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MULTIMODAL PREDICTORS OF COLLATERALS, SALVAGEABLE AND SAVED TISSUE IN ACUTE ISCHEMIC STROKE, AND CLINICAL IMPLICATIONS

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Département des Neurosciences Cliniques

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Thèse de doctorat en Neurosciences

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par

STEFANIA NANNONI
Medical Doctor

Jury

Prof. Lorenz Hirt, Président
Prof. Patrik Michel, Directeur
Dr. Vincent Dunet, Expert
Dr. Gian Marco De Marchis, Expert

Thèse n° 285

Lausanne 2020

Programme doctoral interuniversitaire en Neurosciences des Universités de Lausanne et Genève

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MULTIMODAL PREDICTORS OF COLLATERALS, SALVAGEABLE AND SAVED TISSUE IN ACUTE ISCHEMIC STROKE, AND CLINICAL IMPLICATIONS

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Prof. Niko GELDNER
Directeur de l'Ecole Doctorale

CONTENTS

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2 ABBREVIATIONS LIST

AIS = acute ischemic stroke

ASPECTS = Alberta Stroke Program Early CT Score

ASTRAL = Acute STroke Registry and Analysis of Lausanne

CBS = clot burden score

CTA = CT-angiography

CTP = CT-perfusion

DBP = diastolic blood pressure

DWI = diffusion-weighted magnetic resonance imaging

ESUS = embolic stroke of undetermined source

EVT = endovascular treatment

HR = hazard ratio

IVT = intravenous thrombolysis

LPGH = last proof of good health

LOC = level of consciousness

MCA = middle cerebral artery

MR = mismatch ratio

MRI = Magnetic Resonance Imaging

mRS = modified Rankin scale

mTICI= modified treatment in cerebral infarction score

MVA = multivariate analysis

NCCT = non contrast CT scan

NIHSS = National Institutes of Health Stroke Scale

PFO = patent foramen ovale

OR = odds ratio

ROC = Receiver Operating Characteristic curve

RCT = randomized controlled trial

SBP = systolic blood pressure

TOAST = Trial of ORG 10172 in acute stroke treatment classification

UVA = univariate analysis

3 ABSTRACT

Background - The most effective treatment of acute ischemic stroke (AIS) is a rapid revascularization of the salvageable tissue (cerebral penumbra). It has been proposed that the penumbra can survive because of leptomeningeal collateral circulation. However, the factors that influence the degree of collateral status at baseline are poorly understood, as well as the relationship between collaterals and salvageable tissue. Recently, the extent of penumbra and infarction has been used in randomized clinical trials (RCT) for the selection of AIS patients for late endovascular treatment (EVT) (i.e., after 6 hours from last proof of good health). Still, data on the number of patients eligible for such treatment in real-life scenario are lacking. Similarly, little is known about the efficacy of more liberal selection criteria for late-EVT.

Aims – In this research project, we aimed to investigate clinical and radiological factors associated with better collateral status in a large cohort of AIS patients. We studied the association between penumbra and infarct volumes with the degree of collaterals over time, and we correlated the amount of early ischemic changes on non-contrast imaging with the infarct volumes on perfusion imaging. Focusing on the subgroup of late-arriving AIS patients, we aimed to calculate the proportion of patients eligible for EVT according to trials criteria, and to propose and validate more liberal selection criteria.

Methods – We performed a retrospective study of all consecutive AIS entered in the long-running stroke registry of Lausanne University Hospital (ASTRAL). Patients were selected based on the availability of good quality multimodal imaging (CT-Angiography, CTA, and CT-Perfusion, CTP), reconstructed in a standardized way. For the analysis of late-EVT patients, we enriched the Lausanne data with late treated patients from the stroke registry of Bern University Hospital. The main outcomes of each project were analyzed using appropriate statistical tests, after applying multiple adjustments for potential confounders.

Results – Our study of 857 patients with middle cerebral artery stroke showed that favorable collateral status was associated with several variables, including lower age, non-smoking status, no previous statin use, dyslipidemia and lower serum creatinine. Moreover, we found that better degree of collaterals related to a smaller infarct and greater mismatch ratio, but we could not demonstrate an independent association between better collaterals and higher penumbra volumes. The correlation between ASPECTS and CTP-core was moderate (rho=-0.49), but significantly stronger in the late-arriving patients with large vessel occlusion (rho=-0.57). Our eligibility analysis on 925 late-arriving AIS with complete neuroimaging protocols showed that 5.6% of patients fulfilled trial criteria (DAWN/DEFUSE-3) for late-EVT. This proportion increased to 11.1% when applying more liberal selection criteria. In the combined Lausanne and Bern cohort of 337 late EVT-treated patients, late EVT seemed effective in the presence of a more liberal clinical-ASPECTS mismatch, but not in its absence.

Discussion – Our results showed that risk factors for diffuse vascular pathology (i.e. smoking, aging, renal function impairment) might play a detrimental role in the development and recruitment of collaterals anastomoses. These findings may add to our understanding of collaterals variability at baseline, and also indicate that collateral circulation is crucial in determining the extent of the infarct volume in the initial diagnostic workup. Translating these observations in the setting of late-arriving AIS patients, we demonstrated that EVT could be offered to a larger population of patients if more liberal criteria were adopted. If confirmed in RCT, a

simpler neuroimaging protocol could be used for referring patients for late EVT and for estimation of prognosis.

4 INTRODUCTION

Stroke is the first cause of adult disability and represents one of the leading causes of death worldwide (1). Acute ischemic stroke (AIS) accounts for about 87 percent of all strokes and has a major impact on health system and society. However, treatment options for AIS are still limited. Intravenous (IV) tPA (Alteplase®) remains the only approved therapy for AIS, with administration being restricted to 4.5 hours post known symptom onset (2). Although early thrombolysis improves long-term outcome (3), the short therapeutic window and its limited efficacy in the presence of a large thrombus burden make it an imperfect treatment. As a result, it is estimated that less than 25% of thrombolyzed patients really benefit from this treatment (4).

Endovascular treatment (EVT), that is the removal of blood clots with mechanical devices or thrombolytic drugs administered intra-arterially, has been long recognized as an alternative, more effective treatment in proximal intracranial large vessel occlusion (LVO) in the anterior circulation. EVT has been linked to higher recanalization rates then IV thrombolysis, with good safety. Recently, mechanical thrombectomy (MT) has been shown to be safe and effective in five randomized-controlled trials (RCT) if performed within the first few hours with dedicated endovascular devices such as stent retrievers (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA). These trials have established MT as the new gold standard for such patients (5). In a meta-analysis, EVT was

effective up to 7.3 hours after symptom onset in AIS patients (6), with a suggestion that this treatment window could even be substantially longer. Unfortunately, a large proportion of patients keep presenting beyond this time window, in particular patients with wake-up stroke.

A central consideration in the optimization of patient selection for acute stroke therapies is the concept of the early infarct (core) and the tissue with potentially reversible ischemia (penumbra). Ischemic penumbra is defined as ischemic tissue that is potentially salvageable and is distinguished from the ischemic core that has already sustained irreversible injury (7). Clearly, the target of acute stroke therapies is prevention of infarct growth through salvage of the ischemic penumbra, leading hopefully to better functional outcome. Acute revascularization treatments should therefore ideally be applied to patients with limited core and a significant ischemic penumbra.

Modern neuroimaging techniques, particularly multimodal CT (including non-invasive angiography and perfusion imaging) allow detecting the location of the occluding clot, to evaluate the integrity of collateral circulation and to quantify the salvageable brain tissue.

Arterial collaterals provide alternative blood flow to support brain viability when a primary vessel in the cervicocephalic arterial tree is critically stenosed or occluded. They are pre-existing anastomoses that cross-connect a small number of distal arterioles within the crowns of the cerebral artery trees. The beneficial effect of good collaterals on clinical outcome in AIS patients could be because of reduced severity of ischemia, resulting in potentially longer time windows for tissue salvage. Good collateral status may also increase distribution of thrombolytic to the clot surface, potentially making the clot more susceptible to thrombolysis or thrombectomy(8) .

Variability in native leptomeningeal status can be explained by genetic and environmental determinants. Studies examining the determinants of variability of collaterals in humans are very limited and are often not robust. History of hypertension and higher systolic blood pressure on admission have been associated with poor collateral status at baseline, while statin use has been

associated with good collateral status(9). The presence of metabolic syndrome, hyperuricemia and aging were found as independent predictor of poor baseline leptomeningeal collateral status among patients presenting with AIS (10).

Early PET studies in stroke have identified different tissue regions within a brain area compromised by ischemia(11). The tissue changes with time, the extent of the penumbra and its conversion into infarction is a dynamic process, and irreversible damage spreads from the core of ischemia to its border. In the experimental as well as the clinical PET studies, after focal cerebral ischemia an early heterogeneity of tissue regions— irreversibly damaged, penumbra, and oligaemic viable tissue—could be observed. The concept of the heterogeneity of the penumbra was further supported by DWI and PWI imaging evaluation of lesions and the mismatch early detected after ischemic stroke (12). In the clinical setting of hyperacute stroke, the penumbra and early infarct can be quite accurately measured using automated thresholded techniques on MRI or CT perfusion (CTP)(13).

In the DEFUSE and EPITHET studies, patients with an important “target mismatch” showed better clinical and radiological outcomes following reperfusion than the other patients, probably because the latter have minimal or no salvageable tissue (14, 15). The degree of reperfusion achieved corresponded with clinical recovery in target mismatch patients, and the association between reperfusion and good clinical outcome was not reduced over time. This finding supports the concept that salvageable tissue can persist many hours after stroke onset in selected stroke patients and that time–independent factors, such as the degree of collateral circulation, play an important role in the progression from reversible to irreversible ischemic injury (13). Also, these and other studies show that mere presence of penumbra doesn’t guarantee a better outcome by itself (16). Rapid recanalization, but probably also multiple other, poorly explored factors, play a role in the intertwined relationship between the presence of salvageable tissue, collaterals, recanalization and tissue survival.

It has been hypothesized for a long time that the time clock to best identify treatable patients by thrombolysis and EVT may be replaceable by imaging

criteria, i.e. the demonstration of a small infarct core coupled with an important volume of salvageable brain tissue (17). Through systematic research over more than 10 years, a large amount of evidence for the clinical usefulness of this concept has been accumulated (14-16). This led to the design of imaging-based RCT of EVT for patient arriving late, i.e. more than 6 hours after stroke onset.

The first such published RCT that showed efficacy and safety of late EVT for acute anterior circulation LVO stroke was the DAWN trial (18): among patients with AIS who had last been known to be well 6 to 24 hours earlier and who had a mismatch between (a small) infarct volume on imaging and a (large) clinical deficit, EVT lead to a better functional outcome at 90 days than standard care alone.

A second RCT, the DEFUSE-3 trial, has also shown impressive clinical benefit of thrombectomy in patients with a LVO anterior ischemic stroke presenting 6 to 16 hours after last seen well (19). Here, patients were selected purely radiologically based on a small infarct and a substantial volume of salvageable tissue. Results showed again that in such patients, EVT led to a clearly superior functional outcome at 90-days compared to control patients.

According to these results, selection for endovascular therapy in AIS should not be made on time alone, but physiological criteria based on imaging also need to be considered. The pathophysiological feature predicting a favorable clinical response in patients enrolled in both trials was the presence of a mismatch between the volume of irreversibly damaged brain (infarct volume) and the total volume of critically hypo-perfused brain (penumbra volume). There are several possible definitions of “mismatch”: the DAWN trial enrolled patients having salvageable brain tissue on the basis of "clinical-core mismatch", that is, patients who have a small core stroke volume and a large clinical deficit (National Institutes of Health Stroke Scale (NIHSS) score > 10). This high NIHSS signifies an extensive brain area which is clinically not functional, but still potentially salvageable. In the DEFUSE-3 trial, a pure radiological mismatch definition was used: patients underwent imaging with CTP or MRI diffusion/perfusion and an automated software program (RAPID) was used to determine whether patients

fulfilled the requirements for target mismatch. The trial required a mismatch ratio (the ratio of the volume of ischemic tissue on perfusion imaging to infarct volume) of at least 1.8 and a relatively small volume of core (in this case less than 70 mL). Use of the mismatch concept may be particularly important in later phases of AIS, because growth rates of infarct volume are very variable: for late treatment, patients with slow-growing infarcts have to be selected, whereas patients with rapidly growing infarct cores should not be treated at these late time points anymore (20). It has been hypothesized that this large variability of early infarct growth may be due to the extent of collateral circulation, metabolic and genetic factors.

Whereas the number of early arriving patients eligible for thrombolysis and EVT has now been calculated (21), the number of late arriving patients who are EVT eligible is not truly known in the real world. For the implementation of DAWN and DEFUSE-3 results, the calculation of the proportion of patients eligible for such treatment is of major importance for organization of stroke systems of care. Moreover, the precise measurement of infarct and penumbra volumes with sophisticated imaging may be difficult in the acute stroke scenario due to patient agitation, contrast contraindications, or technical problems with perfusion imaging. Therefore, simpler and more liberal criteria to determinate clinical-core mismatch could be useful for clinical practice. In addition, it is important to know whether the results of the trial criteria are matched in the real life by similarly improved clinical outcome.

4.1 Research questions

The thesis project consists in two main sections: project A) exploring the neuroradiological characteristics of AIS patients assessed with CT-based multimodal imaging; and project B) analyzing the selection criteria for endovascular treatment in the late time window.

4.1.1 *Project **A)** Multimodal imaging in AIS*

The main objective of project A) was to identify predictors of a good clinical status and a salvageable penumbra in a large cohort of AIS patients hospitalized in a university stroke center. More specifically, we planned the following three sequential analyses:

1) We planned to analyze multiple demographic, clinical, metabolic and radiological variables in order to identify those which are independently related with a good collateral status in the hyperacute state of stroke.
2) We aimed to investigate the relationship of collateral status, penumbra and core volumes on CT-perfusion (CTP), and their interaction over the time after stroke onset.
3) We searched for a correlation between early ischemic changes on non-contrast CT scan (assessed by ASPECTS) and core volumes on CTP, testing the strengh of this association:
   - In a large cohort of patients with AIS in the middle cerebral artery territory with availability of good quality CTP;
   - In the subgroup of patients admitted in the late time window and showing a large vessel occlusion (LVO).

   Moreover, we explored the predictive value of both ASPECTS and CTP-core in determining the clinical outcome at 3 months, with a special focus in late-arriving patients with LVO.

4.1.2 *Project **B)** Clinical implication in the late time window*

We planned to calculate eligibility for late thrombectomy in AIS patients arriving late (5-23 hours) using strict trial criteria, to propose more liberal selection criteria for late thrombectomy, and to show the relative value of these criteria on clinical long-term outcome. More specifically, we planned the following two sequential analyses:

1) We calculated the proportion of late EVT eligible patients using strict trial criteria as used in DAWN & DEFUSE-3. Calculations was made for the overall acute stroke population arriving at our hospital, and separately for patients coming from the primary catchment area and from the larger referral base. The proportion of eligibility was calculated for the following four denominators:
   - for all ASTRAL patients (arrival between 0-23 hours);
   - for all late arriving ASTRAL patients (arrival between 5-23 hours);
   - for all late arriving ASTRAL patients (arrival between 5-23 hours) with all required multimodal imaging data available;
   - for all late and very late arriving patients (arrival between 5 hours and 7 days).

   Morover, we searched for independent prehospital predictors of eligibility according to the criteria applied.

2) We proposed more liberal (pragmatic) criteria that could be used to select late arriving patients for EVT.
   - We defined more easy-to use ASPECTS cut-offs through by correlating ASPECTS with core volume on CTP in the ASTRAL database. These ASPECTS cut-offs were combined with other less stringent selection criteria, such as older age, lower stroke severity, and minor prestroke handicap.
   - We then calculated late EVT eligibility based on these more liberal selection criteria. As in point 1), the proportion of eligible patients was determined: separately for the primary catchment area and the larger referral base; for the four denominators mentioned above.
   - Using these criteria, we analyzed the outcome of patient with/without liberal criteria and with/without late EVT through an interaction analysis in order to show the criteria's validity.

5 PROJECT **A)** MULTIMODAL NEUROIMAGING OF AIS PATIENTS

5.1 Determining factors of better leptomeningeal collaterals

5.1.1 *Abstract*

Background

In acute ischemic stroke (AIS) collaterals correlate with infarct size, recanalization rate and clinical outcome. We aimed to identify factors associated with better collateral status in a large series of AIS patients with middle cerebral artery (MCA) occlusion.

Methods

In the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) from 2003 to 2016, we identified all consecutive AIS with proximal MCA occlusion on CT-angiography performed <24 hours. Collaterals were scored from 0 (absent) to 3 (≥100%) and related to multiple demographic, clinical, metabolic and radiological variables in a multivariate regression analysis (MVA).

Results

The 857 included patients had a median age of 72.3 years, 48.4% were female and median admission NIHSS was 16. Better collaterals were associated with younger age (OR=0.99; 95%CI: 0.98-1.00), hemineglect (OR=1.35; 95%CI:

1.03-1.76), absence of visual field defects (OR=0.64 95%CI: 0.46-0.90), eye deviation (OR=0.58; 95%CI: 0.43-0.79) and decreased vigilance (OR=0.62 95%CI: 0.44-0.88). Better collaterals were also associated with dyslipidemia (OR=1.57; 95% CI: 1.16-2.13), no previous statin use (OR=0.69; 95%CI: 0.50-0.95), and lower creatinine levels (OR=0.99 95%CI: 0.99-1.00). On neuroimaging, better collaterals related to higher ASPECTS score (OR=1.27 95% CI: 1.20-1.35) and higher clot burden score (OR=1.09; 95% CI: 1.03-1.14).

Conclusions

Younger age, dyslipidemia and lower creatinine levels were predictors of better collaterals in AIS patients from proximal MCA occlusions. Greater degree of collaterals related to lower stroke severity on admission. On neuroimaging, better collaterals were independently associated with minor early ischemic changes and lower clot burden. These data may add knowledge on pathophysiology of collaterals development and may help to identify patients with better collaterals for late or aggressive recanalization treatments.

5.1.2 *Background*

Leptomeningeal arterial collaterals are pre-existing anastomoses that cross-connect a small number of distal arterioles of the cerebral arteries(22). They provide alternative blood flow to support brain viability when a primary vessel in the cervico-cephalic arteries is critically stenosed or occluded, such as in acute ischemic stroke (AIS). A greater degree of collaterals at baseline has been associated with smaller infarct size (23), improved recanalization rate after endovascular treatment(24) and improved clinical outcome(25, 26).

The magnitude of collateral flow varies greatly between patients. Still, studies examining determinants of this variability are lacking. Besides genetic and environmental factors, statin use has been associated with good collaterals (9), whereas a history of hypertension and higher systolic blood pressure on admission have been associated with poor collateral status at baseline(27).

Recently, the presence of metabolic syndrome, hyperuricemia and aging were found as independent predictors of poor leptomeningeal collateral status (10). Malik et al. confirmed the association between poor collaterals and older age, but did not find a favorable influence of pre-stroke statin use on the patency of collateral circulation (28).

In this study, we investigated factors associated with leptomeningeal collateral status in a large cohort of AIS patients. In particular, we analyzed multiple demographic, clinical, biochemical and radiological variables in order to identify independent predictors of better collaterals in the acute phase of stroke.

5.1.3 *Methods*

Patient selection

All consecutive patients included in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to June 2016 were considered for this study. ASTRAL is a single-center prospective cohort of all AIS patients admitted to the Stroke Center of Lausanne University Hospital within 24 hours of an ischemic stroke (29). It incorporates detailed clinical and laboratory data and multimodal brain imaging techniques. The type and definition of collected variables in ASTRAL is prespecified, and the current analysis was retrospective.

For patient selection, we used the following inclusion criteria: AIS involving the middle cerebral artery (MCA); CT-based multimodal imaging performed <24h of last proof of good health; availability of a CT-angiography (CTA) of good quality showing occlusion of the proximal segments (M1 and/or proximal M2), with or without added more distal and more proximal (carotid siphon, extracranial carotid artery) pathology. Patients with only distal M2 or only M3 occlusions were excluded because visual assessment of collaterals in a small arterial territory was considered insufficiently reliable.

Clinical Variables

Demographic data (age, gender), medical history and vascular risk factors (like previous cerebrovascular events, arterial hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation) were recorded. We collected pre-stroke modified Rankin scale (mRs) and current medications at the time of stroke. We recorded new (i.e. not preexisting) clinical signs and symptoms as noted by the initial assessment in the medical records. Stroke severity by National Institutes of Health Stroke Scale (NIHSS). We measured vital signs (body temperature, blood pressure), metabolic and hematologic parameters at admission and calculated onset-to-door, onset-to brain imaging and onset-to treatment times. Stroke etiology was classified according to the TOAST classification, with dissection and multiple causes added as categories. Clinical outcome was measured at 3 months with the mRs either in person at the outpatient stroke clinic, or by standardized telephone interview by Rankin-certified medical personnel. Favorable outcome was considered as 3 months mRs ≤2.

Imaging protocol and analysis

We assess all individuals with suspected AIS by a multimodal CT scan as part of their standard of care, unless contrast contraindication exists. Non-contrast CT (NCCT) scanning was performed to detect intracranial hemorrhage, hyperdense MCA sign and chronic cerebrovascular lesions (defined as presence of chronic infarct and/or leukoaraiosis ≥1 according to Blennow scale). Early ischemic changes in the MCA territory were recorded to calculate ASPECTS.

CTA in helical mode was performed from the aortic arch to the top of the frontal sinuses (120 KV, 150-260 mAs, 0.625 slice-thickness, 50ml of iodinated contrast at 5ml/s, delay according to the perfusion data). On CTA, we searched for significant extracranial carotid pathology in the ischemic territory, defined as the presence of ≥50% stenosis, occlusion, dissection or floating thrombus. Significant intracranial pathology, i.e. ≥50% stenosis or occlusion, was grouped as proximal if it involved carotid siphon, proximal M1 (i.e. less than 10 mm from

M1 origin) or A1 segment, and distal if it involved distal M1, M2, M3 or A2 segment. We calculated clot burden score (CBS) as indicator of clot extension. The collateral score was visually determined from CTA maximal intensity projection reconstructions and graded according to Tan et al.(30) Absence of collateral flow to the ischemic territory was graded as 0, whereas collateral flow in ≤50%, >50% and ≥100% of the vessels filling in the ischemic territory distal to the occluded artery was graded as 1 (poor collaterals), 2 (moderate collaterals), and 3 (good collaterals), respectively. Interrater agreement for collateral grading 0-1 vs. 2-3 was evaluated on 100 consecutive patient's proximal intracranial occlusions using Cohen's kappa.

Statistical analysis

We first performed a univariate analysis (UVA) between demographic, clinical, metabolic and radiological variables depending on collateral status. All grades of collaterals (0-3) were considered for the primary outcome of the study. All variables from the UVA, independently from their p-value in univariate comparisons, were then used to fit three multivariate logistic models in order to determine the independent associations with better degrees of collateralization. First, we performed a clinical multivariate analysis (MVA-A) using only demographic, clinical and laboratory variables available before the acquisition of CTA. Second, we analyzed the radiological variables that are independently associated with better collaterals (MVA-B). Finally, we did a combined analysis using all demographic, clinical, metabolic and radiological variables in a comprehensive MVA (MVA-C). All analyses were performed using the proportional odds approach. In all MVA analyses, imputation of missing values was carried out using multiple chain equations methodology(31). In this way, we generated five complete datasets. Analysis of each dataset was performed separately. We used backward elimination techniques to select important covariates. The reported results were generated by appropriately combining the results of the five imputed analyses. In all analyses, a type I error of 5% was used (e.g. $p<0.05$). The R package (R version 3.4.1) was used throughout.

Given that the 3 months clinical outcome was considered a secondary, ancillary result, no adjustment was done for this analysis.
Collection, analysis and publication of data in ASTRAL was approved by the institution's ethical commission.

5.1.4 *Results*

Among 2027 patients with AIS involving MCA territory and with good quality acute CTA during the study period, 857 met the inclusion criteria (Figure 1). Median age was 72.3 (interquartile range, IQR 20.5) years, 415 (48.4%) were females and median admission NIHSS was 16 (IQR 9). Median onset to CT time was 2.5 (IQR 3.4) hours. CTA showed M1 occlusion in 620 (72.3%) and proximal M2 occlusion in 237 (27.7%) patients. Collaterals were graded as absent (grade 0) in 77 (9.0 %), poor (grade 1) in 345 (40.3 %), moderate (grade 2) in 307 (35.8 %) and good (grade 3) in 128 (14.9 %) patients. Interrater agreement for collateral grading 0-1 vs. 2-3 was 0.81.
Table 1 and 2 show patient characteristics, laboratory and radiological findings of the study population as well as the results of the univariate analysis. The distribution of vascular risk factors was similar among the collateral scores.
Significant results from the MVAs are shown in Table 3. In the clinical MVA (MVA-A), better collaterals were associated with lower age (OR=0.99, confidence intervals: see Table 3), lower NIHSS on admission (OR=0.94, see also Figure 2) and lower frequency of visual field defects (OR=0.70), eye deviation (OR=0.66) and decreased vigilance (OR=0.60). Better collaterals were also associated with non-smoking status (OR=0.72) and decreased delay to imaging (OR=0.97). When limiting the MVA to radiological variables (MVA-B), better collaterals were associated with a higher ASPECTS score (OR= 1.27), higher CBS (OR=1.15), and absence of chronic cerebrovascular lesions (OR= 0.72).
Combining all data in a comprehensive MVA (MVA-C), better collaterals were associated with lower age (OR= 0.99), hemineglect (OR=1.35), absence of visual field defects (OR= 0.64), eye deviation (OR= 0.58) and decreased

vigilance (OR= 0.62). Better collaterals were also associated with dyslipidemia (OR= 1.57), absence of statin use (OR= 0.96) and lower creatinine levels (OR= 0.99). Moreover, we confirmed the positive association between better collaterals and higher ASPECTS (OR=1.27 and Figure 3) and higher CBS (OR= 1.09 and Figure 4) respectively.

As an ancillary result, we found in unadjusted analysis that a better collateral status was associated with favorable clinical outcome at 3 months (Table 1).

5.1.5 *Discussion*

In this largest retrospective study of collaterals so far, we investigated factors that are associated to their variability in patients with AIS and proximal MCA occlusion. We found that favorable collateral patterns could be predicted by lower age, non-smoking status, no previous statin use, dyslipidemia and lower serum creatinine. Better collaterals were more frequently observed in patients with shorter delay to imaging and absence of chronic cerebrovascular lesions. Moreover, better collaterals were associated with lower stroke severity, lower frequency of cortical signs (except for hemineglect), higher ASPECTS and lower clot burden.

The association between younger age and better collateral score is in agreement with previous findings (10, 28). It has been proposed that aging leads to 'collateral rarefaction', a process causing reduction in collateral density and diameter, probably mediated by prolonged endothelial dysfunction (32). Among vascular risk factors, current smoking was an independent predictor of poorer collaterals in our clinical analysis. The role of smoking in the impairment of collateral extent in the coronary and peripheral bed is well known(33), but studies examining its association with leptomeningeal collateral status in humans are lacking. To the best of our knowledge, there have been no previous reports noting that renal impairment was associated with poor cerebral collaterals. However, hyperuricemia, known to be related to chronic kidney disease, and the presence of metabolic syndrome, have recently been associated with worse collaterals(10). These findings allow us to generate

hypotheses with regard to underlying pathophysiology of collateral formation. Aging, smoking and impaired renal function could reduce collateral extent by either causing endothelial dysfunction or decreasing dilatator capacity of the pial arteries(34).

Somewhat unexpectedly, known or newly diagnosed dyslipidemia was associated with better and statin use with poorer collaterals. Previous reports on coronary artery disease demonstrated a positive association of hypercholesterolemia and collateral extension, probably mediated by elevated levels of vascular endothelial growth factor (35). Regarding statin use, our findings may be viewed as contradictory and not consistent with previous studies suggesting a role for statins in the promotion of arteriogenesis (9, 36). In our study, it seems that untreated (newly diagnosed) hyperlipidemia may be a major promoter of collaterogenesis, rather than known and treated hyperlipidemia (i.e. statin use).

A shorter delay from symptoms onset to baseline imaging was independently associated with better collaterals, supporting the concept of time-dependent 'collateral-failure' (37, 38). In the purely radiological analysis, absence chronic infarcts and leukoaraiosis were associated with better collaterals. Leukoaraiosis might be associated with increased arterial stiffness, which lead to less recruitment of collaterals in the acute phase of occlusive ischemic stroke (39).

In our study, lower rate of cortical signs (i.e. eye deviation and visual field defects) were associated with better collaterals. This is consistent with the anatomical observation that leptomeningeal collaterals mainly supply cortical peripheral areas, whereas deeper structures are predominantly supplied by perforating arteries(40). Only hemineglect did not fit this pattern, possibly indicating that the critical site of temporal damage responsible for hemineglect is mostly supplied by non-anastomosing arterial systems(41). The positive association with higher ASPECTS suggests that a higher degree of collaterals may prevent infarct growth(38). Moreover, higher clot burden may obstruct more orifices of arteries that could provide collateral blood flow. Inversely, one

could hypothesize that collaterals may influence clot length, because patients with poor collaterals may have an increased degree of stasis around the clot and this could lead to a clot extension(42).

The association of collateral status with clinical outcome was not a main goal of our study. Still, the fact that patients with good collaterals showed a better outcome in unadjusted analysis stresses the need to adjust for this variable when reporting outcomes after revascularization treatments.

The limitations of our study include its retrospective design and its single center nature. Also, collaterals were estimated semi-quantitatively and CTA-based collateral assessment may be less precise than invasive contrast angiography. Moreover, the use of single-phase CTA may lead to technique-dependency bias in collaterals evaluation due to variability in the timing of the contrast injection and image acquisition.

In conclusion, our study showed that younger age, non-smoking status, dyslipidemia and lower serum creatinine were predictors of better collaterals in patients with AIS and proximal MCA occlusion. The implications of our findings are several: first, they may add to our understanding of collaterals variability at baseline, indicating that risk factors for diffuse vascular pathology (i.e. smoking, aging, renal function impairment) may play a detrimental role in the development and recruitment of such anastomoses. Conversely, dyslipidemia may exhibit a promoting effect upon angiogenesis. Second, our data suggest that manipulation of physiological parameters such as blood pressure or sugar may not result in better collateral flow, but the latter seems to be largely determined by non-modifiable factors in the acute phase of stroke. Third, the associations between collateral status and ASPECTS, clot burden, and frequent cortical signs suggest that these elements are related and partly interchangeable, measuring similar aspects of the ischemic pathophysiology. These characteristics could be used to identify patients with better collaterals for more aggressive revascularization treatment, even at later timepoints.

5.1.6 *Tables and Figures*

Table 1 Patient characteristics, laboratory and radiological findings in the study population. Odds ratios (OR) with confidence intervals (95% CI) from the univariate analysis of better vs. poorer collaterals are given, with collaterals used as an ordinal variable quantified by four grades.

Table 2 Patients characteristics, laboratory and radiological findings in the study population divided in the four collateral grades. Absence of collateral flow to the ischemic territory was graded as 0, whereas collateral flow in ≤50%, >50% and ≥100% of the vessels filling in the ischemic territory distal to the occluded artery was graded as 1, 2, and 3, respectively.

Table 3 Results of the pre-imaging multivariate analysis (MVA-A), the imaging-only MVA (MVA-B), and the comprehensive MVAs (MVA-C). Only significant associations are shown.

Figure 1 Inclusion and exclusion flow chart.

Figure 2 Correlation between NIHSS on admission and collaterals (ordinal).

Figure 3 Correlation between ASPECTS score and collaterals (ordinal).

Figure 4 Correlation between Clot Burden Score and collaterals (ordinal).

Table 1

Baseline Variable and Follow-up as median ± IQR. or n (%):	**Total pt (N = 857)**	**OR**	**95% CI**
Demographics			
Age (yrs)	72.3 (20.5)	0.99*	0.98 - 1.00
Sex (females)	415 / 857 (48.4%)	1.08	0.84 - 1.38
Onset during sleep	140 / 857 (16.3%)	0.73	0.52 - 1.03
Acute treatment	531 / 857 (62.0%)	1.03	0.80 - 1.33
Admission NIHSS	16.0 (9.0)	0.91*	0.89 - 0.92
New neurological deficit			
Paresis	821 / 849 (96.7%)	0.65	0.33 - 1.29
Dysarthria	628 / 843 (74.5%)	0.70*	0.52 - 0.93
Sensory Deficit	674 / 840 (80.2%)	0.50*	0.37 - 0.69
Visual field defects	619 / 836 (74.0%)	0.34*	0.25 - 0.46
Eye deviation	477 / 835 (57.1%)	0.35*	0.27 - 0.46
Aphasia	435 / 842 (51.7%)	1.04	0.81 - 1.33
Neglect	431 / 835 (51.6%)	0.89	0.69 - 1.14
Vigilance impairment	163 / 836 (19.5%)	0.34*	0.25 - 0.48
Side affected (left)	419 / 857 (48.9%)	1.30	1.01 - 1.67
Premorbid risk factors			
Previous cerebrovascular events	166 / 851 (19.5%)	1.08	0.79 - 1.48
Hypertention	537 / 852 (63.0%)	0.88	0.68 - 1.14
Diabetes	134 / 852 (15.7%)	0.85	0.61 - 1.19
Hyperlipidemia	581 / 851 (68.3%)	1.20	0.92 - 1.57
Current smoking	206 / 841 (24.5%)	0.87	0.65 - 1.17
Atrial Fibrillation	351 / 854 (41.1%)	0.78	0.61 - 1.01
Coronary artery disease	163 / 850 (19.2%)	0.82	0.60 - 1.12
Peripheral artery disease	53 / 840 (6.3%)	0.75	0.45 - 1.25
Alcohol dependence	97 / 851 (11.4%)	1.07	0.73 - 1.56
Obesity	339 / 836 (40.6%)	1.20	0.93 - 1.55
Pre-stroke mRS >2	68 / 850 (8.0%)	0.89	0.57 - 1.40
Treatment before stroke			
Anti-hypertensive use	486 / 840 (57.9%)	0.77*	0.60 - 1.00
Statin use	215 / 846 (25.4%)	0.75	0.57 - 1.00
Anti-diabetic or Insuline use	82 / 841 (9.8%)	0.89	0.58 - 1.34
Baseline clinical measurements			
Body temperature (°C)	36.2 (0.8)	1.08	0.90 - 1.31
Systolic Blood Pressure (mmHg)	150 (35)	0.99	0.94 - 1.04
Laboratory studies			
Blood glucose (g/L)	6.7 (2.1)	0.93*	0.88 - 0.98
Laboratory studies			
Serum creatinine (mg/dL)	87.0 (29.0)	0.99*	0.99 - 1.00

Total cholesterol (mmol/L)	5.1 (1.6)	1.01	0.99 - 1.03
WBC count (cells/mL)	8.2 (3.7)	0.96*	0.94 - 0.99
Hemoglobin (g/dL)	13.7 (2.1)	1.00*	0.99 - 1.01
Onset to CT time (h)	2.5 (3.4)	0.98	0.95 - 1.01
Neuroimaging data			
ASPECTS score	8.0 (4.0)	1.32*	1.25 - 1.39
Chronic or subacute infarct	220 / 857 (25.7%)	0.87	0.66 - 1.15
Significant leukoaraiosis	212 / 857 (24.7%)	0.84	0.63 - 1.11
Hyperdense MCA sign	398 / 857 (46.4%)	0.54*	0.42 - 0.70
Silent infarct	178 / 857 (20.8%)	0.83	0.62 - 1.13
Clot burden score	6.0 (4.0)	1.22*	1.16 - 1.27
Vascular imaging			
Significant extracranial carotid pathology			
Significant stenosis	69 / 856 (8.1%)	0.73	0.46 - 1.16
Any occlusion	184 / 856 (21.5%)	0.59*	0.43 - 0.81
Significant proximal intracranial pathology‡	425 / 857 (49.6%)	0.42*	0.32 - 0.54
Significant distal intracranial pathology‡	796 / 857 (92.9%)	0.75	0.46 - 1.23
Significant extracranial carotid pathology in non-ischemic territory	72 / 857 (8.4%)	1.14	0.74 - 1.77
Significant vascular pathology in non-ischemic territory	119 / 857 (13.9%)	1.02	0.72 - 1.45
TOAST Mechanism †			
Atherosclerosis	114 / 828 (13.8%)	0.81	0.56 - 1.19
Cardiac	396 / 828 (47.8%)		
Dissection	56 / 828 (6.8%)	0.68	0.38 - 1.21
Embolic stroke of undetermined source	179 / 828 (21.6%)	0.82	0.53 - 1.25
Other (rare) causes	34 / 828 (4.0%)	1.02	0.49 - 2.11
Multiple causes	49 / 828 (5.9%)	0.64	0.34 - 1.18
mRS at 3 months			
0-2	308/760 (40.5%)	0.35*	0.26 - 0.46

* Asterisks denote significant findings. † Reference: atherosclerosis. ‡ Definitions: see text.

