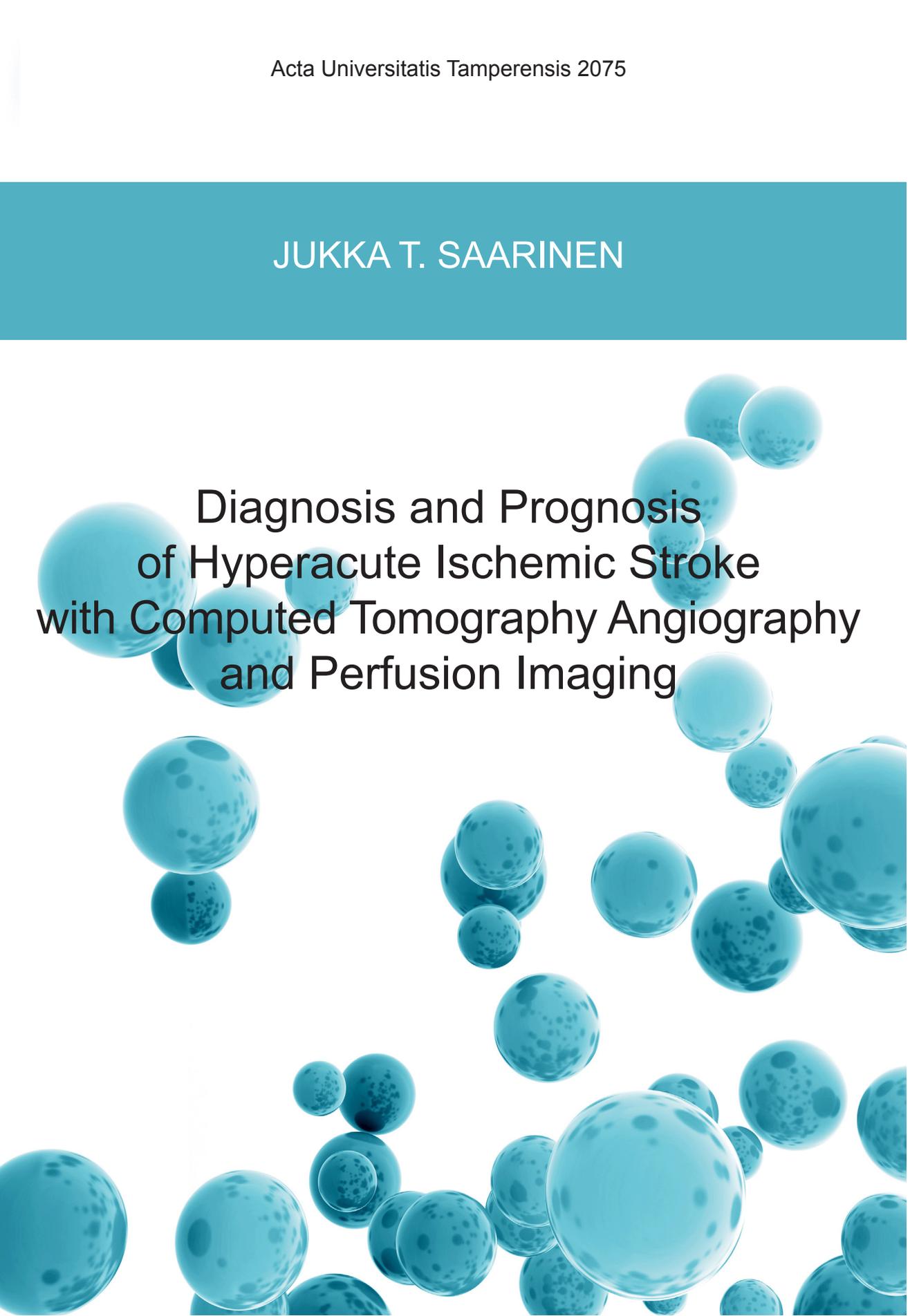


JUKKA T. SAARINEN

Diagnosis and Prognosis  
of Hyperacute Ischemic Stroke  
with Computed Tomography Angiography  
and Perfusion Imaging

The background of the cover features a collection of semi-transparent blue spheres of various sizes, scattered across the white space. The spheres have a subtle gradient and some internal texture, giving them a three-dimensional appearance. They are distributed throughout the page, with a higher density in the lower half.



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ACADEMIC DISSERTATION

To be presented, with the permission of  
the Board of the School of Medicine of the University of Tampere,  
for public discussion in the Main auditorium of building B,  
School of Medicine, Medisiinarinkatu 3, Tampere,  
on 14 August 2015, at 12 o'clock.

UNIVERSITY OF TAMPERE

JUKKA T. SAARINEN

Diagnosis and Prognosis  
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with Computed Tomography Angiography  
and Perfusion Imaging

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# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:

- I) Arsava EM, Saarinen JT, Unal A, Akpınar E, Oguz KK, Topcuoglu MA. Impact of window setting optimization on accuracy of computed tomography and computed tomography angiography source image-based Alberta Stroke Program Early Computed Tomography Score. *J Stroke Cerebrovasc Dis.* 2014 Jan;23(1):12-6. **Arsava EM and Saarinen JT are co-first authors of this article.**
- II) Saarinen JT, Sillanpää N, Rusanen H, Hakomäki J, Huhtala H, Lähteelä A, Dastidar P, Soimakallio S, Elovaara I. The mid-M1 segment of the middle cerebral artery is a cutoff clot location for good outcome in intravenous thrombolysis. *Eur J Neurol.* 2012 Aug;19(8):1121-7.
- III) Saarinen JT, Rusanen H, Sillanpää N. Collateral score complements clot location in predicting the outcome of intravenous thrombolysis. *AJNR Am J Neuroradiol.* 2014 Oct;35(10):1892-6.
- IV) Sillanpää N, Saarinen JT, Rusanen H, Elovaara I, Dastidar P, Soimakallio S. Location of the clot and outcome of perfusion defects in acute anterior circulation stroke treated with intravenous thrombolysis. *AJNR Am J Neuroradiol.* 2013 Jan;34(1):100-6.

Publication II has been used in Niko Sillanpää's thesis Multimodal Computed Tomography in the Evaluation of Acute Ischemic Stroke. *Tampere University Press* 2012.

# ABSTRACT

Stroke continues to be the second leading cause of death worldwide. Brain parenchyma and vascular imaging play a central role in the evaluation of hyperacute stroke patients. Multimodal computed tomography and magnetic resonance imaging have enabled the detection of intracranial hemorrhage, approximation of the volume of reversible and irreversible ischemic changes, and location of the clot and collateral circulation integrity. However, it has not been known how these data can be used in predicting the clinical outcome of ischemic stroke in the presence of intravenous thrombolysis.

In this thesis, a retrospective, observational cohort of 44 hyperacute ischemic stroke patients treated with thrombolytic therapy was examined to determine whether the use of nonstandard, variable window width and center level settings further increases the accuracy of a structured scoring system to detect of early ischemic changes. Another retrospective, observational cohort consisted of 105 patients with detailed clinical information, and we studied the impact of the location of the clot, perfusion computed tomography and collateral circulation in predicting the radiological and clinical outcome of these hyperacute ischemic stroke patients treated with intravenous thrombolysis.

It appeared that the accuracy of the Alberta Stroke Program Early CT Score, which is used to assess the extent of ischemic injury, is markedly improved by the optimization of the window width and center level settings or by the use of computed tomography angiography source images. Three months after ischemic stroke, based on individual sites of occlusions in computed tomography angiography, internal carotid artery, proximal M1 of the middle cerebral artery, distal M1 of the middle cerebral artery, and M2+M3 of the middle cerebral artery

had favorable outcomes of 12%, 24%, 59% and 81% of the cases, respectively. In the regression analysis, after adjusting for National Institutes of Health Stroke Scale, age, sex, and onset-to-treatment time, the clot location was an independent predictor of favorable clinical outcome, and a cut-off between the proximal and the distal M1 segments best differentiated between favorable and unfavorable clinical outcome. A clot in the internal carotid artery resulted in a large cerebral blood volume lesion in perfusion computed tomography. Two-thirds of patients with a proximal occlusion displayed poor collateral filling. Only 36% of patients with a proximal occlusion and good collaterals experienced favorable clinical outcome. In a multivariate analysis, both clot location and collateral score were highly significant and independent predictors of favorable clinical outcome. Good collateral status increased the odds of favorable clinical outcome approximately 9-fold. After dichotomization, a distal clot location had a larger odds ratio compared with the odds ratio of good collaterals.

Our data indicate that the accuracy of detection of early ischemic changes is improved with multimodal computed tomography imaging and that both the location of the clot and the integrity of the collateral circulation are important, independent predictors of clinical outcome in the context of hyperacute ischemic stroke treated with intravenous thrombolysis. Ultimately, the use of advanced imaging selection is a prerequisite to immediate endovascular treatment.

Keywords: ASPECTS, collateral circulation, computed tomography perfusion, computed tomography angiography, ischemic stroke, magnetic resonance imaging, thrombolytic therapy.

# TIIVISTELMÄ

Aivohalvaus on toiseksi yleisin kuolinsyyn maailmassa. Aivojen ja aivoverisuonten kuvantamisella on keskeinen merkitys arvioitaessa aivohalvauspotilaita. Multimodaaliset tietokonetomografia- ja magneettitutkimukset ovat mahdollistaneet aivoverenvuodon havaitsemisen, sekä palautuvan että palautumattoman vaillinaisesta tai puuttuvasta verenvirtauksesta johtuvan aivokudoksen vaurion laajuuden arvioinnin, tukoksen sijainnin paikantamisen ja aivoverisuonten kollateraalikierron arvioinnin. Toistaiseksi ei ole kuitenkaan tarkkaan tiedetty kuinka edellä mainittuja tuloksia voidaan hyödyntää arvioitaessa laskimonsisäistä liuotushoitoa saavien aivoinfarktipotilaiden kliinistä ennustetta.

Tässä väitöstutkimuksessa tarkastelimme aluksi retrospektiivisesti kohorttia, jossa oli 44 liuotushoidon saanutta hyperakuuttia aivoinfarktipotilasta. Tavoitteena oli selvittää parantaako kuvantamisohjelman ikkunoinnin optimointi pisteytysjärjestelmän käytön yhteydessä aivokudoksen varhaisten iskemiamuutosten havaitsemisen tarkkuutta. Tämän lisäksi tarkastelimme retrospektiivisesti 105 potilasta käsittävissä yksityiskohtaisia kliinisiä tietoja sisältävässä kohortissa valtimotukoksen sijainnin, tietokonetomografiaperfuusio-tutkimuksen tulosten ja aivoverisuonten kollateraalikierron merkitystä arvioitaessa laskimonsisäisen liuotushoidon saaneiden hyperakuuttien aivoinfarktipotilaiden radiologista ja kliinistä ennustetta.

Ensimmäisessä tutkimusasetelmassamme kävi ilmi, että aivokudoksen varhaisten iskemiamuutosten laajuuden arviointiin kehitetyn Alberta Stroke Program Early CT Score-pisteytysjärjestelmän tarkkuutta pystyttiin merkittävästi parantamaan tietokonetomografiakuvien ikkunoinnin optimoimisella tai pisteyttämällä tietokonetomografia-angiografiakuvia. Jälkimmäisissä

tutkimuksissamme havaitsimme, että kolme kuukautta aivoinfarktin jälkeen omatoimisia potilaita oli kaulavaltimossa sijainneen tukoksen sairastaneiden joukossa 12%, keskimmäisen aivovaltimon M1-haaran alkuosan tukoksissa 24% ja keskimmäisen aivovaltimon M1-haaran loppuosan tukoksissa 59%. Sekä M2- että M3-haarojen tukoksissa omatoimisia potilaita oli 81%. Logistisessa regressioanalyysissä tukoksen sijainti oli tilastollisesti merkitsevästi itsenäinen omatoimisuuden ennustaja, kun National Institutes of Health Stroke Scale-pisteytys, ikä, sukupuoli ja viive sairastumisesta liuotushoidon aloitukseen oli otettu huomioon. M1-haaran alku- ja loppuosan välillä oli suurin ero arvioitaessa hyvää ja huonoa ennustetta. Kaulavaltimossa oleva tukos johti suureen perfuusiohäiriöön aivojen veritilavuuskartan perusteella tulkittuna tietokonetomografiaperfuusiotutkimuksessa. Kahdella kolmasosalla potilaista joilla oli kaulavaltimon tai keskimmäisen aivovaltimon alkuosan tukos, oli huono aivojen kollateraalikierto. Vain 36% potilaista joilla oli hyvä kollateraalikierto ja kaulavaltimon tai keskimmäisen aivovaltimon alkuosan tukos, oli omatoimisia kolmen kuukauden kuluttua aivoinfarktista. Monimuuttuja-analyysissä sekä tukoksen sijainti että kollateraalikierto ennustivat itsenäisesti ja erittäin merkitsevästi omatoimisuutta. Hyvä kollateraalikierto nosti omatoimisuuden todennäköisyyden yhdeksänkertaiseksi. Tukoksen sijainti keskimmäisen aivovaltimon M1-haaran loppuosassa tai M2- ja M3 haaroissa ennusti omatoimisuutta kuitenkin hyvää kollateraalikiertoa vahvemmin.

Tulostemme perusteella multimodaalisella tietokonetomografialla todettu valtimotukoksen sijainti ja aivojen kollateraalikierto vaikuttivat merkitsevästi ja itsenäisesti kliiniseen kolmen kuukauden ennusteeseen laskimonsisäisellä liuotushoidolla hoidetuilla hyperakuuteilla aivoinfarktipotilailla. Aivojen ja aivoverisuonten kuvantaminen on edellytys oikealle potilasvalinnalle hyperakuutin aivoinfarktin valtimonsisäisiä hoitotoimenpiteitä harkittaessa.

# ABBREVIATIONS

3D	three-dimensional
A1	A1 segment of the anterior cerebral artery
ACA	anterior cerebral artery
ACommA	anterior communicating artery
ADC	apparent diffusion coefficient
AHA	American Heart Association
AIF	arterial input function
aPTT	activated partial thromboplastin time
ASPECTS	Alberta Stroke Program Early CT Score
ASRH	acute stroke-ready hospital
ATP	adenosine triphosphate
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CAS	carotid angioplasty and stenting
CBF	cerebral blood flow
CBS	clot burden score
CBSV	the sum of CBS and CBV ASPECTS
CBV	cerebral blood volume
CCAD	cervicocephalic artery dissections
CCS	Causative Classification System for Ischemic Stroke
CEA	carotid endarterectomy
CEE	conjugated equine estrogens
CI	confidence interval
CNS	central nervous system
CSC	comprehensive stroke center
CT	computed tomography
CTA	computed tomography angiography
CTA-SI	computed tomography angiography source images

CTP	computed tomography perfusion
CW	circle of Willis
DSA	digital subtraction angiography
DWI	diffusion-weighted imaging
ECT	ecarin clotting time
ED	emergency department
EIC	early ischemic change
EKG	electrocardiogram
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HIS	hyperacute ischemic stroke
H-L	Hosmer-Lemeshow
HMCAS	the hyperdense MCA sign
IAT	intra-arterial thrombolysis
ICA	internal carotid artery
ICH	intracranial hemorrhage
INR	International Normalized Ratio
IS	ischemic stroke
IVT	intravenous thrombolysis
LDL-C	low-density lipoprotein cholesterol
M1	M1 segment of the middle cerebral artery
M1D	distal M1 segment of the middle cerebral artery
M1P	proximal M1 segment of the middle cerebral artery
M2	M2 segment of the middle cerebral artery
M3	M3 segment of the middle cerebral artery
M4	M4 segment of the middle cerebral artery
MCA	middle cerebral artery
MIP	maximum intensity projection
MM HG	millimeters of mercury
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MTT	mean transit time
NCCT	noncontrast (nonenhanced) computed tomography
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke

NO	nitric oxide
NOS	nitric oxide synthase
OC	oral contraceptives
OR	odds ratio
PACS	Picture Archiving and Communication Systems
PCA	posterior cerebral artery
PCommA	posterior communicating artery
PFO	patent foramen ovale
PSC	primary stroke center
PWI	perfusion-weighted imaging
RR	risk ratio
rtPA	recombinant tissue plasminogen activator
sICH	symptomatic intracranial hemorrhage
SPSS	Statistical Package for the Social Sciences
SWI	susceptibility-weighted imaging
TEE	transesophageal echocardiography
TIA	transient ischemic attack
T <sub>max</sub>	time-to-maximum
TT	thrombin time
T*TP	time to peak
VA	vertebral artery
VOF	venous output function

# 1. INTRODUCTION

In the year 2000 in Finland, the estimated number of first strokes was 11 500, and this number could increase to 20 100 by 2030 due to the aging of the population [1]. Stroke is the fifth-leading cause of death in men and the third leading cause of death in women in the United States [2]. In contrast, stroke continues to be the second leading cause of death worldwide [3]. This mortality burden has come with more than a doubling of the stroke incidence in low- and middle-income countries, surpassing the incidence rates observed in most high-income countries [4]. The burden of stroke is particularly high in Eastern Europe, North Asia, Central Africa and the South Pacific [5].

