DES Radiodiagnostic et imagerie médicale

Mots-clés : AVC, Thrombectomie Mécanique, transformation hémorragique, Thrombolyse intraveineuse.

Résumé :

Introduction : La transformation hémorragique après thrombectomie mécanique des AVC ischémiques est une complication majeure menaçant la survie et le pronostic fonctionnel des patients. L'objectif de l'étude était d'évaluer les facteurs prédictifs de transformation hémorragique après thrombectomie mécanique.
Méthodes : Nous avons conduit une étude de cohorte à partir du registre prospectif des patients avec AVC ischémique de circulation antérieure ayant bénéficiés d'une thrombectomie mécanique entre 2015 et 2017. Nous avons analysé les données cliniques (antécédents, score NIHSS), biologiques (glycémie, plaquettes, tests de coagulation) et radiologiques (ASPECTS et volume d'infarctus initiaux) de base, les scores de recanalisation angiographiques (mTICI), et la présence d'un remaniement hémorragique sur l'IRM de suivi à J-1 selon la classification ECASS II.
Résultats : Parmi les 643 patients inclus, les facteurs de risque de transformation hémorragique étaient : la thrombolyse intraveineuse, la glycémie, la thrombocytémie à l'admission, le volume lésionnel ischémique initial, le délai de prise en charge ainsi que la recanalisation intracrânienne. Les déterminants d'hémorragie intracrânienne symptomatique (sICH) étaient : le diabète, la thrombolyse intraveineuse, la pression artérielle systolique à l'admission et le volume ischémique. Le délai de prise en charge semblait être un facteur de risque et la recanalisation un facteur protecteur mais ces associations n'étaient pas significatives.
Conclusion : Les facteurs de risque de transformation hémorragique des lésions ischémiques après thrombectomie étaient similaires à ceux après thrombolyse IV à l'exception de l'âge et du NIHSS. La recanalisation était un facteur de risque de transformation hémorragique mais semblait protéger du sICH.

Composition du Jury :

Président : Pr. Jean-Pierre PRUVO

Assesseurs : Pr. Xavier LECLERC, Pr. Charlotte CORDONNIER

Directeur : Dr. Nicolas BRICOUT