Table 2

Baseline Variable and Follow-up as median ± IQR or n (%):	**Collateral Grade**			
	0 (N = 77)	**1 (N = 345)**	**2 (N = 307)**	**3 (N = 128)**
Age (yrs)	74.9 (16.6)	74.9 (19.1)	69.6 (22.5)	69.8 (17.9)
Sex (females)	39 (50.6%)	158 (45.8%)	156 (50.8%)	62 (48.4%)
Admission NIHSS	21.0 (7.0)	17.0 (9.0)	15.0 (9.5)	12.0 (9.5)
New neurological deficit				
Visual field defects	66 (89.2%)	275 (82.1%)	213 (70.8%)	65 (51.6%)
Eye deviation	53 (73.6%)	228 (67.9%)	160 (52.8%)	36 (29.0%)
Aphasia	41 (54.7%)	168 (49.7%)	160 (53.2%)	66 (51.6%)
Neglect	37 (51.4%)	180 (53.4%)	156 (51.7%)	58 (46.8%)
Vigilance impairment	32 (42.7%)	80 (23.8%)	38 (12.6%)	13 (10.5%)
Premorbid risk factors				
Hypertension	45 (59.2%)	226 (65.9%)	193 (63.1%)	73 (57.5%)
Diabetes	11 (14.5%)	60 (17.5%)	47 (15.4%)	16 (12.6%)
Hyperlipidemia	44 (57.9%)	237 (69.1%)	209 (68.5%)	91 (71.7%)
Current smoking	19 (25.3%)	87 (25.8%)	73 (24.2%)	27 (21.3%)
Atrial fibrillation	36 (47.4%)	148 (42.9%)	123 (40.2%)	44 (34.6%)
Pre-stroke mRS >2	6 (8.0%)	28 (8.2%)	27 (8.9%)	7 (5.5%)
Statin use before stroke	21 (27.3%)	97 (28.5%)	72 (23.8%)	25 (19.8%)
Laboratory studies				
Blood glucose (mmol/L)	7.3 (2.6)	6.7 (2.1)	6.6 (1.8)	6.5 (1.9)
Serum creatinine (mg/dL)	87.0 (35.2)	88.0 (29.0)	85.0 (28.5)	86.0 (30.5)
Total cholesterol (mmol/L)	5.2 (1.5)	4.9 (1.6)	5.1 (1.7)	5.5 (1.8)
Onset to CT time (h)	3.2 (8.6)	2.5 (3.4)	2.4 (2.9)	2.7 (2.9)
Neuroimaging data				
ASPECTS score	6.0 (5.0)	7.0 (4.0)	9.0 (3.0)	9.0 (2.0)
Significant leukoaraiosis	18 (23.4%)	91 (26.4%)	82 (26.7%)	21 (16.4%)
Hyperdense MCA sign	55 (71.4%)	168 (48.7%)	131 (42.7%)	44 (34.4%)
Clot burden score	3.0 (5.0)	6.0 (5.0)	6.0 (4.0)	7.0 (3.0)
Extracranial carotid pathology:				
Significant stenosis	5 (6.5%)	35 (10.1%)	18 (5.9%)	11 (8.6%)
Any occlusion	27 (35.1%)	77 (22.3%)	63 (20.6%)	17 (13.3%)
TOAST Mechanism				
Atherosclerosis	5 (6.7%)	46 (13.9%)	45 (15.2%)	18 (14.4%)
Cardiac	38 (50.7%)	158 (47.7%)	139 (46.8%)	61 (48.8%)
mRS at 3 months				
0-2	10 (14.1%)	96 (31.9%)	132 (48.0%)	70 (61.9%)

Table 3

MVA-A			
Clinical variable	**OR**	**95% CI**	***p*-value**
Age	0.99	0.98-1.00	<0.01
Admission NIHSS	0.94	0.92-0.97	<0.01
Visual field defects	0.70	0.49-1.00	0.04
Eye deviation	0.66	0.48-0.91	0.01
Vigilance impairement	0.60	0.41-0.86	<0.01
Current smoking	0.72	0.53-0.98	0.04
Onset to CT time (h)	0.97	0.94-1.00	0.03
MVA-B			
Radiological variable	**OR**	**95% CI**	***p*-value**
ASPECTS score	1.27	1.20-1.34	<0.01
Clot burden score	1.15	1.09-1.20	<0.01
Chronic cerebrovascular lesions	0.72	0.54-0.96	0.03
MVA-C			
Variable	**OR**	**95% CI**	***p*-value**
Age	0.99	0.98-1.00	<0.01
Visual field defects	0.64	0.46-0.90	<0.01
Eye deviation	0.58	0.43-0.79	<0.01
Neglect	1.35	1.03-1.76	0.03
Vigilance impairment	0.62	0.44-0.88	<0.01
Statin use	0.69	0.50-0.95	0.02
Hyperlipidemia	1.57	1.16-2.13	<0.01
Serum creatinine	0.99	0.99-1.00	<0.01
ASPECTS score	1.27	1.20-1.35	<0.01
Clot burden score	1.09	1.03-1.14	<0.01

Figure 1

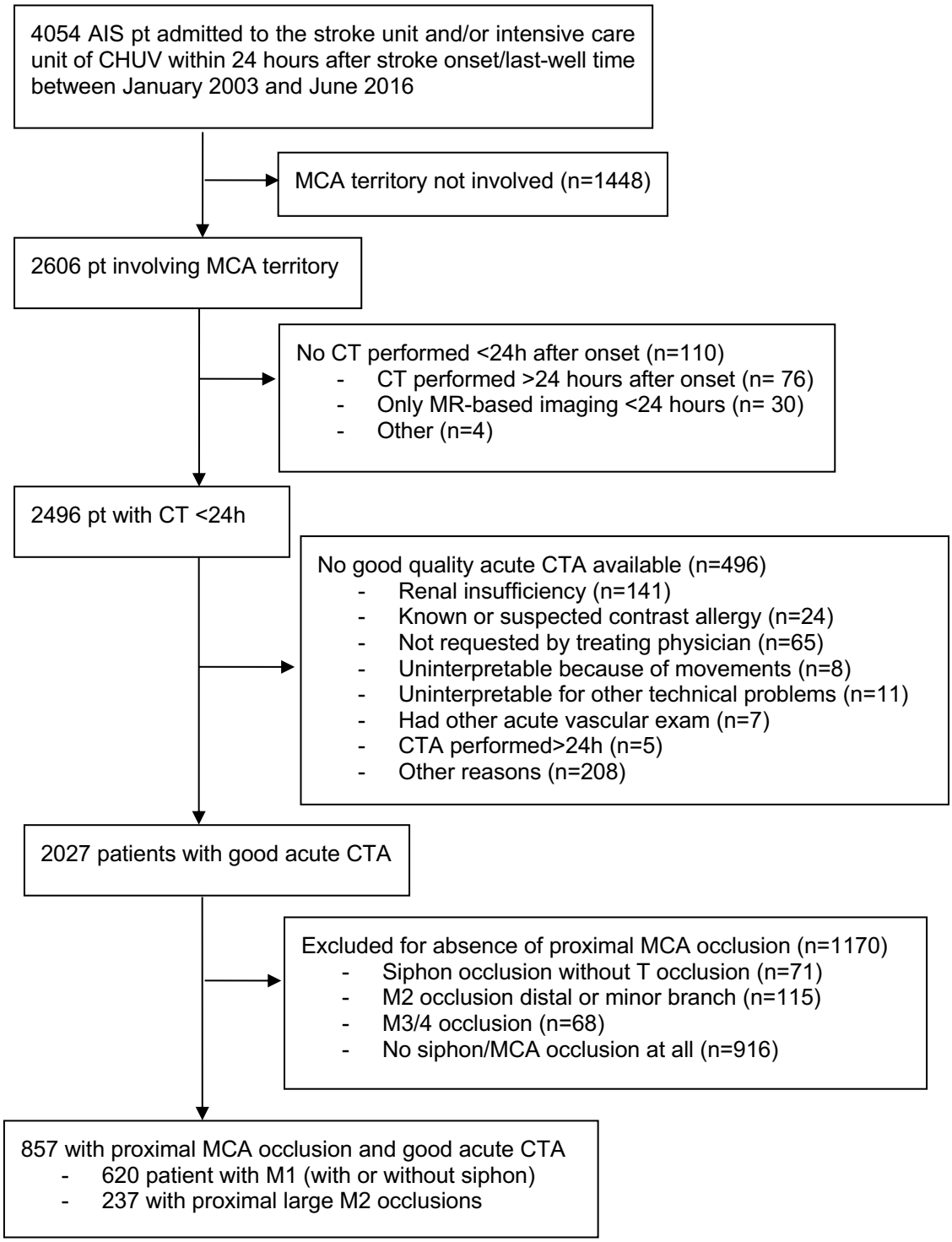

4054 AIS pt admitted to the stroke unit and/or intensive care unit of CHUV within 24 hours after stroke onset/last-well time between January 2003 and June 2016
MCA territory not involved (n=1448)
2606 pt involving MCA territory
No CT performed <24h after onset (n=110)
- CT performed >24 hours after onset (n= 76)
- Only MR-based imaging <24 hours (n= 30)
- Other (n=4)
2496 pt with CT <24h
No good quality acute CTA available (n=496)
- Renal insufficiency (n=141)
- Known or suspected contrast allergy (n=24)
- Not requested by treating physician (n=65)
- Uninterpretable because of movements (n=8)
- Uninterpretable for other technical problems (n=11)
- Had other acute vascular exam (n=7)
- CTA performed>24h (n=5)
- Other reasons (n=208)
2027 patients with good acute CTA
Excluded for absence of proximal MCA occlusion (n=1170)
- Siphon occlusion without T occlusion (n=71)
- M2 occlusion distal or minor branch (n=115)
- M3/4 occlusion (n=68)
- No siphon/MCA occlusion at all (n=916)
857 with proximal MCA occlusion and good acute CTA
- 620 patient with M1 (with or without siphon)
- 237 with proximal large M2 occlusions

Figure 2

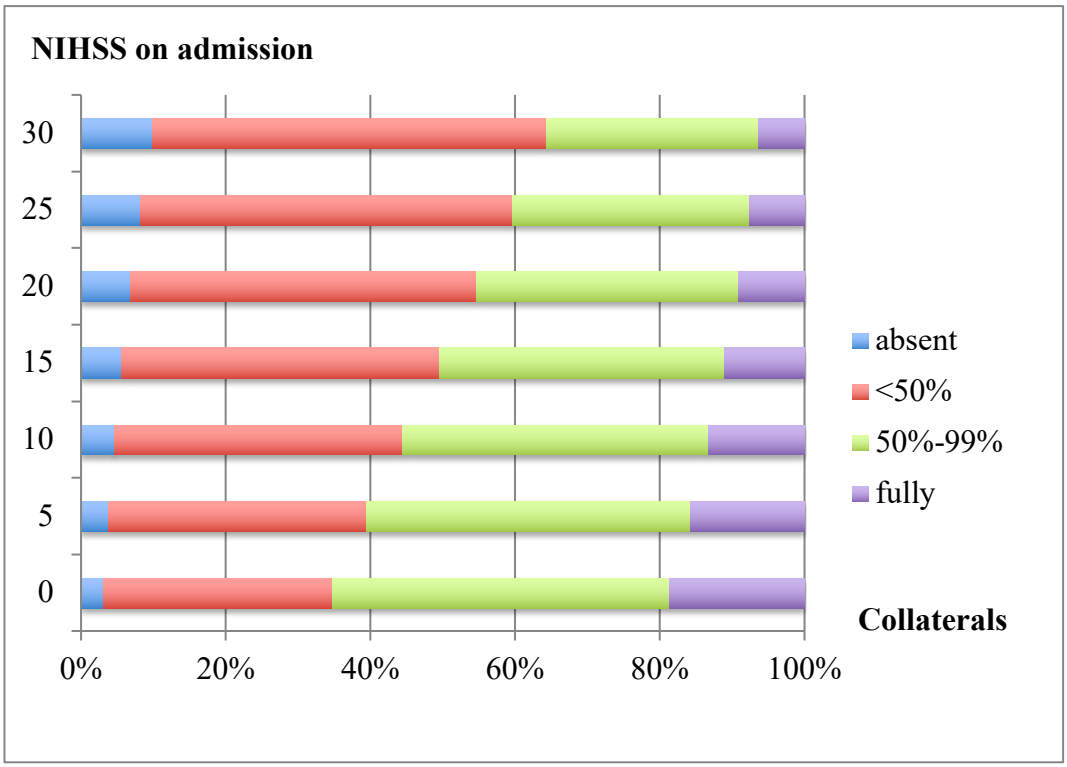

NIHSS on admission
30
25
20
15
10
5
0
0%
20%
40%
60%
80%
100%
absent
<50%
50%-99%
fully
Collaterals

Figure 3

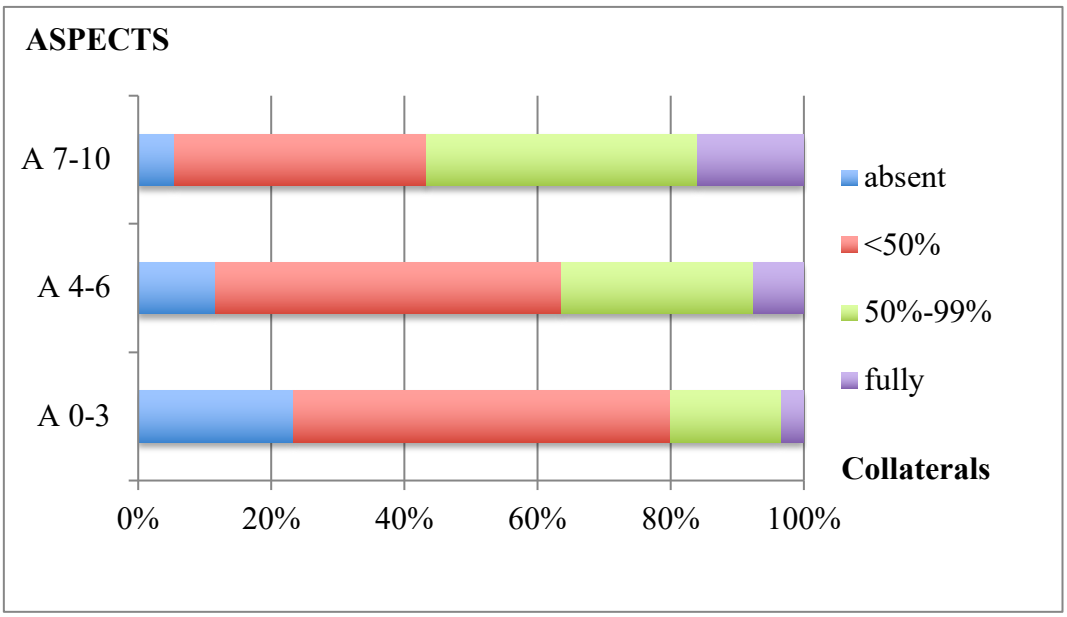
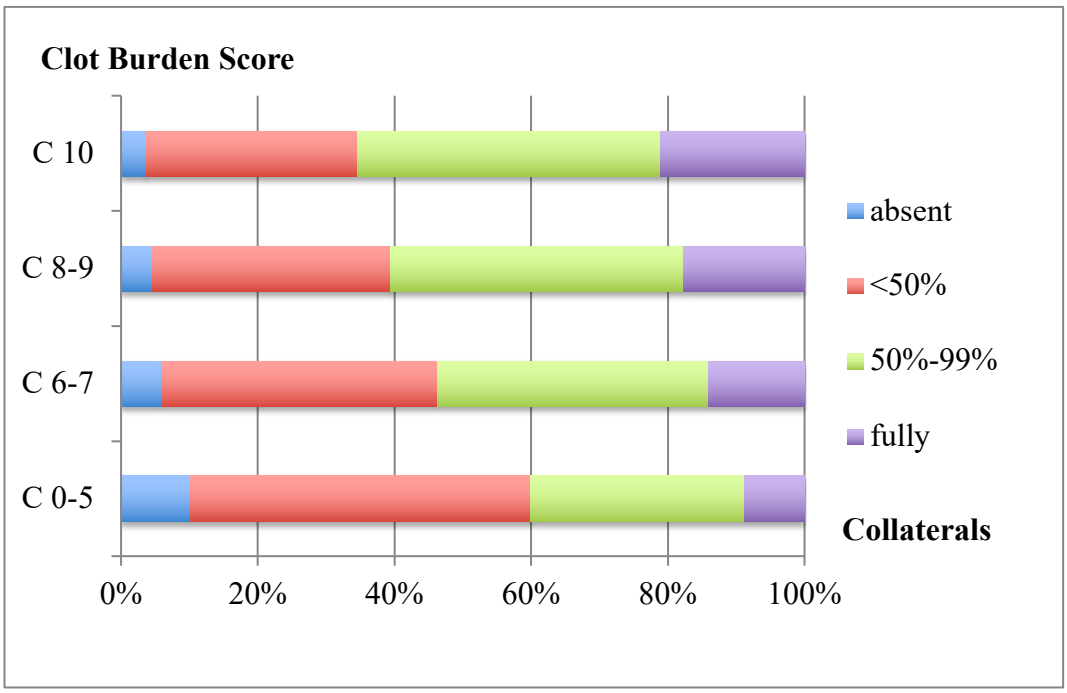

ASPECTS
A 7-10
A 4-6
A 0-3
0%
20%
40%
60%
80%
100%
absent
<50%
50%-99%
fully
Collaterals

Figure 4


Clot Burden Score
C 10
C 8-9
C 6-7
C 0-5
0%
20%
40%
60%
80%
100%
absent
<50%
50%-99%
fully
Collaterals

5.2 Collaterals & core/penumbra volumes on CTP

5.2.1 *Abstract*

Purpose

Determinants of early loss of ischemic tissue (core) or its prolonged survival (penumbra) in acute ischemic stroke (AIS) are poorly understood. We aimed to identify radiological associations of core and penumbra volumes on CT perfusion (CTP) in a large cohort of AIS.

Methods

In the ASTRAL registry (2003-2016), we identified consecutive AIS patients with proximal middle cerebral artery (MCA) occlusion. We calculated core and penumbra volumes using established thresholds, and the mismatch ratio (MR). We graded collaterals into three categories on CT-Angiography. We used clot burden score (CBS) to quantify the clot length. We related CTP volumes to radiological variables in multivariate regression analyses, adjusted for time from stroke onset to first imaging.

Results

The median age of the 415 included patients was 69 years (IQR=21) and 49% were female. Median admission NIHSS was 16(11) and median delay to imaging 2.2(1.9) hours. Lower core volumes were associated with higher ASPECTS (Hazard Ratio =1.08), absence of hyperdense MCA sign (HR=0.70), higher CBS (i.e. smaller clot, HR=1.10) and better collaterals (HR=1.95). Higher penumbra volumes were related to lower CBS (i.e. longer clot, HR=1.08) and proximal intracranial occlusion (HR=1.47), but not to collaterals. Higher MR was found in absence of hyperdense MCA sign (HR=1.28), absence of distal intracranial occlusion (HR=1.39) and with better collaterals (HR=0.52).

Conclusions

In AIS, better collaterals were associated with lower core volumes, but not with higher penumbra volumes. This suggests a major role of collaterals in early tissue loss and their limited significance as marker of salvageable tissue.

5.2.2 *Background*

The most effective treatment in acute ischemic stroke (AIS) is rapid reperfusion of the cerebral penumbra. However, before reperfusion, penumbral tissue may survive from a sustained blood flow through the leptomeningeal collateral circulation (8, 25, 43). Furthermore, the extent of arterial obstruction and metabolic and genetic factors may contribute to the presence and survival of penumbral tissue (7, 44). However, the factors influencing features of the infarct and penumbra at baseline are poorly understood. Similarly, the relationship between collateral status and salvageable tissue has not been sufficiently explored.

Modern neuroimaging techniques, including CT-angiography (CTA) and CT-perfusion (CTP), allow detection of clot location, assessment of collateral circulation and quantification of salvageable brain tissue. Imaging selection may be an efficient tool for selecting patients with a relevant treatment target and optimizing clinical trial design, as evident from recent trials (15, 16, 18, 19, 45, 46). However, it is still uncertain whether imaging parameters and thresholds could identify patients who are more likely to benefit from revascularization treatments.

In this study, we aimed to identify radiological variables independently associated with core volumes, penumbra volumes and the mismatch ratio (MR) in a large cohort of AIS patients with proximal middle cerebral artery (MCA) occlusion. More specifically, we aimed to investigate the relationship between collateral status at baseline and CTP volumes.

5.2.3 *Methods*

Patient selection

For this study, we considered all patients in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to June 2016. ASTRAL collects all consecutive AIS patients admitted to the stroke unit and/or intensive care unit of the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne University Hospital) within 24 hours of the last known well time (29). ASTRAL incorporates detailed clinical and radiological data from modern, mainly CT-based, multimodal brain imaging techniques. The type and definition of collected variables in ASTRAL was pre-specified, and the current analysis was retrospective. The institution's ethical commission approved collection, analysis and publication of data in ASTRAL.

For patient selection, we used the following inclusion criteria: AIS involving the MCA territory (with or without ipsilateral anterior or posterior cerebral artery territory), known stroke onset (with less than one hour of uncertainty), CT-based multimodal imaging of good quality performed <24 hours, CTA showing occlusion of M1 and/or proximal M2 segment (with or without added more distal and proximal pathology) and CTP showing hypoperfusion of at least 10ml in a site consistent with the clinical picture. We excluded patients with only distal M2 or only M3 occlusions as we considered reliability of visual collateral assessment in a small arterial territory insufficient. We also excluded patients with pre-existing radiological infarct in the newly hypoperfused area.

For this analysis, we reviewed: demographic data (age, gender), vascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, current smoking, atrial fibrillation), pre-stroke modified Rankin score (mRS) and National Institutes of Health Stroke Scale (NIHSS) score at admission. We calculated onset-to-brain imaging and onset-to-treatment times. We classified stroke etiology according to the TOAST classification, with dissection and multiple causes added as categories.

CT imaging data acquisition

We assessed patients with suspected AIS by multimodal CT scanning including non-contrast CT (NCCT), CTP, CTA and post-contrast series as part of standard

of care, unless contrast contraindication existed. We performed CT on a 64-multidetector CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). We acquired NCCT and post-contrast series in axial mode from the skull base to the vertex (16cm z-axis coverage) using the following imaging parameters: 120kV peak tube voltage, 320mA tube current, slice thickness 5mm, 32cm scan field of view (SFOV), 512x512 matrix. We acquired all CTP series in axial scan mode with 80kV peak tube voltage, 240mA tube current, 32cm SFOV and 512x512 matrix. We acquired CTP images at the level of the basal ganglia and the third ventricle above the orbits. We used eighteen groups of 16 slices of 5mm (80mm z-axis coverage) and acquired CTP images for 50s in a cine mode with a delay of 5 s after the beginning of injection of 50ml of iodinated contrast (iohexol 300mg/ml) with an injection rate of 5ml per second into an antecubital vein using a power injector. We performed CTA in helical mode from the aortic arch to the top of the frontal sinuses (120 KV, 150-260 mAs, 0.625 slice-thickness, 50ml of iodinated contrast at 5ml/s, delay according to the perfusion data).

CT imaging data analysis

We reviewed NCCT scans to detect intracranial hemorrhage, hyperdense middle cerebral artery sign, chronic stroke lesions and presence of leukoaraiosis (defined as grade ≥1 according to Blennow scale) (47). We recorded early ischemic changes on NCCT in the MCA territory to calculate ASPECTS (48).

CTP data were transferred to a workstation and analyzed by a standardized method to create parametric maps of mean transit time (MTT), cerebral blood flow (CBF) and cerebral blood volume (CBV). We used Philips Medical Systems (Cleveland, OH, USA) deconvolution software. Infarct core and ischemic penumbra volumes were calculated with the software using the appropriate MTT and CBV thresholds, that are MTT >145% of the contralateral side values and CBV >2.0 mL/100 g for the penumbra volume; and MTT >145% of the contralateral side values and CBV <2.0 mL/100 g for the core volume (49). We

calculated MR as the ratio of the total ischemic volume (i.e. core plus penumbra volumes) to the core volume (15).

We reviewed the raw axial and maximal intensity projection CTA images for significant (≥50% stenosis or occlusion) extra- and intracranial arterial pathology leading to the ischemic territory. We grouped significant intracranial pathology in the ischemic carotid territory as proximal if it involved carotid siphon, proximal M1 (i.e. less than 10 mm from M1 origin) or A1 segment, or distal, if it involved distal M1, M2, M3 or A2 segment. For each patient, we calculated the clot burden score (CBS) to evaluate the extent of intracranial thrombus burden in the anterior circulation. CBS is a 10-point scoring system that assigned points for the presence of contrast on CTA within the intracranial internal carotid artery, M1 and M2 branches, and A1 segment. A CBS of 10 indicates absence of a visible large vessel occlusion, whereas a score of 0 corresponds to a complete multisegment occlusion of the carotid axes (50).

We visually determined the collateral score from CTA maximal intensity projection reconstructions and graded according to Tan et al.(30) Absence of collateral flow to the ischemic territory was graded as zero, whereas collateral flow in ≤50%, >50% and 100% of the vessels filling in the ischemic territory distal to the occluded artery were graded as one, 2 and 3 respectively. We added a score of four for individuals with more than 100% filling of the ischemic bed compared to the normal side, as was previously suggested (51). For statistical analysis, we grouped grades 0 and 1 as ‘poor’ collaterals, grade 2 as ‘partial’, and grades 3 and 4 as ‘good’ collaterals; we used these three categories in an ordinal way.

At least one experienced vascular neurologist and one experienced neuroradiologist reviewed NCCT, CTP and CTA images independently. We assessed interrater variability using Cohen's kappa on 100 consecutive acute CTAs with anterior circulation occlusive stroke for NCCT-ASPECTS, CBS and collateral status. In cases of differing evaluation between readers, we reached consensus after joint assessment.

Statistical analysis

We performed multivariate analyses (MVA) on multiple radiological variables at baseline and the three main outcomes, i.e. core volume, penumbra volume and MR. We included in the model the time since stroke onset to brain imaging (in hours) to test the strength of the radiological associations independently of time. We used a Cox's proportional hazards model and preferred the latter to a classic linear model because of the highly skewed distribution of the response variables and the consequent violation of normality and variance stability assumptions. Alternatives to alleviate this problem (e.g. transforming the response or choosing an appropriate distribution for the response) resulted in estimation problems or difficulties in interpreting the analysis outcome. The Cox model avoids distribution specification for the response and facilitates group comparison through the hazard coefficient. Although we usually employ this model with time as response variable and with censoring, the methodology is quite general and we can implement it in cases of other response variable and no censoring.

We can more easily interpret results if we compare probability density functions (PDFs) among groups, rather than hazard functions. The association between hazard function and PDF is displayed in Figure 1. A higher hazard ratio obtained from this model indicates a higher probability of mass concentration in the lower spectrum of the acceptable range of the response variable (52).

We filled in missing data using multiple imputation chain equations technique. Specifically, we initially generated five imputed datasets and analyzed each dataset separately. We used stepwise variable selection methods to select the covariates significantly associated with the response. Finally, the outcome of the five imputed analyses were appropriately combined to produce the results presented (31). We set significance level at 5% throughout. We carried out all l analyses using the statistical package R (version 3.4.2).

5.2.4 *Results*

Out of 2'799 subjects with AIS of known onset and multimodal CT-based imaging performed within 24 hours from onset during the study period, 415 patients met

the inclusion criteria. The inclusion flow-chart of the study population is depicted in Figure 2.

Interrater agreement for reading of CT-based imaging was excellent for ASPECTS (kappa 0.82) and for collaterals (kappa=0.81); it was good for clot burden score (kappa=0.77).

We show demographics and clinical and radiological variables of the study population at baseline in Table 1. Median age of the included patients was 69 years-old (IQR 21) and 49% were female. Median admission NIHSS was 16 (IQR 11) and median delay to imaging was 2.2 hours (IQR 1.9). CTA showed M1 occlusion in 252 (60.7%) and proximal M2 occlusion in 163 (39.3%) patients. We graded leptomeningeal collaterals as “good” in 20.2% patients, "partial" in 36.6% and "poor" in 43.3% patients.

We present significant results from MVA in Table 2. Lower core volumes were independently associated with higher ASPECTS (Hazard Ratio, HR=1.08; 95% confidence interval, CI=1.03-1.12), with absence of hyperdense MCA sign (HR=0.70; 95% CI=0.55-0.89), and with higher CBS (i.e. smaller clot, HR=1.10; 95% CI=1.05-1.15). Moreover, we found an independent association between lower core volumes and better collaterals (HR=1.95; 95% CI=1.44-2.63). Higher penumbra volumes were related to lower CBS (i.e. longer clot, HR=1.08; 95% CI=1.04-1.12) and non-distal intracranial occlusion (HR=1.47; 95% CI=1.11-1.94). We did not find significant association between penumbra volumes and collateral status. Higher MR was found in the absence of hyperdense MCA sign (HR=1.28; 95% CI=1.04-1.59) and absence of distal intracranial occlusion (HR=1.39; 95% CI=1.06-1.82). Finally, higher MR correlated with better collaterals (HR=0.52; 95% CI=0.39-0.70).

We present graphically the significant associations between core volumes and ASPECTS, CBS and collaterals and between MR and collaterals in Figures 3 and 4, and additional significant associations (i.e. between core volumes and hyperdense MCA sign, penumbra volumes and CBS, MR and hyperdense MCA sign and distal intracranial occlusion) in Figure 5.

5.2.5 *Discussion*

In our cohort of 415 AIS patients with proximal MCA occlusion, we found that a better degree of collaterals related to a smaller ischemic core and greater mismatch ratio, but we could not demonstrate an independent association between better collaterals and higher penumbra volumes. Furthermore, proximal occlusions (hyperdense MCA sign) were associated with higher core volumes, and distal occlusions with lesser penumbra volumes. Similarly, longer clot (i.e. lower CBS) correlated with a more extended core and smaller clot (i.e. higher CBS) with less penumbra. These results were independent of time since stroke onset to brain imaging

The negative association between ASPECTS and ischemic core volumes on CTP was expected (53) indicating that quantification of early ischemic changes on NCCT is a reliable measure of infarct cores in anterior circulation stroke.

An inverse relationship between core volume and collateral patency is in agreement with previous reports and supports the major impact of collateral circulation on the early transformation of ischemia into infarct (23, 54). The lack of a correlation between penumbra volumes and collaterals was unexpected and not in agreement with previous studies (44, 55). Most investigators regard collaterals as a compensatory network preserving blood flow in the setting of acute ischemia. However, according to our results measured by CTP, collaterals seem to influence more the extent of the ischemic core rather than sustenance of penumbra. A possible explanation for this finding is that poor collaterals lead to early infarct and good collaterals to benign oligemia, reducing the critical hypoperfusion (penumbra) region between these two thresholds. Alternatively, our finding may reflect an artefact of our imaging protocol: penumbra defined by our CTP acquisition allows for delayed leptomeningeal contrast arrival whereas early arterial phase CTA underestimates collateral status substantially. This could affect more the measurement of penumbra than of core, and may explain the absence of a clear relationship between collaterals and penumbra.

Our data confirm the previously observed association of higher mismatch ratios with good collaterals (23, 25, 56). Nevertheless, we found proportionally more

salvageable tissue in patients with good collaterals due to lower core, rather than to higher penumbra volumes.

Regarding the vascular site of occlusion, we found an association of the hyperdense MCA sign, an indicator of proximal MCA occlusion, with higher core volumes and a less extensive MR. Another study has also shown that increased thrombus attenuation was associated poor baseline collateral status (42). On the other hand, the more distal intracranial occlusions, resulting in greater superficial localization of stroke, were associated with smaller penumbras and a lesser MR, possibly because fewer leptomeningeal collaterals are available in the setting of a cortical infarction.

We expected the association of a higher clot burden (which represents lower CBS) with larger core volumes, probably because extended clots obstruct more arterial branches. Interestingly, higher clot burden was also associated with a larger penumbra volume. This finding was independent of collateral status, suggesting intuitively that larger clots bring larger ischemia volumes, including larger cores and larger penumbras.

The location and size of thrombus along with the degree and extent of collaterals likely determine the amount of damaged and salvageable tissue in acute ischemic stroke from large vessel occlusion. Therefore, as expected, most of these variables are strongly related each other. The major focus of our research has been to identify which radiological features available on non-advanced neuroimaging (NCCT and CTA) help to predict the CTP profile of acute ischemic stroke patients. Taking into account all the potential limitations related to the neuroimaging protocol (as discussed below), our results have several implications. The association of lower core volumes with good collaterals suggests a major role of the latter in early tissue loss. On the other hand, the absence of an independent correlation between penumbra volumes and collaterals might indicate that collateral assessment per se is a poor substitute for penumbral tissue. The implication of our findings for the clinic is that collaterals and core may represent a similar tissue marker and we could perhaps use them interchangeably, whereas collaterals and penumbra volumes do not. Further,

patients with a pattern of small core and good collaterals seem to be the best candidates for acute revascularization treatment, and this independently of the time of stroke onset, as previously suggested (20). Supporting these observations, the recent ESCAPE trial showed highly favorable outcomes for acute thrombectomy based on assessment of collateral flow using multiphasic CTA (46), and independently of stroke onset-to-treatment time (57).

The limitations of our study include its retrospective, non-randomized design and its single-center nature. Moreover, our dataset comes from a tertiary stroke center with a predominantly elderly, Caucasian population, which may not be representative of other settings. Still, demographics and stroke mechanisms of our population (Table 1) is comparable to other Western stroke populations (i.e. SITS-MOST and REGARDS registry).

Regarding the radiological protocol, we used single-phase CTA (sCTA), which may lead to technique-dependent bias in collateral evaluation due to variability in the timing of the contrast injection and image acquisition (58, 59). This represents a major limitation of our study, potentially affecting the absence of an independent relationship between collaterals and penumbra volumes. Compared to sCTA, multi-phase CTA (mCTA), by acquiring temporal information at three data points, has the advantage of a more dynamic and time-resolved assessment of collaterals (60) and is a proven selection tool for endovascular treatment up to 9 hours after stroke onset (46). mCTA also allows the detection of an eventual occult anterograde flow through thrombus, which could contribute, together with the retrograde flow, to the determination of the actual leptomeningeal collateral status (61). Our findings may still be of importance, however, given that sCTA is more frequently used in clinical practice, and that other authors have reported similar findings as we do (23).

The CTP threshold model used for determination of core and penumbra is based on a systematic method of development (49), while other models have been used in the literature with limited direct comparisons between methods (62). We had to exclude a number of patients because of missing values of good quality CTP reconstructions. Finally, we intentionally did not adjust the analysis to clinical and

metabolic variables, aiming for purely radiological associations, although these variables may be relevant for level of perfusion deficit.

In conclusion, our large-sample study of AIS patients with proximal MCA occlusion showed that a better degree of collaterals was related to a smaller ischemic core and consequently a higher mismatch ratio, independently of time from stroke onset. We did not show a correlation between collateral status and penumbra volumes, the latter appearing influenced more by the characteristics of the occlusive thrombus (distal location and shorter length). Our results highlight the importance of the degree of collateral circulation in determining the extent of the core volume in the initial diagnostic workup. Furthermore, our findings may help clinicians in decision-making process when CTP is not available or cannot be performed.

5.2.6 *Tables and Figures*

Table 1 Patient characteristics of the selected clinical and radiological variables at admission.

Table 2 Results from MVA showing significant associations between radiological variables and the three main outcomes, expressed as Hazard Ratio (HR) and 95% confident interval (CI). All results are adjusted for time from stroke onset to brain imaging. Higher HRs signify lower response values (i.e. negative association). Empty fields indicate no significant association. Green values signify a favorable and red, an unfavorable CTP pattern.

Figure 1 Example of the association between hazard and probability density function (PDF). Group B reports a higher hazard function compared to group A (left graph), thus group B patients most frequently have lower values compared to group A patients (right graph). Therefore, the PDFs of group B position to the left of the corresponding PDFs of group A.

Figure 2 Inclusion flow-chart for the study population.

Figure 3

a) Correlation between infarct volume and ASPECTS
b) Correlation between infarct volume and clot burden score
c) Correlation between infarct volume and collaterals
d) Correlation between MR and collaterals

Figure 4 Significant associations between CTP-parameters (core volume and mismatch ratio) and radiological variables at baseline. More specifically: correlation between a) infarct volume and ASPECTS (for ASPECTS=1, 5, 8 and 10); b) between infarct volume and clot burden score (for clot burden score=1,5 and 10); c) between infarct volume and collaterals (for collaterals= non, partial and good); d) between mismatch ratio and collaterals (for collaterals= none, partial and good). Confidence interval are displayed as dashed lines.

Figure 5 Significant and independent associations between CTP-parameters (infarct, penumbra volume and mismatch ratio, MR) and radiological variables at baseline. More specifically: correlation between a) infarct volume and hyperdense MCA sign; b) between MR and hyperdense MCA sign; c) between penumbra volume and clot burden score; d) between MR and distal intracranial pathology.

Table 1

Baseline Clinical and Radiological Variables, as median (± IQR) or n (%):	Total pt (N = 415)
Demographics	
Age, yr	69.0 (20.9)
Sex (females), n	201 / 415 (48.4%)
Vascular risk factors	
Hypertension	254 / 415 (61.2%)
Diabetes	63 / 414 (15.2%)
Hypercholesterolemia	265 / 415 (63.9%)
Current smoking	103 / 413 (24.9%)
Atrial Fibrillation	154 / 415 (37.1%)
Pre-stroke mRS 0-2	398 / 415 (95.9%)
Onset-to-hospital time, h	1.7 (1.6)
NIHSS on admission	16.0 (11.0)
Acute stroke treatment, n	266 /415 (64.1%)
Stroke etiology (TOAST)	
Atherosclerosis	78 / 410 (19.0%)
Cardiac	185 / 410 (45.1%)
Onset-to-CT time, h	2.2 (1.9)
Neuroimaging variables on NCCT	
ASPECTS	8.0 (4.0)
Significant leukoaraiosis, n	77 / 409 (18.8%)
Hyperdense MCA sign, n	168 / 398 (42.2%)
Silent infarct, n	90 / 408 (22.1%)
Neuroimaging variables on CTA	
Collaterals	
Poor	161 / 372 (43.3%)
Partial	136 / 372 (36.6%)
Good	75 / 372 (20.2%)
Clot burden score	6.0 (5.0)
Intracranial occlusion site (most proximal)	
M1 segment of MCA	252 (60.7%)

M2 segment of MCA	163 (39.3%)
Extracranial carotid pathology	
Significant stenosis	41 / 413 (9.9%)
Any occlusion	103 / 413 (24.9%)
Significant proximal° intracranial pathology	197 / 414 (47.6%)
Significant distal° intracranial pathology	339 / 411 (82.5%)
Neuroimaging variables on CTP	
Infarct volume, mL	39.7 (65.6)
Penumbra volume, mL	79.4 (77.0)
Total ischemia volume, mL	133.6 (104.2)
Mismatch Ratio, n	2.8 (4.8)

° Definitions: see text

Table 2

Radiological variables	**Core volume**	**Penumbra volume**	**Mismatch ratio**
ASPECTS	1.08 (1.03-1.12)	-	-
Hyperdense MCA sign	0.70 (0.55-0.89)	-	1.28 (1.04-1.59)
Distal intracranial occlusion	-	1.47 (1.11-1.94)	1.39 (1.06-1.82)
Clot burden score	1.10 (1.05-1.15)	1.08 (1.04-1.12)	-
Better collaterals	1.95 (1.44-2.63)	-	0.52 (0.39-0.70)

Legend: ASPECTS = Alberta stroke program early CT score; MCA = middle cerebral artery; CBS = clot burden score; Distal intracranial occlusion indicates distal M1 or M2 occlusion; MR = Mismatch ratio.