Data from epidemiological studies have demonstrated that the majority (87%) of strokes are ischemic, with the remainder being hemorrhagic (10% intracerebral and 3% subarachnoid) [6]. Common signs and symptoms of stroke include the abrupt onset of any of the following: hemiparesis with or without hemisensory deficits, monocular visual loss, visual field deficits, diplopia, dysarthria and/or aphasia, facial droop, ataxia, a decrease in the level of consciousness and vertigo, in combination with other symptoms. Ischemic stroke (IS) is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal cell death that is attributable to ischemia, based on pathological, imaging, or other objective evidence of ischemic injury in a defined vascular distribution, or clinical evidence of focal ischemic injury, based on symptoms persisting  $\geq 24$  hours or until death, excluding other etiologies. Focal arterial ischemia with transient symptoms (lasting  $< 24$  hours) and without evidence of infarction, is considered a transient ischemic attack (TIA). Symptoms or signs of cerebral venous thrombosis caused by reversible vasogenic edema in the absence of infarction or hemorrhage do not

qualify as stroke [7]. However, *acute neurovascular syndrome* is an appropriate term for cases in patients who have recently developed acute cerebrovascular symptoms and in whom it remains unknown whether the symptoms will resolve or persist [8]. Patients presenting within 6 hours of IS onset also constitute a subcategory of hyperacute ischemic stroke (HIS) patients [9].

Computed tomography (CT) scanning, which also, in the foreseeable future, will be more readily available in most medical centers than magnetic resonance imaging (MRI), is usually able to exclude stroke mimics and to distinguish brain ischemia from hemorrhage. Imaging of the cervical and intracranial arteries with CT angiography (CTA) can also identify occlusive vascular lesions. Today, attention is being focused on the early identification of permanent tissue injury, as well as of viable tissue at risk, widely known as the penumbra. Noncontrast CT (NCCT), CTA and CT perfusion (CTP) are used to identify the area of potentially reversible injury. Ideally, radiological assessment could identify the patients who would benefit from intensive reperfusion therapy. The optimal tool would characterize the size and location of the ischemic core destined for infarction, the size and volume of the penumbra; and the anatomic distribution of vascular occlusion and flow. However, no imaging features have yet been proved to achieve this goal sufficiently for use in selecting patients for specific therapies [7].

To satisfy the need for more precise up-to-date data on the utility and prognostic performance of imaging features derived from multimodal CT imaging in the treatment of HIS patients with intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA), we designed, for this thesis project, retrospective studies including two observational cohorts, consisting of sufficient numbers of consecutive patients with detailed clinical information, including laboratory findings, risk factors and outcomes. Imaging features include Alberta Stroke Program Early CT Score (ASPECTS), the location of the clot by introducing a modified parameter that divided the M1 segment of the MCA into two parts of equal length – the proximal and distal halves (designated as M1P and

M1D) – and collateral score (CS). The impact of the location of the clot on the CTP parametric maps was also investigated. Independence at 3 months was the primary functional outcome measurement.

This thesis has the potential to improve our understanding of the determinants of clinical outcomes in patients with HIS treated with IVT, as well as some aspects of brain imaging in this setting and how to optimize this imaging.

## 2. REVIEW OF THE LITERATURE

### 2.1 ISCHEMIC STROKE PATHOPHYSIOLOGY

The human brain comprises 2% of the weight of the body but requires 20% of the total oxygen consumption. The common pathway of IS involves a lack of sufficient cerebral blood flow (CBF) to perfuse the cerebral tissue due to a thrombosis or an embolism in the arteries leading to or within the brain, resulting in insufficient oxygen and glucose delivery to support cellular homeostasis. This effect elicits multiple processes that lead to cell death: excitotoxicity, acidotoxicity and ionic imbalance, oxidative/nitrative stress, inflammation, apoptosis and peri-infarct depolarization. Within the core of the ischemic territory, where the blood flow is most severely restricted ( $[CBF] < 15\text{ml}/100\text{g}/\text{min}$ ), the mitochondria are completely dysfunctional in adenosine triphosphate (ATP) production, ensuring the occurrence of excitotoxic and necrotic cell death within minutes. In the periphery of the ischemic area – the ischemic penumbra ( $CBF\ 15\text{-}20\text{ml}/100\text{g}/\text{min}$ ) – where collateral blood flow can buffer the full effects of the stroke for hours, cell death occurs less rapidly via active cell death mechanisms, such as apoptosis. The penumbra represents impaired ischemic brain tissue with suppressed cortical function that has the potential to recover following early revascularization, but this region is at a high risk for irreversible injury (infarction) in the absence of early revascularization. The penumbra does not include tissue with mild hypoperfusion (benign oligemia,  $CBF > 20\text{ml}\text{-}55\text{ml}/100\text{g}/\text{min}$ ), which is unlikely to infarct, even in the absence of revascularization [10, 11].

Increasing the systemic blood pressure (BP) can improve the cerebral collateral status, and a small subset of patients with IS in the very acute period might benefit from a modest elevation in systemic BP [12]. It has been reported that patients

with IS who have not received IVT demonstrated the most favorable outcomes with baseline systolic BP of approximately 150 mm Hg [13]. A slightly lower systolic BP of 141 to 150 mm Hg was associated with the most favorable results among patients who received IVT [14].

Ischemic tissue injury also activates nitric oxide synthase (NOS) and increases the generation of nitric oxide (NO), which combines with superoxide to produce peroxynitrite, a potent oxidant. Oxygen radicals trigger apoptotic cell death [15]. Other mechanisms of apoptosis include glutamate release, mitochondrial damage, proteolysis and lipolysis. Oxidative and nitrative stresses also trigger the recruitment and migration of neutrophils and other leukocytes to the cerebral vasculature, thus causing inflammation. This process can lead to parenchymal hemorrhage and vasogenic brain edema. Following delayed reperfusion, there is a surge in the production of free radicals, causing a second wave of oxidative and nitrative stress and further increasing the risk of reperfusion-induced injury [16].

## 2.2 CEREBRAL VASCULAR TERRITORIES

The cerebral circulation can be divided into the anterior and posterior circulation, based on the internal carotid artery (ICA) and vertebral artery (VA) supplies, respectively. The circle of Willis (CW) is a channel that unites the internal carotid and vertebrobasilar systems. Variations of the CW have often been observed [17]. Two major arterial branches, the posterior communicating artery (PComA) and the anterior choroidal artery, arise from the communicating segment of the ICA [18]. The anterior cerebral artery (ACA) and middle cerebral artery (MCA) are the terminal branches of the ICA. From the ACA originates the anterior communicating artery (AComA), and the branches of the ACA supply the medial part of the frontal and parietal lobes. The MCA supplies the majority of the lateral surface of the hemisphere. The MCA is divided into the M1, M2, M3 and M4 segments. From M1 originates the lenticulostriate arteries, which supply blood to

the basal ganglia. The M2 division of the MCA is variable, although it most commonly bifurcates into superior and inferior divisions. The posterior cerebral arteries (PCAs) are the terminal branches of the basilar artery (BA), and they supply the occipital lobes and posteromedial temporal lobes. The branches of the BA and VAs supply the cerebellum, the medulla oblongata and the pons [19].

## 2.3 CAUSES OF ISCHEMIC STROKE

IS is classified based on the presumed mechanism of the focal brain injury. The classic categories, based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST), have been defined as large-artery atherosclerotic infarction, embolism from a cardiac source, small-vessel disease, stroke of other determined etiology, and infarcts of undetermined cause [20]. The Stop Stroke Study TOAST (SSS-TOAST) system consists of the same five major stroke subtypes as in the TOAST classification system. In the SSS-TOAST system, each causative category is subdivided, based on the weight of evidence as “evident,” “probable,” or “possible”. At a minimum, patients should undergo a diagnostic workup to exclude high-risk modifiable conditions as the cause of the ischemic symptoms. At least one potential source of cardiac embolism can be detected using echocardiography in approximately 50 to 70% of patients with IS. Similarly, 12% of patients with a cardiac source of embolism and 22% of patients with a lacunar infarction harbor ipsilateral large artery atherosclerosis, causing stenosis greater than 50% [21]. The Causative Classification of Ischemic Stroke (CCS) is an automated version of the SSS-TOAST. It was developed to maximize inter-examiner reliability in stroke classification. The automated CCS system limits inter-examiner variability in the interpretation of stroke-related characteristics and ensures consistency in data entry, thereby further supporting the reliability of SSS-TOAST in etiologic stroke classification [22].

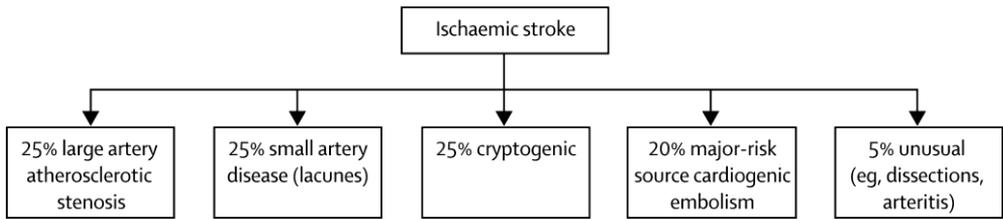


Figure 1

*Distribution of ischemic stroke subtypes in North American and European studies. The distribution in Asian and African populations differs from that in North American and European populations [23].*

### 2.3.1 Large-artery atherosclerosis

Large-artery intracranial occlusive disease is an important stroke subtype, particularly in blacks, Asians, and Hispanics. [24]. In addition, patients with substantial (60-99%) extracranial carotid artery narrowing are at an increased risk of IS in the carotid territory of the brain [25]. Similarly, extracranial VA stenosis is a potential source of posterior circulation IS [26]. According to the phenotype-based A-S-C-O (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause) classification, any atherosclerotic stenosis in an artery supplying the ischemic field with attached luminal thrombus or a mobile thrombus in the aortic arch is definitely a potential cause of the index IS [27].

### 2.3.2 Cardioembolism

Atrial fibrillation (AF) is a potent cardiac source of stroke due to embolism of thrombi that form in the left atrial appendage. The probability of IS linked to atrial flutter is similar to that observed with AF. In addition, paroxysmal and permanent AF should be considered to have equal risks of IS [28]. The main challenge in the prevention of AF-related stroke is detecting undiagnosed AF more effectively. For

patients who have experienced IS with no other apparent cause, prolonged noninvasive rhythm monitoring ( $\approx 30$  days) for AF is reasonable [29, 30]. Both dilated and restrictive cardiomyopathies in sinus rhythm are cardiogenic embolism risk factors for stroke. In particular, a low left ventricular (LV) ejection fraction (EF) is a significant predictor of cardiac thromboembolism. The risk of stroke appears to increase when the EF is  $<30\%$  [31]. A mural thrombus after myocardial infarction also causes a significantly increased risk of embolization [32]. In patients with mitral valve stenosis in sinus rhythm, the mitral valve area has been associated with embolism [33]. There is a particularly high risk of a thromboembolism of a cardiac source shortly after mechanical valve implantation. During the first six months after surgery, the thromboembolic risk is up to seven times greater than that during the subsequent months and years; however, there is an elevated lifelong risk [34]. Patients with bioprosthetic aortic or mitral valve replacement have a high risk of thromboembolism during the first 10 days after surgery, high (mitral) to medium (aortic) risk at 11 to 90 days and medium (mitral) to low (aortic) risk thereafter [35]. Stroke can also occur in patients undergoing cardiac catheterization, pacemaker implantation, or coronary artery bypass surgery [36]. IS occurs in up to 20% of patients with infective endocarditis, with the greatest risk observed for mitral valve endocarditis [37]. The presence of atherosclerotic plaques (particularly plaques  $\geq 4$  mm thick) in the ascending aorta or proximal arch, as detected by transesophageal echocardiography (TEE), is an independent risk factor for IS [38]. Patent foramen ovale (PFO) is an embryonic defect (hole) in the interatrial septum that can be the conduit for an embolism traveling from the deep veins of the legs or pelvis to the brain. However, even among patients with otherwise cryptogenic stroke, approximately one-third of the discovered PFOs were likely to be incidental [39]. Benign primary cardiac tumors or malignant neoplasms also pose risks for embolisms [40].

### 2.3.3 Small-vessel occlusion

Lacunar (small-vessel disease) strokes, most of which result from intrinsic diseases of the small penetrating arteries, comprise approximately 25% of ISs (Fig. 1) and are defined according to a combination of clinical and radiological criteria as follows: events presenting with clinical lacunar stroke syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome) persisting for >24 h or the presence on TIA and diffusion-weighted magnetic resonance imaging (DWI) of small subcortical strokes, corresponding to the qualifying event, without signs or symptoms of cortical dysfunction (aphasia, apraxia, agnosia, agraphia, homonymous visual field defect), ipsilateral cervical carotid stenosis or major-risk cardioembolic sources [41].

### 2.3.4 Other specific causes

The category of other causes accounts for only approximately 1 to 5% of all strokes, and their coexistence with other potential stroke mechanisms is rare [21, 23]. In Western countries, cervicocephalic artery dissections (CCADs) are among the most common causes of stroke in young adults [42]. Inherited thrombophilias (eg, protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden, the prothrombin G20210A mutation, and the methylenetetrahydrofolate reductase [MTHFR] C677T mutation) can be the primary mechanism of pediatric IS [30]. An association between antiphospholipid antibodies and an increased risk of IS has been described in women but not in men [44, 45]. Patients with chronic inflammatory diseases, such as rheumatoid arthritis, should be considered to be at an increased risk for stroke. Inflammation affects the initiation, growth, and stability of atherosclerotic plaques. Furthermore, inflammation has prothrombotic effects. The possible mechanisms underlying the role of inflammation in IS related

to acute infectious diseases (such as influenza) include the induction of procoagulant acute-phase reactants [40]. For patients with sickle cell disease, the risk of having a first stroke could be as high as 24% by the age of 45 years old [46]. Fabry disease is an X-linked glycosphingolipid storage disease, and according to data from the Fabry Registry, 6.9% of the male Fabry disease patients with a median age of 39 years old and 4.3% of the female Fabry disease patients with a median age of 46 years old experienced a stroke [47].