Figure 1

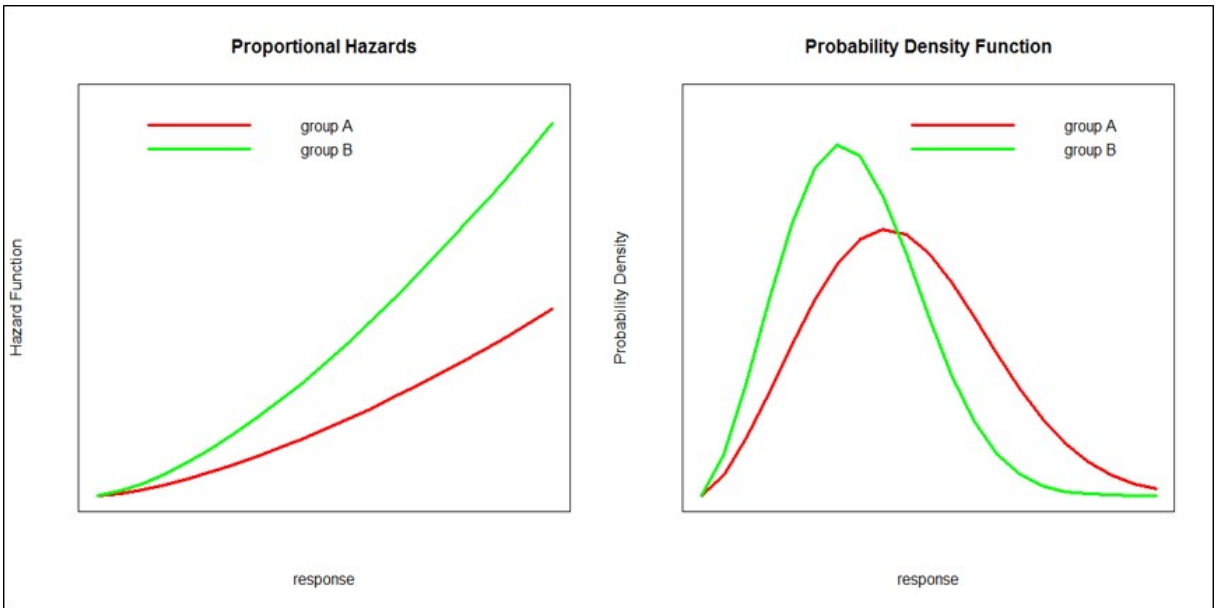

Proportional Hazards
group A
group B
Hazard Function
response
Probability Density Function
group A
group B
Probability Density
response

Figure 2

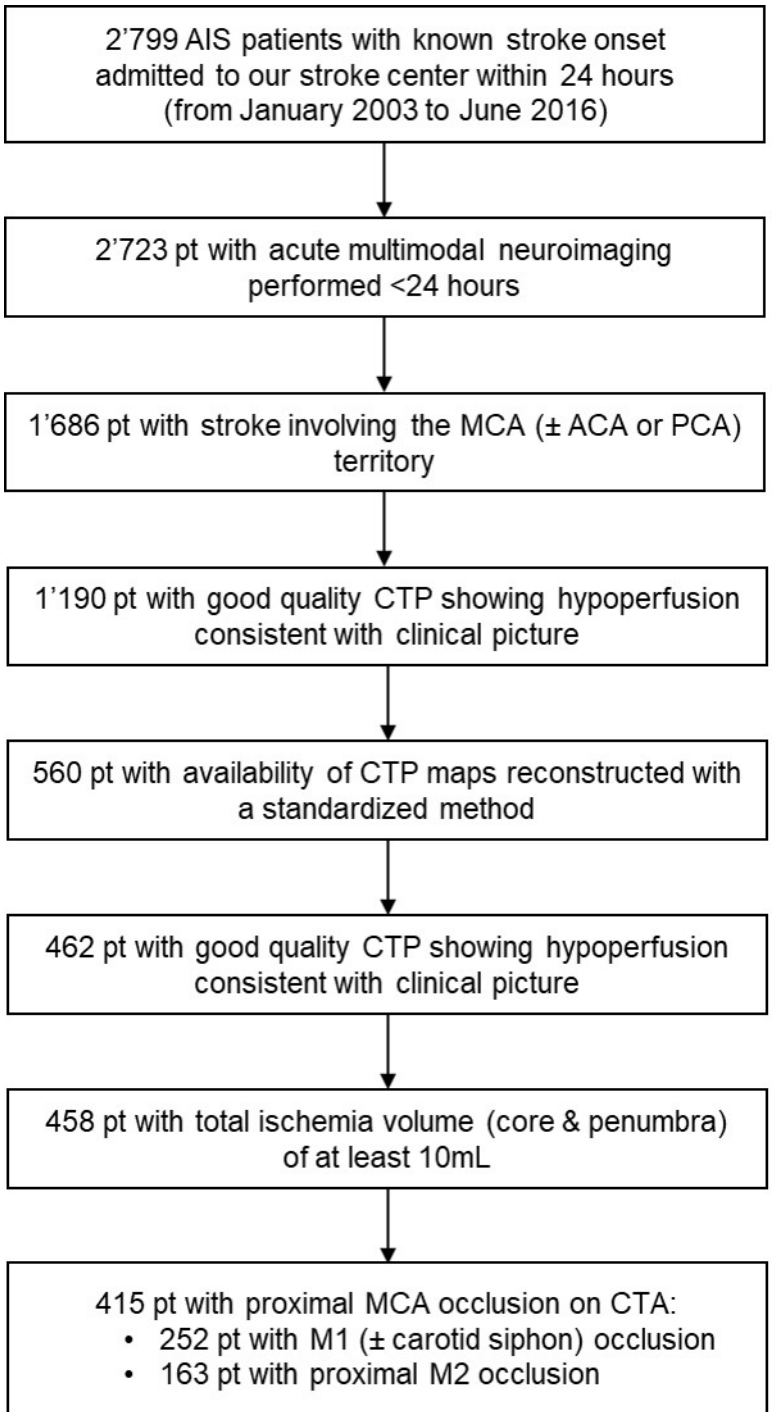

2'799 AIS patients with known stroke onset admitted to our stroke center within 24 hours (from January 2003 to June 2016)
2'723 pt with acute multimodal neuroimaging performed <24 hours
1'686 pt with stroke involving the MCA (± ACA or PCA) territory
1'190 pt with good quality CTP showing hypoperfusion consistent with clinical picture
560 pt with availability of CTP maps reconstructed with a standardized method
462 pt with good quality CTP showing hypoperfusion consistent with clinical picture
458 pt with total ischemia volume (core & penumbra) of at least 10mL
415 pt with proximal MCA occlusion on CTA:
• 252 pt with M1 (± carotid siphon) occlusion
• 163 pt with proximal M2 occlusion

Figure 3

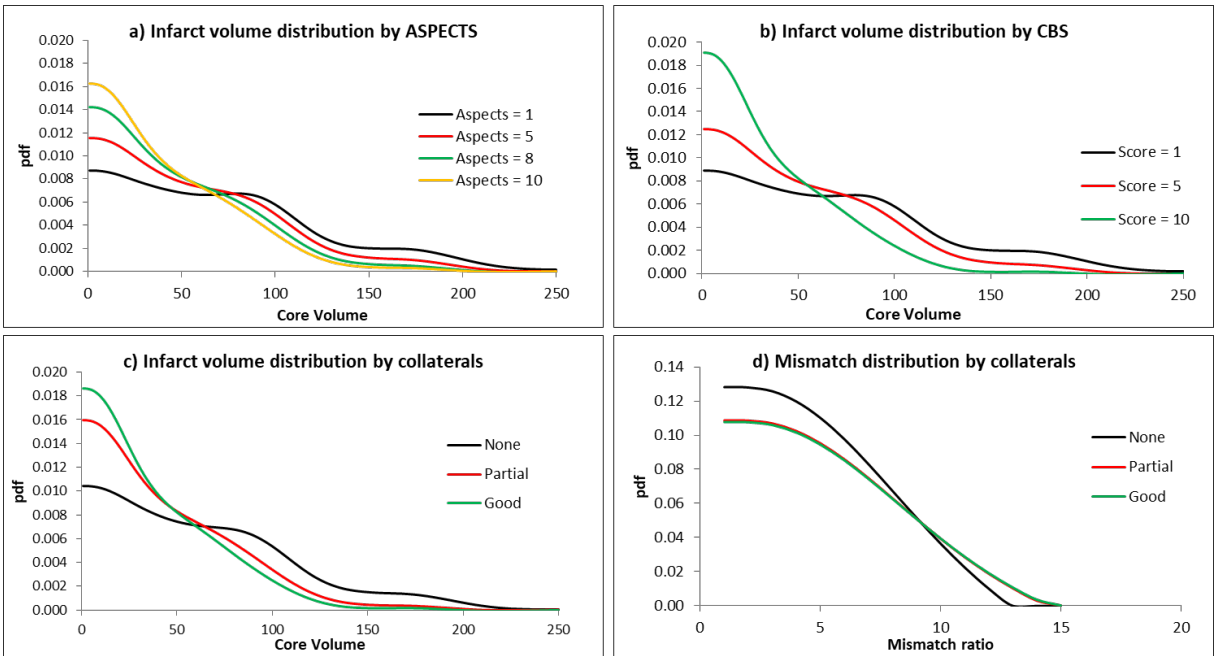
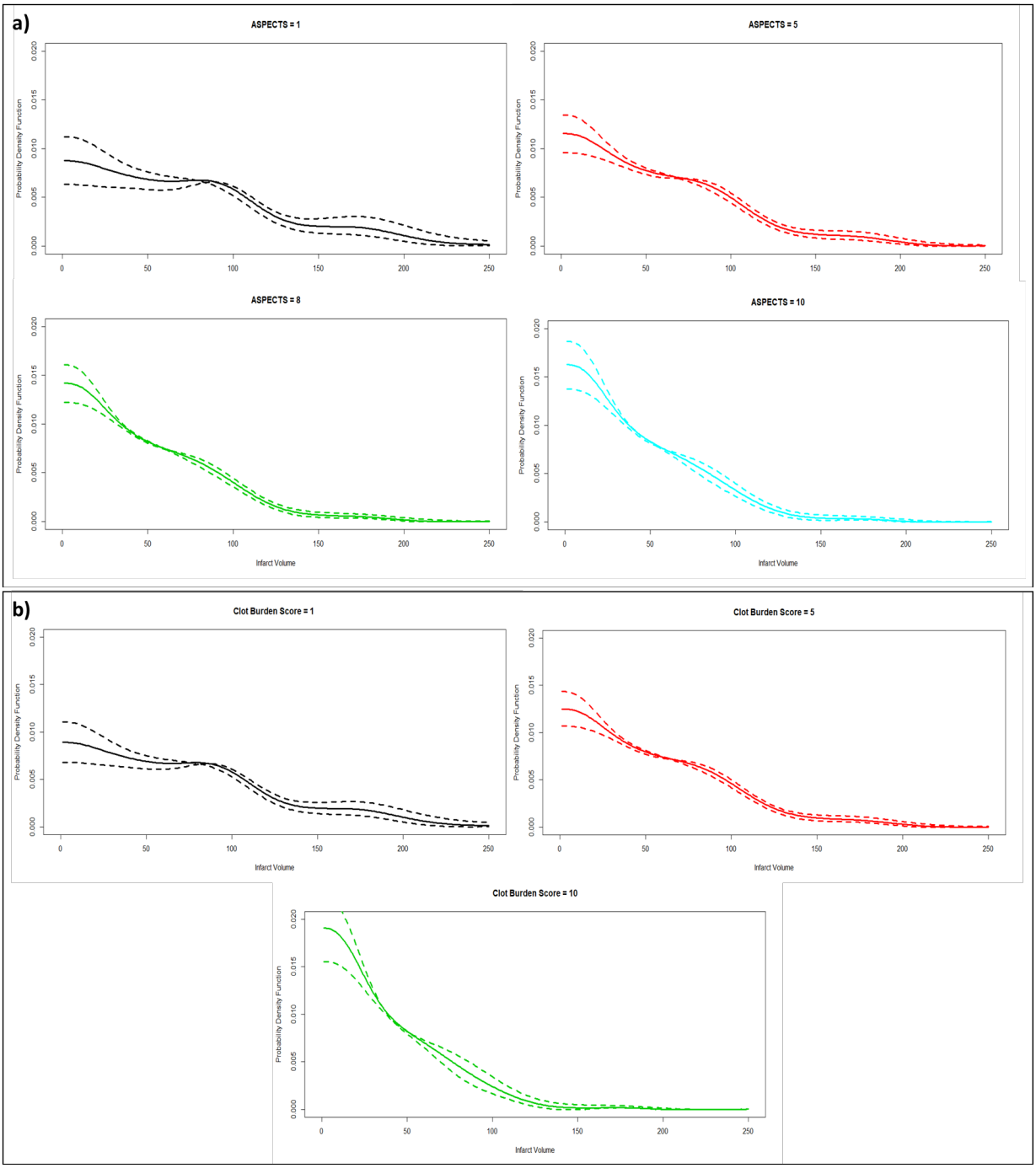
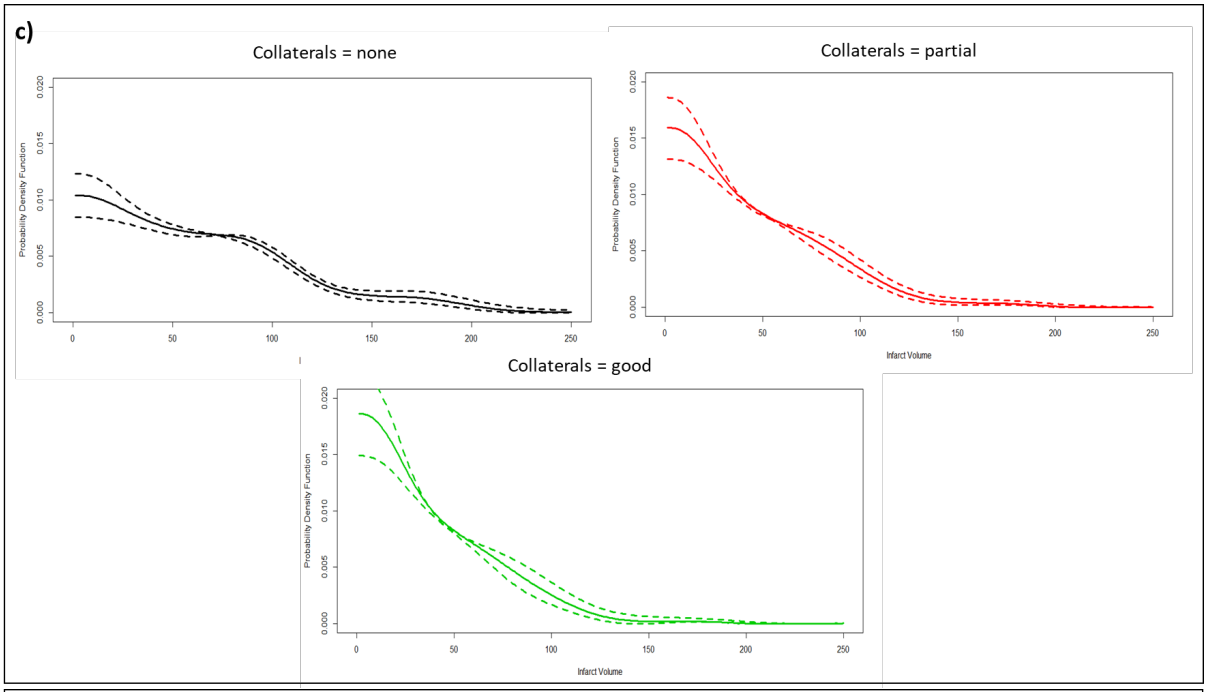

a) Infarct volume distribution by ASPECTS
pdf
Core Volume
Aspects = 1
Aspects = 5
Aspects = 8
Aspects = 10
b) Infarct volume distribution by CBS
pdf
Core Volume
Score = 1
Score = 5
Score = 10
c) Infarct volume distribution by collaterals
pdf
Core Volume
None
Partial
Good
d) Mismatch distribution by collaterals
pdf
Mismatch ratio
None
Partial
Good

Figure 4


a)
ASPECTS = 1
ASPECTS = 5
ASPECTS = 8
ASPECTS = 10
Probability Density Function
Infarct Volume
b)
Clot Burden Score = 1
Clot Burden Score = 5
Clot Burden Score = 10
Probability Density Function
Infarct Volume


c)
Collaterals = none
Collaterals = partial
Collaterals = good
Probability Density Function
Infarct Volume

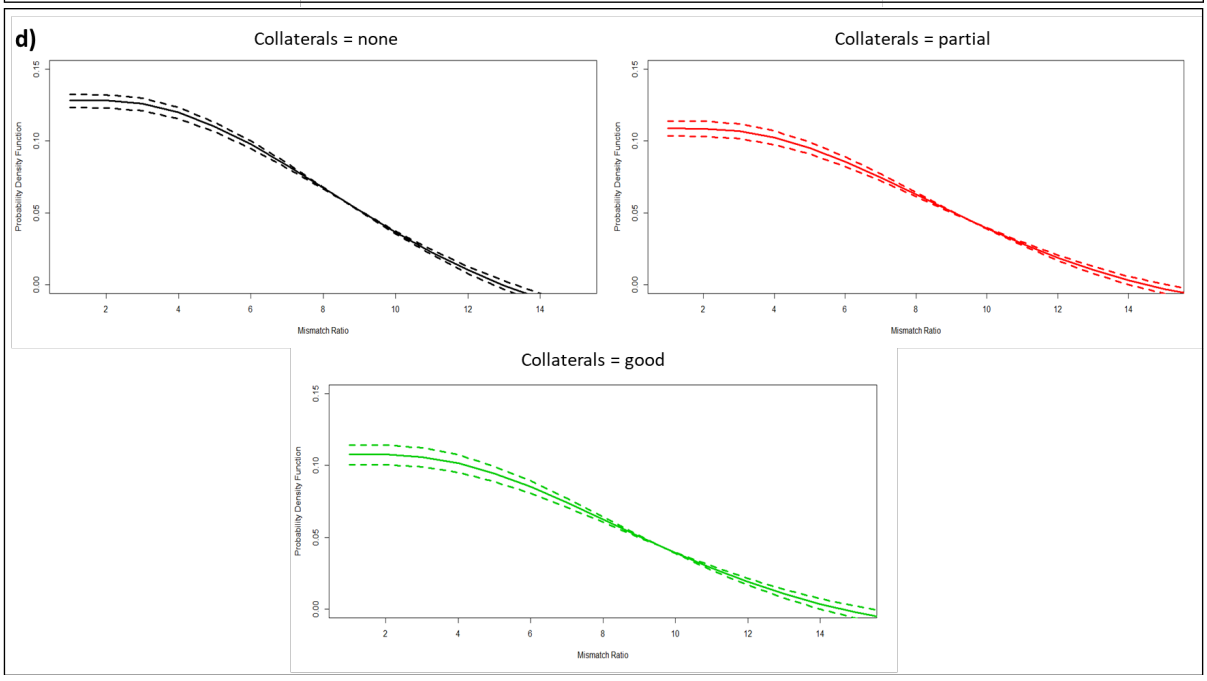
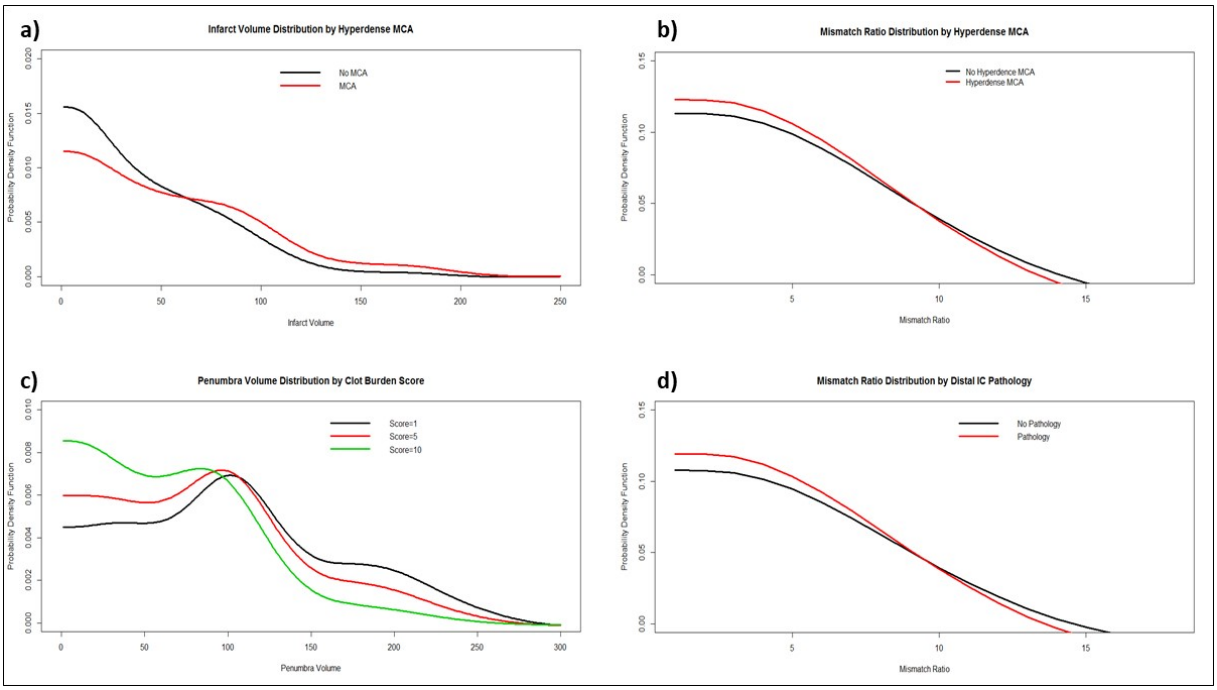

d)
Collaterals = none
Collaterals = partial
Collaterals = good
Probability Density Function
Mismatch Ratio

Figure 5


a)
Infarct Volume Distribution by Hyperdense MCA
No MCA
MCA
Probability Density Function
Infarct Volume
b)
Mismatch Ratio Distribution by Hyperdense MCA
No Hyperdence MCA
Hyperdense MCA
Probability Density Function
Mismatch Ratio
c)
Penumbra Volume Distribution by Clot Burden Score
Score=1
Score=5
Score=10
Probability Density Function
Penumbra Volume
d)
Mismatch Ratio Distribution by Distal IC Pathology
No Pathology
Pathology
Probability Density Function
Mismatch Ratio

5.3 ASPECTS & core volumes on CTP

5.3.1 *Abstract*

Introduction

Both ASPECTS and core volume on CT-Perfusion (CTP) are used to estimate infarct volume in acute ischemic stroke (AIS). To assess the potential value of ASPECTS for acute treatment decisions, we aimed to determine the correlation between ASPECTS and CTP-core, depending on timing and presence of large vessel occlusion (LVO).

Methods

In the ASTRAL registry, we reviewed all middle cerebral artery AIS with standardized reconstructions of CTP maps. Correlation between ASPECTS and CTP-core was calculated for early (<6hours) vs late (6-24hours) times from onset and presence or absence of LVO. Correlation coefficients and multiple linear regression models were used to test associations.

Results

The included 1,046 patients had a median age of 71.4 years (IQR=59.8-79.4), NIHSS of 12(6-18), ASPECTS of 9(7-10) and CTP-core of 13.6 mL (0.6-52.8). The overall correlation between ASPECTS and CTP-core was moderate (ρ=-0.49, p<0.01), but significantly stronger in the late vs early window (ρ=-0.56 and ρ=-0.48 respectively, p=0.05) and in the presence vs absence of LVO (ρ=-0.40 and ρ=-0.20 respectively, p<0.01). In the regression model, the independent association between ASPECTS and CTP-core was twice as strong in late-arriving patients with LVO (β=-0.21 per 10 mL; 95%CI= (-0.27;-0.15), p<0.01) than in the overall population (β=-0.10; 95%CI= (-0.14;-0.07), p<0.01).

Conclusion

The association between ASPECTS and CTP-core in 1,046 AIS patients was moderate, but significantly stronger in patients with longer delay from stroke onset

and presence of LVO. Our findings could support the use of ASPECTS as a surrogate marker of CTP-core in late-arriving AIS patients with LVO.

5.3.2 *Background*

In acute ischemic stroke (AIS), estimating the amount of irreversibly damaged brain tissue is of critical importance in patient selection for reperfusion therapies. Both the Alberta Stroke Program Early CT Score (ASPECTS)(48, 63) and automated core volume on CT perfusion (CTP)(64, 65) have been used to estimate infarct volume in the acute phase of stroke. However, the level of agreement between the two modalities remains uncertain.

ASPECTS is a useful and easily applicable tool for standardized evaluation of the extent of early ischemic changes in anterior circulation strokes on non-contrast CT scans (NCCT). In the original report describing the ASPECTS score(63), and in a subsequent observational study involving 1,135 patients undergoing intravenous thrombolysis (IVT), the ASPECTS grading was shown to be an independent predictor of functional outcome(66). For mechanical thrombectomy performed within 6 hours after onset, a clear benefit was proven for patients with NCCT ASPECTS of 6–10, while for ASPECTS values 0–5, treatment effect was not clear(5).

Recently, the efficacy of endovascular treatment (EVT) beyond the 6-hour time window was demonstrated in two randomized trials using a tissue-based approach: an advanced neuroimaging protocol (with CT Perfusion or DWI) was used to identify AIS patients with a low infarct core despite late presentation(18, 19).

The role of ASPECTS in selecting patients likely to benefit from EVT and for predicting clinical outcome, is not clearly established in the late time window(67, 68). Its use in the setting of late-presenting AIS could enlarge EVT eligibility in centers without availability of advanced neuroimaging techniques, or in patients who have contraindications to such imaging.

The main purposes of our study were, 1) to investigate the correlation between ASPECTS and automated core volume on CTP in a large cohort of AIS patients

with involvement of middle cerebral artery (MCA) territory and 2) to assess the influence of large vessel occlusion (LVO) and time from stroke onset on this correlation and to evaluate the association of ASPECTS with clinical outcome at three months, with a special focus on late-arriving AIS patients (i.e. 6-24 hours after last proof of good health, LPGH).

5.3.3 *Methods*

Study Design and Patient Selection

We performed a retrospective analysis of all consecutive patients entered in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to December 2018. The ASTRAL registry includes all AIS patients admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital (CHUV) within 24 hours after LPGH. For each patient, more than 250 pre-specified demographic, clinical and laboratory variables and multimodal neuroimaging items are prospectively collected, as previously reported(29).

For the current analysis, we selected patients according to the following criteria: acute CT-based multimodal imaging performed <24 hours after LPGH; stroke involving MCA based on clinical findings such as new hemispheric deficits (aphasia, hemineglect, eye deviation towards the side of the hemiparesis) and the simultaneous absence of neuroimaging findings showing posterior circulation stroke; and availability of good quality CTP maps (i.e. with the arterial input function returning to baseline before the end of the acquisition), reconstructed with a standardized method(49).

Demographic data, medical history and vascular risk factors were reviewed. We collected pre-stroke modified Rankin scale (mRs) and current medications at the time of the index event. We recorded neurological symptoms and signs, stroke severity (NIHSS) on admission, and biochemical parameters at baseline. Acute recanalization treatments, including IVT and/or EVT, were administered in accordance with Swiss and European Stroke Organization guidelines(69, 70), and updated with recent positive randomized trial data(18, 19). We calculated LPGH-to-arrival, -to-first imaging, and -to-treatment times. Stroke mechanism

was classified according to the TOAST classification, with dissection, embolic stroke of undetermined source (ESUS) and multiple causes added as categories. Clinical outcome was measured at 3 months using the mRS, either at the outpatient stroke clinic or by standardized telephone interview by Rankin-certified medical staff. Favorable outcome was considered as a 3-month mRS ≤2.
The STROBE method (Strengthening the Reporting of Observational Studies in Epidemiology) was applied. The local ethics commission approved the scientific use of anonymized data from ASTRAL.

Neuroimaging protocol

During the study period, patients admitted to our institution with suspected AIS were examined with a multimodal, mostly CT-based, neuroimaging protocol as standard of care. In patients without contraindications for iodinated contrast, this protocol included NCCT, CT angiography (CTA) and CTP.
Cerebral CT was performed on a 16-multidetector CT scanner (LightSpeed, GE Healthcare, Milwaukee, WI, USA) up to November 2005 and on a 64-multidetector CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) thereafter. NCCT was acquired in axial mode using the following parameters: 120 kV peak tube voltage, 320 mA tube current, slice thickness 5 mm, 32 cm scan field of view (SFOV) and 512x512 matrix. Raw data were reconstructed in the axial plane using filtered-back-projection (FBP) until 2009, and adaptive statistical iterative reconstruction (ASiR) thereafter. Using NCCT, we searched for intracranial hemorrhage, hyperdense MCA sign, chronic stroke lesions, presence of leukoaraiosis and presence and extent of early ischemic changes in the MCA territory to calculate ASPECTS(48).
The cervical and cerebral CTAs were acquired in helical scan mode from the aortic arch to the top of the frontal sinuses, according to the following parameters: 120 kV peak tube voltage, 150-260 mA tube current, 0.9:1 pitch, 0.625 mm slice thickness (1.25 mm before November 2005) and 512x512 matrix. Data acquisition was performed after intravenous injection of 50 ml of iodinated contrast material at a flow rate of 5 ml per second, with a delay according to the

perfusion data. We defined LVO as an internal carotid artery, M1 or proximal M2 occlusion. We calculated clot burden score (CBS) for each patient as an indicator of clot extension(50). We defined tandem occlusion as arterial occlusion affecting both the extra- and intracranial circulation in the same carotid axis. In patients with LVO, collaterals were graded according to Tan et al.(30). We considered collaterals as “good” if more than 50% of the ischemic territory distal to the occluded artery was filled.

CTP images were acquired for 50 s in a cine mode with a delay of 5-7 s after beginning the injection of 50 ml of iodinated contrast at a flow rate of 5 ml per second; four 10 mm slices (40 mm coverage) were imaged before November 2005, and 18 groups of sixteen 5 mm slices (80 mm coverage), thereafter. CTP data were transferred to a workstation and analyzed using the Brilliance Workspace Portal® (Philips Medical Systems, Cleveland, OH, USA). This team performed manual checks and adjustments and corrections of artefacts. The locations of early signs of ischemia and infarct core on CTP were not checked for accordance. A deconvolution approach, based on the central volume principle, was used to create parametric maps of mean transit time (MTT); cerebral blood volume (CBV) was calculated from the area under the time-enhancement curves and cerebral blood flow (CBF) was derived from the formula CBF=CBV/MTT. Infarct core and ischemic penumbra volumes were calculated by applying appropriate MTT and CBV thresholds, which are MTT >145% of the contralateral side values and CBV >2.0 mL/100 g for the penumbra volume, and MTT >145% of the contralateral side values and CBV <2.0 mL/100 g for the core volume(49).

NCCT images were reviewed for ASPECTS retrospectively by an experienced vascular neurologist (PM). This person compared his value to the assessment established by the radiologist in the acute phase and appearing in the official (clinical) radiology report. In cases of disagreement between the two ASPECTS values, the case was discussed at the weekly joint neuroradiology meetings to reach a consensus. We had previously assessed inter-rater variability between the vascular neurologist and senior neuro-radiologist using Cohen's kappa on 100 consecutive acute CT scans with anterior circulation occlusive stroke for

NCCT-ASPECTS, CBS and collateral status (poor vs good). ASPECTS was scored by the Lausanne team, without considering results of the CTP, the latter being performed by a completely independent team in Stanford. Both ASPECTS and CTP were calculated in the acute phase, without knowledge of the long-term clinical outcome.

Statistical Analysis

Categorical and binary variables were summarized as frequencies and percentages, while continuous variables as median and interquartile range (IQR). Statistical correlation between ASPECTS and core volume on CTP was quantified using Spearman's Rho coefficient (ρ). To report the strength and direction of the correlation, we referred to a commonly-used interpretation of the Spearman's correlation coefficient in medical research(71). We calculated the statistical significance of this association both in the overall study population and in several meaningful subpopulations defined by the following settings:

a) Presence and absence of LVO; b) early- and late-arriving-patients and c) known and unknown stroke onset. Furthermore, we compared the correlation coefficients between groups defined by variable combinations of the above-mentioned scenarios (e.g., late-arriving patients with LVO). Comparisons between the different groups of patients were based on z-scores obtained using Fisher's r-to-z transformation of the ρ; this allows determining the statistical significance of the differences by means of tests based on Student's t-distributions. We performed a complete case analysis and no imputation of missing data was done.

To check for independent factors associated with ASPECTS (used as dependent variable), we developed a multivariate linear regression model. We included in the model, variables likely to influence ASPECTS based on pathophysiological considerations (such as age, NIHSS, pre-stroke treatments, vascular risk factors, clot burden, leukoaraiosis, core and penumbra volumes on CTP) and variables that were supposed to influence the relationship between ASPECTS and core volumes (such as the above variables and time from LPGH and LVO and onset

type). The complete list of variables included in the model, along with the p-values obtained using univariate analysis, is shown in Table 1. We used stepwise backward elimination method based on the Akaike Information Criterion (AIC) to select relevant covariates for inclusion in the final model. Then, we checked the sensitivity of our findings by fitting the same model (except for LVO) into the subpopulation of late-presenting patients with LVO. Heteroskedasticity and normality of residuals were checked using graphical methods (QQ and Residuals vs Fitted Plots).

In order to identify independent predictors for good clinical outcome at 3 months (mRS≤2), we fitted a multivariate logistic regression model with stepwise backward elimination method. This model included demographic, clinical and radiological variables at stroke onset that are known to be related to the functional long-term outcome(72, 73) (Table 2). Then, as before, we performed a separate logistic regression analysis on the subgroup of late-arriving patients with LVO, applying the same model (except for LVO).

Finally, to understand better the capability of NCCT and CTP to predict clinical outcome, we performed Receiver Operating Characteristic (ROC) curve analyses for both imaging modalities in patients showing a concordant or discordant NCCT-CTP profile. We defined favorable NCCT if ASPECTS was ≥6 and favorable CTP if the core volume was ≤70 mL, as previously suggested(19, 74).

5.3.4 *Results*

Study population and baseline characteristics

Out of 5,049 AIS patients entered in the ASTRAL registry during the study period, 1,046 were included in the current analysis. The flow chart in Figure 1 describes the reasons for exclusion from the analysis and the main differences between the included and excluded patients.

The median age of the included patients was 71.4 years (IQR= 59.8-79.4) and the median NIHSS was 12 (6-18), as described in Table 3. The median time from LPGH-to-hospital arrival was 2.6 hours (1.3-6.9), and median time from LPGH to imaging was 3.4 hours (1.9-8.5). Two hundred and ninety two patients (27.9%)

were admitted in the late time window; their median LPGH-to-hospital arrival time was 10.2 hours (7.9-13.4), and their median LPGH-to-CT time was 11.5 hours (8.7-15.3).

We previously assessed inter-rater agreement measures for the following CT-based neuroimaging variables, finding almost perfect agreement for ASPECTS (kappa 0.82) and collaterals (kappa=0.81), and good agreement for clot burden score (kappa=0.77).

In the study population, median ASPECTS was 9 (7-10) and median core volume on CTP 13.6 mL (0.6-52.8). On CTA, an LVO was detected in 612 (58.5%) patients and in 151 (51.7%) late-arriving patients. Additional treatment details, stroke etiology and clinical outcome measures are available in Table 3.

Correlation between ASPECTS and CTP-core, and influence of time and LVO

The overall correlation between ASPECTS and CTP core was moderate (ρ=-0.49, p<0.01). The distribution of CTP-core volumes across ASPECTS grades is depicted in Figure 2a and it showed a definitive trend of increasing median baseline CTP-cores as ASPECTS grade decreases. The ASPECTS-CTP core correlation was significantly stronger in the subgroup of patients admitted in the late than in the early time window (ρ=-0.56 and ρ=-0.48 respectively, p=0.05, Figure 3). In addition, this correlation was significantly better in the presence vs absence of an LVO (ρ=-0.40 and ρ=-0.20 respectively, p<0.01, Figure 4). We did not find any significant difference in the ASPECTS-CTP core correlation in the subgroup of patients with known vs unknown stroke onset (ρ=-0.55 and ρ=-0.44 respectively, p=0.12).

Testing the combined covariates “LVO” and “time”, we found that correlation increased up to a moderately strong degree (ρ=-0.57, p<0.01) in the subgroup of late-arriving patients with LVO (Figure 2b). On the other hand, it was poor in early patients, with and without LVO (ρ=-0.36, p<0.01; and ρ=-0.23, p=0.01 respectively).

With the linear multiple regression model, we confirmed an independent association between ASPECTS and CTP-core (β=-0.10 per 10mL; 95%CI= (-0.14;-0.07), p<0.01). Moreover, a higher ASPECTS was independently associated with older age, shorter delay to arrival time, pre-stroke statin use and lower admission glucose. Regarding radiological variables, we found an independent association between a higher ASPECTS and absence of hyperdense MCA sign, absence of LVO, higher CBS and presence of good collaterals (Table 4). In the subpopulation of late-arriving patients with LVO, the association of ASPECTS and CTP-core was twice as strong (β=-0.21 per 10mL; 95%CI= (-0.27;-0.15), p<0.01). Again, older age, shorter delay to arrival time and higher CBS were independently associated with a higher ASPECTS (Table 4).
To check if ASPECTS could reliably identify the CTP core volume thresholds, which have been used in recent clinical trials of late time window, we performed a ROC analysis using a CTP-core of 70 mL (as used in the DEFUSE-3 trial) investigating if a higher ASPECTS was associated with a favorable CTP profile. We found an AUC=0.76 in the overall population and an AUC=0.79 in the subpopulation of late-arriving stroke with LVO (Figure 5). In this latter group, a cut off of ASPECTS≥7 (based on the Youden index) identified patients with a CTP-core <70 mL with a sensitivity of 65.7% and a specificity of 76.7%.

Association of ASPECTS with clinical outcome

The overall percentage of good clinical outcome at three months was 51.9%. Fitting a logistic multiple regression model, ASPECTS emerged as an independent predictor of good outcome in both the overall population (OR=1.10; 95%CI= (1.00-1.20), p=0.05) and late-arriving AIS patients (OR=1.23; 95%CI= (1.02-1.51), p=0.03) (Table 5). Moreover, we found younger age, lower NIHSS on admission and lower frequency of decreased level of consciousness as independently associated with a favorable outcome in our study cohort. Among radiological variables, a smaller clot (i.e. higher CBS) and the absence of tandem occlusion also predicted favorable outcome.

As sensitivity analysis, we compared the predictive capabilities of the models for good clinical outcome at 3 months where ASPECTS is replaced with CTP-core (Table 6). These models showed very similar performance as indicated by the similar coefficients and AICs, in both the overall cohort and in the subpopulation of late-arriving patients with LVO: the Vuong tests for the difference in AICs were not significant (p=0.39 for the overall cohort; p=0.14 for the late-arriving patients with LVO).

Looking at the relationship between imaging concordance and clinical outcome, we identified the following subgroups of patients: patients with favorable NCCT/CTPs (n=756/1046, 72%), patients with poor NCCT/CTPs (n=79, 8%) and patients with discordant NCCT/CTPs (n=211, 20%). The percentages of good outcome across the subgroups were: 61% in patients with both images being favorable, 14% in patients with both unfavorable images, and 32% in patients with discordant images. The areas under the curve (AUCs) for predicting good outcome for each imaging technique in the threes subgroups of patients are reported in Figure 6. We observed a similar but poor prognostic performance of NCCT and CTP in patients with favorable profiles on both modalities. The performance was higher in patients showing both unfavorable NCCT and CTP, without any statistical difference between ASPECTS and CTP. In patients with discordant NCCT and CTP profiles, the performance of both modalities was again modest, with a non-significant higher accuracy for CTP-core compared to ASPECTS.

5.3.5 *Discussion*

In a large cohort of consecutive AIS patients involving the MCA territory, we showed a moderate correlation between ASPECTS and core volume on CTP in the acute phase of stroke. This correlation was significantly better in the presence of an LVO (ICA, M1 or proximal M2 occlusion) and was time-dependent, being stronger in the subgroup of patients potentially eligible for late endovascular treatment (i.e. LVO positive and arriving after 6 hours of last proof of good health).

In the latter, we confirmed an independent role of ASPECTS in determining good clinical outcome at three months, which was similar to CTP-core.

Compared to previous studies reporting a weak(75) to moderate(76) ASPECTS-CTP core correlation, we tested correlation in a larger study cohort and applying multiple adjustments. We demonstrated that the ASPECTS-CTP core association was stronger in patients with LVO than without. This finding was very robust, given that the association was present even after correction for several clinical and radiological variables. We suppose that the presence of a proximal intracranial occlusion leads to higher ischemic core volume, therefore to a higher likelihood of detecting early ischemic changes on NCCT and, as a consequence, to a higher accuracy of ASPECTS on estimating core volume(77). This was especially evident in patients assessed 6 hours after symptoms onset, which probably reflects the progressive development of cytotoxic edema, the histological equivalent of early ischemic changes on NCCT.

We also found that multiple other clinical and radiological variables, in addition to time and presence of an LVO, influence the ASPECTS. Patients with pre-stroke statin use presented with higher ASPECTS, which is in line with previous studies reporting that statin pretreatment enhances collateral perfusion and reduces final infarct volume(78, 79). We also demonstrated that admission hyperglycemia was associated with poorer ASPECTS; this finding is consistent with previous human and animal studies showing that hyperglycemia is associated with early infarct expansion in AIS(80, 81). Regarding radiological variables, we found higher ASPECTS in patients without hyperdense MCA sign, (which is a marker of proximal MCA occlusion) and with higher CBS, (which means smaller clots). Taken together, these results suggest a favorable NCCT profile in patients with distal or small area of vascular occlusion. Moreover, we identified an independent association between higher ASPECTS and good collaterals, further supporting the role of collateral circulation in the early prevention of tissue loss(77).

Our results confirm that in a mixed population of AIS patients, some treated with IVT and/or EVT, baseline ASPECTS is a major determinant of good clinical outcome at three months, after adjusting for known confounders (including age,

pre-stroke disability, stroke severity and admission glycaemia). This has already been shown in the early time window for patients without revascularization treatment(82), treated with IVT(66) and with early EVT(5, 53, 83). In our subgroup of patients admitted late and who had LVO (a minority of whom underwent EVT), we confirmed that higher ASPECTS also remained independently associated with good clinical outcome and we showed that the prognostic value of ASPECTS was similar to core volume on CTP.

Still, relying on imaging alone could lead to erroneous outcome prediction. Our results showed that a good and concordant NCCT/CTP imaging profile on admission was not a sufficient condition for sure translation to a positive clinical outcome, and the performance of both imaging modalities did not seem to contribute to prediction. We can probably explain this by the other numerous variables that may have an impact on the outcome (as emerged from our multivariate model of prediction of good clinical outcome at 3 months). In addition, the small number of patients with LVO who underwent EVT in our cohort might have influenced this finding. We also showed that 20% of patients presented a discordant NCCT/CTP profile, of whom 30% achieved a good outcome. These patients include patients with good ASPECTS despite a large infarct volume, in whom it was demonstrated that a quick and successful revascularization of the hypoperfused region was still associated with high probability of good outcome. In fact, up to 20% of such patients might present a final infarct volume lower than that of the admission volume, due to an overestimation of the latter by CTP in the early hours after stroke onset (84, 85). In the opposite situation of low ASPECTS associated with acceptable core volumes on CTP, a revision of early ischemic NCCT changes should be considered (e.g. to exclude old infarctions or NCCT artefacts), especially for patients imaged in the extended time window and with good collateral circulation.

The clinical implications of our findings include that ASPECTS appears as a quite reliable surrogate marker for the ischemic core in patients with LVO in the later time window. Such a finding supports the possible role of ASPECTS as a selection tool for late mechanical thrombectomy. We previously demonstrated

that the strict application of trials criteria (DAWN, DEFUSE-3) translated into a low proportion of eligible patients for late EVT in the real-word scenario, and that this treatment could be offered to a larger population of patients if more liberal criteria were adopted(86). In this setting, the use of ASPECTS could help with the decision to proceed to thrombectomy in cases of absent, failed or contraindicated advanced imaging, or in situations of CT and CTP discordant profiles(74). Success of late revascularization therapies according to trials criteria could be hopefully replicated by simpler selection criteria. This strategy is currently evaluated in ongoing randomized clinical trials (MR CLEAN-LATE(87); TWIST(88)).

Several limitations of our study need to be acknowledged. First, its single-center retrospective design and the exclusion of patients due to absence of reconstructed CTP volumes could lead to a selection bias; furthermore, an external validation of the study results is lacking. Second, we did not assess the spatial agreement between ASPECTS and CTP-core, and therefore, we could not assess if unequal weighting of brain regions in ASPECTS rating could hamper its correlation with core volumes. Third, the thresholds model used for core and penumbra volume reconstructions was different from those adopted in recent EVT trials(15); however, it is a well-established model, based on a systematic evaluation of all PCT parameters and is the most suitable for the software used in the analysis(49). Finally, given the small number of patients treated with late EVT in our cohort, we could not analyze the impact of ASPECTS on the response to revascularization treatments.

A future potential development of this study includes the comparison between visual ASPECTS and scoring with automated software applications able to detect and quantify early ischemic changes(89).

In conclusion, in our series of 1,046 MCA stroke patients, ASPECTS exhibits a moderate correlation with CTP-based infarct core, which is stronger in late-arriving patients with large vessel occlusion. This could support the use of ASPECTS as a surrogate marker for CTP-core for selection of late endovascular treatment and for estimation of prognosis. Further studies on the effect of an

ASPECTS-based selection for late revascularization therapies are strongly welcomed.

5.3.6 *Tables and Figures*

Table 1 Variables included in multivariate regression model to identify associations with ASPECTS (used as dependent variable), and the p-values obtained in the univariate analysis.