### 2.3.5 Stroke of undetermined etiology

In some patients (20-25%), no likely etiology of an IS will be determined, despite an extensive evaluation [21, 23]. In others, no cause is found; however, the evaluation might have been only cursory. The CCS system requires echocardiography (or other more advanced cardiac investigations) if the clinical history, cardiac examination, and EKG do not reveal a source of cardiac embolism. The category of stroke of undetermined etiology also includes patients with two or more potential causes of stroke; therefore, the physician might be unable to provide a final etiology [20, 22].

## 2.4 RISK FACTORS AND PRIMARY PREVENTION OF ISCHEMIC STROKE

The risk factors or risk markers (attributes or exposures associated with an increased probability of disease but with a relationship that is not necessarily causal) of a first ischemic or hemorrhagic stroke are overlapping. For several risk factors, there is clear, supportive epidemiological evidence, in addition to evidence of a reduction of risk with modifications. In the INTERSTROKE study five risk factors accounted for 83% of the overall risk of IS: hypertension, current smoking, abdominal obesity (waist-to-hip ratio), unhealthy diet, and lack of regular physical activity [48]. People who practice a healthy lifestyle (nonsmoking, a body mass index[BMI]  $<25 \text{ kg/m}^2$ ,  $\geq 30$  minutes/day of moderate activity, consuming alcohol modestly, and scoring within the top 40% of a healthy diet score) experience an 80% lower risk of a first stroke, compared with those who do not [49]. In contrast, some of the risk factors are sex-specific or are more common in women than in men.

### 2.4.1 Generally nonmodifiable risk factors

The risk of IS doubles for each successive decade after the age of 55 years old [50]. The risk for stroke is higher in pregnant women than in nonpregnant women, with the highest stroke risk occurring in the third trimester and postpartum. The physiological changes that occur during pregnancy, specifically venous stasis, edema, and hypercoagulability caused by activated protein C resistance, lower levels of protein S, and increased fibrinogen, as well as pregnancy-related hypertension, combine to make pregnancy and the postpartum period a time of increased risk for stroke [51]. In addition, the use of low-dose (second- and third- generation only) combined oral contraceptives (OCs) was associated with an increased risk of IS [52].

Black race and a family history of stroke have been associated with an increased risk of stroke [40]. Genetic factors might also be associated with arterial dissections, Moyamoya disease, and fibromuscular dysplasia. In contrast, some clear monogenic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Marfan syndrome, retinal vasculopathy with cerebral leukodystrophy, Fabry disease, sickle cell disease, and neurofibromatosis types I and II, are associated with an increased risk of IS [40]. There is an enzyme replacement therapy available for Fabry disease that appears to improve cerebral vessel function [40]. A referral for genetic counseling might be considered for patients with rare genetic causes of stroke [40].

#### 2.4.2 Well-documented and modifiable risk factors

Hypertension is the most common modifiable risk factor for stroke, and it has the highest population-attributable risk [53]. Annual screening for high BP and health-promoting lifestyle modifications are recommended for patients with prehypertension. Reduced intake of sodium, increased intake of potassium and a DASH-style (Dietary Approaches to Stop Hypertension) diet that emphasizes fruits, vegetables, and low-fat dairy products and reduced saturated fat, are recommended for lowering BP. Patients with hypertension should be treated with antihypertensive drugs to achieve a target BP of <140/90 mm Hg [40].

Virtually every multivariable assessment of stroke risk factors has identified cigarette smoking as a potent risk factor for IS, associated with an approximate doubling of the risk for IS even after adjustment for other risk factors [54]. Counseling, in combination with drug therapy using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking [40].

Both case-control studies and prospective epidemiological studies have confirmed that diabetes independently increases the risk of IS [55]. The control of

BP in patients with type 1 or type 2 diabetes and treatment of these patients with an HMG coenzyme-A reductase inhibitor (statin) are recommended to lower the risk of first IS [40].

In the Women's Health Study (WHS), a prospective cohort study of 27 937 US women  $\geq 45$  years of age, higher total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were significantly associated with an increased risk of IS [56]. In addition to therapeutic lifestyle changes, according to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the treatment of blood cholesterol, treatment with a statin medication is recommended for the primary prevention of IS in patients with a high estimated 10-year risk of cardiovascular events to reduce atherosclerotic cardiovascular risk in adults [40, 57].

AF is a potent risk factor for IS [27]. The probability of IS linked to atrial flutter is similar to that observed with AF [28]. Paroxysmal and permanent AF should be considered to have equal risks of IS [29]. The CHA<sub>2</sub>DS<sub>2</sub>-VASc hazard assessment scheme aids clinicians in determining whether to initiate antithrombotic therapy and in identifying the appropriate antithrombotic agent. For CHA<sub>2</sub>DS<sub>2</sub>-VASc, a scoring system awards points for congestive heart failure (1 point), hypertension (1 point), age category of 65 to 74 years old (1 point) or age  $\geq 75$  years old (2 points), diabetes (1 point), prior IS or TIA (2 points), female sex (1 point), and vascular disease other than cerebrovascular disease (1 point) [58]. For patients with valvular AF at a high risk for IS and with an acceptably low risk of hemorrhagic complications, long-term oral anticoagulant therapy with warfarin is recommended at a target International Normalized Ratio (INR) of 2.0 to 3.0. For patients with nonvalvular AF at a high risk for IS and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended. The options include warfarin, dabigatran, apixaban and rivaroxaban [40].

Anticoagulation is indicated in patients with mitral stenosis and left atrial thrombus. Warfarin (target INR, 2.0-3.0) and low-dose aspirin are indicated after

aortic valve replacement with bileaflet mechanical or current-generation, single-tilting-disk prostheses in patients with no risk factors; warfarin (target INR, 2.5-3.5) and low-dose aspirin are indicated in patients with mechanical aortic valve replacement and risk factors; and warfarin (target INR, 2.5-3.5) and low-dose aspirin are indicated after mitral valve replacement with any mechanical valve [40]. No treatment is recommended for the primary prevention of IS in people with PFO [40]. Surgical intervention is recommended for the treatment of atrial myxomas, for symptomatic fibroelastomas and for fibroelastomas that are >1 cm or that appear mobile, even if they are asymptomatic [40]. In addition, several other cardiac conditions are associated with a high risk of IS, as detailed in section 2.3.2.

The presence of an atherosclerotic stenotic lesion in the extracranial ICA or carotid bulb has been associated with an increased risk of IS. Randomized trials have shown that prophylactic carotid endarterectomy (CEA) in appropriately selected patients with carotid stenosis of 80% or more modestly reduces the risk of IS [36].

A meta-analysis found a strong, inverse relationship between servings of fruits and vegetables and subsequent stroke. Compared with persons who consumed <3 servings of fruits and vegetables per day, the relative risk of IS was less in those who consumed  $\geq 3$  servings per day [59]. A higher level of sodium intake was associated with an increased risk of stroke [60]. A trial of the Mediterranean diet showed that those on an energy-unrestricted Mediterranean diet, supplemented with nuts (walnuts, hazelnuts, and almonds) or extra virgin olive oil, had a lower risk of stroke compared to people on a control diet [61].

The risk of IS with conjugated equine estrogens (CEE) is significantly increased in women >60 years of age [62].

Physical activity reduces plasma fibrinogen and platelet activity and elevates plasma tissue plasminogen activator activity. Moderately intense physical activity, compared with inactivity, has a protective effect against total stroke, thus making lack of physical activity a modifiable risk factor [63]. Consequently, it is

recommended that healthy adults perform at least moderate- to vigorous-intensity aerobic physical activity for at least 40 minutes/day, 3 to 4 days/week [40].

Obesity is an independent risk factor for stroke. The traditional classification of weight status is defined by BMI (weight in kilograms divided by the square of the height in meters). There is a graded association between BMI and stroke risk; the risk of IS rises linearly with increasing BMI and in a stepwise fashion for higher BMI categories [64]. Among overweight (BMI = 25 to 29 kg/m<sup>2</sup>) and obese (BMI >30 kg/m<sup>2</sup>) individuals, weight reduction is recommended to reduce the risk of stroke [40].

Subjective depression (feeling sad, blue, or depressed for two or more consecutive weeks over the previous 12 months) was associated in a case-control study with increased risk of stroke incidence [48].

### **2.4.3 Less well-documented or potentially modifiable risk factors**

Migraine with aura is associated with an increased risk of IS, and this association is increased in women, compared to men [65]. Smoking cessation should be strongly recommended in women with migraine with aura [40].

Adherence to a combination of healthy lifestyle practices (a healthy diet, physical activity, abstinence from smoking, moderate alcohol intake, and maintenance of a healthy BMI) has been shown to decrease the incidence of stroke in women [66].

There is strong evidence that heavy alcohol consumption is a risk factor for all stroke subtypes [48]. Prospective, randomized clinical trials showing that light alcohol consumption is beneficial have been lacking, and such trials cannot be performed because it is well established that alcohol dependence is a major health problem. Reduction or elimination of alcohol consumption in heavy drinkers, through established screening and counseling strategies, is recommended [40].

Drugs that are abused can produce acute and severe elevations in BP, cerebral vasospasm, vasculitis, embolization due to infective endocarditis, and hemostatic and hematologic abnormalities resulting in increased blood viscosity and platelet aggregation. Data are lacking for the independent risk of stroke associated with specific drugs of abuse [40]. However, in a prospective study of 48 young patients with IS, 21% had multifocal intracranial stenosis associated with the use of cannabis [67].

Sleep apnea is associated with a variety of other stroke risk factors and could independently contribute to the risk of stroke. Treatment of sleep apnea to reduce the risk of stroke might be reasonable, although its effectiveness for the primary prevention of stroke is unknown [40].

Hyperhomocysteinemia was associated with an increased risk of stroke [42, 43]. The use of B complex vitamins, including cobalamin (B12), pyridoxine (B6), and folic acid, might be considered for the prevention of IS in patients with hyperhomocysteinemia, but the effectiveness of these vitamins has not been well established [40].

Inherited thrombophilias may be associated with a modest increase in the risk of IS, particularly in young adults with cryptogenic events and pediatric stroke [30]. An association between antiphospholipid antibodies and an increased risk of IS has been described in women but not in men [43, 44]. The usefulness of specific treatments (including low-dose aspirin) for primary IS prevention in asymptomatic patients with a hereditary or acquired thrombophilia is not well established [40].

## 2.5 EARLY DIAGNOSIS OF ISCHEMIC STROKE

In the emergency department (ED), patients with suspected hyperacute stroke, based on the clinical history and neurological signs (face, arm, or leg weakness, speech disturbances, visual field defects), should be triaged with the same priority as patients with acute myocardial infarction (AMI). The overall goal is not only to identify patients with possible neurovascular syndrome but also to exclude conditions with stroke-like symptoms (stroke mimics). Common stroke mimics are seizures, syncope, and sepsis [68]. Other stroke mimics are drug toxicity, central nervous system (CNS) tumors, CNS abscesses, Wernicke's encephalopathy, hypertensive encephalopathy, migraine with aura, hypoglycemia, clinical situations of psychogenic origin (conversion disorder) and symptoms of neuroimmunologic diseases, such as multiple sclerosis, polyradiculitis or myasthenia gravis [12]. Thus, it is important to determine the risk factors for arteriosclerosis and cardiac disease, as well as any history of drug abuse, migraine with aura, seizure, infection, trauma, or pregnancy and family history of neurological diseases [40]. The detailed physical examination is important for identifying other potential causes of the symptoms of the patient, potential causes of an IS, coexisting comorbidities, or issues that could impact the management of an IS. The use of a standardized neurological examination ensures that the major components of a neurological examination are performed in a timely and uniform fashion. The National Institutes of Health Stroke Scale (NIHSS), a serial measurement of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories. For example, a mild facial paralysis is given a score of 1, and complete right hemiplegia with aphasia, gaze deviation, visual-field deficit, dysarthria, and sensory loss is given a score of 25 [69].

## 2.6 BRAIN PARENCHYMA AND VASCULAR IMAGING OF ISCHEMIC STROKE

The primary goal of imaging patients with hyperacute stroke symptoms is to distinguish between hemorrhagic stroke and IS. In IS patients, the secondary goals of imaging, before initiating recanalization interventions with IVT or endovascular therapies, include identification of the location and extent of the intravascular clot, as well as the presence and extent of early ischemic changes (EICs), the ischemic core (irreversibly damaged tissue) and the penumbra (hypoperfused tissue at risk for infarction).

With its widespread availability, short scan time, noninvasiveness, and safety, NCCT is the accepted standard-of-care imaging technique for the exclusion of intracranial hemorrhage, and it has been incorporated into the inclusion criteria in randomized clinical trials evaluating the efficacy of IVT [70]. NCCT can also be used to exclude other stroke mimics and to detect EICs [71]. The limitations of CT imaging are its ionizing radiation and its lack of sensitivity to detect acute and small cortical or subcortical infarctions, particularly in the posterior fossa [70].

The accuracy of MRI techniques for the detection of intracranial hemorrhage in the hyperacute stroke setting has been reported as likely equivalent to that of NCCT when gradient recalled echo (GRE) sequences are used [72]. Additionally, T2\*-weighted sequences (including GRE and susceptibility-weighted imaging [SWI] sequences) have the ability to detect clinically silent prior microbleeds that cannot be visualized on NCCT [72]. The pattern of hematoma in the acute phase is DWI hyperintensity and reduced apparent diffusion coefficient (ADC). These features can occasionally be confused with ischemic lesion, although a hematoma presents a more heterogeneous pattern with magnetic susceptibility effects and a brighter DWI hyperintensity than acute ischemic lesions. This heterogeneous appearance is also observed on the T1-weighted images with hypointensity (whereas a hyperacute ischemic lesion usually cannot be observed on T1-weighted sequences), as well as a leaf-like appearance in the periphery. In addition, the

hematoma can be seen as pronounced fluid-attenuated inversion recovery (FLAIR) hyperintensity (the FLAIR hyperintensity is unusual in ischemic lesions before 3 hours). Finally, peripheral T2\*-weighted hypointensity, consistent with the presence of deoxyhemoglobin, is an indicator of hematoma [73]. Accordingly, MRI can be used as the sole initial imaging modality to evaluate hyperacute stroke patients, including candidates for IVT [12]. However, the importance of the presence of large numbers of microbleeds on MRI in thrombolytic decision-making remains uncertain [12]. The limitations of MRI include that it might not be available 24-hours-per-day/7-days-per-week, it is vulnerable to motion artifacts, there are patient contraindications, such as claustrophobia, it might not be accessible with monitors and/or ventilators, and it might not be feasible or safe for patients with metallic implants (pacemakers, implantable defibrillators) [70]. Consequently, 10-15% of patients cannot undergo MRI [74].

### 2.6.1 Early ischemic signs

EICs observed using NCCT (within 6 h of symptom onset) include 1) subtle parenchymal hypoattenuation with or without swelling, which often manifests as a loss of visualization of the gray-white matter interface, 2) isolated parenchymal swelling without hypoattenuation, and 3) focal hyperattenuation of an arterial trunk, which is an additional sign that can be considered a surrogate for ongoing parenchymal ischemia. The presence of the hyperdense middle cerebral artery sign (HMCAS) indicates M1 and proximal M2 segments thrombosis, and the MCA “dot” sign may indicate thrombosis within insular branches (distal M2 and M3 segments). However, most MCA dot signs are correlated with occlusion of more proximal, or horizontal, portion of the MCA rather than of a specific insular branch [75]. To achieve high sensitivity for detecting an HMCAS, CT image slices must be reconstructed using a significantly thinner slice width than that described in standard protocols [76]. EICs are insensitive to the detection of acute ischemic

processes and show, at best, moderate interobserver agreement and reproducibility [71]. However, detection could increase with the use of a structured scoring system, such as the Alberta Stroke Program Early CT Score (ASPECTS) [77], as well as with the use of better gray scale windowing of the CT images to differentiate between normal and abnormal tissues [78]. The ASPECTS is a semiquantitative grading system that was developed to quantify the extent of EICs in the MCA territory. Only parenchymal hypoattenuation is considered a finding in the scoring process. Each hemisphere is divided into 10 regions (Fig. 2). Each of these regions is given a score of 1 point. This point is deducted if the region shows EICs. Thus, negative findings yield a score of 10, and extensive ischemia covering the entire MCA region yields a score of 0 [77].

The window width and center level settings, used for the CT scan review, measured in Hounsfield units (HU), are known to influence diagnostic accuracy. Window width is defined as the range of CT numbers converted into grey levels and displayed on the image monitor. Center level is defined as the central value of the window used for the display of the reconstructed CT image. Early CT-depicted hypoattenuation reflects cytotoxic edema secondary to the failure of ion pumps in response to an inadequate supply of ATP. The attenuation in HU observed with CT scanning in patients with acute stroke is directly proportional to the degree of cytotoxic edema; an increase in tissue water content by 1% results in a 2.5-HU decrease in parenchymal attenuation, which corresponds to an approximately 3% to 5% decrease in x-ray attenuation. An approximately 1-to 30-HU window width and a 28 to 36-HU center level maximize the gray matter and white matter contrast, accentuating the subtle attenuation differences between normal and acutely edematous ischemic brain parenchyma. The effects of changing the window settings have not been formally analyzed for ASPECTS. Consequently, the detection of EICs is facilitated by a soft-copy visual review at a Picture Archiving and Communication Systems (PACS) workstation, without an appreciable increase in the time required for image interpretation [78].

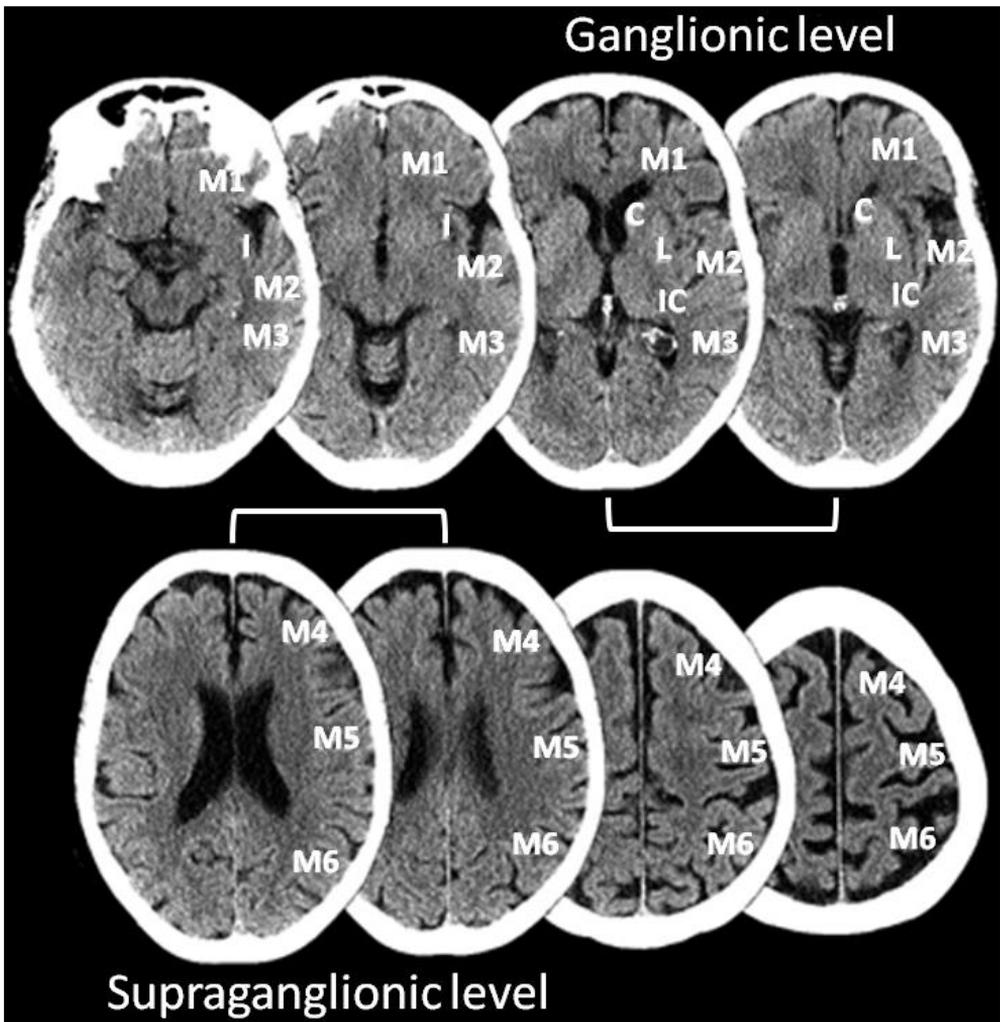


Figure 2

*Axial NCCT images showing the MCA territory regions, as defined by ASPECTS. The ganglionic and supraganglionic levels are indicated by white brackets. C - Caudate nucleus, I - Insular ribbon, IC - Internal capsule, L - Lentiform nucleus, M1 - Anterior MCA cortex, M2 MCA cortex lateral to the insular ribbon, M3 - Posterior MCA cortex, M4, M5, and M6 are the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3, respectively and rostral to the basal ganglia. Subcortical structures are allotted 3 points and the MCA cortex is allotted 7 points. The image is adapted from [www.aspectsinstroke.com](http://www.aspectsinstroke.com).*

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NCCT, noncontrast computed tomography; MCA, middle cerebral artery.

In addition, unprocessed source images from CTA (CTA-SI) have been shown to have increased sensitivity relative to NCCT for detecting EICs [79]. CTA-SI provides an approximation of the cerebral blood volume (CBV), assuming a steady state between the arterial and parenchymal contrast material. The attenuation values for brain tissue on CTA-SI are directly proportional to the amount of contrast material that has arrived within the parenchyma at the time of imaging. When a proximal cerebral artery is occluded, the affected territory is supplied by the collateral circulation, prolonging the arrival time of the contrast material, even during sufficient blood flow. Earlier CTA image acquisition prevents the contrast material from traversing the collateral vessels and reaching the distal bed, thereby increasing the area of hypoattenuation [80]. Thus, CTA-SI with rapid CT acquisition is more an estimate of the reduction of cerebral blood and therefore the contrast distribution to the affected territory than of the expression of cytotoxic edema observed on NCCT. Therefore, a significant overestimation of the size of the infarct occurs with a shortened time from contrast material injection to imaging of the ischemic territory [81]. In contrast, frank hypoattenuation on NCCT is highly specific for irreversible tissue damage [82].

Standard MRI sequences (T1-weighted imaging, T2-weighted imaging, FLAIR) are relatively insensitive to the changes in hyperacute ischemia [83]. In contrast, DWI has very high sensitivity and specificity for the detection of infarcted regions, even at very early time points of symptom onset [84]. An “optimized” diffusion-weighted sequence can even further increase the sensitivity of DWI [85]. DWI detects decreases in the self-diffusion of water molecules, appearing as a hyperintensity on DWI sequences (Fig. 3).

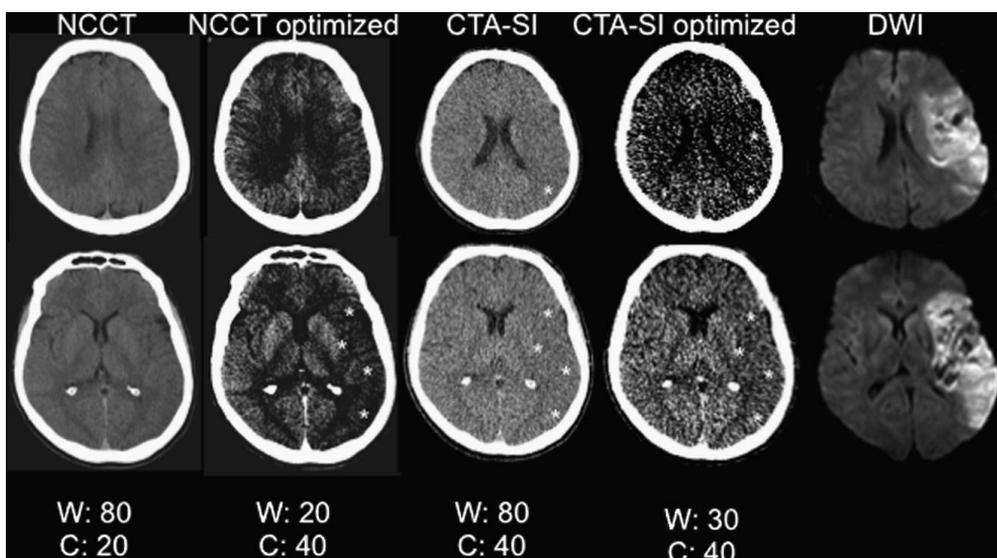


Figure 3

*NCCT and CTA-SI of a 44-year-old male patient with acute-onset right hemiparesis and aphasia, obtained 1 hour after symptom onset. ASPECTS was 10 on NCCT, 6 on NCCT with window setting optimization, 5 on CTA-SI, and 4 on CTA-SI with window setting optimization. ASPECTS on follow-up MRI, as an acute infarct appearing as a hyperintensity on DWI sequences, was 4. ASPECTS regions judged to be abnormal on CT are marked with asterisks. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; DWI, diffusion-weighted imaging; NCCT, noncontrast computed tomography; CTA-SI, computed tomography angiography source images; MRI, magnetic resonance imaging.*

Hyperintensity on DWI sequences associated with a reduced ADC value is detected within minutes of ischemia and is related, at least in part, to cellular energy failure and early cytotoxic edema [86]. DWI lesion reversal is uncommon in ischemic stroke patients treated with IVT beyond the 3-hour time window [87]. DWI is widely regarded as the best imaging modality for estimating the infarct core in the acute setting [80]. Apart from an acute ischemic lesion, the signal hyperintensity on DWI can be due to previous stroke or susceptibility artifacts. For

these reasons, DWI images should always be interpreted with T2 images or with calculation of the ADC value [83]. However, in addition to recent hematoma, other causes of cytotoxic edema (reversible posterior encephalopathy, venous cerebral thrombosis, infectious encephalitis) can cause a reduction in the ADC value on MRI [73, 88].

FLAIR imaging becomes positive during the initial hours of stroke onset. Two situations can be potentially distinguished based on the presence or absence of a “DWI/FLAIR” mismatch (a positive DWI signal with a negative FLAIR signal): 1) DWI hyperintensity with no FLAIR hyperintensity, usually representing a hyperacute lesion; and 2) DWI hyperintensity with pronounced FLAIR hyperintensity (DWI/FLAIR match), for which the time from stroke onset is likely to be  $> 4.5$  hours [73]. A 1.5-Tesla (T) MRI “DWI/FLAIR” mismatch with qualitative or quantitative analysis can aid in determining, with sensitivity and specificity of more than 90%, whether patients were imaged within the first 3 hours after stroke onset [89]. However, with 3-T MRI and a 4.5-hour time window, the accuracy of a “DWI/FLAIR” mismatch to differentiate a HIS is far from perfect [90].

## 2.6.2 Brain perfusion

CTP and perfusion-weighted MRI (PWI) have been widely incorporated into acute multimodal imaging protocols. The heart of the multimodal approach is the perfusion study, which permits the detection of the infarct core and the penumbra, as well as the quantification of salvageable brain tissue. This identification and quantification procedure can be primarily accomplished with high accuracy and full anatomic coverage by MRI. However, CTP has emerged as an alternative to MRI [91]. Brain perfusion imaging provides information about regional cerebral hemodynamics in the form of such features as CBF, CBV, and mean transit time (MTT). CBF indicates the volume of blood moving through a brain volume of

interest per unit of time ( $[CBF] = \text{ml}/100 \text{ g}/\text{min}$ ). CBV describes the total volume of blood in a given brain volume of interest ( $[CBV] = \text{ml}/100 \text{ g}$ ). This volume includes the intracellular, intravascular and extravascular interstitial spaces. MTT describes the average difference in time between the arterial inflow and the venous outflow of a brain region of interest ( $[MTT] = \text{s}$ ). This time is dependent on the average distance travelled. In terms of multimodal CT neuroimaging, the penumbra is the mismatch (subtraction) volume between the CBF or MTT and the CBV, in which the CBV lesion reflects the infarct core, and the CBF or MTT lesion reflects the boundaries of the hypoperfused penumbral tissue (Fig. 4). MTT maps potentially overestimate size of the perfusion defects, while CBV maps may overestimate or underestimate the volume of the irreversibly damaged brain parenchyma, and there is vendor variability in the CTP results [92].

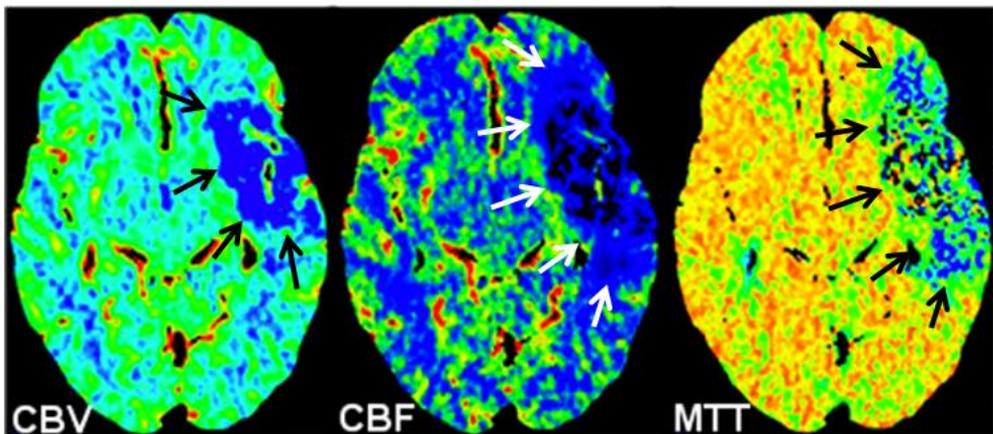


Figure 4

*A patient suffering from a hyperacute ischemic stroke of the left middle cerebral artery territory. CBV lesion reflects the infarct core and the CBF or MTT lesion reflects the boundaries of the penumbra. MTT and CBF–CBV mismatch is present. Arrows mark the boundaries of the perfusion defects. Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time.*

On MRI, the ischemic penumbra is roughly indexed as the area of the PWI-DWI mismatch. However, the CT and MRI definitions of the ischemic core and ischemic penumbra are probabilistic. Therefore, when the terms for the ischemic core and penumbra are used, there should be an explicit qualification in the publication regarding the specific (1) imaging technique; (2) perfusion parameter(s); and (3) threshold(s) under discussion [93]. The RAPid processing of Perfusion and Diffusion (RAPID) system is fully automated system developed to perform real-time identification of diffusion-perfusion mismatch in acute stroke patients based on processed DWI and PWI. In the RAPID system, brain regions displaying altered perfusion are identified on time-to-maximum ( $T_{max}$ ) maps. Here, the  $T_{max}$  parameter serves a bolus-shape-independent estimate of time-delay in blood delivery between a main feeding artery and tissue at a given spatial location, similar to time-to-peak parameter,  $T_{max}$  strongly correlate with hypoperfusion [94].