Table 2 Variables included in multivariate regression model for 3-months good clinical outcome prediction.

Table 3 Demographics, clinical-radiological characteristics, stroke etiology and outcome of the 1,046 patients included in the study. Continuous variables are expressed as median and interquartile range (IQR), categorical variables as frequencies and percentages.

Table 4 Significant results from the multiple regression model with NCCT-ASPECTS as dependent variable, in the overall population and in late arriving (>6 hours from LPGH) AIS patients with LVO. Results are expressed as β coefficient and relative 95% CI.

Table 5 Independent predictors for good clinical outcome at 3 months (mRS≤2), in the overall population and in late arriving (>6 hours from LPGH) AIS patients with LVO. Results are adjusted for pre-stroke mRS and expressed as OR and relative 95% CI.

Table 6 Independent predictors for good clinical outcome at 3 months (mRS≤2), in the overall population and in late arriving (>6 hours from LPGH) AIS patients with LVO, with the ASPECTS variable being replaced by the variable CTP-core. Results are adjusted for pre-stroke mRS and expressed as OR and relative 95% CI.

Figure 1 Flow-chart for patients selection in the current analysis. Results from the univariate comparison between included (n=1,046) and excluded patients (n=4,003) showed that the included patients were younger (median age =71.4 vs 74.4; p<0.001), more frequently female (47.9% vs 43.8%; p=0.017), had a higher NIHSS on admission (median value=12 vs 5; p<0.001), and a lower ASPECTS (median value= 9 vs 10; p<0.001).

Figure 2 Box plot of ASPECTS scores (x-axis) and baseline CTP-core volumes (y-axis) in the overall population (n=1,046, Figure 2a) and in subgroup of late-arriving patients with LVO (n=151, Figure 2b). We observe a moderate ASPECTS - CTP-core correlation in our study cohort (ρ=-0.49) and a stronger correlation among late-arriving patients with LVO (ρ=-0.57).

Figure 3 ASPECTS-CTP core correlations in the subgroup of AIS patients admitted in: a) the early time window (< 6 hours since LPGH); b) the late time window (6-24 hours since LPGH). The correlation was moderate in the early phase (ρ=-0.48) and moderately strong (ρ=-0.56) in the later phase, with a statistically significant difference (p=0.05) between the two groups.

Figure 4 ASPECTS-CTP core correlations in the subgroup of AIS patients: a) without large vessel occlusion (LVO); b) who had LVO. The correlation was weak in patients without LVO (ρ=-0.20) and moderate in the presence of LVO (ρ=-0.40), with a statistically significant difference (p<0.01) between the two groups.

Figure 5 Receiver Operating Characteristic (ROC) curve analyses for the prediction of CTP-core volume<70 mL by ASPECTS, in all included patients (red line) and in the late-arriving patients with LVO (blue line). AUC indicates the area under the curve for each model (with its 95% confidence interval, CI). In LVO patients admitted after 6 hours, a cut off ASPECTS≥7 identified patients with a CTP-core <70 mL with a sensitivity of 65.7% and a specificity of 76.7%.

Figure 6 Receiver Operating Characteristic (ROC) curve analyses for prediction of good outcome at 3 months, by ASPECTS (red line) and CTP (blue line). The

performance of the two imaging modalities was tested in patients showing concordant and favorable NCCT/CTP (n=756), concordant and unfavorable NCCT/CTP (n=79) and discordant NCCT/CTP (n=211), and reported as the area under the curve (AUC) with 95% confidence interval (CI).

Table 1

Variable	*p-value*
Age	**<0.01**
Unknown stroke onset	**<0.01**
LPGH to hospital arrival, h	**<0.01**
Pre-stroke antiplatelets therapy	0.55
Pre-stroke anticoagulation therapy	0.20
Pre-stroke antihypertensives therapy	0.26
Pre-stroke statin therapy	0.28
Hypertension	0.21
Diabetes	0.58
Hyperlipidaemia	0.89
Current smoking	**0.01**
Atrial fibrillation	0.64
Systolic blood pressure on admission, *per* 10 mmHg	**0.04**
Blood glucose on admission, (g/L)	**<0.01**
Hyperdense MCA sign	**<0.01**
Chronic stroke on NCCT	**<0.01**
Severe leukoaraiosis	**<0.01**
LVO	**<0.01**
Good Collaterals	**0.03**
Clot Burden Score	**<0.01**
Infarct volume on CTP, mL	**<0.01**
Penumbra volume on CTP, mL	**<0.01**

Table 2

Variable
Age
Pre-stroke modified Rankin Scale
NIHSS on admission
Decreased level of consciousness on admission
Unknown stroke onset
LPGH to hospital arrival, h
Blood glucose on admission, (g/L)
ASPECTS
Severe leukoaraiosis
LVO
Good Collaterals
Clot Burden Score
Tandem occlusion
Etiology: cardioembolism
IVT
EVT

Table 3

Variable	Patients (n=1,046)
Age, y	71.4 (59.8-79.4)
Sex, F	501 (47.9%)
Pre-stroke mRS	0 (0-1)
Vascular risk factors	
Hypertension	606 (57.9%)
Hyperlipidemia	375 (35.9%)
Atrial fibrillation	210 (20.1%)
Current smoking	256 (24.7%)
Diabetes	130 (12.4%)
Pre-stroke treatments	
Antiplatelet	356 (34.0%)
Anticoagulation	126 (12.1%)
Anti-hypertensive	569 (54.5%)
Statin	269 (25.8%)
Stroke characteristics	
NIHSS on admission	12 (6-18)
Hemiparesis	940 (90.7%)
Visual field defects	566 (54.8%)
Aphasia	522 (50.3%)
Neglect	423 (41.1%)
Vigilance impairment	137 (13.3%)
Onset stroke type	
Unwitnessed onset	99 (9.5%)
Wake-up stroke	217 (20.7%)
Process measures	
LPGH to arrival, min	154 (79-416)
LPGH to CT time, min	206 (115-508)
Baseline measurements	
SBP on admission (mmHg)	153 (137-172)
DBP on admission (mmHg)	85 (75-99)
Body temperature (°C)	36.3 (36.0-36.7)
Blood glucose on admission (g/L)	6.5 (5.7-7.6)
Radiological variables	
ASPECTS	9 (7-10)
Hyperdense MCA sign	286 (34.2%)
Leukoaraiosis	291 (28.6%)
Chronic strokes	234 (23.0%)
Vascular imaging variables	
LVO	612 (58.5%)

ICA occlusion	195 (18.6%)
M1 occlusion*	441 (42.2%)
M2 occlusion*	518 (49.5%)
Good collaterals	382/612 (62.4%)
Clot burden score	7 (4-9)
Tandem occlusion	167 (16.0%)
CTP parameters	
Infarct volume, mL	13.6 (0.6-52.8)
Penumbra volume, mL	49.1 (6.3-106.5)
Mismatch ratio	2.6 (1.3-6.9)
Acute reperfusion therapies	
IVT	359 (34.3%)
LPGH-IVT, min	150 (110-195)
EVT (± preceding IVT)	94 (9.0%)
LPGH-groin puncture, min	353 (218-590)
TICI 2b-3 at the end of EVT	62 (66.0%)
Stroke Mechanism	
Atherosclerotic	157 (15.0%)
Cardioembolism	393 (37.7%)
Dissection	69 (6.6%)
Lacunar	15 (1.4%)
ESUS	153 (14.7%)
Multiple	65 (6.2%)
PFO-related	38 (3.6%)
Other cause/rare	56 (5.4%)
Undetermined/incomplete workup	97 (9.3%)
Outcome measures	
NIHSS at 24 hours	9 (4-17)
Symptomatic HT at 24 hours	139 (13.3%)
3 months mRS 0-2	536 (51.9%)
Death within 3 months	185 (17.9%)

*Means with or without more proximal occlusion.

Table 4

Variables associated with ASPECTS	**Study cohort** (n=1, 046)	**Late AIS with LVO** (n=151)
Age, years	0.02 (0.01;0.03)	0.05 (0.02;0.07)
LPGH to arrival time, hours	-0.11 (-0.15;-0.08)	-0.21 (-0.30;-0.12)
Pre-stroke statin use	0.67 (0.13;1.21)	ns
Acute glucose (g/L)	-0.07 (-0.13;-0.01)	ns
Hyperdense MCA sign	-0.56 (-0.98;-0.14)	ns
LVO*	-0.73 (-1.26;-0.20)	-
CBS	0.14 (0.06;0.21)	0.17 (0.03;0.31)
Good collaterals	0.87 (0.51;1.23)	ns
Core volume, *per* 10 mL	-0.10 (-0.14;-0.07)	-0.21 (-0.27;-0.15)

*included in the predictive model for the entire study cohort only; ns= non-significant

Table 5

Variables associated with good outcome	**Study cohort** (n=1,046)	**Late AIS with LVO** (n=151)
Age, years	0.96 (0.94-0.97)	ns
NIHSS on admission	0.87 (0.84-0.91)	0.86 (0.80-0.93)
Decreased LOC on admission	0.45 (0.24-0.83)	ns
LPGH to arrival time, hour	0.95 (0.91-0.99)	ns
NCCT-ASPECTS	1.10 (1.00-1.20)	1.23 (1.02-1.51)
CBS	1.17 (1.08-1.28)	ns
Tandem occlusion	0.54 (0.32-0.92)	0.23 (0.06-0.76)
	AIC=694.76	*AIC=146.02*

LOC=level of consciousness; AIC=Akaike's Information Criteria

Table 6

Variables associated with good outcome	**Study cohort** (n=1, 046)	**Late AIS with LVO** (n=151)
Age, years	0.96 (0.94-0.97)	ns
NIHSS on admission	0.88 (0.84-0.91)	0.88 (0.81-0.95)
Decreased LOC on admission	0.45 (0.24-0.83)	ns
LPGH to arrival time, hour	0.94 (0.90-0.98)	0.84 (0.73-0.96)
CTP-core	0.99 (0.99-1.00)	0.98 (0.97-1.00)
CBS	1.18 (1.08-1.28)	ns
Tandem occlusion	0.56 (0.33-0.96)	0.21 (0.06-0.72)
	AIC= 693.34	*AIC=140.64*

Figure 1

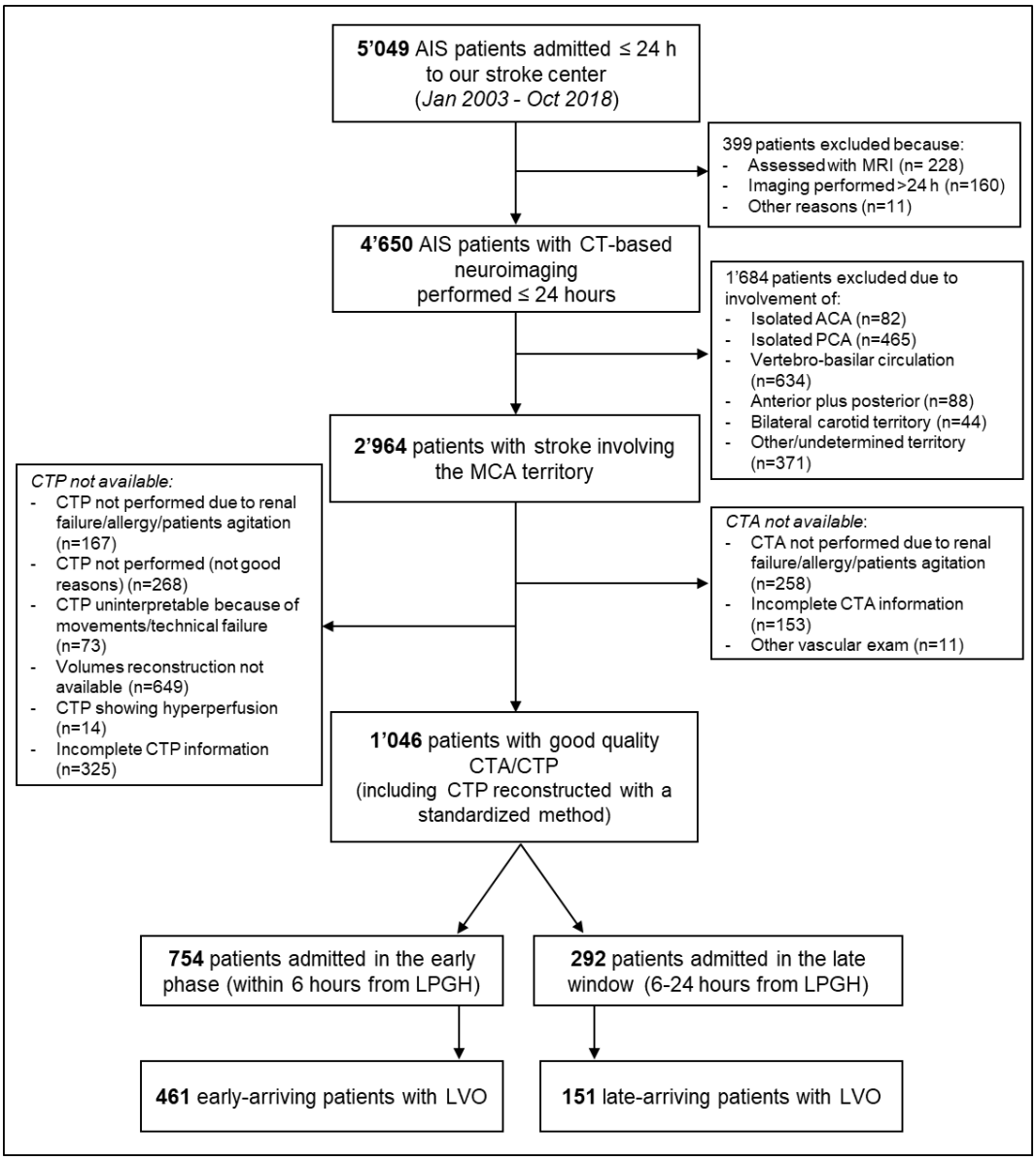
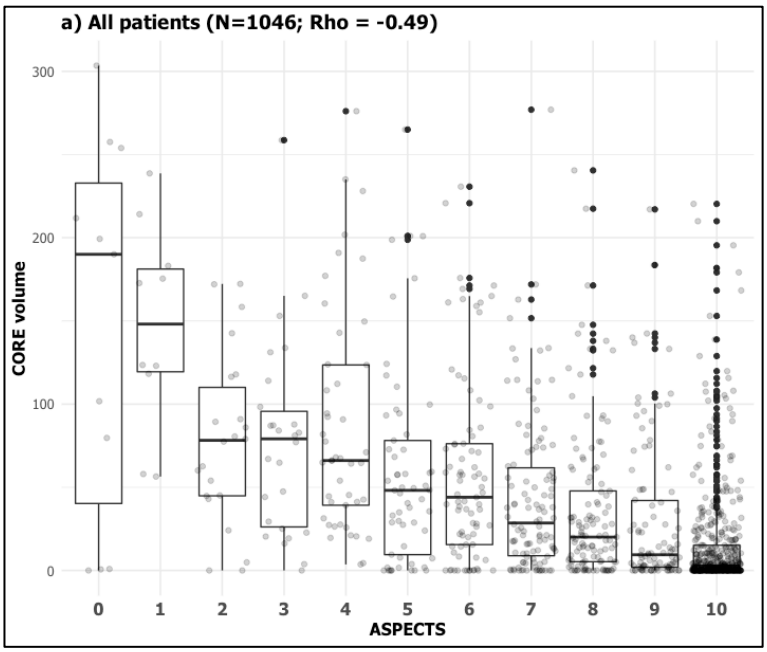

5'049 AIS patients admitted ≤ 24 h to our stroke center (*Jan 2003 - Oct 2018*)
399 patients excluded because:
- Assessed with MRI (n= 228)
- Imaging performed >24 h (n=160)
- Other reasons (n=11)
4'650 AIS patients with CT-based neuroimaging performed ≤ 24 hours
1'684 patients excluded due to involvement of:
- Isolated ACA (n=82)
- Isolated PCA (n=465)
- Vertebro-basilar circulation (n=634)
- Anterior plus posterior (n=88)
- Bilateral carotid territory (n=44)
- Other/undetermined territory (n=371)
2'964 patients with stroke involving the MCA territory
CTP not available:
- CTP not performed due to renal failure/allergy/patients agitation (n=167)
- CTP not performed (not good reasons) (n=268)
- CTP uninterpretable because of movements/technical failure (n=73)
- Volumes reconstruction not available (n=649)
- CTP showing hyperperfusion (n=14)
- Incomplete CTP information (n=325)
CTA not available:
- CTA not performed due to renal failure/allergy/patients agitation (n=258)
- Incomplete CTA information (n=153)
- Other vascular exam (n=11)
1'046 patients with good quality CTA/CTP (including CTP reconstructed with a standardized method)
754 patients admitted in the early phase (within 6 hours from LPGH)
292 patients admitted in the late window (6-24 hours from LPGH)
461 early-arriving patients with LVO
151 late-arriving patients with LVO

Figure 2


a) All patients (N=1046; Rho = -0.49)
CORE volume
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
ASPECTS

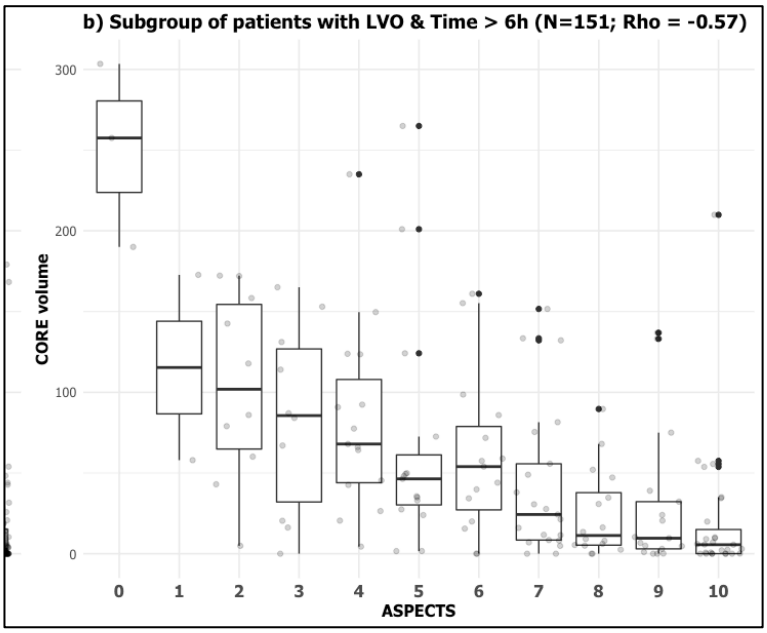

b) Subgroup of patients with LVO & Time > 6h (N=151; Rho = -0.57)
CORE volume
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
ASPECTS

Figure 3

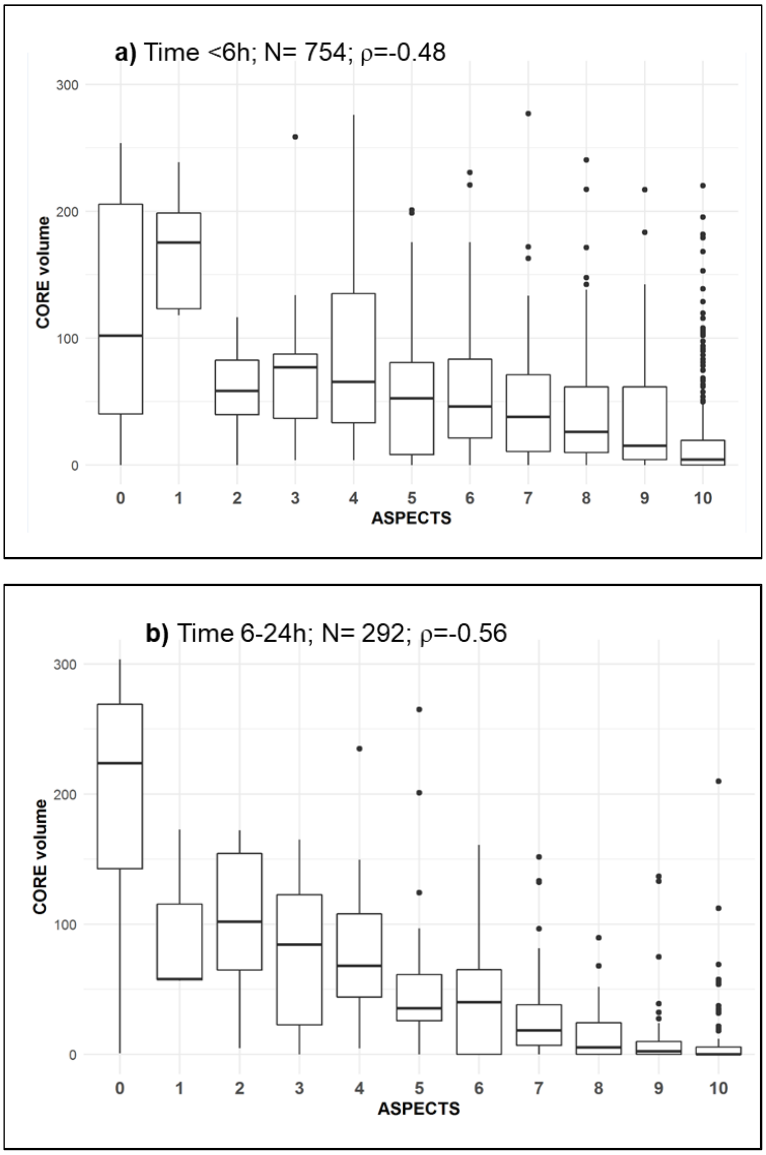

a) Time <6h; N= 754; ρ=-0.48
CORE volume
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
ASPECTS
b) Time 6-24h; N= 292; ρ=-0.56
CORE volume
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
ASPECTS

Figure 4

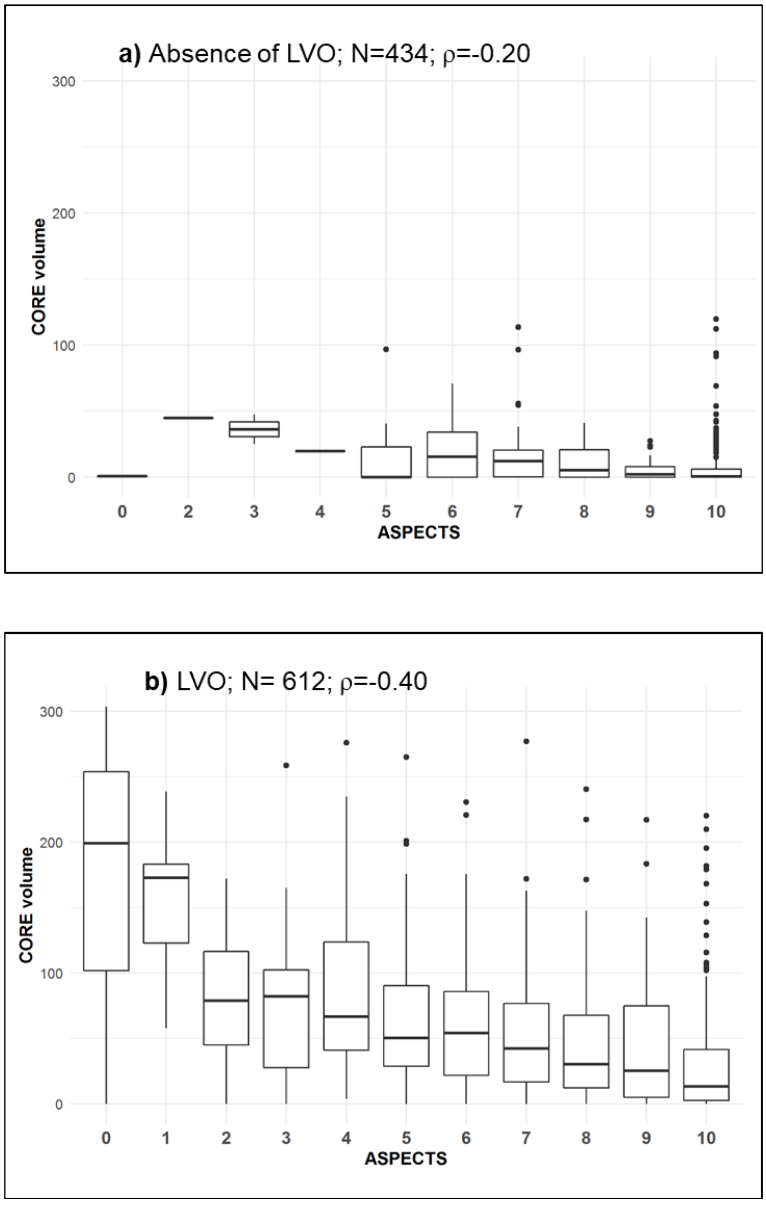
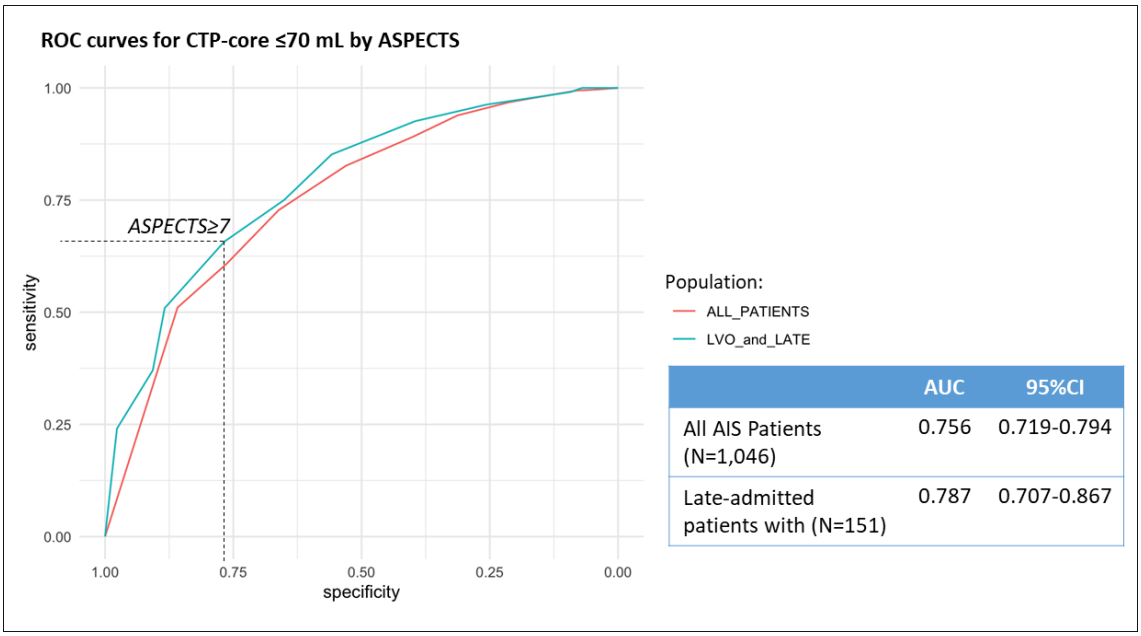
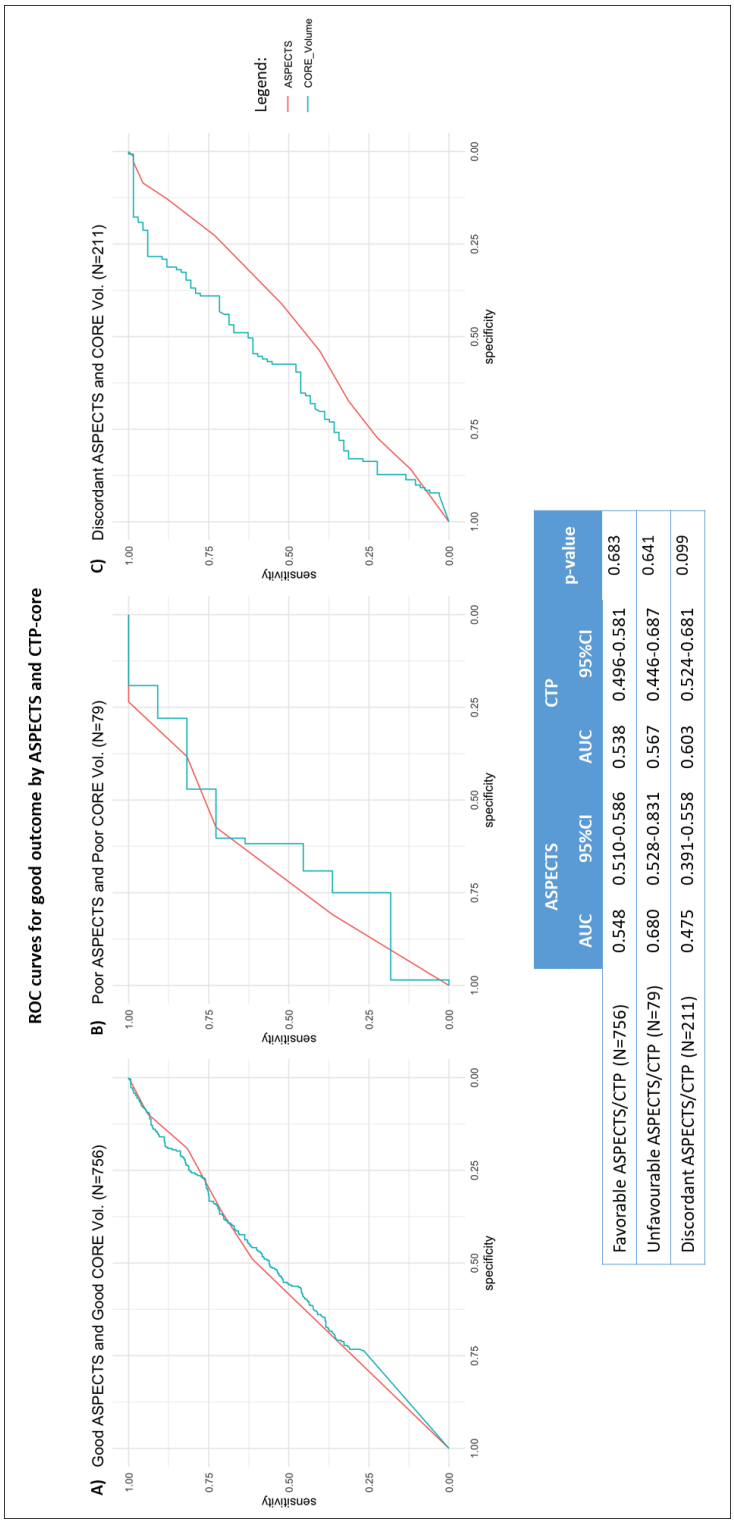

a) Absence of LVO; N=434; ρ=-0.20
CORE volume
300
200
100
0
0
2
3
4
5
6
7
8
9
10
ASPECTS
b) LVO; N= 612; ρ=-0.40
CORE volume
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
ASPECTS

Figure 5



	AUC	95%CI
All AIS Patients (N=1,046)	0.756	0.719-0.794
Late-admitted patients with (N=151)	0.787	0.707-0.867

Figure 6



	ASPECTS		CTP		p-value
	AUC	95%CI	AUC	95%CI	
Favorable ASPECTS/CTP (N=756)	0.548	0.510-0.586	0.538	0.496-0.581	0.683
Unfavourable ASPECTS/CTP (N=79)	0.680	0.528-0.831	0.567	0.446-0.687	0.641
Discordant ASPECTS/CTP (N=211)	0.475	0.391-0.558	0.603	0.524-0.681	0.099

6 PROJECT **B)** CLINICAL IMPLICATIONS IN THE LATE TIME WINDOW

6.1 Real-life eligibility for late endovascular treatment

6.1.1 *Abstract*

Background and purpose

Real-life application of DAWN and DEFUSE-3 trials is poorly investigated. We aimed to identify the proportion of acute ischemic stroke (AIS) patients eligible for late endovascular treatment (EVT) in our stroke center based on trial and more liberal selection criteria.

Methods

All consecutive patients in the ASTRAL registry (2003-2017) admitted between 5-23 hours of last proof of good health were selected if they had complete clinical and radiological datasets. We calculated the proportion of patients eligible for late EVT according to trial (DAWN and/or DEFUSE-3) and more liberal clinical-imaging mismatch criteria (including lower admission NIHSS and ASPECTS for core estimation).

Results

Out of 1'705 AIS patients admitted to our comprehensive stroke center in the late time window, we identified 925 patients with complete clinical and radiological data. Among them, proportions of late EVT eligibility were 2.5% (n=23) with DAWN, 5.1% (n=47) with DEFUSE-3 and 11.1% (n=103) with more liberal criteria. Considering late-arriving patients with LVO (n=221), percentages of eligible patients were 10.4%, 21.3% and 46.6%, respectively. A favorable outcome was observed at comparable rates in treated patients selected by trial or liberal criteria (67% vs 58%, p=0.49).

Conclusions

In a long-term stroke registry, the proportion of late EVT eligibility varied greatly according to selection criteria and referral pattern. Among late-arriving patients referred to our comprehensive stroke center, we found 5.6% eligible according to trial (DAWN/DEFUSE-3) and 11.1% according to liberal criteria. These data indicate that late EVT could be offered to a larger population of patients if more liberal criteria are applied.

6.1.2 *Background*

Endovascular treatment (EVT) for AIS patients with proximal intracranial large vessel occlusion (LVO) is well demonstrated within the first 6 hours after onset when most patients have limited irreversible damage and significant amounts of salvageable brain tissue (5). Recently, two randomized clinical trials showed effectiveness of late EVT up to 24 hours, based on radiological selection of AIS patients having small core volume and either severe clinical symptoms (clinical-core mismatch in the DAWN trial) or a large perfusion deficit (perfusion mismatch in the DEFUSE-3 trial) (18, 19).

Scant data exists on the number of late-arriving patients who are eligible for EVT in the real world (90). The calculation of the proportion of patients eligible for such treatment is of major importance for implementing DAWN and DEFUSE-3 results and consequently, reorganizing stroke systems of care. Moreover, the precise measurement of lesion volumes with sophisticated imaging may be difficult in the

acute stroke scenario due to patient agitation, contrast product contraindications, or technical problems with perfusion imaging. Therefore, simpler and more liberal criteria to determine the clinical-imaging mismatch could be useful in clinical practice.

The main purpose of our study was to identify the proportions of AIS patients eligible for late EVT in our endovascular-capable stroke center, using strict trial (DAWN and/or DEFUSE-3) criteria and more liberal clinical-imaging mismatch criteria. Moreover, we searched for clinical and laboratory variables independently associated with late EVT eligibility according to trial and liberal criteria. Then, we provided a description of our real life cohort treated by late EVT and the outcome analysis at three months.

6.1.3 *Methods*

Study Design

We performed a retrospective analysis of all AIS patients admitted to our comprehensive stroke center from January 2003 to December 2017. We used the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) as our data source(29). ASTRAL is a single center-based cohort of all AIS patients admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital within 24 hours after last proof of good health (LPGH). It incorporates more than 250 pre-specified demographic, clinical, laboratory variables and modern multimodal brain imaging items on over 4'500 consecutive AIS patients. The STROBE method (Strengthening the Reporting of Observational Studies in Epidemiology) was applied. The local ethics commission approved the scientific use of anonymized data from the ASTRAL registry.

Patient Selection

We included late-arriving/treatable patients, i.e. admitted from five to 23 hours after LPGH (including patients with unknown daytime stroke onset and wake-up stroke). This time window allowed patients to be potentially treated by endovascular procedure between 6 and 24 hours. Then, we selected patients

with complete datasets allowing eligibility calculation according to trial criteria, including availability of good quality CT-perfusion (CTP).

Patients were defined as eligible according to the DAWN and DEFUSE-3 enrolment criteria, as reported previously (91, 92). In our study cohort, we applied the DEFUSE-3 criteria up to 23 hours; this allowed a combined evaluation of trial eligibility in the late time window and was based on the assumption that clinical outcomes were better in later than earlier treated patients(20).

In addition, we proposed more liberal and pragmatic selection criteria for late EVT eligibility that included: less severe stroke on admission (NIHSS ≥5), mild pre-stroke disability (modified Rankin Scale, mRS ≤2), non-contrast CT (NCCT) ASPECTS cut-offs for core volume estimation (≥5) and presence of internal carotid artery (ICA), M1, proximal M2 or basilar artery (BA) occlusions on CT-angiography (CTA). Moreover, the liberal criteria required a clinical-imaging mismatch in the anterior circulation strokes defined as: NIHSS 5-9 and ASPECTS ≥8; or NIHSS ≥10 and ASPECTS ≥7; or NIHSS ≥20 and ASPECTS ≥5. For posterior circulation (pc) stroke, eligibility required pc-ASPECTS ≥8 and absence of bilateral (transverse) pontine or midbrain infarction. The choice of ASPECTS for infarct core estimation reflects the intent of the liberal criteria to offer EVT to a wider proportion of late arriving patients, even in centers where access to advanced imaging is limited.

We measured clinical outcome at three months using the mRS, either in person at the outpatient stroke clinic or in a standardized telephone interview by Rankin-certified medical personnel. Favorable outcome was defined as mRS ≤2.

Neuroimaging protocol

Multimodal CT-based imaging, including NCCT, CTP, CTA and post-contrast series, was performed in patients with suspected AIS as standard of care, unless contrast contraindication existed. We performed CT on a 16-detector CT scanner until November 2005 and on a 64-multidetector CT scanner

thereafter (LightSpeed VCT or Revolution, GE Healthcare, Milwaukee, WI, USA). We acquired NCCT and post-contrast series in axial scan mode from the skull base to the vertex (16cm z-axis coverage) using the following imaging parameters: 120kV peak tube voltage, 320mA tube current, 5mm slice thickness, 32cm scan field of view (SFOV), 512x512 matrix. All CTP series were acquired with 80kV peak tube voltage, 240mA tube current, 32cm SFOV and 512x512 matrix. Images were centered on the level of the basal ganglia and third ventricle. We used 40mm z-axis coverage until November 2005, 80mm z-axis coverage until November 2015 and 120mm z-axis coverage thereafter. CTP images were acquired for 50s in cine mode before January 2011 and in shuttle mode thereafter. Delay was 5-7 s after beginning injection of 50ml of iodinated contrast (Accupaque 300, iohexol 300mg/ml, GE Healthcare, Glattbrugg, Switzerland) in an antecubital vein at a flow rate of 5ml per second followed by 50ml of 0.9% NaCl solution at the same flow rate.

We previously assessed interrater variability using Cohen's kappa on 100 consecutive CT scans of acute anterior circulation occlusive strokes and found an excellent agreement for ASPECTS (kappa 0.82). The use of ASPECTS for core volume estimation was supported by unpublished data from ASTRAL showing a moderate correlation between ASPECTS and core volume on CTP in the presence of LVO and in a late time window (Spearman ρ=-0.58, $p<0.001$). This assumption is in agreement with previous reports (53, 75) and supported by the fact that hypoattenuation on CT was proven highly specific for irreversible ischemic brain damage (93).

We analyzed CTP data using the Brilliance Workspace Portal® (Philips Medical Systems, Cleveland, OH, USA) deconvolution software. The core and penumbra volumes were automatically generated using the appropriate mean transit time (MTT) and cerebral blood volume (CBV) thresholds (penumbra: MTT >145% of the contralateral side value, CBV >2.0 mL/100 g; core: MTT >145% of the contralateral side value, CBV <2.0 mL/100 g) (49). We calculated mismatch ratio (MR) as the ratio of the total ischemic volume (i.e. core plus penumbra volumes) to the core volume.

Statistical Analysis

We calculated the numbers of late EVT eligible patients according to the three sets of selection criteria (DAWN, DEFUSE-3, liberal). We chose the following denominators: A) all AIS patients arriving within 24 hours; B) all late-arriving patients (5-23 hours); C) late-arriving patients with the necessary multimodal imaging available; D) late-arriving patients with emergent LVO. We selected two scenarios: 1) the stroke population arriving at our comprehensive stroke center, 2) the population from the primary catchment area (i.e. patients for whom our institution is the hospital of reference, independently of the need of specialized stroke treatment).

We first performed a univariate comparison of the three groups of eligible patients according to their baseline characteristics. In order to account for correlations between the criteria, we used the method of generalized estimation equations (GEE) (94). This method allows modelling correlated multiple outcomes, using an approach inspired by quasi-likelihood. In our situation, the estimated parameters are odds ratio (OR), quantifying the association between a variable and the probability to satisfy each criterion and ratios of odds ratios (ORR), quantifying the relative strength of the associations.

Then, we performed a multivariate analysis to identify independent variables associated with late EVT eligibility according to trial and liberal criteria. All demographic, clinical and laboratory variables at baseline, as well as pre-stroke treatments and vascular risk factors were included in this analysis. We used a logistic regression model and implemented a variable selection method via backwards elimination of variables with least significant ORs, until all ORs were significant. When needed, we inserted the last eliminated variable back into the model until good calibration was reached. We used non-significance of the Hosmer-Lemeshow test as criterion for good calibration. In all analyses, the level of significance was set at 5%. All analyses were performed with R version 3.4.2 software.

6.1.4 *Results*

Study population

During the observational period, four denominators emerged according to the methods described above: we identified A) 4’653 AIS patients arriving between 0 and 24 hours; B) 1'705 (36.6%) late-arriving (5-23 hours from LPGH) AIS patients; C) 925 (19.9%) late-arriving AIS patients with complete clinical and radiological datasets for investigating eligibility criteria; and D) 221 (4.7%) late-arriving patients with LVO. The flow chart of eligible patients is depicted in Figure 1. Additional information on the population selection process is available in Table 1.

In the main group of interest, C, the median age was 72.3 (IQR=20.5) years, 444 (48.0%) patients were female and median NIHSS on admission was 5 (8). Two hundred and twenty-seven (24.5%) patients were distant referrals, sent from community hospitals or bypassing distant ERs. Other characteristics of group C are shown in Table 2.

Frequency of late EVT eligibility

For DAWN eligibility, 96 patients were excluded for clinical reasons, mainly lower stroke severity on admission (NIHSS<10, n=60) (Figure 1). In addition, 90 patients did not meet the radiological criteria. A small numbers of patients (n=12) did not present the minimal clinical-core mismatch. Finally, only 23 patients were eligible for late EVT according to the DAWN criteria.

When applying the DEFUSE-3 criteria, 60 patients were excluded on a clinical basis. Moreover, approximately half of the patients did not present radiological inclusion criteria, mainly due to the distal site of vascular occlusion (n=48). The required radiological mismatch was absent in 8 patients, leading to 47 eligible patients according to DEFUSE-3 trial criteria. Overall, 52 patients satisfied DAWN and/or DEFUSE trial criteria.

Using our more liberal evaluation, we excluded 42 patients due to clinical reasons, mainly based on higher pre-stroke disability. An additional 42 patients did not exhibit the radiological criteria. We did not find the more liberal clinical-

core mismatch in 34 patients and finally identified 103 eligible patients. Ten of the patients presented a posterior stroke from BA occlusion that we considered eligible.

In the population from the primary catchment area only (n=698), 12 patients were eligible for late EVT based on DAWN criteria, 18 on DEFUSE-3 criteria and 53 with less stringent criteria (Figure 2).

The proportions of late EVT eligibility for the three denominators A, B and C are depicted in Figure 3, shown for the primary catchment area (Figure 3a) and comprehensive (Figure 3b) populations. Among late-arriving patients with complete clinic-radiological assessment (i.e. denominator C) proportions of late EVT eligibility were 2.5% with DAWN, 5.1% with DEFUSE-3 and 11.1% with more liberal criteria. Considering only the primary catchment area, percentages were 1.7%, 2.6% and 7.6%, respectively.

The proportions of late EVT eligibility for patients with emergent LVO (i.e. denominator D) are shown in Figure 4. DAWN criteria would allow treating 10.4% late-arriving patients with LVO, while 21.3% would be eligible according to DEFUSE-3 selection criteria. Adopting our liberal approach, 46.6% of LVO patients would be suitable for late EVT.

Characteristics of the eligible patients

We found a partial overlap between the three eligibility groups. Fifty-two patients fulfilled strict trial criteria (DAWN and/or DEFUSE-3). All but five DAWN-eligible patients were also DEFUSE-3-eligible (18/23, 78.3%) and 18/47 (38.3%) DEFUSE-3-eligible patients were also DAWN-eligible. Among the 103 liberal-criteria patients, 45 fulfilled strict trial criteria. Only seven trial-based patients did not match the liberal criteria; these patients did not present the less stringent clinical-core mismatch but all showed the pure radiological mismatch (Figure 5).

In the univariate comparison of baseline characteristics (Table 3), the two groups of trial-criteria patients appeared similar, except for a higher NIHSS on admission and a higher prevalence of smoking in the DAWN-eligible patients. When comparing the trial and liberal eligible-patients (Table 4), we found the following

radiological differences: trial-based patients presented lower ASPECTS, higher frequency of M1 occlusions, higher core volumes, higher penumbra volumes and higher MR.

Factors associated with late EVT eligibility

Among all late-arriving AIS patients, EVT eligibility based on the strict trial criteria was independently associated with neurological signs such as hemiparesis, visual field defects and eye deviation and with a shorter delay to hospital arrival. The variables implicated in determining EVT eligibility using the more liberal criteria were lower pre-stroke disability, higher NIHSS on admission, eye deviation, hypercholesterolemia and shorter delay to hospital arrival (Table 5).

EVT procedures performed in real life and outcome analysis

Sixty-four patients arriving in the late time window underwent EVT over the study period. Four (6.4%) and 13 (20.3%) treated patients fulfilled the DAWN and DEFUSE-3 criteria, respectively. Thirty-nine of the treated patients (60.9%) complied with the proposed liberal approach. The proportion of late EVT among all revascularization procedures increased from 7% in the 5 years preceding presentation of the DAWN results (May 2017) to 21% after presentation, resulting in a relative increase of 200% in the last eight months of the study period (Figure 6). A favorable outcome was observed at comparable rates in treated patients selected by trial or liberal criteria (67% vs 58% respectively, p=0.49) (Table 5).

6.1.5 *Discussion*

In this study, we performed a single stroke-center analysis to determine the percentage of patients who could benefit from endovascular therapy in the extended time window. We found that the proportion of late EVT eligibility varied greatly according to selection criteria and referral patterns. Among AIS patients admitted late to our comprehensive stroke center and assessed with a multimodal neuroimaging protocol, we found that 2.5% were eligible according to DAWN and 5.1% to DEFUSE-3 criteria. This proportion reached 11.1% applying more liberal

selection criteria. Considering only the local population in the primary catchment area, these percentages dropped to 1.7%, 2.6% and 7.6%, respectively.

A previous study performed in our stroke center reported that 10.5% of all AIS presenting within 6 hours of symptom onset were eligible for EVT according to the AHA/ASA guidelines (21). The frequency of EVT eligibility was higher (17.7%) if less restrictive criteria were adopted. We expected these percentages to be lower in the late-arriving AIS population, mainly because of the strict selection criteria used in the randomized clinical trials, but also because patients with LVO seem to arrive earlier at the hospital (95). Another published study on late EVT eligibility in a stroke center found that 1.7% of all AIS patients qualified for DAWN enrolment and 2.2% for the DEFUSE-3 trial (90). To the best of our knowledge, our study is the first to examine late EVT eligibility in a real-life scenario.

Several factors could contribute to the low eligibility for late EVT in real life. First, a substantial proportion of late-arriving patients were excluded due to lack of complete neuroimaging protocol. In addition to the well-known contraindications to iodinated contrast (allergy, renal impairment), we did not obtain perfusion imaging for a non-negligible number of patients in our CT-based emergency center due to ordering failures or moving patients. Second, we found that approximately two-thirds of late-presenting AIS patients did not meet the clinical inclusion criteria required by the trials, due to age (>85 y), important pre-stroke disability (mRS≥2) or too low NIHSS on admission. Third, late-presenting LVO strokes exhibited commonly larger core volumes than the thresholds (50 and 70 mL) needed for trial eligibility.

As a meaningful finding, we identified an LVO in 23.9% of late-arriving AIS patients. This defines a target subpopulation of stroke patients that should be promptly identified as potentially suitable for revascularization treatment. Our analysis showed that about one out of four late-arriving patients with LVO could be treatable if trial criteria were adopted. The application of more liberal criteria in this population could allow treating up to one out of two patients.

We showed that DEFUSE-3 criteria, including patients with lower NIHSS score, higher pre-stroke disability and larger core volumes allowed enrolling a higher

proportion of patients compared to the DAWN trial. As a result, all DAWN eligible patients, except for those >85 y were also DEFUSE-3 eligible in our cohort. Taken together, patients satisfying criteria of at least one of the two trials, DAWN and/or DEFUSE-3, extended EVT eligibility to 5.6% (n=52/925) of late AIS patients admitted to our comprehensive center. Our proposed more liberal selection criteria, characterized by lower NIHSS on admission and a mRS of up to 2, extended EVT eligibility to twice as many patients. Moreover, using ASPECTS for core volume estimations, the liberal approach seems more feasible in the real word clinical practice.

In our study, eligible patients according to trial criteria were best identified using clinical factors, including hemiparesis, visual field defects and eye deviation. As predictors of liberal eligibility, we confirmed eye deviation, but also found hypercholesterolemia and the expected lower pre-stroke disability and higher admission NIHSS. In keeping with infarct growth over time (96) and the usual associated reduction of salvageable tissue, we found that delay from stroke onset (or LPGH) to hospital arrival predicts lower eligibility according to both trial and liberal criteria. Despite the fact that carefully selected late and unknown onset patients have major benefit from recanalization (18-20), “time is still brain” both in the pre- and intra-hospital phase.

Although the number of late-treated patients in our center is insufficient for an appropriately adjusted clinical outcome analysis, we showed a similar rate of favorable outcome in late-treated patients satisfying strict or liberal criteria. This finding might indicate that a proportion of trial-ineligible patients may still benefit from late treatments if less stringent criteria are used, as recently suggested (97, 98). Moreover, data from EVT-treated patients in earlier phases (up to 8 hours from onset) showed that revascularization therapy was still associated with favorable clinical outcome in the presence of higher core volumes (i.e. ASPECTS ≤5 on DWI)(99). Similarly, it has been demonstrated that patients not fulfilling guideline criteria for EVT within 6 hours after onset still benefit from mechanical thrombectomy, even in cases exceeding recommendations for onset-to-groin

puncture time (100). These studies might support a progressive widening of EVT selection criteria in the late time window.

Our study could have several and significant implications for triage, resource allocation and hospital referral re-organization in order to maximize patient selection for mechanical thrombectomy in the extended time-window. The higher frequency of patients who could receive late EVT in the comprehensive stroke center compared to the local catchment area shows that endovascular-capable centers need to develop emergency medical services and close collaborations with referral facilities in order to deliver advanced treatments. Moreover, we observed a large increase in registered late EVT procedures after presentation of the DAWN results, suggesting that recanalization procedures could be implemented rapidly and successfully in clinical practice.

Strengths of our monocentric study are the large number of AIS patients with a thorough, homogeneous workup and the consecutive availability of patients with advanced acute neuroimaging since 2003.

Our study has several limitations, mainly due to its retrospective and single center nature. First, eligibility in our wider catchment area might be not entirely representative because of fewer referrals before the presentation of the DAWN results; still, our analysis of the primary catchment area should correct for this error. Moreover, advanced neuroimaging information, especially regarding perfusion imaging of referred patients, was not available for a minority (n=373, 21.9%) of late-arriving AIS patients and this likely underestimated the proportion of patients with late-EVT criteria. Regarding the neuroimaging protocol, we included only AIS patients with CT-based assessment of core and penumbra volumes due to the small number of MRI-assessed patients in the ASTRAL registry (n=42, 0.05% of late-arriving population); therefore we were not able to investigate the imaging modality differences on eligibility and outcome analyses. In addition, the threshold model used for core and penumbra volume reconstructions was different from those adopted in the CT arms of the recent EVT trials (15), which may affect the evaluation of the DAWN and DEFUSE-3 criteria in the clinical practice. Even if not validated in a clinical trial setting, it is a

well-established model, based on a systematic evaluation of all PCT parameters (49). Finally, our number of treated patients is too small for meaningful interpretation and therefore, outcome analysis results should be considered with caution.

In conclusion, in our comprehensive stroke center, depending on inclusion criteria used (trial vs liberal), 5.6 to 11.1% of late treatable AIS patients with complete neuroimaging protocols may be eligible for revascularization procedures. This translates to 23.5% and 46.6% of late-arriving AIS patients with LVO admitted to our institution, respectively. Overall, we demonstrated that by applying a more liberal approach than strict trial criteria, EVT could be offered to twice as many patients. We should invest effort to re-organize stroke care systems and achieve comparable rates in real life.

6.1.6 *Tables and Figures*

Table 1 Reasons for lack of CTA and CTP data in our comprehensive stroke centre.

Table 2 Demographics, clinical and radiological characteristics of AIS patients admitted late (5-23 hours after LPGH) to our comprehensive stroke centre (from 2003-2017) with complete multimodal CT-based neuroimaging protocols (n=925). We express values as medians and interquartile rage (IQR) for continuous variables and absolute counts and percentages for categorical variables.

Table 3 Demographics, clinical and radiological characteristics of patients eligible for late EVT according to DAWN and DEFUSE-3 criteria. We report results from the univariate comparison between DAWN and DEFUSE-3 eligible patients as ORR and their 95%CI.

Table 4 Demographics, clinical and radiological characteristics of patients eligible for late EVT according to trial (DAWN and/or DEFUSE-3) and liberal criteria. We

present results from the univariate analysis between trial and liberal-eligible patients as ORR and their 95%CI.

Table 5 Independent predictors for late EVT eligibility according to trial and liberal criteria in late arriving AIS patients (n=925) are presented. Only significant results are shown. The model for liberal eligibility also included the variables, known onset, statin use, smoking and systolic blood pressure on admission; they were included to obtain a good calibration of the model according to the Hosmer-Lemeshow test. The time unit for LPGH-to-arrival time is 30 minutes.

Figure 1 Flow chart eligibility in our comprehensive stroke center. First, we identified four denominators: A) total number of AIS patients admitted to our institution between 0 and 24 hours over the study period; B) the number of AIS patients admitted late (5-23 hours);C) the number of late AIS patients with complete datasets; and D) late-arriving patients with emergent LVO. Secondly, we applied the DAWN criteria, DEFUSE-3 criteria and more liberal selection criteria to identify AIS patients eligible for late EVT accordingly. *see Table 1 for additional information about radiological exclusion criteria.

Figure 2 Flow diagram of eligibility in our primary catchment area. We identified four denominators for eligibility assessment: A) total AIS patients admitted to our stroke unit from 0-24 hours; B) the number of AIS patients admitted late (5-23 hours); C) the number of late AIS patients with complete datasets and D) the late-arriving patients with emerging LVO. Then, we applied DAWN, DEFUSE-3 criteria and our more liberal selection criteria to identify the AIS patients accordingly eligible for late EVT.

Figure 3 Proportion of AIS patients eligible for late EVT according to DAWN, DEFUSE-3 and more liberal criteria from all AIS patients admitted in the first 24 hours of LPGH, patients admitted late (5-23 hours) and patients admitted late

with complete neuroimaging protocols. The data refers to our primary catchment area (a) and our comprehensive stroke center (b).

Figure 4. Proportions of EVT eligible patients among: 1) late-arriving patients with large vessel occlusion (LVO) admitted to our comprehensive stroke centre (SC) and 2) late-arriving patients with LVO referred by our the primary catchment area (stroke unit, SU). We found different proportions according to the selection criteria applied, i.e. liberal (in green), DEFUSE-3 (blue) and DAWN (red).

Figure 5 DAWN (n=23, in red), DEFUSE-3 (n=47, in green) and liberal (n=103, in blue) late EVT-eligible patients in our late-arriving AIS population. Circles show the partial overlaps between the three groups of patients: 52 patients fulfilled DAWN and/or DEFUSE-3 criteria whereas 45 liberal patients also matched trial criteria. All but 5 DAWN-eligible patients were also DEFUSE-3-eligible, and 18/47 (38.3%) DEFUSE-3-eligible patients were also DAWN eligible. Only seven trial-eligible patients did not present the liberal criteria.

Figure 6. Number of acute endovascular treatments (EVT) for acute ischemic stroke performed in our comprehensive stroke centre from 2007 to 2017. The columns indicate the annual numbers of real EVT procedures of different strategies and timing: EVT performed in the first 6 hours after LPGH (red), intravenous thrombolysis (IVT) bridged with EVT in the first 6 hours after LPGH (violet) and EVT performed between 6 and 24 hours after LTSW. We observed a global increase in the number of patients treated by EVT at any time and in particular, a large increase in the number of patients treated with late EVT. The proportion of effective late EVT increased from 7% (38/536) in the 5 years prior to DAWN results (May 2017) to 21% (17/78) after DAWN results, resulting in a global increase of 200% in the last eight months of the study period.

Table 1.

Reason	Patients (n)
No CT-based imaging protocol performed <24h after LPGH	**148**
• Performed after 24 hours	106
• MRI only-based imaging	42
Acute CTA not available	**250**
• Other acute vascular exam	38
• Vascular imaging performed after 24 h	196
• Insufficient quality CTA	16
Good quality CTP not available	**373**
• Acute CTP not done	327
– Allergy/renal reasons	7
– Thought to be vertebro-basilar	155
– Not requested by physician	120
– Not attempted due to movement	18
– Other reasons	27
• Technical failure	31
• Uninterpretable from movement	3
• No reconstructions available	12

Table 2.

Variable	Included patients (n=925)
Age, y	72.3 (20.5)
Sex, F	444 (48.0%)
Pre-stroke mRS	0 (1)
Referrals	227 (24.5%)
Stroke characteristics	
NIHSS on admission	5 (8)
Visual field defects	275 (29.7%)
Aphasia	288 (31.1%)
Neglect	177 (19.1%)
Vigilance impairment	105 (11.4%)
Unwitnessed stroke onset	635 (68.6%)
Wake-up stroke	495 (53.5%)
Daytime unknown onset	140 (15.1%)
Process measures	
LPGH-to-arrival time, min	695 (435)
LPGH-to-CT time, min	823 (485)
Pre-stroke treatments	
Antiplatelet	305 (33.0%)
Anticoagulation	99 (10.7%)
Anti-hypertensive	510 (55.1%)
Statin	256 (27.7%)
Vascular risk factors	
Hypertension	567 (61.3%)
Diabetes	149 (16.1%)
Hyperlipidaemia	359 (38.8%)
Current smoking	250 (27.0%)
Baseline clinical measurements	
Body temperature (°C)	36.4 (0.8)
Systolic Blood Pressure (mmHg)	154 (35)
Diastolic Blood Pressure (mmHg)	84 (21)
Laboratory studies	
Blood glucose (g/L)	6.4 (2.0)
Radiological variables	
ASPECTS	10 (2)
ICA, M1 and/or proximal M2 occlusion	206 (22.3%)
BA occlusion	15 (1.6%)
No hypoperfusion on CTP	337 (36.4%)

Infarct volume, mL	2.7 (29)°
Penumbra volume, mL	19.5 (79)°
Good collaterals	90 (43.6%)*
TOAST Mechanism	
Atherosclerotic	119 (12.9%)
Cardioembolism	254 (27.5%)
ESUS	137 (14.8%)
Real EVT	
Late EVT performed	48 (5.2%)
LPGH-groin puncture, min	688 (420)

° indicates that the median infarct and penumbra volumes refer to the 588 patients with a hypoperfusion lesion on CTP.

* indicates that the collateral grades refer to the 206 patients with ICA and/M1 and/or proximal M2 occlusion on CTA.

Table 3.

Variable	DAWN eligible (n=23)	DEFUSE-3 eligible (n=47)	ORR (95% CI) DAWN / DEFUSE-3
Age, y	68.2 (20.4)	66.6 (21.5)	1.01 (0.98 - 1.02)
Sex, F	14 (60.9%)	28 (59.6%)	1.04 (0.48 - 2.25)
Pre-stroke mRS	0 (1)	0 (1)	0.98 (0.72 - 1.35)
Stroke characteristics			
NIHSS on admission	16 (5)	15 (8)	**1.02 (1.01 - 1.04)***
Visual field defects	16 (69.6%)	33 (70.2%)	0.92 (0.4 - 2.11)
Aphasia	10 (43.5%)	24 (51.1%)	0.71 (0.34 - 1.48)
Neglect	11 (47.8%)	19 (40.4%)	1.32 (0.63 - 2.74)
Vigilance impairment	5 (21.7%)	8 (17.0%)	1.35 (0.67 - 2.73)
Wake-up stroke	16 (69.6%)	27 (57.5%)	1.71 (0.80 - 3.63)
Process measures			
LPGH-to-arrival time, min	646 (327)	560 (299)	1.03 (0.99 - 1.07)
LPGH-to-CT time, min	747 (353)	603 (295)	1.01 (0.99 - 1.04)
Pre-stroke treatments			
Antiplatelet	6 (26.1%)	15 (31.9%)	0.75 (0.33 - 1.69)
Anticoagulation	4 (17.4%)	6 (12.8%)	1.45 (0.57 - 3.66)
Anti-hypertensive	11 (47.8%)	25 (54.4%)	0.77 (0.38 - 1.56)
Statin	5 (21.7%)	14 (30.4%)	0.63 (0.27 - 1.43)
Vascular risk factors			
Hypertension	13 (56.5%)	26 (55.3%)	1.06 (0.52 - 2.16)
Diabetes	1 (4.4%)	5 (10.6%)	0.38 (0.06 - 2.31)
Hyperlipidaemia	8 (34.8%)	20 (43.5%)	0.68 (0.33 - 1.41)
Current smoking	7 (30.4%)	9 (19.6%)	**1.84 (1.03 - 3.31)***
Radiological variables			
ASPECTS	8 (0.5)	8 (2.5)	0.96 (0.90 - 1.03)
ICA occlusion	10 (43.5%)	13 (27.7%)	1.96 (0.90 - 4.27)
M1 occlusion°	18 (78.3%)	41 (87.2%)	0.42 (0.17 - 1.07)
Infarct volume, mL	9.1 (11.3)	17 (32.6)	0.79 (0.62 - 1.01)
Penumbra volume, mL	114.6 (81.05)	108 (53.6)	0.96 (0.90 - 1.02)
MR	8.26 (17.53)	7.52 (17.3)	0.99 (0.98 - 1.01)
Good collaterals	7 (31.82%)	16 (37.2%)	0.69 (0.31 - 1.57)
TOAST Mechanism			
Atherosclerotic	4 (18.2%)	9 (20.5%)	0.85 (0.32 - 2.27)
Cardioembolism	8 (36.4%)	21 (47.7%)	0.60 (0.28 - 1.29)
Real EVT			
Late EVT performed	4 (17.4%)	13 (27.7%)	0.45 (0.15 - 1.32)
LPGH-groin puncture, min	501 (205)	641 (146)	0.91 (0.73 - 1.12)
Favourable outcome			

In all patients	9 (40.9%)	24 (53.3%)	0.61 (0.29 - 1.31)
In patients with EVT	1/3 (33.3%)	8/11 (72.7%)	0.14 (0.01 - 1.81)

*Denotes significant results. °Means with or without more proximal occlusion.

Table 4.

Variable	Trial-eligible group (n=52)	Liberal-eligible group (n=103)	ORR (95% CI) Trials / Liberal
Age, y	67.7 (22.6)	72.3 (22.0)	0.99 (0.98 – 1.00)
Sex, F	29 (55.6%)	53 (51.5%)	1.19 (0.75 – 1.89)
Pre-stroke mRS	0 (1)	0 (1)	0.89 (0.72 – 1.11)
Stroke characteristics			
NIHSS on admission	15 (8)	15 (9)	0.98 (0.96 – 1.00)
Visual field defects	35 (67.3%)	64 (62.1%)	1.11 (0.67 - 1.85)
Aphasia	27 (51.9%)	53 (52.0%)	0.93 (0.59 - 1.49)
Neglect	22 (42.3%)	37 (36.6%)	1.20 (0.76 - 1.89)
Vigilance impairment	8 (15.4%)	24 (23.5%)	0.52 (0.26 - 1.04)
Wake-up stroke	32 (61.5%)	55 (53.4%)	1.43 (0.88 - 2.33)
Process measures			
LPGH-to-arrival time, min	577 (316)	526 (363)	1.01 (0.97 - 1.04)
LPGH-to-CT time, min	615 (304)	587 (379)	1.08 (1.00 – 1.15)
Pre-stroke treatments			
Antiplatelet	16 (30.8%)	34 (33.0%)	0.89 (0.54 - 1.47)
Anticoagulation	7 (13.5%)	9 (8.7%)	1.69 (0.94 - 3.03)
Anti-hypertensive	27 (52.9%)	56 (55.5%)	0.90 (0.56 - 1.43)
Statin	14 (27.5%)	27 (26.7%)	1.04 (0.62 - 1.75)
Vascular risk factors			
Hypertension	30 (57.7%)	60 (58.8%)	0.96 (0.60 - 1.54)
Diabetes	5 (9.6%)	16 (15.7%)	0.56 (0.25 - 1.23)
Hyperlipidaemia	20 (39.2%)	45 (44.6%)	0.78 (0.48 - 1.27)
Current smoking	9 (17.7%)	23 (22.6%)	0.74 (0.38 - 1.41)
Radiological variables			
ASPECTS	8 (2)	9 (2)	**0.93 (0.87 - 0.99)***
ICA occlusion	16 (30.1%)	25 (24.3%)	1.20 (0.69 - 2.13)
M1 occlusion°	44 (84.6%)	56 (54.4%)	**4.17 (2.04 - 9.09)***
Proximal M2 occlusion°	37 (71.1%)	68 (66.0%)	1.01 (0.58 - 1.74)
BA occlusion	0 (0%)	10 (9.7%)	NA
Infarct volume, mL	16.1 (32.8)	13.4 (39.0)	**1.07 (1.02 - 1.11)***
Penumbra volume, mL	106.5 (61.6)	90.5 (84.6)	**1.06 (1.02 - 1.10)***
MR	6.0 (17.1)	4.3 (15.5)	**1.01 (1.01 - 1.02)***
Good collaterals	17 (36.1%)	33 (34.4%)	0.82 (0.47 - 1.43)
TOAST Mechanism			
Atherosclerotic	10 (20.4%)	16 (16.3%)	1.32 (0.69 - 2.56)
Cardioembolism	22 (44.9%)	44 (44.9%)	0.95 (0.58 - 1.54)
Undetermined (incl. ESUS)	13 (26.5%)	29 (29.6%)	0.83 (0.48 - 1.45)
Real EVT			

Late EVT performed	14 (26.9%)	27 (26.2%)	1.49 (0.76 - 2.92)
LPGH-to-groin puncture, min	643 (145)	641 (300)	1.03 (0.97 - 1.10)
Favourable outcome			
In all patients	25 (50.0%)	48 (48.0%)	1.20 (0.74 – 1.96)
In patients with EVT	8/12 (66.7%)	14/24 (58.3%)	2.04 (0.39 – 11.1)

*Denotes significant results. °Means with or without more proximal occlusion.

Table 5.

Predictors	Trial (DAWN and/or DEFUSE-3) eligibility		*Liberal* eligibility	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Pre-stroke mRS	-	-	0.64 (0.48-0.86)	<0.01
Hypercholesterolemia	-	-	2.79 (1.43-5.46)	<0.01
NIHSS	-	-	1.12 (1.07-1.16)	<0.01
Eye Deviation	2.94 (1.44-6.01)	<0.01	2.06 (1.08-3.92)	0.03
Visual field defects	2.75 (1.32-5.70)	0.01	-	-
Hemiparesis	4.72 (1.10-20.30)	0.04	-	-
LPGH-to-arrival time	0.95 (0.91-0.98)	<0.01	0.94 (0.91-0.97)	<0.01

Figure 1.

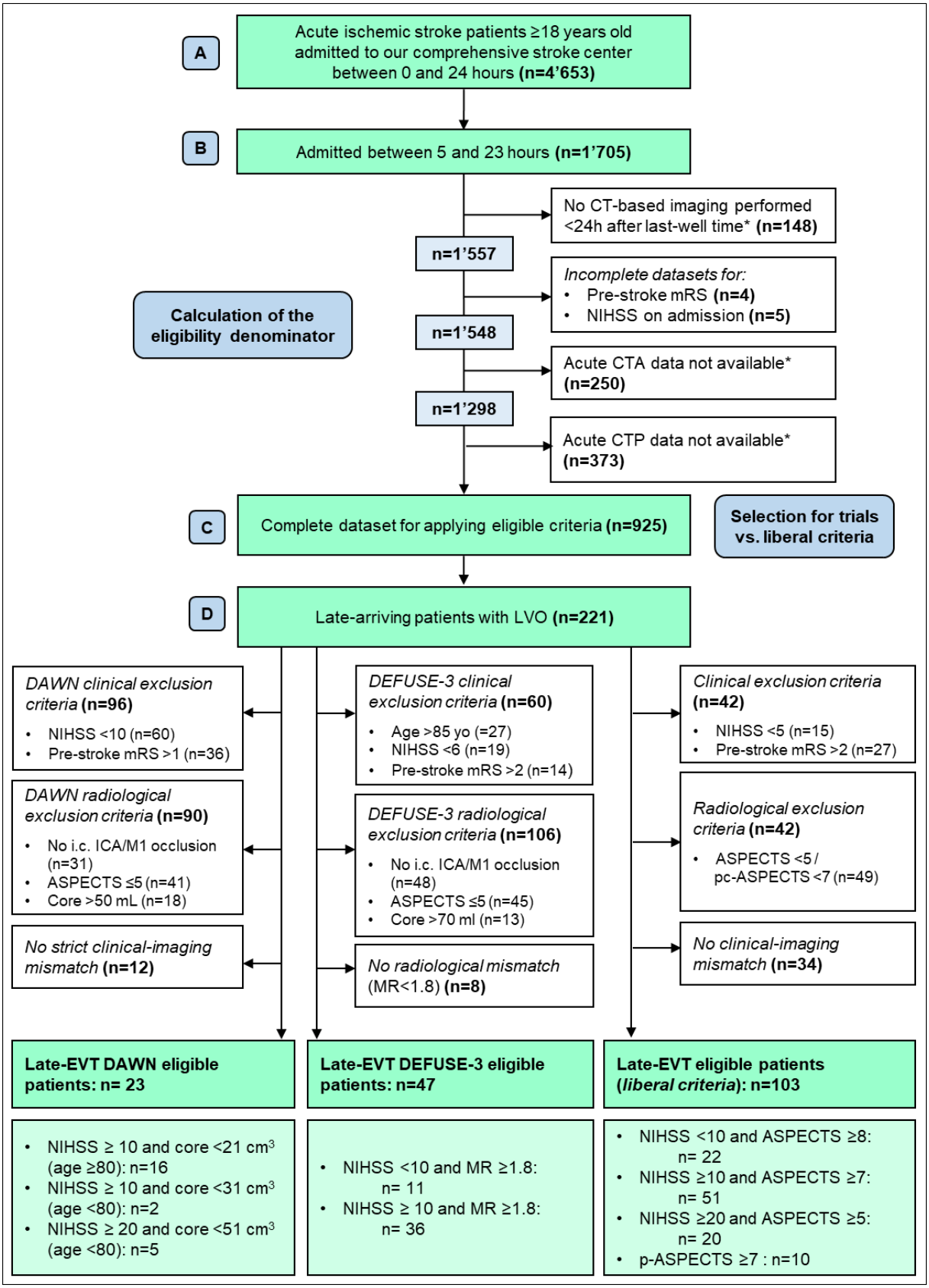

A
Acute ischemic stroke patients ≥18 years old admitted to our comprehensive stroke center between 0 and 24 hours (n=4'653)
B
Admitted between 5 and 23 hours (n=1'705)
No CT-based imaging performed <24h after last-well time* (n=148)
n=1'557
Incomplete datasets for:
• Pre-stroke mRS (n=4)
• NIHSS on admission (n=5)
Calculation of the eligibility denominator
n=1'548
Acute CTA data not available* (n=250)
n=1'298
Acute CTP data not available* (n=373)
C
Complete dataset for applying eligible criteria (n=925)
Selection for trials vs. liberal criteria
D
Late-arriving patients with LVO (n=221)
DAWN clinical exclusion criteria (n=96)
• NIHSS <10 (n=60)
• Pre-stroke mRS >1 (n=36)
DEFUSE-3 clinical exclusion criteria (n=60)
• Age >85 yo (=27)
• NIHSS <6 (n=19)
• Pre-stroke mRS >2 (n=14)
Clinical exclusion criteria (n=42)
• NIHSS <5 (n=15)
• Pre-stroke mRS >2 (n=27)
DAWN radiological exclusion criteria (n=90)
• No i.c. ICA/M1 occlusion (n=31)
• ASPECTS ≤5 (n=41)
• Core >50 mL (n=18)
DEFUSE-3 radiological exclusion criteria (n=106)
• No i.c. ICA/M1 occlusion (n=48)
• ASPECTS ≤5 (n=45)
• Core >70 ml (n=13)
Radiological exclusion criteria (n=42)
• ASPECTS <5 / pc-ASPECTS <7 (n=49)
No strict clinical-imaging mismatch (n=12)
No radiological mismatch (MR<1.8) (n=8)
No clinical-imaging mismatch (n=34)
Late-EVT DAWN eligible patients: n= 23
Late-EVT DEFUSE-3 eligible patients: n=47
Late-EVT eligible patients (liberal criteria): n=103
• NIHSS ≥ 10 and core <21 cm3 (age ≥80): n=16
• NIHSS ≥ 10 and core <31 cm3 (age <80): n=2
• NIHSS ≥ 20 and core <51 cm3 (age <80): n=5
• NIHSS <10 and MR ≥1.8: n= 11
• NIHSS ≥ 10 and MR ≥1.8: n= 36
• NIHSS <10 and ASPECTS ≥8: n= 22
• NIHSS ≥10 and ASPECTS ≥7: n= 51
• NIHSS ≥20 and ASPECTS ≥5: n= 20
• p-ASPECTS ≥7 : n=10

Figure 2.

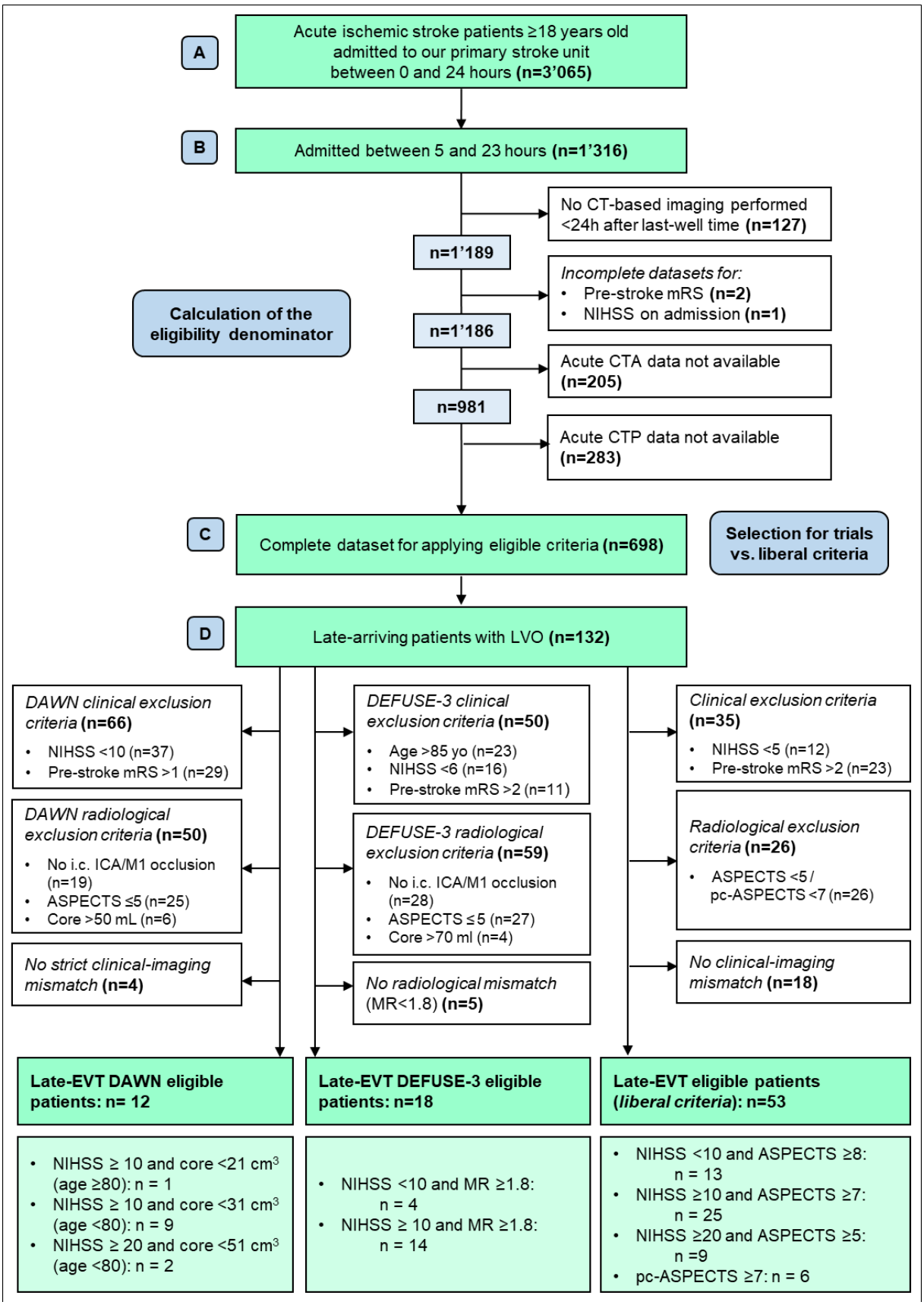

A
Acute ischemic stroke patients ≥18 years old admitted to our primary stroke unit between 0 and 24 hours (n=3'065)
B
Admitted between 5 and 23 hours (n=1'316)
No CT-based imaging performed <24h after last-well time (n=127)
n=1'189
Incomplete datasets for:
• Pre-stroke mRS (n=2)
• NIHSS on admission (n=1)
Calculation of the eligibility denominator
n=1'186
Acute CTA data not available (n=205)
n=981
Acute CTP data not available (n=283)
C
Complete dataset for applying eligible criteria (n=698)
Selection for trials vs. liberal criteria
D
Late-arriving patients with LVO (n=132)
DAWN clinical exclusion criteria (n=66)
• NIHSS <10 (n=37)
• Pre-stroke mRS >1 (n=29)
DEFUSE-3 clinical exclusion criteria (n=50)
• Age >85 yo (n=23)
• NIHSS <6 (n=16)
• Pre-stroke mRS >2 (n=11)
Clinical exclusion criteria (n=35)
• NIHSS <5 (n=12)
• Pre-stroke mRS >2 (n=23)
DAWN radiological exclusion criteria (n=50)
• No i.c. ICA/M1 occlusion (n=19)
• ASPECTS ≤5 (n=25)
• Core >50 mL (n=6)
DEFUSE-3 radiological exclusion criteria (n=59)
• No i.c. ICA/M1 occlusion (n=28)
• ASPECTS ≤ 5 (n=27)
• Core >70 ml (n=4)
Radiological exclusion criteria (n=26)
• ASPECTS <5 / pc-ASPECTS <7 (n=26)
No strict clinical-imaging mismatch (n=4)
No radiological mismatch (MR<1.8) (n=5)
No clinical-imaging mismatch (n=18)
Late-EVT DAWN eligible patients: n= 12
Late-EVT DEFUSE-3 eligible patients: n=18
Late-EVT eligible patients (liberal criteria): n=53
• NIHSS ≥ 10 and core <21 cm3 (age ≥80): n = 1
• NIHSS ≥ 10 and core <31 cm3 (age <80): n = 9
• NIHSS ≥ 20 and core <51 cm3 (age <80): n = 2
• NIHSS <10 and MR ≥1.8: n = 4
• NIHSS ≥ 10 and MR ≥1.8: n = 14
• NIHSS <10 and ASPECTS ≥8: n = 13
• NIHSS ≥10 and ASPECTS ≥7: n = 25
• NIHSS ≥20 and ASPECTS ≥5: n =9
• pc-ASPECTS ≥7: n = 6

Figure 3.