The advantages of the multimodal CT approach over MRI include more rapid imaging and CTP features that can be more easily quantified compared to their PWI counterparts, owing in part to the linear relationship between the iodinated CT contrast concentration and the resulting CT image density, which is a relationship that does not hold for the concentration of gadolinium versus the MRI signal intensity [12]. However, the use of iodinated contrast carries a small risk of nephrotoxicity [95]. In addition, gadolinium reactions are uncommon but can be dangerous. In general, gadolinium should be avoided in the presence of advanced renal failure [12]. Perfusion imaging has many applications beyond the characterization of the penumbra, including enhanced sensitivity and accuracy of stroke diagnosis (excluding stroke mimics) and improved assessment of the ischemic core. There is mounting evidence supporting the poor performance of NCCT during the first 3 hours after stroke onset compared to more advanced imaging with DWI, PWI or CTP [96]. The effect of the location of the clot on CTP examination findings for the anterior circulation has seldom been directly addressed in previous studies, particularly in the context of early IVT.

### 2.6.3 Vessel stenosis and occlusion

CTA has been reported to have high sensitivity and specificity for detecting intracranial stenoses and occlusions compared with digital subtraction angiography (DSA), which is regarded as the gold standard for assessing the degree of stenosis in the intracranial vessels [97]. In contrast, intracranial MRA with nonenhanced three-dimensional (3D) time of flight (3D TOF) techniques has a sensitivity ranging from 60% to 85% for stenoses and from 80% to 90% for occlusions compared with CTA or DSA, although it cannot reliably identify distal occlusions [98]. However, it should be borne in mind that failure to visualize an artery on 3D TOF can also represent severe slowing in an artery that is nevertheless patent. In addition, a T2\*-weighted sequence can be used to assess the site of occlusion through an artifact described as the “susceptibility vessel sign” (SVS). The SVS is the MRI correlate of the HMCAS observed on NECT [99]. Nearly half of all patients with IS have an occlusion of the large intracranial vessels, such as the BA, carotid terminus (carotid T), or MCA [100]. Large-vessel occlusions are significantly associated with patient mortality and with decreased probability of a favorable outcome [100]. Furthermore, large-artery occlusions have been associated with greater risks of stroke after TIA and minor stroke [101].

### 2.6.4 Collateral circulation

Collateral vessels as a vascular network can potentially bypass the devastating effects of a blocked cerebral artery. In patients with natural histories of proximal intracranial arterial occlusion, good collateral flow appears to be more important than the level of proximal intracranial arterial occlusion in determining favorable outcomes [102]. An angiographic grading system for regional collateral flow predicts the extent and location of a cerebral infarction [103]. Collaterals were graded as follows: 0 = no collaterals, absent collaterals; 1 = minimal collaterals,

collaterals filling  $\leq 50\%$  of the occluded territory; 2 = intermediate collaterals, collaterals filling  $>50\%$  but  $<100\%$  of the occluded territory; 3 = maximal collaterals, collaterals filling 100% of the occluded territory (Fig. 5).

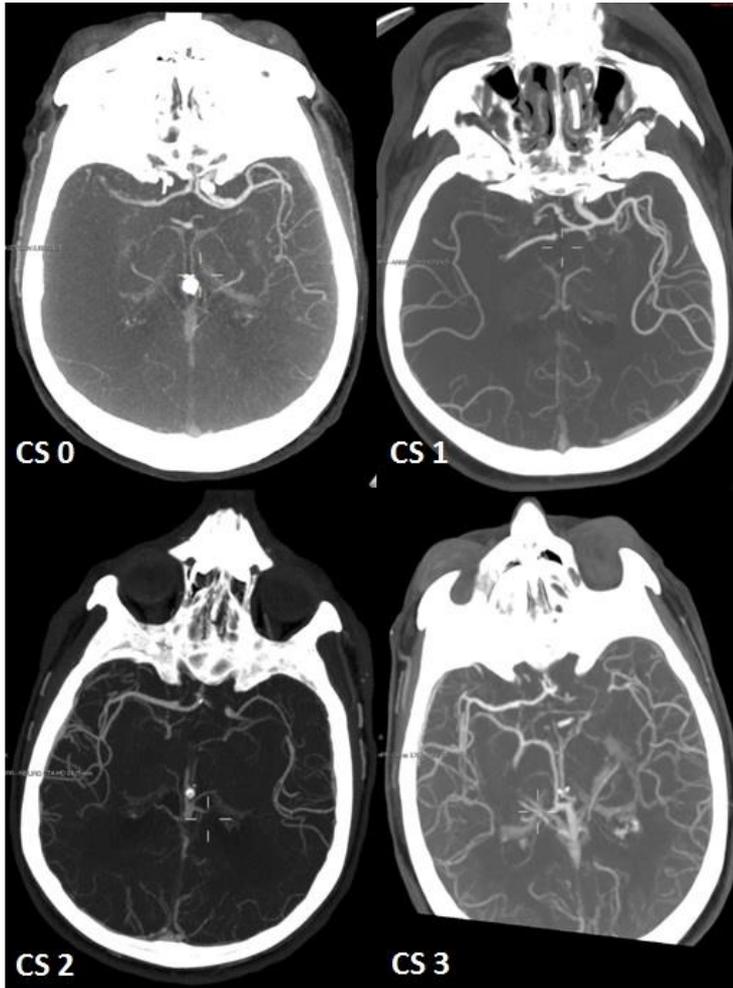


Figure 5

*Single-phase CTA of patients with hyperacute right MCA occlusions. CS 0 = no collaterals, CS 1 = minimal collaterals, CS 2 = intermediate collaterals and CS 3 = maximal collaterals. Abbreviations: CS, collateral score; CTA, computed tomography angiography; MCA, middle cerebral artery.*

The richness of collateral flow on single-phase (conventional) CTA maximum intensity projections (MIPs) predicts the final infarct volume in both patients with persistent arterial occlusion and those experiencing recanalization. Patients with poor collateral circulation at baseline are prone to further infarct growth prior to recanalization because irreversible changes occur early; patients with rich collateral circulation ultimately have smaller infarcts, even in the setting of persistent occlusion [104]. Another collateral scoring system based also on intracranial CTA MIPs was devised by Souza et al. This system was scored as follows: 0 = absent collaterals in >50% of an M2 branch territory; 1 = diminished collaterals in >50% of an M2 branch territory; 2 = diminished collaterals in <50% of an M2 branch territory; 3 = collaterals equivalent to the contralateral hemisphere; and 4 = increased collaterals compared to the contralateral hemisphere [105]. Single-phase CTA does not provide temporal resolution; therefore, collateral status may be mischaracterized in many patients. Dynamic CTA is a technique that derives time-resolved images of pial arterial filling from CTP images; however, dynamic CTA requires postprocessing and whole-brain CTP. In contrast, multiphase (arterial, arteriovenous, and venous phases) dynamic CTA rapidly provides easily interpretable information about the degree and extent of pial arterial filling in the whole brain in a time-resolved manner. In addition, interrater reliability for multiphase CTA is excellent. In multi-phase collateral scoring (0-5) collaterals are considered to be poor when they are distal to occlusion, compared to backfilling arteries to similar arteries in the asymptomatic contralateral hemisphere, there are no vessels visible in any phase within the occluded vascular territory or there are only a few vessels visible or no or minimal collaterals are visible in a region greater than 50% of the MCA territory [106].

The effects of leptomeningeal collateral circulation with regard to the location of the clot in predicting the clinical outcomes of patients treated with IVT have seldom been directly addressed in previous studies.

## 2.7 EARLY MANAGEMENT OF PATIENTS WITH ISCHEMIC STROKE

Prehospital care providers must perform initial assessments and intervene if necessary to provide cardiopulmonary support. In addition, providers must clearly establish the time of onset of symptoms. If the patient wakes from sleep or is found with symptoms of a stroke, the time of onset of symptoms is defined as the last time the patient was observed to be normal. Providers must be able to transport the patient and to provide pre-arrival notification to an acute stroke-ready hospital (ASRH) [107]. ASRHs are hospitals that have made an institutional commitment to evaluate, diagnose, and treat most ED stroke patients effectively and efficiently. Additionally, ASRHs have well-developed relationships with regional primary stroke centers (PSCs) and comprehensive stroke centers (CSCs) [12]. Continuous cardiac monitoring begins in the prehospital setting and is indicated for at least the first 24 hours after stroke throughout the initial assessment and management [108]. Because stroke is a primary failure of focal tissue oxygenation and energy supply, supplemental oxygen should be provided to maintain an oxygen saturation  $>94\%$ , sources of hyperthermia (temperature  $>38^{\circ}\text{C}$ ) should be identified and treated, and antipyretic medications should be administered to lower the temperature of hyperthermic patients. In addition, hypovolemia should be corrected with intravenous normal saline, it is reasonable to treat hyperglycemia, and in patients with markedly elevated blood pressure (SBD  $>220$  mmHg, DBP  $>120$  mmHg), the goal should be to lower blood pressure by 15% over the first 24 hours after the onset of stroke [12].

### 2.7.1 Intravenous thrombolytic therapy of hyperacute ischemic stroke

The use of IVT with rtPA for hyperacute anterior circulation IS is associated with improved outcomes for a broad spectrum of patients who can be treated within 3

hours of symptom onset [109] and for a more selective spectrum of patients who can be treated between 3 and 4.5 hours after symptom onset [110]. The effects of treatment in patients older than 80 years of age are as great as in patients younger than 80 years of age, and there is a greater benefit of IVT in patients with increasingly severe strokes [111]. Treatment with IVT has also been associated with increased rates of intracranial hemorrhage, which can be fatal [109-110]. The rate of symptomatic intracranial hemorrhage (sICH) depends on the definition of sICH [14, 109, 112]. The average absolute increased risk of early death from sICH is approximately 2%, but by 3 months, overall mortality is similar between patients treated with IVT and controls [113]. In addition to the risk of sICH, other potential adverse effects include systemic bleeding, myocardial rupture if IVT is administered within a few days of AMI, and reactions such as anaphylaxis or orolingual angioedema, although these events are rare [12]. Regulatory precedents established by the Food and Drug Administration (FDA) and the Department of Health and Human Services in the United States and by the World Medical Association provide international support for the use of IVT in patients lacking decision-making capacity, in the absence of a substitute decision-maker (surrogate) within the treatment window [114].

In Sweden, according to the Riks-Stroke registry, 6.7% of IS patients received thrombolytic therapy from 2007 to 2010. Among patients treated with thrombolysis, the proportion with minor stroke (NIHSS 0-5) increased from 22.1% in 2007 to 28.7% in 2010 [115]. A CSC of Helsinki University Hospital in Finland has organized regional stroke care around the CSC, and among HIS patients transported directly to the Helsinki University Hospital, 31% receive IVT. Because many patients who are not candidates for IVT are admitted to other hospitals, the population-based regional thrombolysis rate is 16% [116].

Stroke expertise and neuroimaging interpretation in ASRHs often appear in the forms of telemedicine and teleradiology. Telemedicine (also called telestroke) has been broadly defined as *the use of telecommunications technologies to provide medical*

*information and services*, including an integrated audio and visual remote assessment coupled with the use of teleradiology for the remote review of brain images. Telemedicine can provide 24-hours-per-day/7-days-per-week acute stroke expertise to hospitals without full-time neurological or radiological services [117]. Telestroke optimizes the use of IVT to treat patients in hospitals without an on-site neurologist, decreases the time to initiate IVT, and provides treatment with a safety similar to that in PSCs [118]. Evidence for the safety of IVT delivery without a neurologist stroke specialist present by telemedicine or by telephone consultation is less robust [12]. However, there has been no evidence of increased risks of mortality, ICH, or a reduced functional recovery in IS patients treated by emergency physicians without a stroke team [119].

It is estimated that each 15-minute delay in IVT treatment can result, on average, in the equivalent of a 1-month reduction of healthy life for each treated patient [120]. Because the benefit of IVT therapy is time dependent, treatment should be initiated as rapidly as possible. With multiple concurrent strategies, it is possible to decrease the median door-to-needle time to 20 minutes. The key is to undertake as few actions as possible after the patient has arrived at the emergency room and as many as possible before this point while the patient is being transported [116]. Thus, health systems should set a goal to increase their percentage of IS patients treated with IVT within 60 minutes of presentation to the hospital to at least 80% [12].

There is potentially a trade-off between more rapid time to treatment and diagnostic accuracy. In a series of 512 IVT-treated patients, 21% did not have an infarct on post-treatment DWI or on follow-up neuroimaging. In the stroke mimics group (14%), the average age was 55 years old, 60% were female, and the median admission NIHSS was 7. However, compared to the IS patients, the stroke mimics were 5 times more likely to have an NIHSS of 1-4. In the TIA group (7%), including patients with a clinical diagnosis of cocaine-associated vasospasm, the average age was 61 years old, 32% were female, and the median admission NIHSS

was 7. In both groups, the median discharge NIHSS was 0, and there were no instances of sICH [121].

Imaging in patients who are potential candidates for IVT should not delay the administration of IVT. The entire multimodal CT evaluation does not delay IVT, which can be performed directly in the CT scanner once the NCCT is completed and while the CTA and/or CTP are being obtained [70]. Rapid MRI sequences require between 5 and 10 minutes and cover the entire brain without radiation.

**Table 1.**

Absolute exclusion characteristics of patients with ischemic stroke who could be treated with intravenous thrombolysis within 3 hours of symptom onset [12]

<b>Exclusion criteria</b>
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding, acute bleeding diathesis, including but not limited to Platelet count <100 000/mm <sup>3</sup>
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

*Abbreviations: CT, computed tomography; INR, international normalized ratio.*

An ASPECTS of  $\leq 5$  can be used as a guideline when evaluating  $>1/3$  of the region of territory involvement [12, 119]. In addition, among patients with very extensive EICs (ASPECTS of  $<3$ ), no benefit from rtPA has been demonstrated [122]. The laboratory result required in all patients prior to the initiation of rtPA therapy (bolus) is the determination of glucose levels; finger-stick measurement devices are acceptable for this measurement. The rtPA infusion should be discontinued if other laboratory results (activated partial thromboplastin time [aPTT], INR, platelet count, ecarin clotting time [ECT] or thrombin time [TT]) are abnormal [12].

The relative exclusion criteria for IVT include only minor or spontaneously rapidly improving symptoms, pregnancy, seizure at onset with postictal residual neurological impairments, major surgery or serious trauma within the previous 14 days, recent gastrointestinal or urinary tract hemorrhage (within the previous 21 days) and recent AMI (within the previous 3 months) [12]. In addition, the relative exclusion criteria within 3 to 4.5 hours after symptom onset include an age  $>80$  years old, severe stroke (NIHSS $>25$ ), taking of an oral anticoagulant regardless of INR and histories of both diabetes and prior IS [12].

The ultimate purpose of IVT is to achieve recanalization (arterial patency) and reperfusion (anterograde flow), which can potentially lead to revascularization. A formal meta-analysis confirmed a strong correlation of recanalization with improved functional outcomes and reduced mortality in IS, suggesting that recanalization is an appropriate biomarker of therapeutic activity. However, recanalization rates after IVT were low when the occlusion involved a large intracranial artery, with rates of 14% for ICAs and 55% for MCAs but information regarding clinical outcome was not presented according to target vessels [123]. Economic studies conducted in developed countries and in the most population-rich developing country (China) have demonstrated that IVT is cost-effective for IS [124].

Treatment protocols for patients with a basilar artery occlusion differ markedly, e.g., consistently including concomitant full-dose intravenous heparin and allowing for an onset to treatment time (OTT) of up to 48 hours in patients with progressing symptoms [125].

## 2.7.2 Endovascular interventions for hyperacute ischemic stroke

The options for endovascular treatment to improve recanalization rates include intra-arterial thrombolysis (IAT), mechanical thrombectomy devices and acute angioplasty and stenting. Angioplasty and stenting of extracranial ICA (or extracranial VAs) are predominantly performed for IS prevention, rather than for acute stroke treatment. However, this therapy has been used on an emergency basis in the setting of acute stroke for 2 situations in particular: when the primary cause of the stroke is attenuation or cessation of flow in the extracranial ICA or VA, such as with total or near-total occlusion caused by severe atherosclerosis or dissection and when catheter access to a culprit intracranial clot is impeded by severe stenosis of the extracranial ICA, and angioplasty/stenting of the ICA is required prior to treatment of a more distal intracranial occlusion [12].

.Evidence for a benefit in the treatment of IAT with a duration of <6 hours caused by occlusions of the MCA (not ICA) in carefully selected patients (age  $\leq 68$  years old, NIHSS 4-10 and NCCT hypodensity  $\leq 5.25$  ml), who are not otherwise candidates for IVT, is derived primarily from 2 randomized trials: the randomized Prolyse in Acute Cerebral Thromboembolism II (PROACT II) and the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) [12, 126]. In one study, IAT was more beneficial, in terms of favorable modified Rankin Scale at 3 months, than IVT in the specific group of stroke patients presenting with HMCAS on NCCT, although IAT was initiated later [127]. The modified Rankin scale (mRS) is a simplified overall assessment of function, in which a score of 0

indicates the absence of symptoms, 0-1 is an excellent outcome, 0-2 indicates independence, 5 is severe disability, and 6 denotes death [69].

The Interventional Management of Stroke III (IMS III) trial used an innovative design in which patients in whom IVT was administered within 3 hours after IS onset were randomly assigned to receive IVT alone or IVT followed by endovascular treatment. The majority of the patients in the endovascular treatment group had intra-arterial rtPA administered during the procedure. Despite a higher rate of partial or complete recanalization at 24 hours in the endovascular group, clinical outcomes were similar in the two groups, and the trial was stopped early due to futility [128]. In contrast, in a post-hoc model, it was estimated that endovascular therapy after IVT is the preferred treatment, compared with IVT alone. However, if the time from onset to reperfusion, as measured according to Thrombolysis in Cerebral Infarction (TICI) grades 2 or 3 (indicating partial or complete re-perfusion), exceeds 5 hours and 47 minutes, IVT alone is the recommended strategy [129].

Currently, 4 devices have been approved by the FDA for recanalization of arterial occlusion in patients with IS. Retrievable stents constitute the newest approach to endovascular recanalization. When mechanical thrombectomy is pursued, stent retrievers are preferred to coil retrievers. These stent retrievers are deployed within symptomatic intracranial thrombi to immediately reperfuse the tissue, and they are then used to engage and retrieve the clot. Removal of the stent eliminates the need for acute double-antiplatelet therapy, as is needed for permanent stent placement.

In the trial comparing endovascular treatment with stent retrievers to standard treatment, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), retrievable stents were used in 190 of the 233 patients (82%) in the intervention group, and simultaneous acute cervical carotid stenting was performed in 30 patients (13%). Good reperfusion rate was 59% in the intervention group, and there was a shift in

the distribution of the mRS scores of 0-5 at 90 days in favor of the intervention, regardless of age. However, in the presence of extracranial ICA occlusion, admission NCCT ASPECTS of <8 or NIHSS <20, the adjusted ORs were accompanied by wide CIs [130].

In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE), retrievable stents were used in 130 of the 151 participants (86%) who underwent an endovascular procedure, and the good reperfusion rate was 72%. In contrast, in the control group, successful recanalization was observed in 41 of 110 (37.3%) who received IVT and 2 of 28 (7%) who did not. The proportion of patients with a mRS score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group and mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group. However, in the presence of carotid T- or L- occlusion, admission NCCT ASPECTS of <8 or age >80 years, the adjusted ORs were accompanied by wide CIs [131].

In the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial, the Solitaire FR (Flow Restoration) retrievable stent was deployed to 28 of the 35 patients in the endovascular group and 33 of 35 (94%) experienced recanalization by 24 hours. In the IVT only group, recanalization rate was 15 of 35 (43%). Endovascular therapy improved functional outcome at 90 days, with more patients achieving functional independence (71% vs. 40%). Subgroup analyses could not be performed given the small number of patients [132].

The Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial also compared IVT followed by neurovascular thrombectomy with the use of a retrievable stent (Solitaire FR or Solitaire 2 device) for IVT alone. 83 endovascular arm patients in whom Solitaire device were used 73 (88%) exhibited substantial or complete reperfusion defined as perfusion of half or greater of the vascular distribution of the occluded artery. The proportion of

outcomes indicating functional independence at 90 days was significantly higher in the intervention group than in the control group, with an absolute difference of 25% (60% vs. 35%). There was no evidence of heterogeneity in the treatment effect in the subgroups. In the subgroup displaying an ASPECTS of 6-7, 10 of 24 patients were independent in the intervention group compared to 5 of 19 in the IVT alone group [133].

The Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to an Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) compared thrombectomy with medical therapy alone in eligible patients who received IVT within 4.5 hours after the onset of symptoms without revascularization after 30 minutes of t-PA infusion or who exhibited a contraindication to IVT. Substantial or complete reperfusion in the thrombectomy group was achieved in 67 of 102 (66%) patients. The absolute between-group difference in the proportion of patients who were functionally independent was 15.5%, favoring thrombectomy (43.7% vs. 28.2%). The benefits appeared to be least consistent in subgroups that were defined according to age ( $\geq 70$  years) or time window ( $>4.5$  hours from onset to randomization) [134].

In all of the endovascular studies of stent retrievers mentioned above, there was no sign of increased bleeding risk compared with IVT alone, and an overall trend toward a reduction in mortality due to thrombectomy [130-134]. Meta-analyses of data from multiple trials will be required to clarify the benefits of thrombectomy in different clinical and neuroimaging subgroups.

## 2.8 EARLY PROGNOSIS OF ISCHEMIC STROKE

There is no simple formula for predicting the prognosis of an individual patient in acute neurovascular syndrome. In the case of symptom resolution during transportation or hospital evaluation, patients can be mistakenly categorized as TIA patients. However, 1/3 of patients with definite specialist-confirmed TIA have positive DWI findings [135]. It is recommended that multimodal neuroimaging of the brain and cerebral vasculature with MRI should be performed in TIA patients to confirm the diagnosis of stroke, identify the underlying etiology, and assess immediate complications and the risk of future stroke [70]. In a multicenter study, among positive DWI patients, the recurrent IS rate at 7 days was 7.1% and among negative DWI patients IS rate at 7 days was 0.4%. Corresponding rates for any infarction, regardless of age, in NCCT-imaged patients were 12.8% and 3.0%, respectively [136]. In a Japanese cohort, a multivariable-adjusted model revealed that dual TIA and carotid stenosis were both significant predictors of IS after TIA, whereas abnormal DWI was not. The addition of intracranial arterial stenosis and the exclusion of abnormal DWI improved the predictive ability for IS risk [137].

Based on the preclinical information (ABCD<sup>3</sup>) and after completion of initial investigations in secondary care settings (ABCD<sup>3</sup>-I), assessment schemes have been developed to predict IS. An age  $\geq 60$  years old, BP  $\geq 140/90$  mm Hg, speech impairment without weakness, a symptom duration of 10-59 min and the presence of diabetes each provide one point. In addition, unilateral weakness, a symptom duration  $\geq 60$  min, dual TIA (TIA prompting medical attention plus at least one other TIA in the preceding 7 days), ipsilateral  $\geq 50\%$  stenosis of the ICA and acute DWI hyperintensity each provide two points. The total ranges of the scores are thus 0-9 and 0-13 for ABCD<sup>3</sup> and ABCD<sup>3</sup>-I, respectively. For example, the 7-day stroke risk in patients with an ABCD<sup>3</sup>-I score of 0-7 was 0.5% compared with 4.1% in those with a score of 8 or greater [138].

In patients presenting with acute IS symptoms and no indicated or available revascularization therapy, advanced age, stroke severity measured by the NIHSS score and unfavorable pattern of leptomeningeal collaterals were associated with mortality and dependency [102].

The DRAGON score was developed for early estimation of the patient prognosis for IVT candidates. It consists of parameters that are available soon after patient admission and prior to IVT administration. The parameters include HMCAS or EICs on admission NCCT, prestroke mRS >1, age, glucose level on admission, OTT and NIHSS on admission. The DRAGON score reliably identifies patients who are very likely benefit from IVT (mRS 0-2), as well as those with a high likelihood of a miserable outcome (mRS 5-6) despite IVT. Proportions of patients with favorable outcome (mRS 0-2) were 96%, 88%, 74%, and 0% for 0-1, 2, 3, and 8-10 points, respectively. [139]. According to the SITS-MOST register, HMCAS is not an independent predictor of sICH but of mortality and independence [140]. The DRAGON score has been validated in both anterior and posterior circulation strokes [141]. In addition, the DRAGON score was recently adapted for patients undergoing MRI instead of CT as the first-line imaging modality. In the MRI-DRAGON score, a proximal (M1) MCA occlusion on MRA is used instead of HMCAS, and DWI ASPECTS of  $\leq 5$  is used rather than EIC on NCCT [142]. The rationale for the DWI ASPECTS threshold of  $\leq 5$  was obtained from a study in which multivariate logistic regression analysis demonstrated that a DWI ASPECTS of  $\leq 5$  was the only independent predictor of a bad outcome. In that study, a bad outcome was defined as an NIHSS score  $\geq 20$  at 7 days after IVT [143].

The associated optimal DWI-ASPECTS cut-off points for infarct volumetric thresholds  $\geq 100$  ml,  $\geq 75$  ml,  $\geq 50$  ml, and  $\geq 25$  ml, were estimated to be  $\leq 3$ ,  $\leq 4$ ,  $\leq 5$ , and  $\leq 7$ , respectively [144]. Furthermore, the clinical responsiveness to the IVT and IS outcome appears to depend more on the baseline DWI (infarct volume  $\leq 25$  ml) and PWI lesion volumes than on the extent of the perfusion-diffusion

mismatch [145]. In contrast, in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) trial, target mismatch patients, who had a MRI profile that suggested salvageable tissue was present, had early reperfusion following endovascular stroke treatment had more favorable clinical outcomes. No association between reperfusion and favorable outcomes was determined in patients without a target mismatch [146]. For ASPECTS based on NCCT in patients treated with IVT within 3 hours, a baseline ASPECTS of 7 or less sharply distinguished independence and death at 3 months [147].

The length of the clot is a limitation of the effectiveness of IVT. Detected with NCCT, short MCA clots (length <5 mm) are highly likely to be dissolved completely, but recanalization can be expected in <1% of cases if the thrombotic clot extends further than 8 mm [148]. However, it is unknown how the location of the extracranial or intracranial clot affects the 3-month functional outcomes of patients treated with IVT for whether if CTA imaging has further prognostic value compared to the parameters used, for example to calculate the DRAGON score.

## 2.9 POST-ACUTE INPATIENT CARE AND SECONDARY PREVENTION OF ISCHEMIC STROKE

The key to safe and effective stroke care is rapid transfer to a stroke unit. The benefits from treatment in a stroke unit are comparable to the effects achieved with IVT. The utility of induced hypothermia for the treatment of patients with IS has not been well established, and further trials are recommended [12]. The interdisciplinary team, consisting of a physician, a nurse with specialized training or experience in rehabilitation, an occupational therapist, a physical therapist and a speech-language pathologist, focuses on providing basic supportive care and preventing major post-stroke complications that can dramatically impede the rehabilitation process and prevent desired patient outcomes. These major complications are pulmonary embolisms and deep vein thrombosis, skin integrity

issues, spasticity, aspiration, malnutrition, severe sleep apnea, seizures, and falls [149]. Thus, it is recommended that swallowing be assessed before the patient begins eating, drinking, or receiving oral medications, and patients with suspected pneumonia or urinary tract infections should be treated with appropriate antibiotics. In addition, patients who cannot consume solid food or liquids orally should receive nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tube feeding to maintain hydration and nutrition while undergoing efforts to restore swallowing. There is currently no clinical evidence that targeting the blood glucose at a particular level during acute IS will improve outcomes. After the patient's condition is stabilized, secondary prevention measures to prevent long-term complications and measures to provide rehabilitation, patient and family education, and family support are initiated [12].

The initiation of BP therapy is indicated for previously untreated patients with IS or TIA who, after the first several days, have an established systolic BP  $\geq 140$  mm Hg systolic or diastolic BP  $\geq 90$  mm Hg, and the resumption of BP therapy is indicated for previously treated patients with known hypertension for the prevention of recurrent stroke and of other vascular events in those who have had an IS or TIA and are beyond the first several days after the event [30].

Statin therapy is recommended to reduce the risks of stroke and cardiovascular events in patients with IS or TIA presumed to be of atherosclerotic origin, regardless of the level of LDL-C [30].

The use of existing guidelines for glycemic control and cardiovascular risk factor management is recommended for patients with an IS or TIA who also have diabetes or pre-diabetes. Furthermore, all patients with IS or TIA should be screened for obesity with the measurement of BMI, and patients with signs of undernutrition should be referred for individualized nutritional counseling [30]. Healthcare providers should strongly advise every patient with IS or TIA who has smoked in the past year to quit, and patients who are heavy drinkers should eliminate or reduce their consumption of alcohol [30].

In patients with a IS or TIA within the past 6 months and ipsilateral severe (70%-99%) carotid artery stenosis as documented by noninvasive imaging (MRA or CTA), CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6%. In addition, in patients with a recent IS or TIA and ipsilateral moderate (50%-69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities. Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis [30].

Carotid angioplasty and stenting (CAS) constitute an alternative to CEA among patients with symptomatic severe stenosis (>70%) in whom anatomic or medical conditions are present that greatly increase the risk of surgery or when other specific circumstances are present, such as radiation-induced stenosis or restenosis after CEA. In younger patients (< 70 years old), CAS is equivalent to CEA in terms of the risk of periprocedural complications and the long-term risk for ipsilateral IS. In contrast, endovascular stenting of patients with extracranial vertebral stenosis should be considered only when patients are experiencing symptoms despite optimal medical therapy [30]. In patients with an IS or TIA caused by 50% to 99% stenosis of a major intracranial artery, aggressive medical management with aspirin rather than warfarin, maintenance of a SBP less than 140 mm Hg and statin therapy are recommended over intracranial stenting [30].

Warfarin (with a target INR of 2.5), apixaban and dabigatran are indicated for the prevention of recurrent IS in patients with nonvalvular AF. In addition, rivaroxaban is reasonable for the prevention of recurrent stroke. For patients with AF who are unable to take oral anticoagulants, aspirin alone is recommended [30]. Treatment with warfarin (target INR 2.5) for 3 months is recommended in most patients with IS or TIA in the setting of AMI complicated by left ventricular mural thrombus formation, identified by echocardiography or another imaging modalities. Furthermore, in patients with IS or TIA in sinus rhythm who have left

atrial or left ventricular thrombus demonstrated by echocardiography or another imaging modality, warfarin is recommended for  $\geq 3$  months [30].