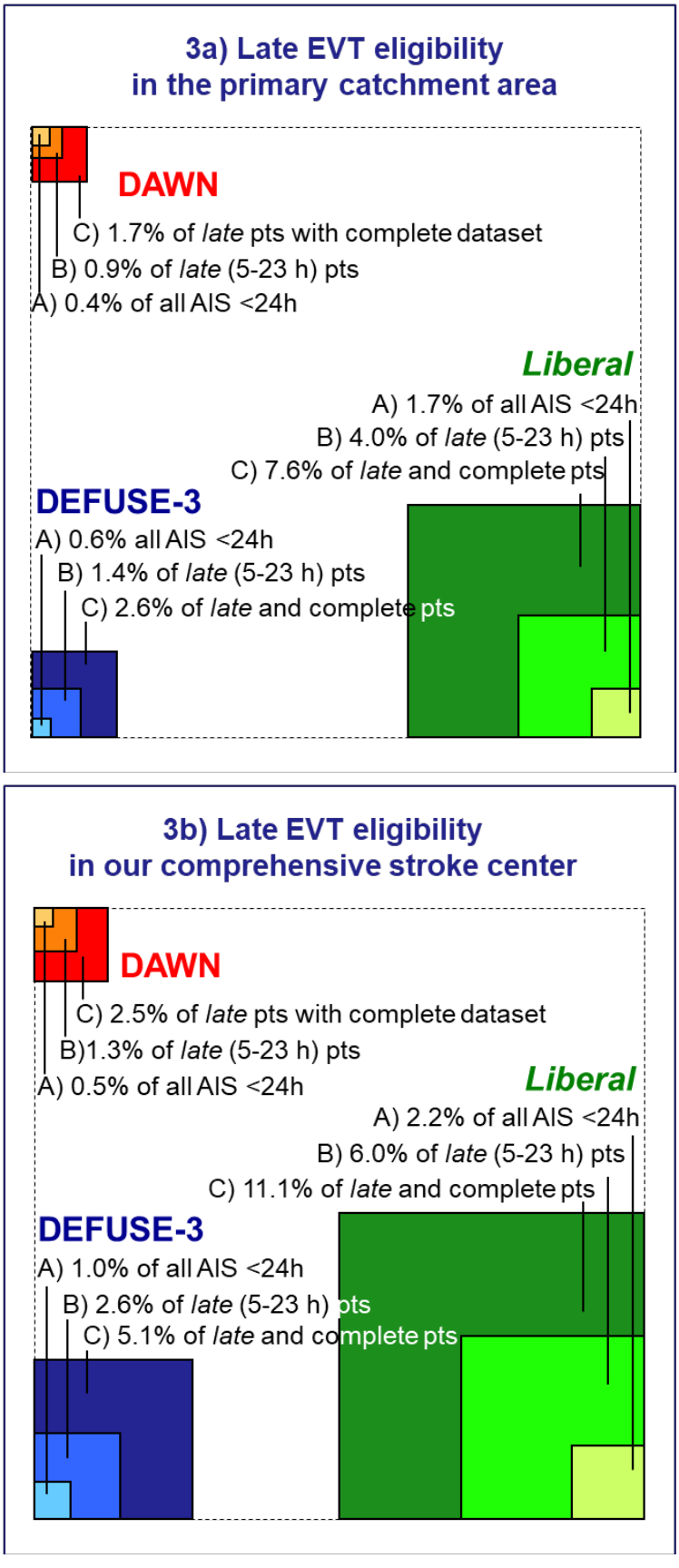

3a) Late EVT eligibility
in the primary catchment area
DAWN
C) 1.7% of late pts with complete dataset
B) 0.9% of late (5-23 h) pts
A) 0.4% of all AIS <24h
Liberal
A) 1.7% of all AIS <24h
B) 4.0% of late (5-23 h) pts
C) 7.6% of late and complete pts
DEFUSE-3
A) 0.6% all AIS <24h
B) 1.4% of late (5-23 h) pts
C) 2.6% of late and complete pts
3b) Late EVT eligibility
in our comprehensive stroke center
DAWN
C) 2.5% of late pts with complete dataset
B)1.3% of late (5-23 h) pts
A) 0.5% of all AIS <24h
Liberal
A) 2.2% of all AIS <24h
B) 6.0% of late (5-23 h) pts
C) 11.1% of late and complete pts
DEFUSE-3
A) 1.0% of all AIS <24h
B) 2.6% of late (5-23 h) pts
C) 5.1% of late and complete pts

Figure 4.

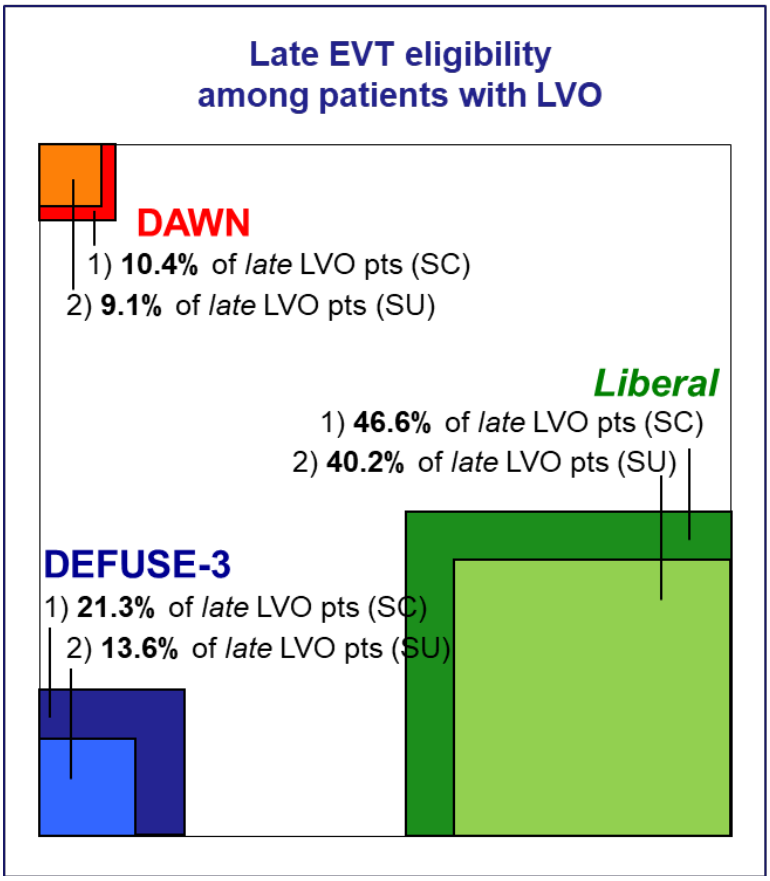

Late EVT eligibility
among patients with LVO
DAWN
1) 10.4% of late LVO pts (SC)
2) 9.1% of late LVO pts (SU)
Liberal
1) 46.6% of late LVO pts (SC)
2) 40.2% of late LVO pts (SU)
DEFUSE-3
1) 21.3% of late LVO pts (SC)
2) 13.6% of late LVO pts (SU)

Figure 5.

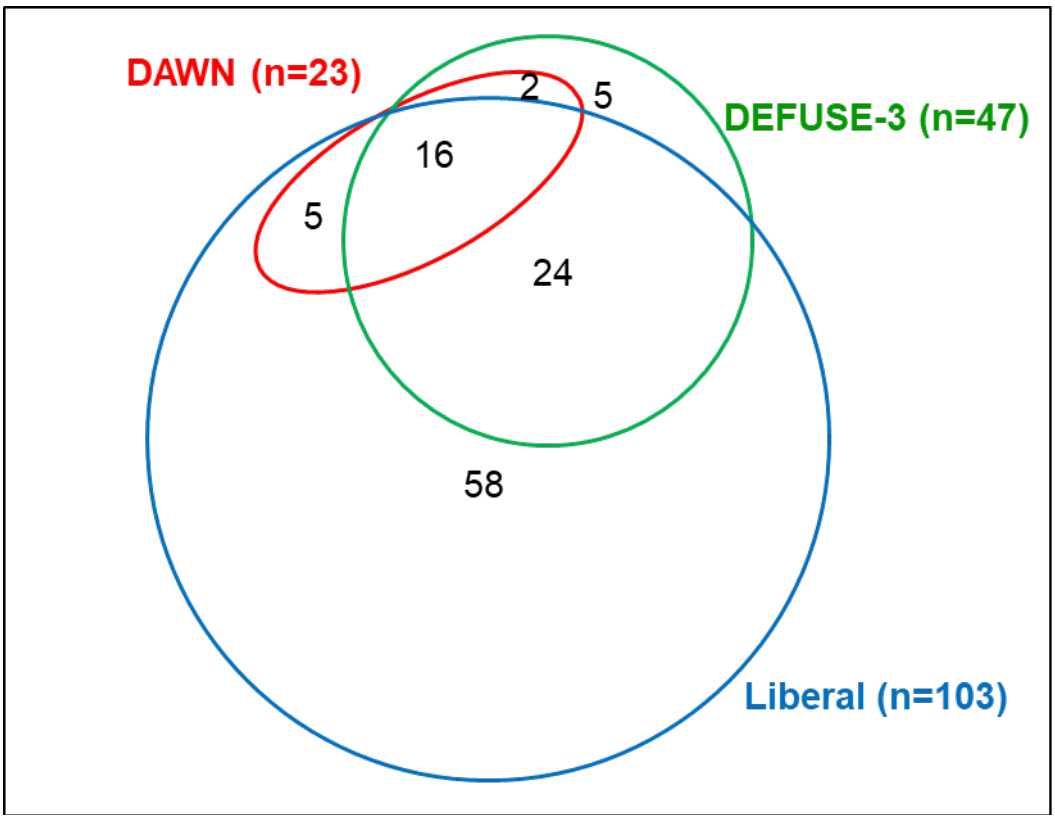
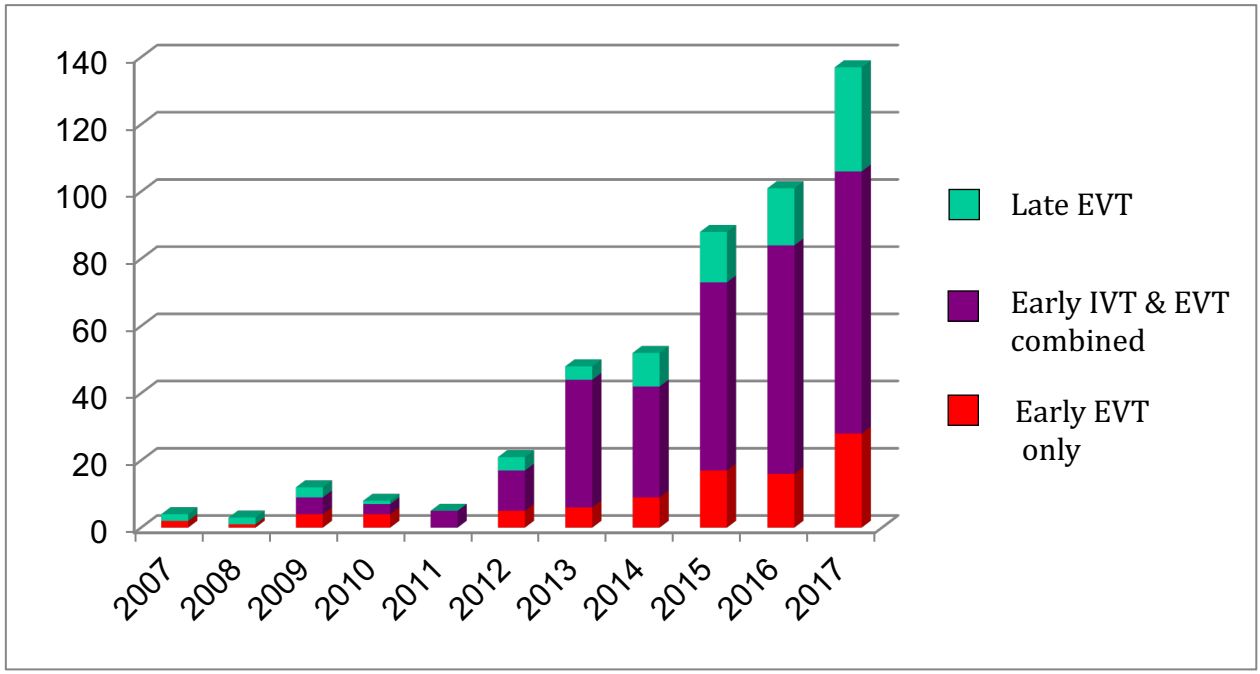


Figure 6.


140
120
100
80
60
40
20
0
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Late EVT
Early IVT & EVT combined
Early EVT only

6.2 ASPECTS-based selection for late endovascular treatment: experience from two Swiss stroke centers

6.2.1 *Abstract*

Introduction

The DAWN trial demonstrated the effectiveness of late endovascular treatment (EVT) in acute ischemic stroke (AIS) patients selected on the basis of a clinical-core mismatch. We retrospectively explored if a clinical-APECTS mismatch was associated with clinical benefit after late EVT.

Methods

We reviewed all consecutive AIS patients admitted 6-24 hours after last proof of good health (LPGH) in two stroke centers, with admission NIHSS≥10 and internal carotid artery or M1 occlusion. We defined liberal patients in the presence of clinical-ASPECTS mismatch (NIHSS≥10 and ASPECTS≥7; or NIHSS≥20 and ASPECTS≥5). We assessed the effect of late EVT in the clinical-ASPECTS mismatch positive and negative groups, using ordinal shift analysis of the 3 months modified Rankin Scale (mRS), and adjusting for several confounders.

Results

The included 337 patients had a median age of 73 years (IQR=61-82), admission NIHSS of 18 (15-22) and baseline ASPECTS of 7 (5-9). Out of 196 (58.2%) liberal patients, late EVT was performed in 146 (74.5%) patients. Among 141 (41.8%) non-liberal patients, 72 (51.1%) patients received EVT. In the adjusted analysis, late EVT was associated significantly with better outcome in the presence of clinical-ASPECTS mismatch (adjusted Odd Ratio, aOR=2.83; 95% confidence interval, CI: 1.48-5.58) but not in its absence (aOR=1.32; 95%CI: 0.61-2.84) (p-value for the interaction term between liberal criteria and late EVT=0.073).

Conclusions

In our exploratory multicenter analysis, late EVT seems effective in the presence of a clinical-ASPECTS mismatch, but not in its absence. If confirmed in

randomized trials, this finding could support the use of an ASPECTS-based selection for late EVT decisions, obviating the need for advanced imaging.

6.2.2 *Background*

Recent randomized clinical trials have provided class I evidence for the efficacy of endovascular treatment (EVT) in acute ischemic stroke (AIS) patients from anterior proximal occlusion in the late-time window, if properly selected based on their neuroimaging profile (18, 19, 101). However, we previously demonstrated that the proportion of late-admitted AIS eligible for EVT according to strict clinical trial criteria was low in the real-life scenario (86).

Enlarging the selection criteria for late EVT could allow a larger population of AIS patients to benefit from the revascularization procedures. Notably, the use of a simpler neuroimaging protocol could help with the decision to proceed with mechanical thrombectomy in case of absent, failed or contraindicated advanced imaging, or in situations of discordant imaging profile (74).

The Alberta Stroke Program Early CT Score (ASPECTS) is an easily applicable tool to estimate the amount of irreversibly damaged brain tissue in the middle cerebral artery (MCA) territory strokes (63). Originally designed for non-contrast CT scan (NCCT), it has been also applied to diffusion-weighted imaging (DWI) sequences, after adjustment (102). However, the role of ASPECTS in selecting patients who are most likely to benefit from EVT is not clearly established in the late time window (67, 68). Also, to the best of our knowledge, its use in association of clinical stroke severity as a surrogate of the core-penumbra mismatch (18) has not been evaluated.

The main aim of our study was to analyze the clinical outcome of late-arriving AIS patients with anterior LVO depending on the presence of a clinical-ASPECTS mismatch and of treatment with mechanical thrombectomy in two comprehensive stroke centers.

6.2.3 *Methods*

Study design and study population

We performed a retrospective analysis of consecutive AIS patients who received mechanical thrombectomy in the late time window in the comprehensive stroke centers of Lausanne and Berne University Hospitals from January 2010 to December 2018. Data were extracted from the prospectively constructed stroke registry of each institution, whose details have been previously published (29, 103).

For the current analysis, we adopted the following inclusion criteria: anterior circulation stroke with large vessel occlusion (LVO; i.e. occlusion of intracranial internal carotid artery, and/or M1 segment of the MCA); NIHSS on admission ≥10; mechanical thrombectomy started between 6 and 24 since last proof of good health (LPGH); and availability of 3-months functional status, assessed with the modified Rankin scale (mRS).

EVT guidelines have evolved during the study period. EVT was performed till 2014 if treatment could be initiated within 6 hours, NIHSS was ≥6, CTA disclosed a proximal intracranial vessel occlusion (104, 105) and CT-perfusion (CTP) showed > 50% of penumbra in anterior circulation strokes. Later arriving patients and unknown onset patients were treated in selected cases if CTP showed >50% penumbra and informed consent was available. Since 10/2014, CTP criteria were replaced by ASPECTS ≥5 and lower NIHSS limit was replaced by the presence of a disabling deficit (106), similar to the European criteria (107). Since May 2017, patients were treated with the same criteria but up to 8 hours (108). After 8 hours, treatment was offered with modified DAWN criteria, i.e. in the presence of an NIHSS ≥10 and ASPECTS ≥7, or if stroke was disabling, NIHSS was 1-10, and ASPECTS was ≥8 (109, 110). Since January 2018, late treatment was alternatively based on any NIHSS, core <70 mL and mismatch ratio ((penumbra + core)/core) >1.8, according to DEFUSE-3 criteria, and in accordance with European (70) and American recommendations (101).

For the current analysis, we defined “clinical-ASPECTS mismatch” as the presence of NIHSS ≥10 combined with ASPECTS ≥7 or NIHSS ≥20 associated

with ASPECTS ≥5. The ASPECTS was visually scored on the first unenhanced neuroimaging modality (NCCT or DWI) obtained on admission. The clinical-ASPECTS definition was inspired by the clinical-core mismatch used in the DAWN trial (18), and based on the ASPECTS/CTP-core correlation that we previously calculated. In order to adjust for the higher sensibility of DWI, one point was added before analysis for DWI-ASPECTS (102). Unlike the DAWN trial, we did not applied any age or pre-stroke functional disability cut-off, in order to present a closer picture to the real-life scenario. We therefore identified a group of "liberal-EVT" of treated patients with clinical-ASPECTS mismatch, and a group "non-liberal-EVT" patients, including treated patients with ASPECTS <5, or not showing a clinical-ASPECTS mismatch.

As control group, we selected all consecutive AIS admitted to the Lausanne University Hospital in the late time window, and not receiving EVT (intravenous thrombolysis, IVT, allowed). The inclusion period for this group was extended from 2005 to 2018 to ensure a satisfactory sample size. The same clinical (i.e. NIHSS ≥10) and radiological (ICA or M1 occlusion) inclusion criteria were applied. Similarly, we identified two groups of non-treated patients: the "liberal-no EVT" group, corresponding to non-treated patients showing the clinical-ASPECTS mismatch, and "non-liberal-no EVT" group, i.e. non treated patients with ASPECTS <5 or without the clinical-ASPECTS mismatch.

The primary outcome of the study was the shift towards better functional outcome in the 3-months modified Rankin Scale (mRS) in "liberal-EVT" group compared to the "liberal no EVT" group, and in the "liberal-EVT vs "non -liberal EVT" groups. As secondary outcomes, we chose the improvement of the NIHSS at 24 hours from the baseline (delta NIHSS), and the rates of symptomatic hemorrhagic transformation (sICH) defined according the ECASS II criteria (111).

Statistics

We first analyzed demographic, clinical, biological, and radiological variables from the acute phase of stroke, performing comparisons between the 4 study groups defined by the presence of clinical-ASPECTS mismatch (liberal versus

non-liberal) and acute treatment modality (late EVT versus no EVT). Baseline characteristics of the cohort were summarized both overall and separately for each group of patients, reporting frequencies and percentages for binary and categorical variables, and medians and inter-quartile ranges (IQR) for continuous measures. Comparisons were conducted using appropriate statistical testing, i.e., Mann-Whitney U for continuous variables and Chi-squared or Fisher Exact test for categorical variables.

The primary outcome was analyzed using both univariate and multivariate methods. We fitted ordered logit regression models, with interaction terms between the variables “liberal criteria” and “EVT”, with the response variable being the shift towards favorable outcome (i.e., lower mRS) at 3 months. Assumption of proportional odds has been tested and it was deemed reasonable. We obtained 4 different odds ratios (ORs) comparing the 4 different groups of patients and the OR for the interaction term. First, unadjusted ORs were calculated, and then a multivariate analysis was performed, in which a list of variables was used to adjust the ORs of interest. These included variable that had been shown to influence outcome or because their unbalanced distribution among the 4 groups. The final, adjusted, model included the followings: age, pre-stroke mRS<3, LPGH to hospital arrival time, admission NIHSS, admission glucose level, baseline ASPECTS, and IV thrombolysis.

Secondary outcomes were analyzed using comparative univariate logistic or linear regression models (depending on the nature of the outcome variable). Adjusted analyses were not performed for secondary outcomes.

Given the retrospective registry-based analysis of data, a formal sample size calculation was not performed. We performed complete case analyses, with only observations with complete information being considered; hence no formal treatment of missing data was done.

Statistical analyses were performed using STATA version 15 and R version 4.0.

This study was approved by the hospital’s Institutional Review Board of each center for retrospective data collection and review.

6.2.4 *Results*

Out of 2,167 AIS patients who received EVT during the study period (2010-2018) in the two participating stroke centers, 482 (22.2%) were treated between 6 and 24 hours from LPGH. Of these, 218 (10.1%) patients presented an admission NIHSS ≥10 and ICA/M1 occlusion, and were therefore included in the EVT-arm. To select the non-EVT arm, we screened 1,675 AIS patients admitted in the late time window to Lausanne stroke center between 2005-2018, and we identified 119 (7.1%) patients who did not received EVT and presented the clinico-radiological inclusion criteria. The flow chart for the selection of the study population is available in Figure 1.

Therefore, the overall study cohort consisted of 337 AIS, with 172 patients from Lausanne and 165 patients from Berne. Their baseline demographics, clinic and radiological features are presented in Table 1. The median age was 73 (IQR=61-82), with 52% females. The median NIHSS on admission was 18 (15-22) and median LPGH to hospital arrival was 9.2 (5.9-12.9) hours. The median ASPECTS was 7 (5-9) and 24% of patients presented tandem occlusions.

One hundred ninety-six (58.2%) patients presented a clinical-ASPECTS mismatch (i.e. “liberal” patients), of whom 146 (74.5%) received EVT. Among 141 (41.8%) patients without clinical-ASPECTS mismatch (i.e. “non-liberal” patients), EVT was performed in 72 (51.1%) patients.

The four groups of patients were well balanced for demographics, stroke severity and vascular risk factors, with the exception of diabetes (higher in the liberal non-EVT group) (Table 1). Patients who did not received EVT showed a lower proportion of pre-stroke independency, longer delay from LPGH to hospital arrival and higher frequency of wake-up strokes. Regarding neuroimaging, more EVT patients were assessed by MRI. The median ASPECTS of non-liberal patients were lower compared to the liberal ones. Patients who did not received EVT were also treated less frequently with IVT.

EVT-patients with the clinical-ASPECTS mismatch presented shorter delay between the groin puncture and the recanalization when compared to patients

without. However, the median number of passes used and the rate of successful recanalization (i.e. mTICI≥2b) were similar between the two groups.

At 24 hours, liberal patients treated with late EVT showed a greater improvement in the NIHSS score compared to non-treated and non-liberal patients (Table 2). Patients receiving EVT showed higher rate of sICH (5% in liberal patients, 13% in non-liberal patients). At 3 months, only 25% of all patients achieved functional independency. This rate was significantly lower in non-treated patients, especially in those without clinical-ASPECTS mismatch (7%). Also, non-treated patients presented higher rate of mortality (42% in liberal patients, 49% in non-liberal ones).

The unadjusted ordinal shift analysis for 3-months mRS showed that late EVT was associated with better outcome than no EVT in both liberal (OR=2.27) and non-liberal patients (OR=2.34). Also, among patients treated with late EVT, patients showing the clinical-ASPECTS mismatch presented better outcome compared to those without (OR=1.74) (Table 3). After adjusting for confounders, a favorable effect of late EVT on clinical outcome emerged in the liberal group (OR=2.83), but no more in the non-liberal group. In this model, moreover, we found a near significant positive interaction between liberal criteria and late EVT (p=0.073).

6.2.5 *Discussion*

In our large, retrospective analysis of a two centers cohort of late-arriving stroke patients undergoing EVT in routine clinical practice, we demonstrated a clinical benefit of the revascularization procedure in patients showing a mismatch between the stroke severity (assessed by NIHSS) and the amount of irreversibly damaged cerebral tissue (evaluated with the ASPECTS). After adjustment for multiple confounders, we found a near significant positive interaction between the treatment effect in the late time window and the selection of patients according to the proposed clinical-ASPECTS mismatch. In thus selected patients, treatment was also associated with early neurological improvement, similar risk of symptomatic hemorrhagic transformation and lower mortality rate.

Real-world data regarding prevalence, treatments, and outcomes of LVO patients admitted in the extended time window fulfilling and not fulfilling DAWN and/or DEFUSE-3 criteria are very limited (97, 98). These reports suggest that a less restrictive cut-off on infarct core volume was still able to select patients responding to late EVT. However, a simpler neuroimaging protocol for patients' selection for mechanical thrombectomy beyond 6 hours has not been tested yet, except in small case series (67, 112). Our retrospective data show that a clinical-ASPECTS mismatch concept has potential value and safety to select patients for late thrombectomy, and that it might be not necessary to use more sophisticated perfusion imaging for this population.

Previous reports showed a moderate correlation between ASPECTS and core volumes on CTP (53, 75). Still, we previously demonstrated that ASPECTS assessment on NCCT seemed to be more accurate in later time windows and in patients with LVO, supporting the findings of our current analysis.

Rates of good outcomes in our EVT cohort (36% in liberal patients and 22% in non-liberal patients) were lower compared to those found in the HERMES meta-analysis for EVT<6 hours (5), and in the DAWN (49%) and DEFUSE-3 (45%) trials. This could be explained by the real-life scenario of our study, potentially including patients with higher degrees of pre-stroke disability. The non-treated group of our study also showed a rather poor natural course (with 16% patients achieving a good outcome), which was similar to the rates of functional independence in the control arm of DAWN (13%) and DEFUSE-3 (17%). Several factors, including the low frequency of the systemic lytic agents in the late time windows, and very low rates of spontaneous recanalization could contribute to this unfavorable outcome.

We found acceptable safety measures in our cohort of late EVT patient using "liberal" imaging criteria: late EVT was not associated with higher risk of sICH in patients showing a clinical-ASPECTS mismatch (5% in treated patients vs 4% in non-treated patients), with similar rates to those reported in late EVT trials. However, we found an increased risk of sICH for patients treated with late EVT not having the clinical-ASPECTS mismatch (13%). The median ASPECTS of

these patients was low (3); therefore, our result is in line with the higher risk of intracranial hemorrhage after early EVT shown for patients with ASPECTS 0-4 (113).

We acknowledge several limitations of our study. First, the nonrandomized and retrospective nature of the study might limit the generalization of the results. Second, it is possible that variables related to the decision to perform endovascular treatment have influenced our results; we have attempted to reduce this potential bias by including several of these variables in the adjustment for our final model. Third, the limited number of patients in each subgroup may lead to type II errors, i.e. a minor effect of EVT could also be present in patients without clinical-ASPECTS mismatch. Fourth, the difference of neuroimaging modalities adopted in each center (with DWI- based ASPECTS mostly adopted in the EVT-group, and NCCT-based ASPECTS used for the non-treated group) might have influenced our results. Last, due to the long study period, especially for the non-treated arm, the outcomes measures might have been influenced by the improvement of revascularization treatments and general stroke care over time.

In conclusion, in our retrospective analysis of consecutive stroke patients with proximal vessel occlusion, there seemed to be a more favorable outcome with late endovascular treatment in the setting of a mismatch between clinical severity and ASPECTS. This result could suggest a potential role of simpler neuroimaging protocols in late revascularization decisions, but confirmation by randomized controlled studies is needed.

6.2.6 *Tables and Figures*

Table 1 Baseline characteristics of the all included patients, and of the four groups of patients selected on the basis of liberal criteria (Liberal, Non-liberal) and late endovascular treatment (EVT, no EVT). Values are expressed as absolute counts and percentage for categorical variables, or medians and interquartile range (IQR) for continuous variables. P-values are given for the

univariate difference between the four groups (or between the two EVT-groups for EVT-related variables).

Table 2 Clinical outcome measures of the included patients, presented in the overall cohort and in the four groups of interests. UVA results from the comparison between groups are provided.

Table 3 Results from the shift analyses for favorable outcome at 3 months (assessed with modified Rankin Scale) according to presence of liberal selection criteria and late endovascular treatment. Results are shown as odds ratios (OR) and their 95% confidence interval (CI), both for unadjusted and adjusted comparison.

Figure 1 Flow-chart of the study population, showing the inclusion of patients treated with late-EVT (from Lausanne and Bern stroke center)) and the selection of control patients who did not received late-EVT (from Lausanne stroke center only).

Table 1

Variables	**Total cohort** (N=337)	**Liberal EVT** (N=146)	**Liberal no EVT** (N=50)	**Non-liberal EVT** (N=72)	**Non-liberal no EVT** (N=69)	*p*-value
Patients from Lausanne stroke center, n (%)	172 (51)	41 (28)	50 (100)	60 (83)	69 (100)	<0.001*
Age, median (IQR)	73 (61-82)	76 (62-84)	73 (58-83)	72 (56-81)	73 (63-83)	0.718
Sexe (F), n (%)	176 (52)	80 (55)	28 (56)	31(43)	37 (54)	0.371
Pre-stroke mRS<2, n (%)	268 (80)	129 (88)	29 (58)	65 (90)	45 (65)	<0.001*
Vascular risk factors						
Hypertension, n (%)	217 (64)	102 (70)	30 (60)	45 (63)	40 (58)	0.288
Diabetes, n (%)	59 (18)	30 (21)	14 (28)	7 (10)	8 (12)	0.024*
Dyslipidemia, n (%)	218 (65)	91 (63)	36 (72)	48 (68)	43 (62)	0.619
Smoking, n (%)	81 (24)	33 (23)	11 (22)	18 (25)	19 (28)	0.887
Treatment at stroke onset						
Anticoagulation, n (%)	44 (13)	25 (17)	8 (16)	5 (7)	6 (9)	0.106
Antiplatelet, n (%)	102 (30)	41 (28)	15 (30)	23 (32)	23 (33)	0.879
Lipid Lowering drugs, n (%)	82 (24)	35 (24)	14 (28)	20 (28)	13 (19)	0.579
NIHSS on admission	18 (15-22)	18 (14-22)	19 (15-23)	17 (15-20)	19 (16-24)	0.067
Glucose on admission, mmol/L	7.1 (6.2-8.6)	7.0 (6.1-8.5)	7.1 (6.2-8.9)	7.1 (6.0-8.4)	7.2 (6.5-8.6)	0.742
LPGH to presentation, min	549 (353-775)	492 (337-713)	614 (720-773)	424 (303-428)	741 (548-938)	<0.001*
Wake-up stroke, n (%)	169 (50)	62 (42)	34 (68)	32 (44)	41 (59)	0.004*

Table 1 (continued)

Variables	**Total cohort** (N=337)	**Liberal EVT** (N=146)	**Liberal no EVT** (N=50)	**Non-liberal EVT** (N=72)	**Non-liberal no EVT** (N=69)	*p*-value
Neuroimaging variables						
MRI on admission, n (%)	96 (37)	59 (63)	0 (0)	37 (79)	0 (0)	<0.001*
Baseline ASPECTS	7 (5-9)	8 (7-9)	8 (7-9)	5 (3-6)	3 (2-5)	<0.001*
Intracranial ICA occlusion, n (%)	149 (44)	54 (37)	25 (50)	32 (44)	38 (55)	0.070
Tandem occlusion, n (%)	81 (24)	31 (21)	16 (32)	14 (19)	20 (29)	0.249
IV thrombolysis, n (%)	50 (15)	31 (21)	3 (6)	14 (19)	2 (3)	0.001*
EVT-related variables						
LPGH to groin puncture, min	583 (423-789)	602 (432-819)	-	539 (403-689)	-	0.150
Groin puncture to recanalization, min	44 (28-70)	40 (27-67)	-	51 (33-80)	-	0.031*
General anesthesia, n (%)	185 (86)	123 (85)	-	62 (87)	-	0.623
Number of passes, n	1 (1-2)	1 (1-2)	-	1.5 (1-3)	-	0.568
Successful recanalization, n (%)	177 (81)	122 (84)	-	55 (76)	-	0.202

Table 2

Variables	**Total cohort** (N=337)	**Liberal EVT** (N=146)	**Liberal no EVT** (N=50)	**Non-liberal EVT** (N=72)	**Non-liberal no EVT** (N=69)	*p*-value
Delta NIHSS at 24h, median (IQR)	-1 (-7;0)	-6 (-10;0)	-1 (-2;0)	0 (-6;2)	0(-1;1)	<0.001*
Symptomatic HT, n (%)	18 (6)	7 (5)	2 (4)	9 (13)	0 (0)	0.017*
3 months mRS=0-2, n (%)	85 (25)	53 (36)	11(22)	16 (22)	5 (7)	<0.001*
3 months mRS, median (IQR)	4 (2-6)	4 (2-6)	5 (3-6)	4 (3-6)	5 (4-6)	0.001*
Death <3 months, n (%)	115 (34)	35 (24)	21 (42)	25 (35)	34 (49)	0.002*

Table 3

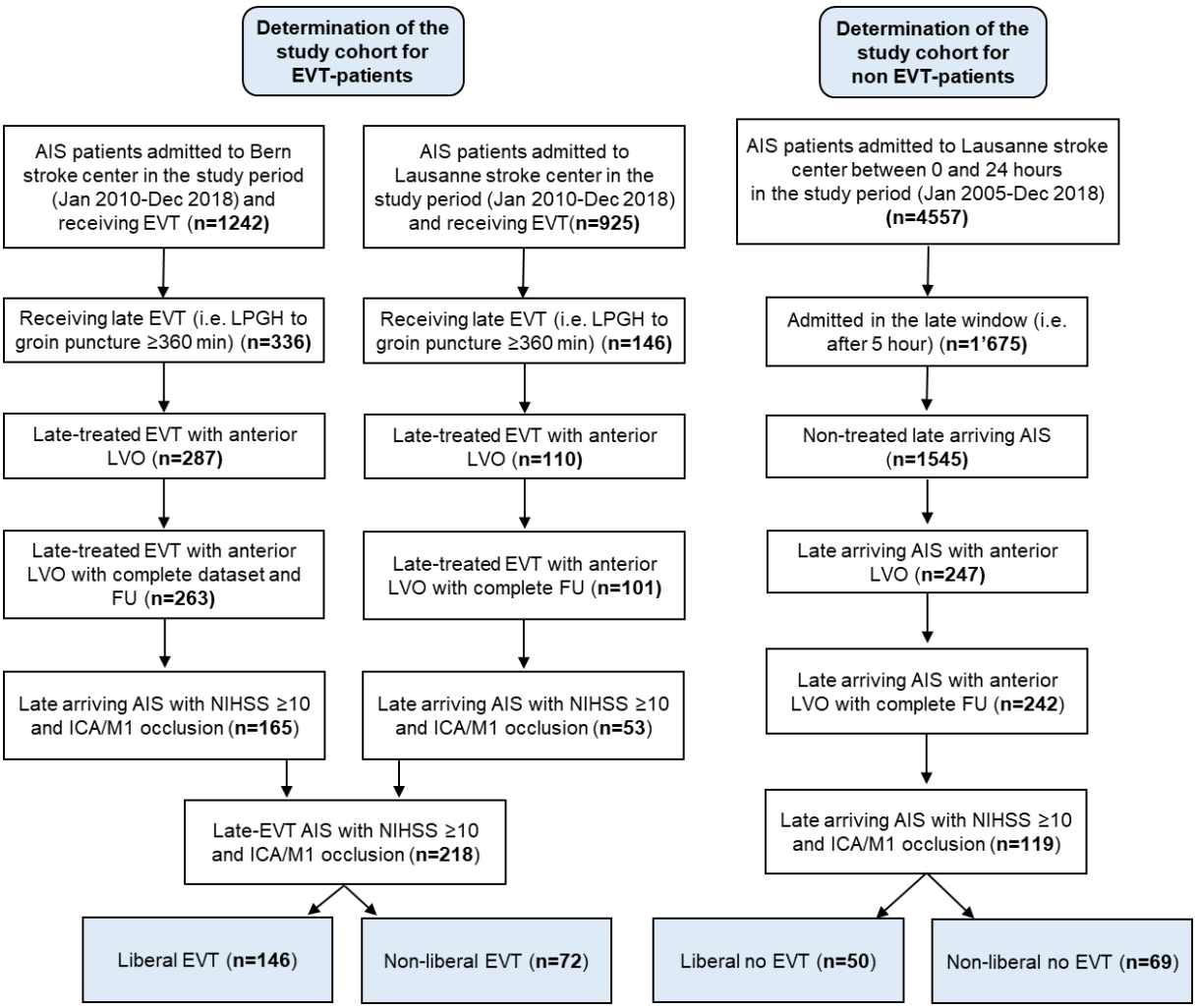
Unadjusted comparison	**Patients group**	**OR**	**95%CI**	**p-value**
EVT *vs* No-EVT	*Liberal*	2.27	1.21-4.16	0.007*
	Non-liberal	2.34	1.26-4.42	0.008*
Liberal *vs* Non-liberal	*EVT*	1.74	1.06-2.90	0.030*
	No EVT	1.68	0.83-3.38	0.147
Interaction°		1.10	0.47-2.58	0.832
Adjusted comparison⁺	**Patients group**	**OR**	**95%CI**	**p-value**
EVT *vs* No-EVT	*Liberal*	2.83	1.48-5.58	0.002*
	Non-liberal	1.32	0.61-2.84	0.484
Liberal *vs* Non-liberal	*EVT*	0.82	0.36-1.84	0.624
	No EVT	2.11	0.55-8.31	0.282
Interaction°		2.33	0.93-5.94	0.073

*Means significant results.

°Refers to the interaction term between the presence of liberal criteria and late-EVT performed.

⁺Adjusted for: age, pre-stroke mRS, LPGH to presentation, NIHSS on admission, glucose on admission, baseline ASPECTS, IV thrombolysis.

Figure 1


Determination of the study cohort for EVT-patients
Determination of the study cohort for non EVT-patients
AIS patients admitted to Bern stroke center in the study period (Jan 2010-Dec 2018) and receiving EVT (n=1242)
AIS patients admitted to Lausanne stroke center in the study period (Jan 2010-Dec 2018) and receiving EVT(n=925)
AIS patients admitted to Lausanne stroke center between 0 and 24 hours in the study period (Jan 2005-Dec 2018) (n=4557)
Receiving late EVT (i.e. LPGH to groin puncture ≥360 min) (n=336)
Receiving late EVT (i.e. LPGH to groin puncture ≥360 min) (n=146)
Admitted in the late window (i.e. after 5 hour) (n=1'675)
Late-treated EVT with anterior LVO (n=287)
Late-treated EVT with anterior LVO (n=110)
Non-treated late arriving AIS (n=1545)
Late-treated EVT with anterior LVO with complete dataset and FU (n=263)
Late-treated EVT with anterior LVO with complete FU (n=101)
Late arriving AIS with anterior LVO (n=247)
Late arriving AIS with NIHSS ≥10 and ICA/M1 occlusion (n=165)
Late arriving AIS with NIHSS ≥10 and ICA/M1 occlusion (n=53)
Late arriving AIS with anterior LVO with complete FU (n=242)
Late-EVT AIS with NIHSS ≥10 and ICA/M1 occlusion (n=218)
Late arriving AIS with NIHSS ≥10 and ICA/M1 occlusion (n=119)
Liberal EVT (n=146)
Non-liberal EVT (n=72)
Liberal no EVT (n=50)
Non-liberal no EVT (n=69)

7 CONCLUSIONS AND FUTURE DIRECTIONS

This research has examined different radiological and clinical aspects of AIS patients. The radiological part of the project has identified multiple determinants of better collateral circulation in the acute phase of stroke, some of them potentially modifiable. We also demonstrated that the degree of collateral status at the baseline is independently related to the amount of cerebral tissue that is already irreversibly damaged on hospital admission. Overall, our results showed that risk factors for diffuse vascular pathology (i.e. smoking, aging, renal function impairment) might play a detrimental role in the development and recruitment of collaterals anastomoses. These findings may contribute to our understanding of collaterals variability at baseline, and also indicate that collateral circulation is crucial in determining the extent of the infarct volume in the initial diagnostic workup. Understanding these factors and relationships, more targeted acute stroke treatment based on multimodal neuroimaging may be possible, replacing the current time-based approach with radiological selection criteria. We could also improve our ability to predict outcome (survival) of ischemic but still viable tissue, and treatment response. Also, patients that may benefit from maintenance or augmentation of collateral flow could be identified and offered such treatment as a therapeutic target.

Translating these observations in the setting of late-arriving AIS patients, we demonstrated that EVT could be offered to a larger amount of patients if more liberal criteria were adopted: the proportion of late-EVT eligible patients was 5.6% according to strict trial criteria, and almost double (11.1%) with our proposed less stringent criteria. These criteria might allow to consider for EVT patients with older age, minor pre-stroke disability and absence of reconstructed perfusion images. In our exploratory analysis of late-EVT treated patients, we were able to show a positive effect of the treatment in patients having a mismatch between clinical severity and ASPECTS, suggesting that a simpler estimation of the ischemic changes could be sufficient for referring patients for late EVT.

These results could be used to help planning the organisation and resource needs in stroke system of care, using our real world estimation of eligible patients for late EVT. Also, our analysis may be used to estimate potential economic long-term savings from this stroke therapy using different sets of criteria, resulting possibly in differential effects and patient volumes. These health economical aspects are important to justify implementation of such treatment options in the health care systems. Finally, if confirmed in RCT, a simpler neuroimaging protocol could be used in the decision to proceed to thrombectomy in cases of absent, failed or contraindicated advanced imaging, and could help for estimation of stroke prognosis.