In patients with IS or TIA who have rheumatic mitral valve disease and AF, warfarin with an INR target of 2.5 is recommended. In patients with a mechanical aortic valve and a history of IS or TIA before its insertion and in patients with a mechanical mitral valve without history of IS or TIA, warfarin is recommended with an INR target of 2.5. In contrast, for patients with a mechanical mitral valve and a history of IS or TIA before its insertion, warfarin is recommended with an INR target of 3.0. In addition for patients with a mechanical mitral or aortic valve who have a history of IS or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin to warfarin therapy is recommended. In contrast, in patients with a bioprosthetic aortic or mitral valve, a history of IS or TIA before its insertion, and no other indications for anticoagulation therapy beyond 3 to 6 months from the time of valve placement, long-term therapy with aspirin is preferable to long-term anticoagulation [30].

In patients with noncardioembolic IS or TIA, aspirin (50-325 mg/d) monotherapy within 24 to 48 hours after symptom onset or a combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated as an initial therapy after IS or TIA. Clopidogrel (75 mg) monotherapy is a reasonable option for the secondary prevention of stroke, as an alternative to aspirin or combination aspirin/dipyridamole [30]. In patients with an IS or TIA and evidence of aortic arch atheroma, antiplatelet and statin therapies are recommended. In patients with IS or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy for at least 3 to 6 months is reasonable [30].

In patients with an IS or TIA and a PFO, who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended. However, in patients with IS or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on the stroke characteristics. Antiplatelet therapy is

recommended for patients who have abnormal findings on coagulation testing after an initial IS or TIA. In patients with IS or TIA who have antiphospholipid antibodies but do not fulfill the criteria for antiphospholipid syndrome, antiplatelet therapy is recommended. In patients with IS or TIA who meet the criteria for antiphospholipid syndrome, anticoagulant therapy might be considered, depending on the perception of the risks of recurrent thrombotic events and bleeding [30].

### 3. AIMS OF THE STUDY

- (I) To determine whether the use of optimized window settings in computed tomography analysis has an effect on the accuracy of the detection of early ischemic changes in hyperacute ischemic stroke patients
- (II) To analyze the impact of the location of the clot on the radiological and clinical outcomes of hyperacute ischemic stroke patients treated with intravenous thrombolysis
- (III) To analyze the impact of leptomeningeal collateral circulation in predicting the radiological and clinical outcomes of hyperacute ischemic stroke patients treated with intravenous thrombolysis
- (IV) To describe the relation of computed tomography perfusion features to clinical outcome in hyperacute ischemic stroke patients treated with intravenous thrombolysis

## 4. MATERIALS AND METHODS

### 4.1 DATA COLLECTION AT HACETTEPE UNIVERSITY HOSPITAL (I)

We retrospectively analyzed a consecutive series of 74 HIS patients who received IVT or IAT from January 2005 to August 2009 at Hacettepe University Hospital in Ankara, Turkey. At this hospital, all patients presenting symptoms consistent with HIS routinely undergo NCCT and CTA. Patients with minor strokes (NIHSS 0-5) are not eligible for thrombolytic therapy unless isolated aphasia or homonymous hemianopia due to a lack of the scientific evidence is present [150]. Our study was restricted to patients who sustained HIS within the MCA territory and who underwent MRI within 14 days after receiving thrombolytic treatment. The study protocol was approved by the local institutional review board. J.T.S made substantial contributions to the acquisition and analysis of the neuroimaging data.

### 4.2 DATA COLLECTION AT TAMPERE UNIVERSITY HOSPITAL (II-IV)

Our retrospective observational cohort study was approved by the ethics committee of Tampere University Hospital. From January 2004 to December 2007, 315 anterior or posterior circulation HIS patients were treated with IVT and were followed up for 3 months in the Department of Neurology of Tampere University Hospital. CTA was performed at admission in the vast majority (90%; 285 of 315) of patients. The inclusion criteria were hyperacute anterior circulation vessel occlusion confirmed by CTA and treatment with standard IVT administration. The IVT protocol was consistent with the guidelines of the

American Heart Association/American Stroke Association [12]. From 2004 to 2007, intra-arterial interventions were not performed for anterior circulation occlusions at Tampere University Hospital. J.T.S made substantial contributions to the conception of the study and the acquisition and interpretation of the clinical data.

### **4.3 CLINICAL VARIABLES IN THE HACETTEPE UNIVERSITY HOSPITAL COHORT (I)**

The baseline characteristics of the study population included age, sex, admission NIHSS score, time from stroke onset to NCCT, time from stroke onset to CTA, time from onset of stroke to initiation of thrombolysis, type of thrombolytic treatment, time from stroke onset to MRI and stroke subtype.

### **4.4 CLINICAL VARIABLES IN THE TAMPERE UNIVERSITY HOSPITAL COHORT (II-IV)**

The baseline clinical characteristics included age, sex, antithrombotic therapy prior to HIS, prestroke functional status (mRS), time from both symptom onset and imaging to the initiation of IVT and clinical risk factors for IS (hypertension, diabetes, coronary artery disease [CAD] and atrial fibrillation). These data were collected from the patient records. The clinical evaluation results at the time of admission were prospectively stored according to a specific protocol, and they consisted of BP and the NIHSS score at the time of initiation of rtPA. The admission levels of hemoglobin, INR, glucose and glycated hemoglobin were obtained from the laboratory database. Systematic ECG monitoring and further vascular and heart imaging were performed in the stroke unit and the neurology ward, and the results of these studies were retrieved. Follow-up NCCT and NIHSS scoring were performed for all of the patients 24 h after administration of the

rtPA. The CCS system was used by a certified CCS rater (J.T.S.) to assess the stroke etiology [22].

Functional status (mRS), which was scored 3 months after the HIS, was the primary outcome measurement. From 2004 to 2005, the 3-month mRS score was prospectively recorded based on follow-up visits to a neurologist and from 2006 to 2007 based on phone interviews by a neurologist. Death during the primary university hospital episode or discharge from the neurology ward to a rehabilitation facility was considered to signify an unfavorable clinical outcome at discharge. This status was used as the secondary outcome measurement. The seven (7%) patients who were discharged temporarily to primary healthcare centers due only to adjustment of their warfarin dose were included in the favorable discharge group, along with the patients who were discharged directly to their homes. All of the prospectively stored clinical data were carefully evaluated for potential errors (J.T.S.).

## 4.5 IMAGING PARAMETERS IN THE HACETTEPE UNIVERSITY HOSPITAL COHORT (I)

NCCT and CTA were performed using a commercially available multidetector row scanner (2-slice scanner SOMATOM Emotion Duo or 16-slice scanner Sensation 16; Siemens Medical Systems, Erlangen, Germany). The image acquisition parameters for NCCT were as follows: sequential mode, 5-mm slice thickness, 120-130 kV, and 200 mA. CTA was obtained using a helical scanning technique after a single bolus injection of 100-130 ml of nonionic contrast medium into an antecubital vein at a rate of 3-4 ml/second, using a dynamic contrast bolus detection technique for the acquisition timing (CareBolus; Siemens Medical Systems). The CTA parameters were as follows: SOMATOM Emotion Duo: 130 kV foramen magnum to vertex, 50 mA, slice thickness of 2 mm, reconstruction

increment of 0.7 mm; Sensation 16: 120 kV aortic arch to vertex, 100 mA, slice width of 1 mm, slice collimation of 0.75 mm, reconstruction increment of 0.7 mm.

MRI was performed with a 1.5-T scanner (Magnetom TIM; Siemens Medical Systems). The protocol included an axial T2-weighted turbo spin echo (repetition time [TR]/echo time [TE], 3800/90 ms; matrix, 256 × 256), FLAIR (TR/TE/inversion time [TI]: 9000/100/2100 ms; matrix, 224 × 256), and DWI (single-shot echo planar, applied 3 b values with a maximum of 1000 s/mm<sup>2</sup> and a TR/TE of 4800/120 ms; matrix, 96 × 256) sequences, all with a slice thickness of 5 mm, a 10% interslice distance, and a 220- to 240-mm field of view.

## 4.6 IMAGING PARAMETERS IN THE TAMPERE UNIVERSITY HOSPITAL COHORT (II-IV)

NCCT scans were obtained using two different multidetector scanners: a General Electric LightSpeed 16-slice scanner (GE Healthcare, Milwaukee, WI, USA) and a Philips Brilliance 64-slice scanner (Philips, Cleveland, OH, USA). Brain NCCT was performed using the following parameters: 64-row, 120 kV, 430 mA, collimation 12 x 1.25 mm, rotation 1.5 s and 16-row, 120 kV, 320 mA, collimation 16 x 1.25 mm, and rotation 1 s. Contiguous slices were reconstructed to a thickness of 5 mm over the entire scanning range (64-row) or to a thickness of 5 mm in the skull base and 7.5 mm in the supratentorial region (16-row).

CTA was performed using a scanning range extending from the C2 vertebra to the vertex of the skull. The imaging parameters were 120 kV, 212 mA (using dynamic tube current modulation), collimation of 64 x 0.625 mm, rotation of 0.75 s, pitch factor of 0.923 (64-row) or 120 kV, 160 mA, collimation of 16 x 0.625 mm, rotation of 0.8 s, and pitch factor of 0.938 (16-row). Contiguous slices were reconstructed to a thickness of 0.9 mm with a 0.45-mm overlap (64-row) or to a thickness of 1.25 mm (16-row). The contrast agent (iobitridol, Xenetix, 350 mgI/ml, Guerbet, Aulnay-sous-Bois, France) was administered via an antecubital

18-gauge cannula using a double-piston power injector at a flow rate of 4 ml/s to inject 70 ml of contrast agent followed by a 50-ml saline flush. Manual bolus triggering was used.

CTP was performed using the following parameters: 80 kV, 200 mA (effective), collimation of 32 x 1.25 mm, rotation of 0.4 s (64-row) or 80 kV, 200 mA, collimation of 8 x 2.5 mm, and rotation of 1 s (16-row). A total of 120 slices, encompassing a range of 80 mm, were generated in 55 s using a protocol that utilized two alternating table positions to increase the z-axis coverage, i.e., a “shuttle mode” (64-row), or 200 slices encompassing a range of 20 mm were generated in 50 s in a stationary table position (16-row). Contiguous slices were reconstructed to a thickness of 10 mm (64-row) or 5 mm (16-row) at even time intervals. The imaging range was positioned such that the ASPECTS levels were covered. The remaining 80-mm range (64-row) was positioned both cranially and caudally to the ASPECTS levels, with the exact balance dependent upon the clinical presentation. The contrast agent (Xenetix, 350 mgI/ml) was administered via an antecubital 18-gauge cannula using a double-piston power injector at a flow rate of 5 ml/s with 60 ml of contrast agent, followed by a 40-ml saline flush.

#### **4.7 IMAGE ANALYSIS IN THE HACETTEPE UNIVERSITY HOSPITAL COHORT (I)**

Three stroke neurologists, 1 neurology resident, and 1 radiologist retrospectively assigned 4 separate ASPECTS calculations of the CT examinations of the patients obtained at the time of admission in the following order: 1) NCCT using standard window width (W)/center level (C) settings (W: 80; C: 20), 2) NCCT using optimized window width/center level settings, 3) CTA-SI using standard window width/center level settings (W: 80; C: 40), and 4) CTA-SI using optimized window width/center level settings. The optimization of the window width/center level settings was left to the discretion of the rater and thus showed a certain amount of

variability between the raters and the patients. The raters were aware of the neurological deficits of the patients but were blinded to their previous ASPECTS ratings and MRI data. The patient order was random, and it differed for each set of CT-based evaluations. Follow-up ASPECTS was graded on MRI DWI or FLAIR images by a neuroradiologist (K.K.O.) who was blinded to clinical and CT data and who had not performed any of the CT-based ASPECTS ratings described above.

#### **4.8 IMAGE ANALYSIS IN THE TAMPERE UNIVERSITY HOSPITAL COHORT (II-IV)**

NCCT examinations were reviewed using dedicated medical imaging workstations. CTA and CTP images were analyzed, and areas and volumes were measured using the Advantage Workstation, version 3.2 (GE Healthcare, Milwaukee, WI, USA). CTA images were reviewed by examining both the raw data and MIP images. Parametric perfusion maps were generated using CT Perfusion 3 software (GE Healthcare), which uses a deconvolution-based algorithm. The ACA was used as a source for the arterial input function (AIF), and the region of interest for the venous output function (VOF) was positioned in the superior sagittal sinus. These curves were considered noisy if there was a clear dip or spike in the curve that could affect the calculations. Minor rippling of the signal, although it is a phenomenon caused by sources of noise, was not recorded as noise in this context. A persistently poor image quality was corrected when feasible by manually adjusting the parameters that control the motion artifact correction algorithm in the software.

The principles of the ASPECTS scoring of NCCT and CTP maps are described in section 2.6.1. The location of the image section closest to an ASPECTS level was considered suboptimal if the location did not exactly correspond to the reference level described in the literature [151] but allowed for reliable scoring. ASPECTS was considered uninterpretable if the section was obviously a different

anatomic region, for example, the cranial parts of the basal ganglia when evaluating the upper level.

MTT maps were used to detect at-risk tissue, and CBV maps were used to approximate the infarct core. The perfusion mismatch was calculated as the difference between the ASPECTS scored for the maps. When characterizing a perfusion defect, we used a semiquantitative approach in which the presence of a perfusion defect was determined visually from color-coded maps by comparing the appearance of the affected location to that of healthy tissue in the contralateral hemisphere. Based on theoretical considerations and to increase the measurement accuracy, we required the area measured in the visually identified location to be larger than 25 mm<sup>2</sup> with a mean MTT > 7 s (or mean CBV < 2.5 ml/100 g; adapted from Wintermark et al. [152]). Further validation was performed by requiring a mean relative MTT > 249% for the penumbra, a mean relative CBF < 31% and a mean relative CBV < 58% for the infarct core, compared with the contralateral side [153, 154].

The location of the clot was recorded based on the most proximal position of the occlusion. The M1 segment of the MCA was divided into two parts of equal length: the proximal and distal halves (designated as M1P and M1D).

The clot burden score (CBS) is an imaging score based on the location and the extent of the clot detected using CTA. In this scoring scheme, a score of 0 to 10 is assigned based on the number and location of arterial segments affected in the anterior circulation. Similar to ASPECTS, the absence of an occlusion is scored with 10 points, and points are deducted if non-opaque arterial segments are revealed by the contrast agent. CBS is correlated with clinical and radiological outcomes [155]. A prognostic variable CBSV combining the CBV ASPECTS and the clot-burden scores was recently introduced and a threshold value of 15 in the prediction of a favorable clinical outcome was derived for CBSV [156].

The examinations were reviewed in the following order: NCCT, CTA and finally CTP, paralleling the clinical work flow. The reviewers were blinded to the

clinical data apart from the side and nature of the acute symptoms. The location of the clot was determined, the CBS was scored, and NCCT and CTP ASPECTS were assigned by two radiologists. In cases in which the scoring differed, a consensus score was determined by agreement upon. The overall consensus opinion was compared in general terms to the original report by an experienced neuroradiologist, and if significant discrepancies were present, that neuroradiologist was further consulted. Perfusion-defect areas and final infarct volumes were measured by one radiologist. The boundaries of the affected areas were determined visually, and the absolute- and relative-value thresholds described above were applied. Volumes were calculated by multiplying the measured area by the slice thickness.

Infarcts with a volume of  $\leq 10$  ml on the 24-hour NCCT were defined as minor infarcts, and those  $\geq 100$  ml were considered extensive infarcts.

The status of the leptomeningeal collateral circulation was evaluated by using the scoring system devised by Souza et al. [105]. CS was scored independently by 2 radiologists. In cases in which the scoring or the assignment differed, agreement was accomplished by consensus. The intraclass correlation coefficient (ICC) between a staff radiologist and an experienced neuroradiologist for a test sample ( $n = 20$ ) for the CS was 0.87. Cohen  $\kappa$  was 0.68 for the CS (0.90 after dichotomization).