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9 ARTICLES

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ORIGINAL COMMUNICATION

Determining factors of better leptomeningeal collaterals: a study of 857 consecutive acute ischemic stroke patients

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Abstract

Background In acute ischemic stroke (AIS) collaterals correlate with infarct size, recanalization rate and clinical outcome. We aimed to identify factors associated with better collateral status in a large series of AIS patients with middle cerebral artery (MCA) occlusion.

Methods In the Acute STroke Registry and Analysis of Lausanne (ASTRAL) from 2003 to 2016, we identified all consecutive AIS with proximal MCA occlusion on CT-angiography performed < 24 h. Collaterals were scored from 0 (absent) to 3 (≥ 100%) and related to multiple demographic, clinical, metabolic and radiological variables in a multivariate regression analysis (MVA).

Results The 857 included patients had a median age of 72.3 years, 48.4% were female and median admission NIHSS was 16. Better collaterals were associated with younger age (OR 0.99; 95% CI 0.98–1.00), hemineglect (OR 1.35; 95% CI 1.03–1.76), absence of visual field defects (OR 0.64; 95% CI 0.46–0.90), eye deviation (OR 0.58; 95% CI 0.43–0.79) and decreased vigilance (OR 0.62; 95% CI 0.44–0.88). Better collaterals were also associated with dyslipidemia (OR 1.57; 95% CI 1.16–2.13), no previous statin use (OR 0.69; 95% CI 0.50–0.95), and lower creatinine levels (OR 0.99; 95% CI 0.99–1.00). On neuroimaging, better collaterals related to higher ASPECTS score (OR 1.27; 95% CI 1.20–1.35) and higher clot burden score (OR 1.09; 95% CI 1.03–1.14).

Conclusions Younger age, dyslipidemia and lower creatinine levels were predictors of better collaterals in AIS patients from proximal MCA occlusions. Greater degree of collaterals related to lower stroke severity on admission. On neuroimaging, better collaterals were independently associated with minor early ischemic changes and lower clot burden. These data may add knowledge on pathophysiology of collaterals development and may help to identify patients with better collaterals for late or aggressive recanalization treatments.

Keywords Acute ischemic stroke · Collateral circulation · Computed tomography-angiography (CTA) · Acute neuroimaging

Abbreviations

AIS	Acute ischemic stroke
CBS	Clot burden score
MCA	Middle cerebral artery

Introduction

Leptomeningeal arterial collaterals are pre-existing anastomoses that cross-connect a small number of distal arterioles of the cerebral arteries [1]. They provide alternative blood flow to support brain viability when a primary vessel in the cervico-cephalic arteries is critically stenosed or occluded, such as in acute ischemic stroke (AIS). A

Preliminary results of our study have been presented on the International Stroke Conference 2017 in Houston (USA) as a poster. Definitive results have been presented as an oral communication on the European Stroke Organization Conference 2017, taking place in Prague (Czech Republic).

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greater degree of collaterals at baseline has been associated with smaller infarct size [2], improved recanalization rate after endovascular treatment [3] and improved clinical outcome [4, 5].

The magnitude of collateral flow varies greatly between patients. Still, studies examining determinants of this variability are lacking. Besides genetic and environmental factors, statin use has been associated with good collaterals [6], whereas a history of hypertension and higher systolic blood pressure on admission have been associated with poor collateral status at baseline [7]. Recently, the presence of metabolic syndrome, hyperuricemia and aging were found as independent predictors of poor leptomeningeal collateral status [8]. Malik et al. confirmed the association between poor collaterals and older age, but did not find a favourable influence of pre-stroke statin use on the patency of collateral circulation [9].

The main aim of our study was to investigate factors associated with the degree of leptomeningeal collateral status in a large cohort of AIS patients. In particular, we performed a comprehensive analysis of a large number of possibly associated variables, including demographic, clinical, biochemical, and radiological variables, to identify independent predictors of better collaterals in the acute phase of stroke.

Methods

Patient selection

All consecutive patients included in the Acute STroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to June 2016 were considered for this study. ASTRAL is a single-center prospective cohort of all AIS patients admitted to the Stroke Center of Lausanne University Hospital within 24 h of an ischemic stroke [10]. It incorporates detailed clinical and laboratory data and multimodal brain imaging techniques. The type and definition of collected variables in ASTRAL is prespecified, and the current analysis was retrospective.

For patient selection, we used the following inclusion criteria: AIS involving the middle cerebral artery (MCA); CT-based multimodal imaging performed < 24 h of last proof of good health; availability of a CT-angiography (CTA) of good quality showing occlusion of the proximal segments (M1 and/or proximal M2), with or without added more distal and more proximal (carotid siphon, extracranial carotid artery) pathology. Patients with only distal M2 or only M3 occlusions were excluded because visual assessment of collaterals in a small arterial territory was considered insufficiently reliable.

Clinical variables

Demographic data (age and gender), medical history and vascular risk factors (such as previous cerebrovascular events, arterial hypertension, diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation) were recorded. We collected pre-stroke modified Rankin scale (mRs) and current medications at the time of stroke. We recorded "new neurological deficits", that are new (i.e. not preexisting), focal neurological deficits, such as visual field defects, eye deviation, aphasia, neglect and vigilance impairment, assessed by a neurologist during the initial evaluation of a patient with suspected acute ischemic stroke, as noted in the medical records. Stroke severity was scored by National Institutes of Health Stroke Scale (NIHSS). We measured vital signs (body temperature, and blood pressure), metabolic and hematologic parameters at admission and calculated onset-to-door, onset-to brain imaging and onset-to treatment times. Stroke etiology was classified according to the TOAST classification, with dissection and multiple causes added as categories. Clinical outcome was measured at 3 months with the mRs either in person at the outpatient stroke clinic, or by standardized telephone interview by Rankin-certified medical personnel. Favorable outcome was considered as 3 months mRs ≤ 2.

Imaging protocol and analysis

We assess all individuals with suspected AIS by a multimodal CT scan as part of their standard of care, unless contrast contraindication exists. Non-contrast CT (NCCT) scanning was performed to detect intracranial haemorrhage, hyperdense MCA sign and chronic cerebrovascular lesions (defined as presence of chronic infarct and/or leukoaraiosis ≥ 1 according to Blennow scale). Early ischemic changes in the MCA territory were recorded to calculate ASPECTS.

CTA in helical mode was performed from the aortic arch to the top of the frontal sinuses (120 KV, 150–260 mAs, 0.625 slice-thickness, 50 ml of iodinated contrast at 5 ml/s, delay according to the perfusion data). On CTA, we searched for significant extracranial carotid pathology in the ischemic territory, defined as the presence of ≥ 50% stenosis, occlusion, dissection or floating thrombus. Significant intracranial pathology, i.e. ≥ 50% stenosis or occlusion, was grouped as proximal if it involved carotid siphon, proximal M1 (i.e. less than 10 mm from M1 origin) or A1 segment, and distal if it involved distal M1, M2, M3 or A2 segment. We calculated clot burden score (CBS) as indicator of clot extension. The collateral score was visually determined from CTA maximal intensity projection

reconstructions and graded according to Tan et al. [11] Absence of collateral flow to the ischemic territory was graded as 0, whereas collateral flow in ≤ 50%, > 50% and ≥ 100% of the vessels filling in the ischemic territory distal to the occluded artery was graded as 1 (poor collaterals), 2 (moderate collaterals), and 3 (good collaterals), respectively. Interrater agreement for collateral grading 0–1 vs. 2–3 was evaluated on 100 consecutive patient's proximal intracranial occlusions using Cohen's kappa.

Statistical analysis

We first performed a univariate analysis (UVA) between demographic, clinical, metabolic and radiological variables depending on collateral status. All grades of collaterals, considered as ordinal categorical variable (0–3), were considered for the primary outcome of the study.

All variables from the UVA, independently from their statistical significance in univariate comparisons, were then used to fit three multivariate logistic models to determine the independent associations with better degrees of collateralization. First, we performed a clinical multivariate analysis (MVA-A) using only demographic, clinical and laboratory variables available before the acquisition of CTA, to provide clinicians with indicators of patients likely to have good collaterals. Second, we analyzed the radiological variables that are independently associated with better collaterals (MVA-B), to provide radiologists with additional information about NCCT variables capable to predict good collaterals. Third, we combined the variables from the two above mentioned models and used all demographic, clinical, metabolic and radiological variables in a comprehensive MVA (MVA-C). This comprehensive analysis aimed to show the most powerful (clinical or radiological) associations, and better understand the pathophysiology of good collaterals.

All analyses were performed using the proportional odds approach. In all MVA analyses, imputation of missing values was carried out using multiple chain equations methodology [12]. In this way, we generated five complete datasets. Analysis of each dataset was performed separately. We used backward elimination techniques to report only covariates significantly associated with the outcome, listed in Table 2. The reported results were obtained by appropriately combining the results of the five imputed analyses. In all analyses, type I errors of 5% to test each regression coefficients separately were used. The R package (R version 3.4.1) was used throughout.

Given that the 3 months clinical outcome was considered a secondary, ancillary result, no adjustment was done for this analysis.

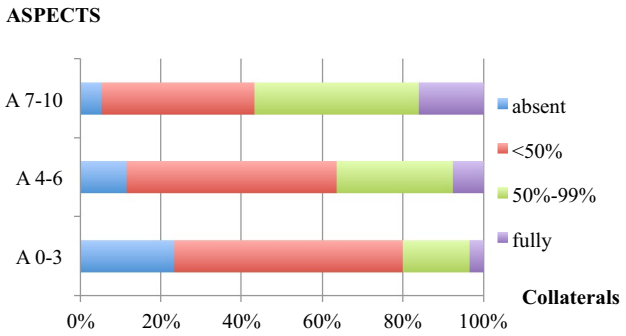

Fig. 1 Correlation between ASPECTS score and collaterals (ordinal)

Results

Among 2027 patients with AIS involving MCA territory and with good quality acute CTA during the study period, 857 met the inclusion criteria (Suppl. Fig. 1S). Median age was 72.3 (interquartile range, IQR 20.5) years, 415 (48.4%) were females and median admission NIHSS was 16 (IQR 9). Median onset to CT time was 2.5 (IQR 3.4) h. CTA showed M1 occlusion in 620 (72.3%) and proximal M2 occlusion in 237 (27.7%) patients. Collaterals were graded as absent (grade 0) in 77 (9.0%), poor (grade 1) in 345 (40.3%), moderate (grade 2) in 307 (35.8%) and good (grade 3) in 128 (14.9%) patients. Interrater agreement for collateral grading 0–1 vs. 2–3 was 0.81.

Table 1 shows patient characteristics, laboratory and radiological findings of the study population as well as the results of the univariate analysis (Suppl. Tables 1S and 2S, are extended versions of Table 1). The distribution of vascular risk factors was similar among the collateral scores.

Significant results from the MVAs are shown in Table 2. In the clinical MVA (MVA-A), better collaterals were associated with lower age (OR 0.99, confidence intervals: see Table 2), lower NIHSS on admission (OR 0.94, see also Suppl. Fig. 2S) and lower frequency of visual field defects (OR 0.70), eye deviation (OR 0.66) and decreased vigilance (OR 0.60). Better collaterals were also associated with non-smoking status (OR 0.72) and decreased delay to imaging (OR 0.97). When limiting the MVA to radiological variables (MVA-B), better collaterals were associated with a higher ASPECTS score (OR 1.27), higher CBS (OR 1.15), and absence of chronic cerebrovascular lesions (OR 0.72).

Combining all data in a comprehensive MVA (MVA-C), better collaterals were associated with lower age (OR 0.99), hemineglect (OR 1.35), absence of visual field defects (OR 0.64), eye deviation (OR 0.58) and decreased vigilance (OR 0.62). Better collaterals were also associated with dyslipidemia (OR 1.57), absence of statin use (OR 0.96) and lower creatinine levels (OR 0.99). Moreover, we confirmed the positive association between better

Table 1 Patient characteristics, laboratory and radiological findings in the study population

Baseline variable and follow-up as median ± IQR or *n* (%)	Total pt (*N* = 857)	OR	95% CI
Age (years)	72.3 (20.5)	0.99*	0.98–1.00
Sex (females)	415/857 (48.4%)	1.08	0.84–1.38
Admission NIHSS	16.0 (9.0)	0.91*	0.89–0.92
New neurological deficit			
Visual field defects	619/836 (74.0%)	0.34*	0.25–0.46
Eye deviation	477/835 (57.1%)	0.35*	0.27–0.46
Aphasia	435/842 (51.7%)	1.04	0.81–1.33
Neglect	431/835 (51.6%)	0.89	0.69–1.14
Vigilance impairment	163/836 (19.5%)	0.34*	0.25–0.48
Premorbid risk factors			
Hypertension	537/852 (63.0%)	0.88	0.68–1.14
Diabetes	134/852 (15.7%)	0.85	0.61–1.19
Hyperlipidemia	581/851 (68.3%)	1.20	0.92–1.57
Current smoking	206/841 (24.5%)	0.87	0.65–1.17
Atrial fibrillation	351/854 (41.1%)	0.78	0.61–1.01
Pre-stroke mRS > 2	68/850 (8.0%)	0.89	0.57–1.40
Statin use before stroke	215/846 (25.4%)	0.75	0.57–1.00
Laboratory studies			
Blood glucose (mmol/L)	6.7 (2.0)	0.93*	0.88–0.98
Serum creatinine (mg/dL)	87.0 (29.0)	0.99*	0.99–1.00
Total cholesterol (mmol/L)	5.1 (1.6)	1.01	0.99–1.03
Onset to CT time (h)	2.5 (3.4)	0.98	0.95–1.01
Neuroimaging data			
ASPECTS score	8.0 (4.0)	1.32*	1.25–1.39
Significant leukoaraiosis	212/857 (24.7%)	0.84	0.63–1.11
Hyperdense MCA sign	398/857 (46.4%)	0.54*	0.42–0.70
Clot burden score	6.0 (4.0)	1.22*	1.16–1.27
Significant extracranial carotid pathology			
Significant stenosis	69/856 (8.1%)	0.73	0.46–1.16
Any occlusion	184/856 (21.5%)	0.59*	0.43–0.81
TOAST mechanism[†]			
Atherosclerosis	114/828 (13.8%)	0.81	0.56–1.19
Cardiac	396/828 (47.8%)		
mRS at 3 months			
0–2	308/760 (40.5%)	0.35*	0.26–0.46

Odds ratios (OR) with confidence intervals (95% CI) from the univariate analysis of better vs. poorer collaterals are given, with collaterals used as an ordinal variable quantified by four grades

*Asterisks denote significant findings

[†]Reference: atherosclerosis

collaterals and higher ASPECTS (OR 1.27 and Fig. 1) and higher CBS (OR 1.09 and Fig. 2), respectively.

As an ancillary result, we found in unadjusted analysis that a better collateral status was associated with favorable clinical outcome at 3 months (Table 1).

Discussion

In this largest retrospective study of collaterals so far, we investigated factors that are associated to their variability

Table 2 Results of the pre-imaging multivariate analysis (MVA-A), the imaging-only MVA (MVA-B), and the comprehensive MVAs (MVA-C)

	OR	95% CI	*p* value
MVA-A (clinical variable)			
Age	0.99	0.98–1.00	<0.01
Admission NIHSS	0.94	0.92–0.97	<0.01
Visual field defects	0.70	0.49–1.00	0.04
Eye deviation	0.66	0.48–0.91	0.01
Vigilance impairement	0.60	0.41–0.86	<0.01
Current smoking	0.72	0.53–0.98	0.04
Onset to CT time (h)	0.97	0.94–1.00	0.03
MVA-B (radiological variable)			
ASPECTS score	1.27	1.20–1.34	<0.01
Clot burden score	1.15	1.09–1.20	<0.01
Chronic cerebrovascular lesions	0.72	0.54–0.96	0.03
MVA-C (variable)			
Age	0.99	0.98–1.00	<0.01
Visual field defects	0.64	0.46–0.90	<0.01
Eye deviation	0.58	0.43–0.79	<0.01
Neglect	1.35	1.03–1.76	0.03
Vigilance impairment	0.62	0.44–0.88	<0.01
Statin use	0.69	0.50–0.95	0.02
Hyperlipidemia	1.57	1.16–2.13	<0.01
Serum creatinine	0.99	0.99–1.00	<0.01
ASPECTS score	1.27	1.20–1.35	<0.01
Clot burden score	1.09	1.03–1.14	<0.01

Only significant associations are shown

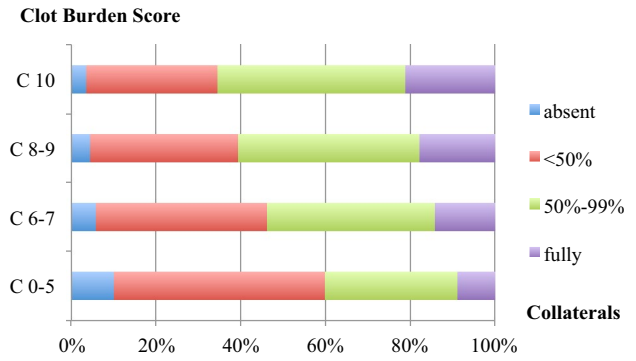

Fig. 2 Correlation between Clot Burden Score and collaterals (ordinal)

in patients with AIS and proximal MCA occlusion. We found that favorable collateral patterns could be predicted by lower age, non-smoking status, no previous statin use, dyslipidemia and lower serum creatinine. Better collaterals were more frequently observed in patients with shorter delay to imaging and absence of chronic cerebrovascular lesions. Moreover, better collaterals were associated with lower stroke severity, lower frequency of cortical signs (except for hemineglect), higher ASPECTS and lower clot burden.

The association between younger age and better collateral score is in agreement with previous findings [8, 9]. It has been proposed that aging leads to 'collateral rarefaction', a process causing reduction in collateral density and diameter, probably mediated by prolonged endothelial dysfunction [13]. Among vascular risk factors, current smoking was an independent predictor of poorer collaterals in our clinical analysis. The role of smoking in the impairment of collateral extent in the coronary and peripheral bed is well known [14], but studies examining its association with leptomeningeal collateral status in humans are lacking. To the best of our knowledge, there have been no previous reports noting that renal impairment was associated with poor cerebral collaterals. However, hyperuricemia, known to be related to chronic kidney disease, and the presence of metabolic syndrome, have recently been associated with worse collaterals [8]. These findings allow us to generate hypotheses with regard to underlying pathophysiology of collateral formation. Aging, smoking and impaired renal function could reduce collateral extent by either causing endothelial dysfunction or decreasing dilatatory capacity of the pial arteries [15].

Somewhat unexpectedly, known or newly diagnosed dyslipidemia was associated with better and statin use with poorer collaterals. Previous reports on coronary artery disease demonstrated a positive association of hypercholesterolemia and collateral extension, probably mediated by elevated levels of vascular endothelial growth factor [16]. Regarding statin use, our findings may be viewed as contradictory and not consistent with previous studies suggesting a role for statins in the promotion of arteriogenesis [6, 17]. In our study, it seems that untreated (newly diagnosed) hyperlipidemia may be a major promoter of collaterogenesis, rather than known and treated hyperlipidemia (i.e. statine use).

A shorter delay from symptoms onset to baseline imaging was independently associated with better collaterals, supporting the concept of time-dependent 'collateral-failure' [18, 19]. In the purely radiological analysis, absence chronic infarcts and leukoaraiosis were associated with better collaterals. Leukoaraiosis might be associated with increased arterial stiffness, which lead to less recruitment of collaterals in the acute phase of occlusive ischemic stroke [20].

In our study, lower rate of cortical signs (i.e. eye deviation and visual field defects) were associated with better collaterals. This is consistent with the anatomical observation that leptomeningeal collaterals mainly supply cortical peripheral areas, whereas deeper structures are predominantly supplied by perforating arteries [21]. Only hemineglect did not fit this pattern, possibly indicating that the critical site of temporal damage responsible for hemineglect is mostly

supplied by non-anastomosing arterial systems [22]. The positive association with higher ASPECTS suggests that a higher degree of collaterals may prevent infarct growth [19]. Moreover, higher clot burden may obstruct more orifices of arteries that could provide collateral blood flow. Inversely, one could hypothesize that collaterals may influence clot length, because patients with poor collaterals may have an increased degree of stasis around the clot and this could lead to a clot extension [23].

The association of collateral status with clinical outcome was not a main goal of our study. Still, the fact that patients with good collaterals showed a better outcome in unadjusted analysis stresses the need to adjust for this variable when reporting outcomes after revascularization treatments.

The limitations of our study include its retrospective design and its single center nature. In addition, collaterals were estimated semi-quantitatively and CTA-based collateral assessment may be less precise than invasive contrast angiography. Moreover, the use of single-phase CTA may lead to technique-dependency bias in collaterals evaluation due to variability in the timing of the contrast injection and image acquisition.

Conclusions

Our study showed that younger age, non-smoking status, dyslipidemia and lower serum creatinine were predictors of better collaterals in patients with AIS and proximal MCA occlusion. The implications of our findings are several: first, they may add to our understanding of collaterals variability at baseline, indicating that risk factors for diffuse vascular pathology (i.e. smoking, aging, renal function impairment) may play a detrimental role in the development and recruitment of such anastomoses. Conversely, dyslipidemia may exhibit a promoting effect upon angiogenesis. Second, our data suggest that manipulation of physiological parameters such as blood pressure or sugar may not result in better collateral flow, but the latter seems to be largely determined by non-modifiable factors in the acute phase of stroke. Third, the associations between collateral status and ASPECTS, clot burden, and frequent cortical signs suggest that these elements are related and partly interchangeable, measuring similar aspects of the ischemic pathophysiology. These characteristics could be used to identify patients with better collaterals for more aggressive revascularization treatment, even at later timepoints.

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Author contributions SN studied the concept and design, helped in analysis and interpretation, and preparation of the article. GS, CWC and DS helped in interpretation of data and critical revision of the article for important intellectual content. DL carried out data analysis and interpretation and helped in preparation of the article. AE helped in data acquisition and analysis. PJM helped in radiological data acquisition and critical revision of the article for important intellectual content. MW contributed to the conception and design, and helped in the interpretation of radiological data. PM studied the concept and design, and helped in data acquisition, analysis and interpretation, critical revision of the article for important intellectual content, study supervision.

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Compliance with ethical standards

Conflicts of interest In the last 3 years, Prof. P. Michel received research grants from the Swiss Heart Foundation, Boehringer Ingelheim and BMS through his institution; speaker fees from Boehringer Ingelheim, Bayer, Daiichi Sankyo, Medtronic and Amgen; honoraria from scientific advisory boards from Boehringer Ingelheim, Bayer, Pfizer and BMS and consulting fees from Medtronic, Astra-Zeneca and Amgen. His institution (CHUV), receives all of the support for stroke education and research. Dr. G. Sirimarco served on scientific advisory boards for Amgen and Daiichi Sankyo. Dr. C.W. Cereda received research grants from the Swiss Heart Foundation, Advisory Board of Research (EOC) and Boehringer Ingelheim in the last 3 years through his institution; honoraria from scientific advisory boards from Boehringer Ingelheim, Bayer and Pfizer. The other authors report no conflicts of interest.

Ethical standards Collection, analysis and publication of data in ASTRAL was approved by the institution's ethical commission.

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DIAGNOSTIC NEURORADIOLOGY

Collaterals are a major determinant of the core but not the penumbra volume in acute ischemic stroke

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Abstract

Purpose Determinants of early loss of ischemic tissue (core) or its prolonged survival (penumbra) in acute ischemic stroke (AIS) are poorly understood. We aimed to identify radiological associations of core and penumbra volumes on CT perfusion (CTP) in a large cohort of AIS.

Methods In the ASTRAL registry (2003–2016), we identified consecutive AIS patients with proximal middle cerebral artery (MCA) occlusion. We calculated core and penumbra volumes using established thresholds and the mismatch ratio (MR). We graded collaterals into three categories on CT-angiography. We used clot burden score (CBS) to quantify the clot length. We related CTP volumes to radiological variables in multivariate regression analyses, adjusted for time from stroke onset to first imaging.

Results The median age of the 415 included patients was 69 years (IQR = 21) and 49% were female. Median admission NIHSS was 16 (11) and median delay to imaging 2.2 h (1.9). *Lower core volumes* were associated with higher ASPECTS (hazard ratio = 1.08), absence of hyperdense MCA sign (HR = 0.70), higher CBS (i.e., smaller clot, HR = 1.10), and better collaterals (HR = 1.95). *Higher penumbra volumes* were related to lower CBS (i.e., longer clot, HR = 1.08) and proximal intracranial occlusion (HR = 1.47), but not to collaterals. *Higher MR* was found in absence of hyperdense MCA sign (HR = 1.28), absence of distal intracranial occlusion (HR = 1.39), and with better collaterals (HR = 0.52).

Conclusions In AIS, better collaterals were associated with lower core volumes, but not with higher penumbra volumes. This suggests a major role of collaterals in early tissue loss and their limited significance as marker of salvageable tissue.

Keywords Acute ischemic stroke · Collateral circulation · CT perfusion · Core volume · Penumbra volume

Results have been previously presented at the European Stroke Organization Conference 2018, Gothenburg, Sweden, as a poster.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00234-019-02224-x) contains supplementary material, which is available to authorized users.

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Abbreviations

AIS	Acute ischemic stroke
ASPECTS	Alberta Stroke Program Early CT Score
CBS	Clot burden score
CTA	CT-angiography
CTP	CT perfusion
MCA	Middle cerebral artery
MR	Mismatch ratio
mRS	Modified Rankin score
NIHSS	National Institutes of Health Stroke Scale

Introduction

The most effective treatment in acute ischemic stroke (AIS) is rapid reperfusion of the cerebral penumbra. However, before reperfusion, penumbral tissue may survive from a sustained

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blood flow through the leptomeningeal collateral circulation [1–3]. Furthermore, the extent of arterial obstruction and metabolic and genetic factors may contribute to the presence and survival of penumbral tissue [4, 5]. However, the factors influencing features of the infarct and penumbra at baseline are poorly understood. Similarly, the relationship between collateral status and salvageable tissue has not been sufficiently explored.

Modern neuroimaging techniques, including CT-angiography (CTA) and CT perfusion (CTP), allow detection of clot location, assessment of collateral circulation, and quantification of salvageable brain tissue. Imaging selection may be an efficient tool for selecting patients with a relevant treatment target and optimizing clinical trial design, as evident from recent trials [6–11]. However, it is still uncertain whether imaging parameters and thresholds could identify patients who are more likely to benefit from revascularization treatments.

In this study, we aimed to identify radiological variables independently associated with core volumes, penumbra volumes, and the mismatch ratio (MR) in a large cohort of AIS patients with proximal middle cerebral artery (MCA) occlusion. More specifically, we aimed to investigate the relationship between collateral status at baseline and CTP volumes.

Methods

Patient selection

For this study, we considered all patients in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to June 2016. ASTRAL collects all consecutive AIS patients admitted to the stroke unit and/or intensive care unit of the Centre Hospitalier Universitaire Vaudois (CHUV, Lausanne University Hospital) within 24 h of the last known well time [12]. ASTRAL incorporates detailed clinical and radiological data from modern, mainly CT-based, multimodal brain imaging techniques. The type and definition of collected variables in ASTRAL was pre-specified, and the current analysis was retrospective. The institution's ethical commission approved collection, analysis, and publication of data in ASTRAL.

For patient selection, we used the following inclusion criteria: AIS involving the MCA territory (with or without ipsilateral anterior or posterior cerebral artery territory), known stroke onset (with less than 1 h of uncertainty), CT-based multimodal imaging of good quality performed < 24 h, CTA showing occlusion of M1 and/or proximal M2 segment (with or without added more distal and proximal pathology), and CTP showing hypoperfusion of at least 10 ml in a site consistent with the clinical picture. We excluded patients with only distal M2 or only M3 occlusions as we considered reliability of visual collateral assessment in a small arterial territory insufficient. We also excluded patients with pre-existing radiological infarct in the newly hypoperfused area.

For this analysis, we reviewed demographic data (age, gender), vascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, current smoking, atrial fibrillation), pre-stroke modified Rankin score (mRS), and National Institutes of Health Stroke Scale (NIHSS) score at admission. We calculated onset-to-brain imaging and onset-to-treatment times. We classified stroke etiology according to the TOAST classification, with dissection and multiple causes added as categories.

CT imaging data acquisition

We assessed patients with suspected AIS by multimodal CT scanning including non-contrast CT (NCCT), CTP, CTA, and post-contrast series as part of standard of care, unless contrast contraindication existed. We performed CT on a 64-multidetector CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). We acquired NCCT and post-contrast series in axial mode from the skull base to the vertex (16 cm z-axis coverage) using the following imaging parameters: 120 kV peak tube voltage, 320 mA tube current, slice thickness 5 mm, 32 cm scan field of view (SFOV), 512 × 512 matrix. We acquired all PCT series in axial scan mode with 80 kV peak tube voltage, 240 mA tube current, 32 cm SFOV, and 512 × 512 matrix. We acquired CTP images at the level of the basal ganglia and the third ventricle above the orbits. We used 18 groups of 16 slices of 5 mm (80 mm z-axis coverage) and acquired CTP images for 50 s in a cine mode with a delay of 5 s after the beginning of injection of 50 ml of iodinated contrast (iohexol 300 mg/ml) with an injection rate of 5 ml per second into an antecubital vein using a power injector. We performed CTA in helical mode from the aortic arch to the top of the frontal sinuses (120 KV, 150–260 mA s, 0.625 slice thickness, 50 ml of iodinated contrast at 5 ml/s, delay according to the perfusion data).

CT imaging data analysis

We reviewed NCCT scans to detect intracranial hemorrhage, hyperdense middle cerebral artery sign, chronic stroke lesions, and presence of leukoaraiosis (defined as grade ≥ 1 according to Blennow scale) [13]. We recorded early ischemic changes on NCCT in the MCA territory to calculate ASPECTS [14].

PCT data were transferred to a workstation and analyzed by a standardized method to create parametric maps of mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV). We used Philips Medical Systems (Cleveland, OH, USA) deconvolution software. Infarct core and ischemic penumbra volumes were calculated with the software using the appropriate MTT and CBV thresholds, which are MTT > 145% of the contralateral side values and CBV > 2.0 mL/100 g for the penumbra volume and MTT > 145% of the contralateral side values and CBV < 2.0 mL/100 g for the core volume [15]. We calculated MR as the ratio

of the total ischemic volume (i.e., core plus penumbra volumes) to the core volume [6].

We reviewed the raw axial and maximal intensity projection CTA images for significant (≥ 50% stenosis or occlusion) extra- and intracranial arterial pathology leading to the ischemic territory. We grouped significant intracranial pathology in the ischemic carotid territory as proximal if it involved carotid siphon, proximal M1 (i.e., less than 10 mm from M1 origin) or A1 segment, or distal, if it involved distal M1, M2, M3, or A2 segment. For each patient, we calculated the clot burden score (CBS) to evaluate the extent of intracranial thrombus burden in the anterior circulation. CBS is a 10-point scoring system that assigned points for the presence of contrast on CTA within the intracranial internal carotid artery, M1 and M2 branches, and A1 segment. A CBS of 10 indicates absence of a visible large vessel occlusion, whereas a score of 0 corresponds to a complete multisegment occlusion of the carotid axes [16].

We visually determined the collateral score from CTA maximal intensity projection reconstructions and graded according to Tan et al. [17] Absence of collateral flow to the ischemic territory was graded as 0, whereas collateral flow in ≤ 50%, > 50%, and 100% of the vessels filling in the ischemic territory distal to the occluded artery were graded as 1, 2, and 3, respectively. We added a score of four for individuals with more than 100% filling of the ischemic bed compared to the normal side, as was previously suggested [18]. For statistical analysis, we grouped grades 0 and 1 as "poor" collaterals, grade 2 as "partial," and grades 3 and 4 as "good" collaterals; we used these three categories in an ordinal way.

At least one experienced vascular neurologist and one experienced neuroradiologist reviewed NCCT, CTP, and CTA images independently. We assessed interrater variability using Cohen's kappa on 100 consecutive acute CTAs with anterior circulation occlusive stroke for NCCT-ASPECTS, CBS, and collateral status. In cases of differing evaluation between readers, we reached consensus after joint assessment.

Statistical analysis

We performed multivariate analyses (MVAs) on multiple radiological variables at baseline and the three main outcomes, i.e., core volume, penumbra volume, and MR. We included in the model the time since stroke onset to brain imaging (in hours) to test the strength of the radiological associations independently of time.

We used a Cox's proportional hazards model and preferred the latter to a classic linear model because of the highly skewed distribution of the response variables and the consequent violation of normality and variance stability assumptions. Alternatives to alleviate this problem (e.g., transforming the response or choosing an appropriate distribution for the response) resulted in estimation problems or difficulties in interpreting the analysis outcome. The Cox model avoids distribution specification for the response and facilitates group comparison through the hazard coefficient. Although we usually employ this model with time as response variable and with censoring, the methodology is quite general and we can implement it in cases of other response variable and no censoring.

We can more easily interpret results if we compare probability density functions (PDFs) among groups, rather than hazard functions. The association between hazard function and PDF is displayed in Fig. 1S (available in on line Supplementary materials). A higher hazard ratio obtained from this model indicates a higher probability of mass concentration in the lower spectrum of the acceptable range of the response variable [19].

We filled in missing data using multiple imputation chain equations technique. Specifically, we initially generated five imputed datasets and analyzed each dataset separately. We used stepwise variable selection methods to select the covariates significantly associated with the response. Finally, the outcome of the five imputed analyses were appropriately combined to produce the results presented [20]. We set significance level at 5% throughout. We carried out all analyses using the statistical package R (version 3.4.2).

Results

Out of 2799 subjects with AIS of known onset and multimodal CT-based imaging performed within 24 h from onset during the study period, 415 patients met the inclusion criteria. The inclusion flowchart of the study population is depicted in online Fig. 2S.

Interrater agreement for reading of CT-based imaging was excellent for ASPECTS (kappa 0.82) and for collaterals (kappa = 0.81); it was good for clot burden score (kappa = 0.77).

We show demographics and clinical and radiological variables of the study population at baseline in Table 1. Median age of the included patients was 69 years old (IQR 21) and 49% were female. Median admission NIHSS was 16 (IQR 11) and median delay to imaging was 2.2 h (IQR 1.9). CTA showed M1 occlusion in 252 (60.7%) and proximal M2 occlusion in 163 (39.3%) patients. We graded leptomeningeal collaterals as "good" in 20.2% patients, "partial" in 36.6%, and "poor" in 43.3% patients.

We present significant results from MVA in Table 2. *Lower core volumes* were independently associated with higher ASPECTS (hazard ratio, HR = 1.08; 95% confidence interval, CI = 1.03–1.12), with absence of hyperdense MCA sign (HR = 0.70; 95% CI = 0.55–0.89), and with higher CBS (i.e., smaller clot, HR = 1.10; 95% CI = 1.05–1.15). Moreover, we found an independent association between lower core volumes and better collaterals (HR = 1.95; 95% CI = 1.44–2.63). *Higher penumbra volumes* were related to lower CBS (i.e., longer clot, HR = 1.08; 95% CI = 1.04–1.12) and non-distal intracranial occlusion (HR = 1.47; 95% CI = 1.11–1.94). We did not find significant association between penumbra

Table 1 Patient characteristics of the selected clinical and radiological variables at admission. Definitions: see text

Baseline clinical and radiological variables	Total pt ($N = 415$)
As median (± IQR) or *n* (%):	
Demographics	
Age, year	69.0 (20.9)
Sex (females), *n*	201/415 (48.4%)
Vascular risk factors	
Hypertension	254 / 415 (61.2%)
Diabetes	63 / 414 (15.2%)
Hypercholesterolemia	265 / 415 (63.9%)
Current smoking	103 / 413 (24.9%)
Atrial fibrillation	154 / 415 (37.1%)
Pre-stroke mRS 0–2	398 / 415 (95.9%)
Onset-to-hospital time, h	1.7 (1.6)
NIHSS on admission	16.0 (11.0)
Acute stroke treatment, *n*	266 /415 (64.1%)
Stroke etiology (TOAST)	
Atherosclerosis	78 / 410 (19.0%)
Cardiac	185 / 410 (45.1%)
Onset-to-CT time, h	2.2 (1.9)
Neuroimaging variables on NCCT	
ASPECTS	8.0 (4.0)
Significant leukoaraiosis, n	77 / 409 (18.8%)
Hyperdense MCA sign, n	168 / 398 (42.2%)
Silent infarct, *n*	90 / 408 (22.1%)
Neuroimaging variables on CTA	
Collaterals	
Poor	161 / 372 (43.3%)
Partial	136 / 372 (36.6%)
Good	75 / 372 (20.2%)
Clot burden score	6.0 (5.0)
Intracranial occlusion site (most proximal)	
M1 segment of MCA	252 (60.7%)
M2 segment of MCA	163 (39.3%)
Extracranial carotid pathology	
Significant stenosis	41 / 413 (9.9%)
Any occlusion	103 / 413 (24.9%)
Significant proximal° intracranial pathology	197 / 414 (47.6%)
Significant distal° intracranial pathology	339 / 411 (82.5%)
Neuroimaging variables on CTP	
Infarct volume, mL	39.7 (65.6)
Penumbra volume, mL	79.4 (77.0)
Total ischemia volume, mL	133.6 (104.2)
Mismatch ratio, *n*	2.8 (4.8)

volumes and collateral status. *Higher MR* was found in the absence of hyperdense MCA sign (HR = 1.28; 95% CI = 1.04–1.59) and absence of distal intracranial occlusion (HR = 1.39; 95% CI = 1.06–1.82). Finally, higher MR correlated with better collaterals (HR = 0.52; 95% CI = 0.39–0.70).

We present graphically the significant associations between core volumes and ASPECTS, CBS, and collaterals and between MR and collaterals in Fig. 1 and additional significant associations (i.e., between core volumes and hyperdense MCA sign, penumbra volumes and CBS, MR and hyperdense MCA sign and distal intracranial occlusion) in online Fig. 3S.

Discussion

In our cohort of 415 AIS patients with proximal MCA occlusion, we found that a better degree of collaterals related to a smaller ischemic core and greater mismatch ratio, but we could not demonstrate an independent association between better collaterals and higher penumbra volumes. Furthermore, proximal occlusions (hyperdense MCA sign) were associated with higher core volumes and distal occlusions with lesser penumbra volumes. Similarly, longer clot (i.e., lower CBS) correlated with a more extended core and smaller clot (i.e. higher CBS) with less penumbra. These results were independent of time since stroke onset to brain imaging.

The negative association between ASPECTS and ischemic core volumes on CTP was expected [21] indicating that quantification of early ischemic changes on NCCT is a reliable measure of infarct cores in anterior circulation stroke.

An inverse relationship between core volume and collateral patency is in agreement with previous reports and supports the major impact of collateral circulation on the early transformation of ischemia into infarct [22, 23]. The lack of a correlation between penumbra volumes and collaterals was unexpected and not in agreement with previous studies [4, 24]. Most investigators regard collaterals as a compensatory network preserving blood flow in the setting of acute ischemia. However, according to our results measured by CTP, collaterals seem to influence more the extent of the ischemic core rather than sustenance of penumbra. A possible explanation for this finding is that poor collaterals lead to early infarct and good collaterals to benign oligemia, reducing the critical hypoperfusion (penumbra) region between these two thresholds. Alternatively, our finding may reflect an artifact of our imaging protocol: penumbra defined by our CTP acquisition allows for delayed leptomeningeal contrast arrival whereas early arterial phase CTA underestimates collateral status substantially. This could affect more the measurement of penumbra than of core and may explain the absence of a clear relationship between collaterals and penumbra.

Our data confirm the previously observed association of higher mismatch ratios with good collaterals [1, 22, 25]. Nevertheless, we found proportionally more salvageable tissue

Table 2 Results from MVA showing significant associations between radiological variables and the three main outcomes, expressed as hazard ratio (HR) and 95% confident interval (CI). All results are adjusted for time from stroke onset to brain imaging. Higher HRs signify lower response values (i.e., negative association). Empty fields indicate no significant association. Italicized values signify a favorable and bold italicized an unfavorable CTP pattern

Radiological variables	Core volume	Penumbra volume	Mismatch ratio
ASPECTS	*1.08 (1.03–1.12)*	–	–
Hyperdense	***0.70***	–	***1.28***
MCA sign	***(0.55–0.89)***		***(1.04–1.59)***
Distal intracranial occlusion	–	***1.47 (1.11–1.94)***	***1.39 (1.06–1.82)***
Clot burden score	*1.10 (1.05–1.15)*	***1.08 (1.04–1.12)***	–
Better collaterals	*1.95 (1.44–2.63)*	–	*0.52 (0.39–0.70)*

Distal intracranial occlusion indicates distal M1 or M2 occlusion

ASPECTS Alberta Stroke Program Early CT Score, *MCA* middle cerebral artery, *CBS* clot burden score, *MR* mismatch ratio

in patients with good collaterals due to lower core, rather than to higher penumbra volumes.

Regarding the vascular site of occlusion, we found an association of the hyperdense MCA sign, an indicator of proximal MCA occlusion, with higher core volumes and a less extensive MR. Another study has also shown that increased thrombus attenuation was associated poor baseline collateral status [26]. On the other hand, the more distal intracranial occlusions, resulting in greater superficial localization of stroke, were associated with smaller penumbras and a lesser MR, possibly because fewer leptomeningeal collaterals are available in the setting of a cortical infarction.

We expected the association of a higher clot burden (which represents lower CBS) with larger core volumes, probably because extended clots obstruct more arterial branches. Interestingly, higher clot burden was also associated with a larger penumbra volume. This finding was independent of collateral status, suggesting intuitively that larger clots bring larger ischemia volumes, including larger cores and larger penumbras.

The location and size of thrombus along with the degree and extent of collaterals likely determine the amount of damaged and salvageable tissue in acute ischemic stroke from large vessel occlusion. Therefore, as expected, most of these

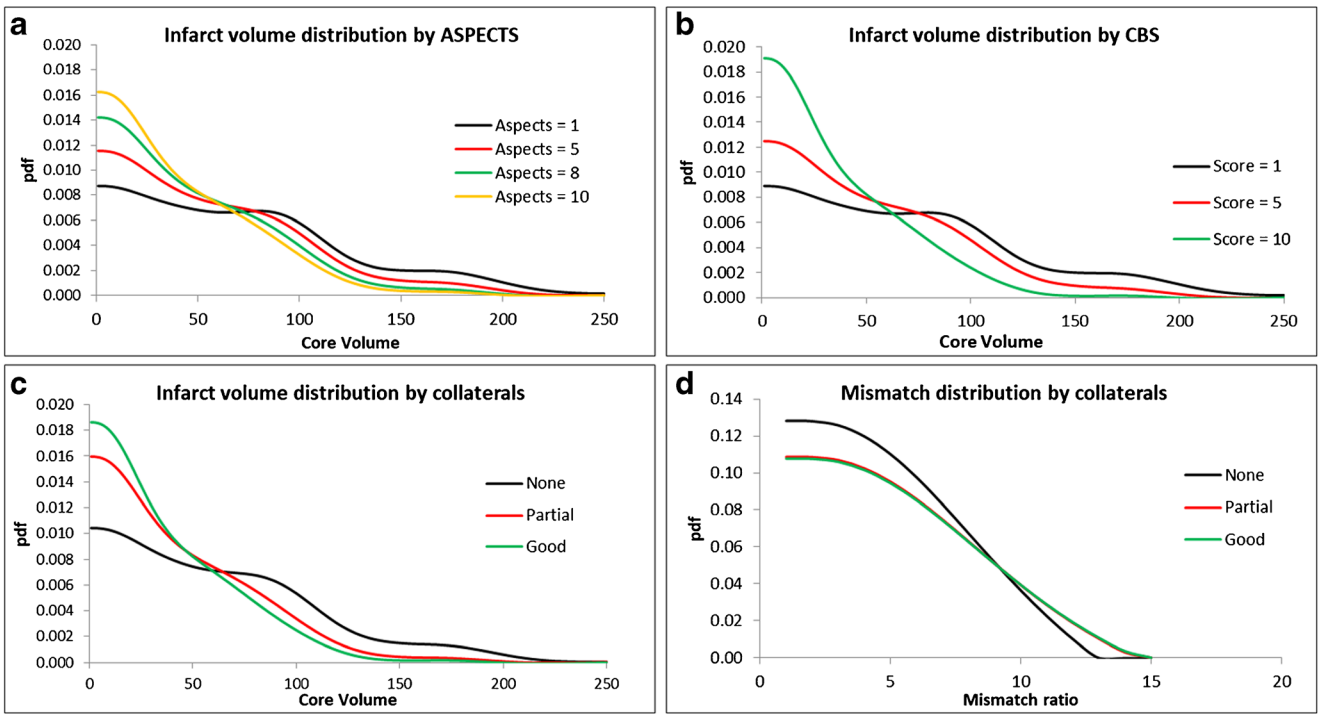

Fig. 1 **a** Correlation between infarct volume and ASPECTS. **b** Correlation between infarct volume and clot burden score. **c** Correlation between infarct volume and collaterals. **d** Correlation between MR and collaterals

variables are strongly related to each other. The major focus of our research has been to identify which radiological features available on non-advanced neuroimaging (NCCT and CTA) help to predict the CTP profile of acute ischemic stroke patients. Taking into account all the potential limitations related to the neuroimaging protocol (as discussed below), our results have several implications. The association of lower core volumes with good collaterals suggests a major role of the latter in early tissue loss. On the other hand, the absence of an independent correlation between penumbra volumes and collaterals might indicate that collateral assessment per se is a poor substitute for penumbral tissue. The implication of our findings for the clinic is that collaterals and core may represent a similar tissue marker, and we could perhaps use them interchangeably, whereas collaterals and penumbra volumes do not. Further, patients with a pattern of small core and good collaterals seem to be the best candidates for acute revascularization treatment, and this independently of the time of stroke onset, as previously suggested [27]. Supporting these observations, the recent ESCAPE trial showed highly favorable outcomes for acute thrombectomy based on assessment of collateral flow using multiphasic CTA [9] and independently of stroke onset-to-treatment time [28].

The limitations of our study include its retrospective, non-randomized design and its single-center nature. Moreover, our dataset comes from a tertiary stroke center with a predominantly elderly, Caucasian population, which may not be representative of other settings. Still, demographics and stroke mechanisms of our population (Table 1) are comparable to other Western stroke populations (i.e., SITS-MOST and REGARDS registry).

Regarding the radiological protocol, we used single-phase CTA (sCTA), which may lead to technique-dependent bias in collateral evaluation due to variability in the timing of the contrast injection and image acquisition [29, 30]. This represents a major limitation of our study, potentially affecting the absence of an independent relationship between collaterals and penumbra volumes. Compared to sCTA, multi-phase CTA (mCTA), by acquiring temporal information at three data points, has the advantage of a more dynamic and time-resolved assessment of collaterals [31] and is a proven selection tool for endovascular treatment up to 9 h after stroke onset [9]. mCTA also allows the detection of an eventual occult anterograde flow through thrombus, which could contribute, together with the retrograde flow, to the determination of the actual leptomeningeal collateral status [32]. Our findings may still be of importance, however, given that sCTA is more frequently used in clinical practice, and that other authors have reported similar findings as we do [22].

The CTP threshold model used for determination of core and penumbra is based on a systematic method of development [15], while other models have been used in the literature with limited direct comparisons between methods [33]. We had to exclude a number of patients because of missing values of good-quality CTP reconstructions. Finally, we intentionally did not adjust the analysis to clinical and metabolic variables, aiming for purely radiological associations, although these variables may be relevant for level of perfusion deficit.

Conclusion

Our large-sample study of AIS patients with proximal MCA occlusion showed that a better degree of collaterals was related to a smaller ischemic core and consequently a higher mismatch ratio, independently of time from stroke onset. We did not show a correlation between collateral status and penumbra volumes, the latter appearing influenced more by the characteristics of the occlusive thrombus (distal location and shorter length). Our results highlight the importance of the degree of collateral circulation in determining the extent of the core volume in the initial diagnostic workup. Furthermore, our findings may help clinicians in decision-making process when CTP is not available or cannot be performed.

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Author's contribution SN studied the concept and design and helped in the analysis and interpretation and preparation of the article. CWC, GS and DS helped in the interpretation of data and critical revision of the article for important intellectual content. DL carried out data analysis and interpretation and helped in the preparation of the article. AE helped in data acquisition and analysis. VD helped in data acquisition and critical revision of the article for important intellectual content. MW contributed to the conception and design and helped in the interpretation of data. PM studied the concept and design and helped in the data acquisition, analysis, and interpretation and critical revision of the article for important intellectual content, study supervision.

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Compliance with ethical standards

Conflict of interest In the last 3 years, PM received research grants from the Swiss Heart Foundation, Boehringer-Ingelheim and BMS through his institution; speaker fees from Boehringer-Ingelheim, Bayer, Daiichi-Sankyo, Medtronic and Amgen; honoraria from scientific advisory boards from Boehringer-Ingelheim, Bayer, Pfizer and BMS; and consulting fees from Medtronic, Astra-Zeneca and Amgen. PM's institution (CHUV) receives all of the support for stroke education and research. GS served on scientific advisory boards for Amgen and Daiichi-Sankyo. CWC received research grants from the Swiss Heart Foundation, Advisory Board of Research (EOC) and Boehringer-Ingelheim in the last 3 years through his institution, and honoraria from scientific advisory boards from Boehringer-Ingelheim, Bayer and Pfizer.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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ORIGINAL RESEARCH

Eligibility for late endovascular treatment using DAWN, DEFUSE-3, and more liberal selection criteria in a stroke center

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ABSTRACT

Background and purpose The real-life application of DAWN and DEFUSE-3 trials has been poorly investigated. We aimed to identify the proportion of patients with acute ischemic stroke (AIS) eligible for late endovascular treatment (EVT) in our stroke center based on trial and more liberal selection criteria.

Methods All consecutive patients in our stroke registry (2003–2017) admitted within 5–23 hours of last proof of good health were selected if they had complete clinical and radiological datasets. We calculated the proportion of patients eligible for late EVT according to trial (DAWN and/or DEFUSE-3) and more liberal clinical/imaging mismatch criteria (including lower admission National Institutes of Health Stroke Scale score and Alberta Stroke Program Early CT Score for core estimation).

Results Of 1705 patients with AIS admitted to our comprehensive stroke center in the late time window, we identified 925 patients with complete clinical and radiological data. Among them, the proportions of late EVT eligibility were 2.5% (n=23) with DAWN, 5.1% (n=47) with DEFUSE-3, and 11.1% (n=103) with more liberal criteria. Considering late-arriving patients with large vessel occlusion (n=221), the percentages of eligible patients were 10.4%, 21.3%, and 46.6%, respectively. A favorable outcome was observed at comparable rates in treated patients selected by trial or liberal criteria (67% vs 58%, p=0.49).

Conclusions In a long-term stroke registry, the proportion of late EVT eligibility varied greatly according to selection criteria and referral pattern. Among late-arriving patients referred to our comprehensive stroke center, we found 5.6% eligible according to trial (DAWN/DEFUSE-3) and 11.1% according to liberal criteria. These data indicate that late EVT could be offered to a larger population of patients if more liberal criteria are applied.

INTRODUCTION

Endovascular treatment (EVT) for patients with acute ischemic stroke (AIS) with proximal intracranial large vessel occlusion (LVO) is well demonstrated within the first 6 hours after onset when most patients have limited irreversible damage and significant amounts of salvageable brain tissue.[1] Recently, two randomized clinical trials showed the effectiveness of late EVT up to 24 hours, based on radiological selection of patients with AIS having small core volume and either severe clinical symptoms (clinical-core mismatch in the DAWN trial) or a large perfusion deficit (perfusion mismatch in the DEFUSE-3 trial).[2 3]

Scant data exist on the number of late-arriving patients who are eligible for EVT in the real world.[4] The calculation of the proportion of patients eligible for such treatment is of major importance for implementing DAWN and DEFUSE-3 results and, consequently, reorganizing stroke systems of care. Moreover, the precise measurement of lesion volumes with sophisticated imaging may be difficult in the acute stroke scenario due to patient agitation, contrast product contraindications, or technical problems with perfusion imaging. Therefore, simpler and more liberal criteria to determine the clinical/imaging mismatch could be useful in clinical practice.

The main purpose of our study was to identify the proportions of patients with AIS eligible for late EVT in our endovascular-capable stroke center using strict trial (DAWN and/or DEFUSE-3) criteria and more liberal clinical/imaging mismatch criteria. Moreover, we searched for clinical and laboratory variables independently associated with late EVT eligibility according to trial and liberal criteria. Then, we provided a description of our real-life cohort treated by late EVT and the outcome analysis at 3 months.

MATERIALS AND METHODS

Study design

We performed a retrospective analysis of all patients with AIS admitted to our comprehensive stroke center from January 2003 to December 2017, using the Acute STroke Registry and Analysis of Lausanne (ASTRAL) as our data source.[5] ASTRAL is a single center-based cohort of all AIS patients admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital within 24 hours after last proof of good health (LPGH). It incorporates more than 250 prespecified demographic, clinical, laboratory variables and modern multimodal brain imaging items on over 4500 consecutive patients with AIS. The STROBE method (Strengthening the Reporting of Observational Studies in Epidemiology) was applied. The local ethics commission

approved the scientific use of anonymized data from the ASTRAL registry.

Patient selection

We included late-arriving/treatable patients—that is, those admitted 5–23 hours after LPGH (including patients with unknown daytime stroke onset and wake-up stroke). This time window allowed patients to be potentially treated by an endovascular procedure between 6 and 24 hours. We then selected patients with complete datasets allowing an eligibility calculation according to trial criteria, including availability of good quality CT perfusion (CTP).

Patients were defined eligible according to the DAWN and DEFUSE-3 enrolment criteria, as reported previously.[6 7] In our study cohort we applied the DEFUSE-3 criteria up to 23 hours; this allowed a combined evaluation of trial eligibility in the late time window and was based on the assumption that clinical outcomes were better in later than earlier treated patients.[8]

In addition, we proposed more liberal and pragmatic selection criteria for late EVT that included less severe stroke on admission (National Institutes of Health Stroke Scale (NIHSS) score ≥5), mild pre-stroke disability (modified Rankin Scale (mRS) ≤2), non-contrast CT (NCCT) Alberta Stroke Program Early CT Score (ASPECTS) cut-offs for core volume estimation (≥5), and presence of internal carotid artery (ICA), M1, proximal M2 or basilar artery occlusions on CT angiography (CTA). Moreover, the liberal criteria required a clinical/imaging mismatch in the anterior circulation strokes defined as: NIHSS 5–9 and ASPECTS ≥8; or NIHSS ≥10 and ASPECTS ≥7; or NIHSS ≥20 and ASPECTS ≥5. For posterior circulation (pc) stroke, eligibility required pc-ASPECTS ≥8 and absence of bilateral (transverse) pontine or midbrain infarction. The choice of ASPECTS for infarct core estimation reflects the intent of the liberal criteria to offer EVT to a wider proportion of late-arriving patients, even in centers where access to advanced imaging is limited.

We measured clinical outcome at 3 months using the mRS, either in person at the outpatient stroke clinic or in a standardized telephone interview by Rankin-certified medical personnel. A favorable outcome was defined as mRS ≤2.

Neuroimaging protocol

Multimodal CT-based imaging including NCCT, CTP, CTA, and post-contrast series, was performed in patients with suspected AIS as standard of care unless contrast contraindication existed. We performed CT on a 16-detector CT scanner until November 2005 and on a 64-multidetector CT scanner thereafter (LightSpeed VCT or Revolution, GE Healthcare, Milwaukee, Wisconsin, USA). We acquired NCCT and post-contrast series in axial scan mode from the skull base to the vertex (16 cm z-axis coverage) using the following imaging parameters: 120 kV peak tube voltage, 320 mA tube current, 5 mm slice thickness, 32 cm scan field of view (SFOV), 512×512 matrix. All CTP series were acquired with 80 kV peak tube voltage, 240 mA tube current, 32 cm SFOV, and 512×512 matrix. Images were centred on the level of the basal ganglia and third ventricle. We used 40 mm z-axis coverage until November 2005, 80 mm z-axis coverage until November 2015, and 120 mm z-axis coverage thereafter. CTP images were acquired for 50 s in cine mode before January 2011 and in shuttle mode thereafter. Delay was 5–7 s after beginning injection of 50 mL of iodinated contrast (Accupaque 300, iohexol 300 mg/mL, GE Healthcare, Glattbrugg, Switzerland) in an antecubital vein at a flow rate of 5 mL/s followed by 50 mL of 0.9% NaCl solution at the same flow rate.

We previously assessed inter-rater variability using Cohen's kappa on 100 consecutive CT scans of acute anterior circulation occlusive strokes and found an excellent agreement for ASPECTS (kappa 0.82). The use of ASPECTS for core volume estimation was supported by unpublished data from ASTRAL showing a moderate correlation between ASPECTS and core volume on CTP in the presence of LVO and in a late time window (Spearman $\rho = -0.58$, $p < 0.001$). This assumption is in agreement with previous reports[9 10] and supported by the fact that hypoattenuation on CT was proved to be highly specific for irreversible ischemic brain damage.[11]

We analysed CTP data using the Brilliance Workspace Portal (Philips Medical Systems, Cleveland, Ohio, USA) deconvolution software. The core and penumbra volumes were automatically generated using the appropriate mean transit time (MTT) and cerebral blood volume (CBV) thresholds (penumbra: MTT >145% of the contralateral side value, CBV ≥2.0 mL/100 g; core: MTT >145% of the contralateral side value, CBV <2.0 mL/100 g).[12] We calculated the mismatch ratio as the ratio of the total ischemic volume (ie, core plus penumbra volumes) to the core volume.

Statistical analysis

We calculated the numbers of late EVT eligible patients according to the three sets of selection criteria (DAWN, DEFUSE-3, liberal). We chose the following denominators: (a) all AIS patients arriving within 24 hours; (b) all late-arriving patients (5–23 hours); (c) late-arriving patients with the necessary multimodal imaging available; (d) late-arriving patients with emergent LVO. We selected two scenarios: (1) the stroke population arriving at our comprehensive stroke center; and (2) the population from the primary catchment area (ie, patients for whom our institution is the hospital of reference, independently of the need for specialized stroke treatment).

We first performed a univariate comparison of the three groups of eligible patients according to their baseline characteristics. In order to account for correlations between the criteria, we used the method of generalized estimation equations (GEE).[13] This method allows modelling correlated multiple outcomes using an approach inspired by quasi-likelihood. In our situation, the estimated parameters are OR, quantifying the association between a variable and the probability to satisfy each criterion, and ratios of odds ratios (ORR), quantifying the relative strength of the associations.

We then performed a multivariate analysis to identify independent variables associated with late EVT eligibility according to trial and liberal criteria. All demographic, clinical, and laboratory variables at baseline, as well as pre-stroke treatments and vascular risk factors, were included in this analysis. We used a logistic regression model and implemented a variable selection method via backwards elimination of variables with least significant ORs, until all ORs were significant. When needed, we inserted the last eliminated variable back into the model until good calibration was reached. We used non-significance of the Hosmer–Lemeshow test as the criterion for good calibration. In all analyses the level of significance was set at 5%. All analyses were performed with R version 3.4.2 software.

RESULTS

Study population

During the observational period, four denominators emerged according to the methods described above: we identified (A) 4653 patients with AIS arriving between 0 and 24 hours; (B) 1705

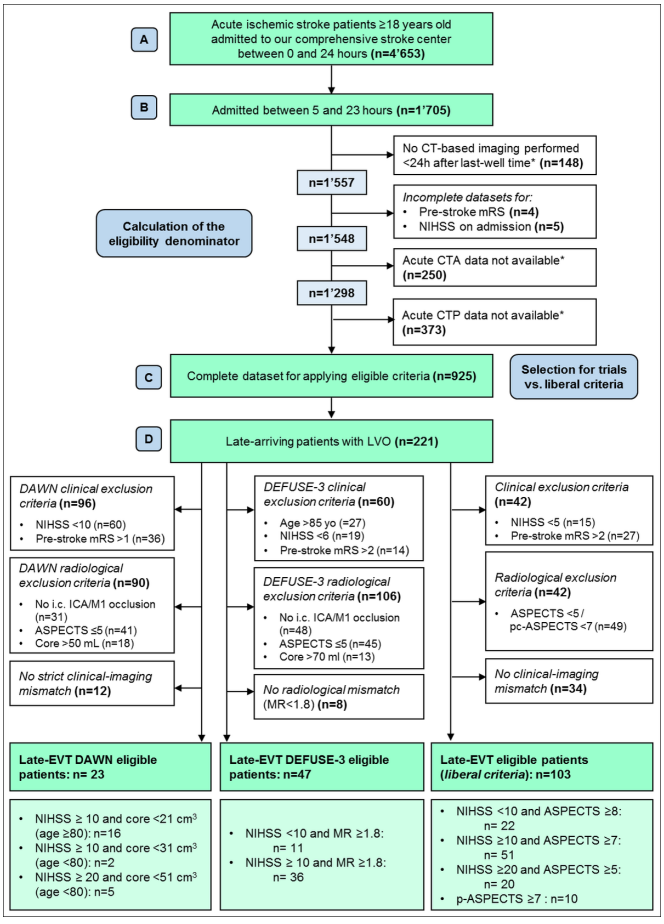

Figure 1 Flow chart eligibility in our comprehensive stroke center. We first identified four denominators: (A) total number of patients with acute ischemic stroke (AIS) admitted to our institution between 0 and 24 hours over the study period; (B) number of patients with AIS admitted late (5–23 hours); (C) number of late AIS patients with complete datasets; and (D) late-arriving patients with emergent LVO. We then applied the DAWN criteria, DEFUSE-3 criteria, and more liberal selection criteria to identify patients with AIS eligible for late endovascular treatment (EVT) accordingly. *See online supplementary table e–1 for additional information about radiological exclusion criteria.

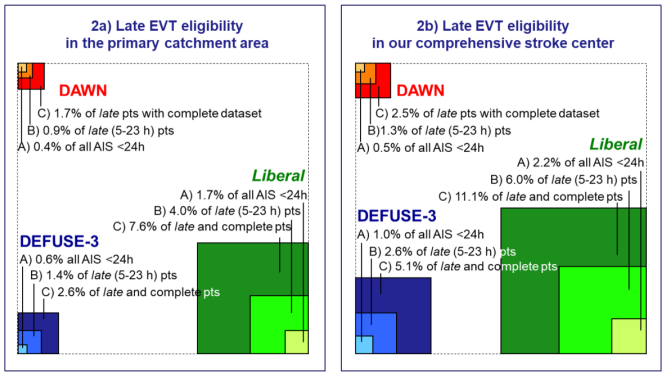

Figure 2 Proportion of patients with acute ischemic stroke (AIS) eligible for late endovascular treatment (EVT) according to DAWN, DEFUSE-3, and more liberal criteria from all patients with AIS admitted in the first 24 hours of last proof of good health, patients admitted late (5–23 hours), and patients admitted late with complete neuroimaging protocols. The data refer to our primary catchment area (A) and our comprehensive stroke centre (B).

(36.6%) late-arriving (5–23 hours from LPGH) AIS patients; (C) 925 (19.9%) late-arriving AIS patients with complete clinical and radiological datasets for investigating eligibility criteria; and (D) 221 (4.7%) late-arriving patients with LVO. The flow chart of eligible patients is depicted in figure 1. Additional information on the population selection process is available in online supplementary table e–1.

In the main group of interest (C), the median age was 72.3 (IQR 20.5) years, 444 (48.0%) patients were female, and median NIHSS score on admission was 5 (8). Two hundred and twenty-seven (24.5%) patients were distant referrals, sent from community hospitals or bypassing distant emergency departments. Other characteristics of group C are shown in online supplementary table e–2.

Frequency of late EVT eligibility

For DAWN eligibility, 96 patients were excluded for clinical reasons, mainly lower stroke severity on admission (NIHSS <10, n=60) (figure 1). In addition, 90 patients did not meet the radiological criteria. A small number of patients (n=12) did not have the minimal clinical/core mismatch. Finally, only 23 patients were eligible for late EVT according to the DAWN criteria.

When applying the DEFUSE-3 criteria, 60 patients were excluded on a clinical basis. Moreover, approximately half of the patients did not have radiological inclusion criteria, mainly due to the distal site of vascular occlusion (n=48). The required radiological mismatch was absent in 8 patients, leading to 47 eligible patients according to DEFUSE-3 trial criteria. Overall, 52 patients satisfied DAWN and/or DEFUSE trial criteria.

Using our more liberal evaluation, we excluded 42 patients for clinical reasons, mainly based on higher pre-stroke disability. An additional 42 patients did not exhibit the radiological criteria. We did not find the more liberal clinical/core mismatch in 34 patients and finally identified 103 eligible patients. Ten of the patients presented with a posterior stroke from basilar artery occlusion which we considered eligible.

In the population from the primary catchment area only (n=698), 12 patients were eligible for late EVT based on DAWN criteria, 18 on DEFUSE-3 criteria, and 53 with less stringent criteria (online supplementary figure e–1).

The proportions of late EVT eligibility for the three denominators A, B, and C are shown in figure 2 for the primary catchment area (figure 2a) and comprehensive (figure 2b) populations. Among late-arriving patients with complete clinico-radiological assessment (ie, denominator C), the proportions of late EVT eligibility were 2.5% with DAWN, 5.1% with DEFUSE-3, and 11.1% with more liberal criteria. Considering only the primary catchment area, the percentages were 1.7%, 2.6%, and 7.6%, respectively.

The proportions of late EVT eligibility for patients with emergent LVO (ie, denominator D) are shown in online supplementary figure e–2. DAWN criteria would allow treating 10.4% of late-arriving patients with LVO, while 21.3% would be eligible according to DEFUSE-3 selection criteria. Adopting our liberal approach, 46.6% of patients with LVO would be suitable for late EVT.

Characteristics of the eligible patients

We found a partial overlap between the three eligibility groups. Fifty-two patients fulfilled the strict trial criteria (DAWN and/or DEFUSE-3). All but five DAWN-eligible patients were also DEFUSE-3-eligible (18/23, 78.3%) and 18/47 (38.3%)

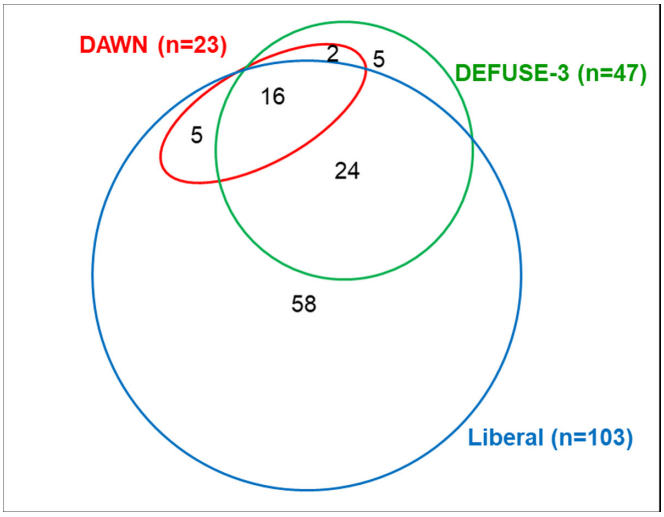

Figure 3 DAWN (n=23, in red), DEFUSE-3 (n=47, in green), and liberal (n=103, in blue) late endovascular treatment (EVT)-eligible patients in our late-arriving acute ischemic stroke population. Circles show the partial overlaps between the three groups of patients: 52 patients fulfilled DAWN and/or DEFUSE-3 criteria whereas 45 liberal patients also matched the trial criteria. All but five DAWN-eligible patients were also DEFUSE-3-eligible, and 18/47 (38.3%) DEFUSE-3-eligible patients were also DAWN-eligible. Only seven trial-eligible patients did not present the liberal criteria.

DEFUSE-3-eligible patients were also DAWN-eligible. Among the 103 liberal criteria patients, 45 fulfilled the strict trial criteria. Only seven trial-based patients did not match the liberal criteria; these patients did not present the less stringent clinical/core mismatch but all showed the pure radiological mismatch (figure 3).

In the univariate comparison of baseline characteristics (online supplementary table e–3), the two groups of trial criteria patients appeared similar, except for a higher NIHSS on admission and a higher prevalence of smoking in the DAWN-eligible patients. When comparing the trial and liberal eligible patients (table 1), we found the following radiological differences: trial-based patients had lower ASPECTS, higher frequency of M1 occlusions, higher core volumes, higher penumbra volumes, and higher mismatch ratio.

Factors associated with late EVT eligibility

Among all late-arriving patients with AIS, EVT eligibility based on the strict trial criteria was independently associated with neurological signs such as hemiparesis, visual field defects and eye deviation, and with a shorter delay to hospital arrival. The variables implicated in determining EVT eligibility using the more liberal criteria were: lower pre-stroke disability, higher NIHSS on admission, eye deviation, hypercholesterolemia, and shorter delay to hospital arrival (table 2).

EVT procedures performed in real life and outcome analysis

Sixty-four patients arriving in the late time window underwent EVT over the study period. Four (6.4%) and 13 (20.3%) treated patients fulfilled the DAWN and DEFUSE-3 criteria, respectively. Thirty-nine of the treated patients (60.9%) complied with the proposed liberal approach. The proportion of late EVT among all revascularization procedures increased from 7% in the 5 years preceding presentation of the DAWN results (May 2017) to 21% after presentation, resulting in a relative increase of 200% in the

Table 1 Demographics, clinical, and radiological characteristics of patients eligible for late EVT according to trial (DAWN and/or DEFUSE-3) and liberal criteria

Variable	Trial-eligible group (n=52)	Liberal-eligible group (n=103)	ORR (95% CI) Trials/Liberal
Age, years	67.7 (22.6)	72.3 (22.0)	0.99 (0.98 to 1.00)
Sex, F	29 (55.6%)	53 (51.5%)	1.19 (0.75 to 1.89)
Pre-stroke mRS	0 (1)	0 (1)	0.89 (0.72 to 1.11)
Stroke characteristics			
NIHSS on admission	15 (8)	15 (9)	0.98 (0.96 to 1.00)
Visual field defects	35 (67.3%)	64 (62.1%)	1.11 (0.67 to 1.85)
Aphasia	27 (51.9%)	53 (52.0%)	0.93 (0.59 to 1.49)
Neglect	22 (42.3%)	37 (36.6%)	1.20 (0.76 to 1.89)
Vigilance impairment	8 (15.4%)	24 (23.5%)	0.52 (0.26 to 1.04)
Wake-up stroke	32 (61.5%)	55 (53.4%)	1.43 (0.88 to 2.33)
Process measures			
LPGH-to-arrival time, min	577 (316)	526 (363)	1.01 (0.97 to 1.04)
LPGH-to-CT time, min	615 (304)	587 (379)	1.08 (1.00 to 1.15)
Pre-stroke treatments			
Antiplatelet	16 (30.8%)	34 (33.0%)	0.89 (0.54 to 1.47)
Anticoagulation	7 (13.5%)	9 (8.7%)	1.69 (0.94 to 3.03)
Antihypertensive	27 (52.9%)	56 (55.5%)	0.90 (0.56 to 1.43)
Statin	14 (27.5%)	27 (26.7%)	1.04 (0.62 to 1.75)
Vascular risk factors			
Hypertension	30 (57.7%)	60 (58.8%)	0.96 (0.60 to 1.54)
Diabetes	5 (9.6%)	16 (15.7%)	0.56 (0.25 to 1.23)
Hyperlipidaemia	20 (39.2%)	45 (44.6%)	0.78 (0.48 to 1.27)
Current smoking	9 (17.7%)	23 (22.6%)	0.74 (0.38 to 1.41)
Radiological variables			
ASPECTS	8 (2)	9 (2)	**0.93 (0.87 to 0.99)***
ICA occlusion	16 (30.1%)	25 (24.3%)	1.20 (0.69 to 2.13)
M1 occlusion†	44 (84.6%)	56 (54.4%)	**4.17 (2.04 to 9.09)***
Proximal M2 occlusion†	37 (71.1%)	68 (66.0%)	1.01 (0.58 to 1.74)
Basilar artery occlusion	0 (0%)	10 (9.7%)	NA
Infarct volume, mL	16.1 (32.8)	13.4 (39.0)	**1.07 (1.02 to 1.11)***
Penumbra volume, mL	106.5 (61.6)	90.5 (84.6)	**1.06 (1.02 to 1.10)***
MR	6.0 (17.1)	4.3 (15.5)	**1.01 (1.01 to 1.02)***
Good collaterals	17 (36.1%)	33 (34.4%)	0.82 (0.47 to 1.43)
TOAST mechanism			
Atherosclerotic	10 (20.4%)	16 (16.3%)	1.32 (0.69 to 2.56)
Cardioembolism	22 (44.9%)	44 (44.9%)	0.95 (0.58 to 1.54)
Undetermined (including ESUS)	13 (26.5%)	29 (29.6%)	0.83 (0.48 to 1.45)
Real EVT			
Late EVT performed	14 (26.9%)	27 (26.2%)	1.49 (0.76 to 2.92)
LPGH-to-groin puncture, min	643 (145)	641 (300)	1.03 (0.97 to 1.10)
Favourable outcome			
In all patients	25 (50.0%)	48 (48.0%)	1.20 (0.74 to 1.96)
In patients with EVT	8/12 (66.7%)	14/24 (58.3%)	2.04 (0.39 to 11.1)

Results from the univariate analysis between trial and liberal-eligible patients are presented as ratios of odds ratios (ORR) and their 95% CI.
*Denotes significant results.
†With or without more proximal occlusion.
ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; ICA, internal carotid artery; LPGH, last proof of good health; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ORR, ratio of odds ratios.

Table 2 Independent predictors for late EVT eligibility according to trial and liberal criteria in late-arriving patients with AIS (n=925)

	Trial (DAWN and/or DEFUSE-3) eligibility		Liberal eligibility	
Predictors	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Pre-stroke mRS	–	–	0.64 (0.48 to 0.86)	<0.01
Hypercholesterolemia	–	–	2.79 (1.43 to 5.46)	<0.01
NIHSS	–	–	1.12 (1.07 to 1.16)	<0.01
Eye deviation	2.94 (1.44 to 6.01)	<0.01	2.06 (1.08 to 3.92)	0.03
Visual field defects	2.75 (1.32 to 5.70)	0.01	–	–
Hemiparesis	4.72 (1.10 to 20.30)	0.04	–	–
LPGH-to-arrival time	0.95 (0.91 to 0.98)	<0.01	0.94 (0.91 to 0.97)	<0.01

Only significant results are shown. The model for liberal eligibility also included the variables known onset, statin use, smoking, and systolic blood pressure on admission, which were included to obtain a good calibration of the model according to the Hosmer–Lemeshow test. The time unit for LPGH-to-arrival time is 30 min.
AIS, acute ischemic stroke; EVT, endovascular treatment; LPGH, last proof of good health; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

last 8 months of the study period (online supplementary figure e–3). A favorable outcome was observed at comparable rates in treated patients selected by trial or liberal criteria (67% vs 58% respectively, p=0.49) (table 1).

DISCUSSION

In this study we performed a single-center analysis to determine the percentage of patients who could benefit from EVT in the extended time window. We found that the proportion of patients with late EVT eligibility varied greatly according to the selection criteria and referral patterns. Among patients with AIS admitted late to our comprehensive stroke center and assessed with a multimodal neuroimaging protocol, we found that 2.5% were eligible according to DAWN trial criteria and 5.1% according to DEFUSE-3 trial criteria. This proportion reached 11.1% when more liberal selection criteria were applied. Considering only the local population in the primary catchment area, these percentages fell to 1.7%, 2.6%, and 7.6%, respectively.

A previous study performed in our stroke center reported that 10.5% of all patients with AIS presenting within 6 hours of symptom onset were eligible for EVT according to the American Heart Association/American Stroke Association guidelines.[14] The frequency of EVT eligibility was higher (17.7%) if less restrictive criteria were adopted. We expected these percentages to be lower in the late-arriving AIS population, mainly because of the strict selection criteria used in the randomized clinical trials, but also because patients with LVO seem to arrive earlier at the hospital.[15] Another published study on late EVT eligibility in a stroke center found that 1.7% of all patients with AIS qualified for enrolment in the DAWN trial and 2.2% for enrolment in the DEFUSE-3 trial.[4] To the best of our knowledge, our study is the first to examine late EVT eligibility in a real-life scenario.

Several factors could contribute to the low eligibility for late EVT in real life. First, a substantial proportion of late-arriving patients were excluded due to lack of a complete neuroimaging protocol. In addition to the well-known contraindications to iodinated contrast (allergy, renal impairment), we did not obtain perfusion imaging for a non-negligible number of patients in our CT-based emergency center due to ordering failures or moving patients. Second, we found that approximately two-thirds of late-presenting AIS patients did not meet the clinical inclusion criteria required by the trials due to age (>85 years), important pre-stroke disability (mRS >2), or too low NIHSS score on admission. Third, late-presenting LVO strokes commonly had larger core volumes than the thresholds (50 and 70 mL) needed for trial eligibility.

As a meaningful finding, we identified a LVO in 23.9% of late-arriving patients with AIS. This defines a target subpopulation of stroke patients that should be promptly identified as potentially suitable for revascularization treatment. Our analysis showed that about one out of four late-arriving patients with LVO could be treatable if trial criteria were adopted. The application of more liberal criteria in this population could allow treating up to one of two patients.

We showed that DEFUSE-3 criteria, including patients with lower NIHSS score, higher pre-stroke disability, and larger core volumes, allowed enrolling a higher proportion of patients compared with the DAWN trial criteria. As a result, all DAWN-eligible patients except for those aged >85 years were also eligible for the DEFUSE-3 trial in our cohort. Taken together, patients satisfying criteria of at least one of the two trials (DAWN and/or DEFUSE-3) extended EVT eligibility to 5.6% (n=52/925) of AIS patients admitted late to our comprehensive center. Our proposed more liberal selection criteria, characterized by lower NIHSS on admission and mRS of up to 2, extended EVT eligibility to twice as many patients. Moreover, using ASPECTS for core volume estimations, the liberal approach seems more feasible in the real-word clinical practice.

In our study, eligible patients according to trial criteria were best identified using clinical factors including hemiparesis, visual field defects, and eye deviation. As predictors of liberal eligibility, we confirmed eye deviation but also found hypercholesterolemia and the expected lower pre-stroke disability and higher admission NIHSS. In keeping with infarct growth over time[16] and the usual associated reduction of salvageable tissue, we found that delay from stroke onset (or LPGH) to hospital arrival predicts lower eligibility according to both trial and liberal criteria. Despite the fact that carefully selected late and unknown onset patients have major benefit from recanalization,[2 3 8] 'time is still brain' both in the pre- and intra-hospital phase.

Although the number of late-treated patients in our center is insufficient for an appropriately adjusted clinical outcome analysis, we showed a similar rate of favorable outcome in late-treated patients satisfying strict or liberal criteria. This finding might indicate that a proportion of trial-ineligible patients may still benefit from late treatments if less stringent criteria are used, as recently suggested.[17 18] Moreover, data from EVT-treated patients in earlier phases (up to 8 hours from onset) showed that revascularization therapy was still associated with a favorable clinical outcome in the presence of higher core volumes (ie, ASPECTS ≤5 on diffusion-weighted imaging).[19] Similarly, it has been shown that patients not fulfilling guideline criteria for EVT

within 6 hours after onset still benefit from mechanical thrombectomy, even in cases exceeding recommendations for onset-to-groin puncture time.[20] These studies might support a progressive widening of EVT selection criteria in the late time window.

Our study could have several and significant implications for triage, resource allocation, and hospital referral re-organization in order to maximize patient selection for mechanical thrombectomy in the extended time window. The higher frequency of patients who could receive late EVT in the comprehensive stroke center compared with the local catchment area shows that endovascular-capable centers need to develop emergency medical services and close collaborations with referral facilities in order to deliver advanced treatments. Moreover, we observed a large increase in registered late EVT procedures after presentation of the DAWN results, suggesting that recanalization procedures could be implemented rapidly and successfully in clinical practice.

The strengths of our single-center study are the large number of patients with AIS with a thorough homogeneous work-up and the consecutive availability of patients with advanced acute neuroimaging since 2003.

Our study has several limitations, mainly due to its retrospective and single-center nature. First, eligibility in our wider catchment area might not be entirely representative because of fewer referrals before the presentation of the DAWN results; however, our analysis of the primary catchment area should correct for this error. Moreover, advanced neuroimaging information, especially regarding perfusion imaging of referred patients, was not available for a minority (n=373, 21.9%) of late-arriving AIS patients and this likely underestimated the proportion of patients with late EVT criteria. Regarding the neuroimaging protocol, we included only patients with AIS with CT-based assessment of core and penumbra volumes due to the small number of MRI-assessed patients in the ASTRAL registry (n=42, 0.05% of late-arriving population); therefore, we were not able to investigate the imaging modality differences on eligibility and outcome analyses. In addition, the threshold model used for core and penumbra volume reconstructions was different from that adopted in the CT arms of the recent EVT trials,[21] which may affect the evaluation of the DAWN and DEFUSE-3 criteria in clinical practice. Even if not validated in a clinical trial setting, it is a well-established model, based on a systematic evaluation of all perfusion-CT parameters.[12] Finally, our number of treated patients is too small for meaningful interpretation and therefore outcome analysis results should be treated with caution.

CONCLUSIONS

In our comprehensive stroke center, depending on the inclusion criteria used (trial vs liberal), 5.6% to 11.1% of late treatable AIS patients with complete neuroimaging protocols may be eligible for revascularization procedures. This translates to 23.5% and 46.6%, respectively, of late-arriving AIS patients with LVO admitted to our institution. Overall, we showed that, by applying a more liberal approach than strict trial criteria, EVT could be offered to twice as many patients. Efforts should be invested to re-organize stroke care systems and achieve comparable rates in real life.

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