## 4.9 STATISTICAL METHODS USED AT HACETTEPE UNIVERSITY HOSPITAL (I)

ICC was used to assess the interexaminer agreement of the CT-based ASPECTS ratings. The absolute value of the difference between MRI-based ASPECTS and CT-based ASPECTS were calculated for all of the ratings to determine the degree of disparity between initial estimates of EICs on CT and the follow-up lesion on MRI. Friedman's test was used to analyze the effect of window settings

optimization on the difference between the initial and follow-up images. All of the numerical variables are expressed as the means  $\pm$  standard deviations (SDs) or as medians (interquartile ranges [IQRs]) as appropriate. A 2-tailed P value  $<.05$  was considered significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM, Armonk, NY, USA).

#### 4.10 STATISTICAL METHODS USED AT TAMPERE UNIVERSITY HOSPITAL (II-IV)

A biostatistician was consulted. The data were analyzed with SPSS, version 18 (SPSS Inc., Chicago, IL, USA) [II, IV] and SPSS version 19 (IBM, Armonk, NY, USA) [III]. In all of the studies, two-sided values of  $P < 0.05$  were considered statistically significant. Group comparisons for baseline variables were performed using Student's t-test, the chi-squared ( $\chi^2$ ) test, Fisher's exact test and the Kruskal-Wallis test [II], one-way ANOVA or Fisher's exact test [IV] and Student's t-test, the  $\chi^2$  test, Fisher's exact test, the Mann-Whitney U-test, and the Kruskal-Wallis test [III]. Bonferroni's correction for multiple comparisons was applied when necessary [II]. ICCs between a staff radiologist and an experienced neuroradiologist were calculated for CBS and ASPECTS assignments in a test sample ( $n=20$ ):  $ICC_{CBS}=0.86$ ,  $ICC_{NCCT0h}=0.86$ ,  $ICC_{MTT}=0.79$ ,  $ICC_{CBV}=0.73$  and  $ICC_{NCCT24h}=0.93$ . The median interobserver agreement indices for areas and volumes were  $AREA_{MTT}$ : 68%,  $AREA_{CBV}$ : 90% and  $VOLUME_{INFARCT}$ : 80%. Cohen's kappa for the location of the clot was 0.94 [II].

Patients who had a 3-month mRS  $\leq 2$  or who were discharged to their homes from the neurology ward were considered to have experienced a favorable clinical outcome. Patients with collateral scores from 2 to 4 had good collateral vessel filling. Binary logistic regression modeling, using these outcome measurements as the dependent variables was repeated for different variables of interest. NIHSS, age, sex, time from onset to treatment and clinical risk factors were examined as

potential confounders and were tested both in univariate models and with the clot location and collateral score [II, III]. The calibration of the models was evaluated using the Hosmer-Lemeshow test, and the discrimination was assessed with the C-statistic [II, III]. Odds ratios (ORs) with 95% CIs were calculated for each covariate. The sensitivity, specificity and CI calculations were performed using standard procedures. The normal and extended McNemar's tests were used to compare the overall diagnostic performance, sensitivities and specificities [II].

Analysis of covariance (ANCOVA) was used for the imaging features with onset-to-imaging time as a covariate. Pair-wise post-hoc testing was performed using Šidák correction for multiple comparisons [IV].

## 5. RESULTS

### 5.1 DETECTION OF EARLY ISCHEMIC CHANGES IN HYPERACUTE ISCHEMIC STROKE (I)

A total of 44 out of 74 patients met the inclusion criteria. Two main reasons for exclusion were missing NCCT because the patients had been referred from other institutions or posterior circulation strokes. Table 2 summarizes the clinical characteristics of the study cohort.

Table 3 summarizes the interexaminer agreement of CT-based ASPECTS ratings and the pooled results of all of the examiners with regard to the differences between CT- and MRI-based ASPECTS. The raters adjusted the window settings to mean values of W:  $22 \pm 12$  C:  $37 \pm 3$  for NCCT and W:  $43 \pm 14$  C:  $45 \pm 4$  for CTA-SI during evaluation of ASPECTS at optimized window settings.

Table 2.

Baseline characteristics of the study population (n = 44)

Age, years, mean $\pm$ SD	62 $\pm$ 13
Male sex, n (%)	23 (52%)
Admission NIHSS score, median (IQR)	16 (12-19)
Time from IS onset to initiation of thrombolysis, minutes, mean $\pm$ SD	138 $\pm$ 37
Type of thrombolytic treatment, n (%)	
IV rtPA	32 (73)
Intra-arterial thrombolysis	5 (11)
Combined IV rtPA and intra-arterial thrombolysis	7 (16)
Time from IS onset to NCCT, minutes, mean $\pm$ SD	81 $\pm$ 33
Time from IS onset to CTA, minutes, mean $\pm$ SD	90 $\pm$ 38
Time from IS onset to MRI, days, median (IQR)	1.2 (0.5-3.0)
Stroke subtype, n (%)	
Large-artery atherosclerosis	8 (18)
Cardioembolic	30 (68)
Small-artery occlusion	0 (0)
Other	1 (2)
Undetermined	5 (11)

*Abbreviations: CTA, computed tomography angiography; IQR, interquartile range; IS, ischemic stroke; IV, intravenous; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Score; NCCT, noncontrast computed tomography; rtPA, recombinant tissue plasminogen activator; SD, standard deviation.*

Table 3.

## Interrater agreement and accuracy of CT-based ASPECTS

	Intraclass correlation coefficient (95% confidence intervals)	CT-based ASPECTS		Difference of CT-based ASPECTS with respect to MRI-ASPECTS	
		Median (IQR)	Mean $\pm$ SD	Median (IQR)	Mean $\pm$ SD
NCCT, standard settings	0.79 (0.66-0.88)	9 (8-10)	8.7 $\pm$ 1.6	4 (2-6)	4.1 $\pm$ 2.2
NCCT, optimized settings	0.81 (0.70-0.89)	9 (7-10)	8.3 $\pm$ 1.8	3 (2-5)	3.7 $\pm$ 2.3
CTA-SI, standard settings	0.81 (0.68-0.89)	8 (7-9)	7.5 $\pm$ 2.3	3 (1-4)	3.0 $\pm$ 2.2
CTA-SI, optimized settings	0.85 (0.76-0.91)	8 (6-9)	7.2 $\pm$ 2.3	2 (1-4)	2.7 $\pm$ 2.1

*Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NCCT, noncontrast computed tomography; CT, computed tomography; CTA-SI, computed tomography angiography source images; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation.*

The mean and median ASPECTS on the follow-up MRI were  $4.6 \pm 2.4$  and 5, respectively (IQR, 3-7). The greatest difference was evident when ASPECTS was determined on NCCT with standard window settings. This difference sequentially decreased when the scores were assessed on NCCT after window setting optimization, CTA-SI without optimization and CTA-SI with optimization ( $p < 0.01$ ). Pairwise comparisons corrected for multiple comparisons revealed a statistically significant improvement between each pair of ratings ( $p < 0.005$ ) and the improvement introduced by the window setting optimization and CTA-SI was consistent among all of the raters irrespective of experience or specialty (Fig.6).

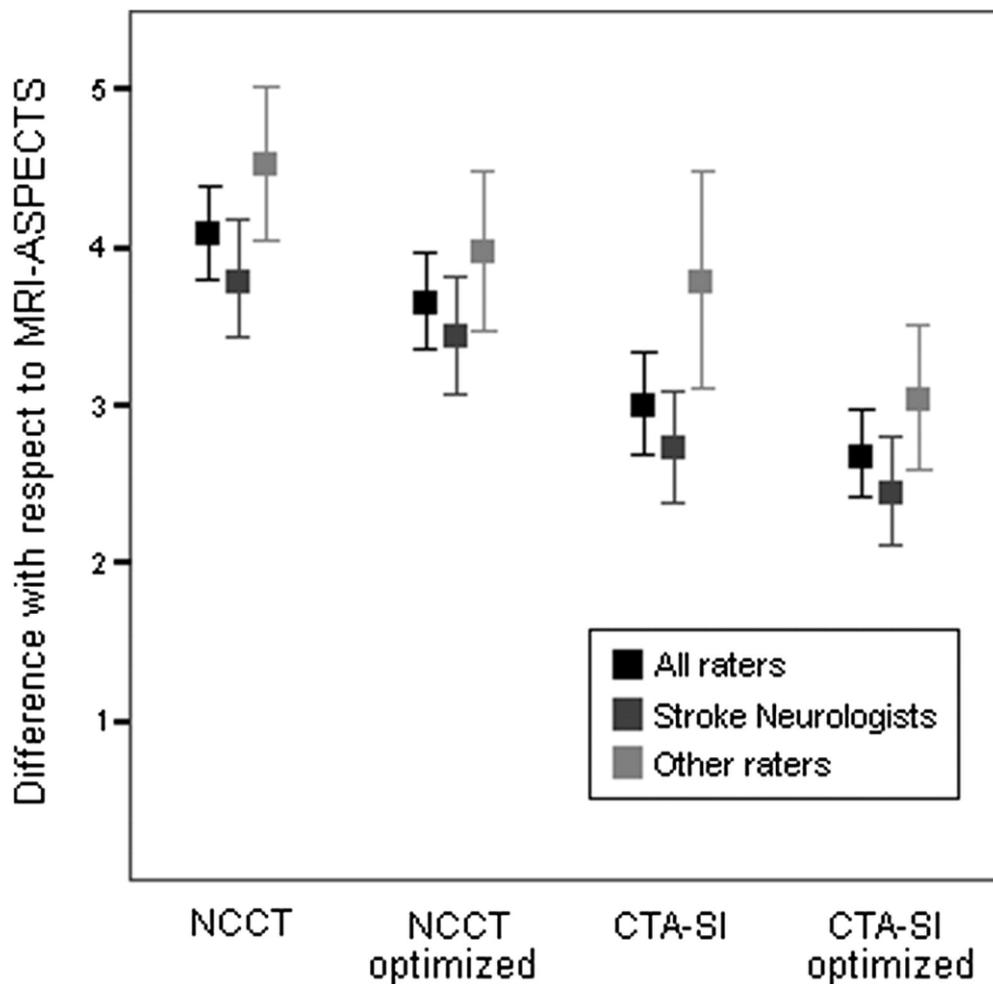


Figure 6

*The mean difference between the CT- and MRI-based ASPECTS ratings. There was a statistically significant improvement in each set of ratings. The improved accuracy of CTA-SI using the optimized window settings displayed a similar trend among stroke neurologists and other raters. Error bars represent 95% confidence intervals. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NCCT, noncontrast computed tomography; CTA-SI, computed tomography angiography source images; MRI, magnetic resonance imaging.*

## 5.2 THE IMPACT OF THE LOCATION OF THE CLOT AND COLLATERAL CIRCULATION ON THE RADIOLOGICAL AND CLINICAL OUTCOME (II-III)

One hundred five of 285 patients (37%) met the inclusion criteria: acute anterior circulation vessel occlusion followed by IVT. A clot was not detected in 142 (50%) cases, and 38 (13%) patients had a posterior circulation clot. One patient could not be reached on day 90 for the evaluation of mRS. Fifty-four (52%) patients experienced a favorable clinical outcome (mRS  $\leq$  2) at 3 months. Thirty-eight (36%) patients had a proximally located (distal ICA and/or M1P segment of MCA) occlusion, and 58 (55%) patients had a good collateral status (CS 2–4). Overall, 29 (28%), 18 (17%), 20 (19%), 36 (34%), and 2 (2%) patients had CSs of 0, 1, 2, 3, and 4, respectively. The first data column in Table 4 summarizes the baseline characteristics of the study cohort. The differences in baseline characteristics between patients with good and poor collateral status, favorable and unfavorable clinical outcome and proximal and distal occlusions are provided in the other columns of Table 4. The number of patients with different clot locations is described in Fig. 7. The median time from imaging to the initiation of IVT was 35 minutes. The median preictal mRS was 1, and the median 3-month mRS was 2. There were no patients with a preictal mRS > 2 in the study population. At 24 h, a local hemorrhagic complication or parenchymal hemorrhage that was distant from the site of the infarct was detected in 7 out of 105 cases (7%) in NCCT. The hemorrhage was symptomatic in 5 (5%) cases. According to the 5-subtype CCS, the etiology was large artery atherosclerosis in 23 (22%), cardiac embolism in 55 (52%) and other uncommon causes in 6 (6%) patients. Twenty-one (20%) patients had IS of undetermined cause.

Table 4.

Baseline characteristics of all patients and by collateral status, outcome at 3 months after intravenous thrombolysis and the location of the clot. P<sub>1</sub>= p-value comparing the poor and good collateral status, P<sub>2</sub>= p-value comparing the mRS ≤2 and mRS 3-6 groups. P<sub>3</sub>= p-value comparing the proximal and distal clot groups.

Characteristic	All patients (n=105)	CS 0-1 (n=47)	CS 2-4 (n=58)	P <sub>1</sub>	mRS ≤2 at day 90 (n=54)	mRS 3-6 at day 90 (n=50)	P <sub>2</sub>	Proximal clot (ICA+M1P, n=38)	Distal clot (M1D+M2+M3, n=67)	P <sub>3</sub>
Age, mean (SD)	68.8 (13.5)	70.1 (14.4)	67.8 (12.7)	0.38	66.4 (13.1)	71.3 (13.6)	0.06	66.0 (15.1)	70.4 (12.3)	0.11
Male sex, n (%)	60 (57)	29 (62)	31 (53)	0.40	32 (59)	28 (56)	0.74	27 (71)	33 (49)	0.03
NIHSS before treatment, median (IQR)	13 (10)	15 (7)	11 (12)	0.02	9 (10)	17 (7)	<0.001	18 (7)	11 (10)	<0.001
NIHSS 24 h after IVT, median (IQR)	6 (14)	14 (14)	3 (7)	<0.001	2 (4)	16 (11)	<0.001	15 (10)	3 (7)	<0.001
ASPECTS at admission NCCT, median (IQR)	10 (2)	8 (3)	10 (0)	<0.001	10 (1)	9 (2)	0.20	9 (3)	10 (2)	0.07
ASPECTS at 24 h NCCT, median (IQR)	7 (5)	5 (4)	8.5 (3)	<0.001	9 (3)	5 (4)	<0.001	4 (5)	8 (4)	<0.001

Characteristic	All patients (n=105)	CS 0-1 (n=47)	CS 2-4 (n=58)	P <sub>1</sub>	mRS ≤2 at day 90 (n=54)	mRS 3-6 at day 90 (n=50)	P <sub>2</sub>	Proximal clot (ICA+M1P, n=38)	Distal clot (M1D+M2+M3, n=67)	P <sub>3</sub>
Collateral Score, median (IQR)	2 (3)	0 (1)	3 (1)	<0.001	3 (1)	1 (2)	<0.001	1 (3)	2 (2)	0.01
OTT (min), mean (SD)	132 (27)	124 (26)	138 (27)	0.008	133 (26)	129 (29)	0.46	131 (31)	132 (25)	0.85
Hypertension, n (%)	69 (66)	31 (66)	38 (66)	0.96	36 (67)	33 (66.)	0.94	22 (58)	47 (70)	0.20
Diabetes, n (%)	17 (16)	9 (19)	8 (14)	0.46	6 (11)	11 (22)	0.13	8 (21)	9 (13)	0.31
AF, n (%)	41 (39)	19 (40)	22 (38)	0.79	23 (43)	18 (36)	0.49	12 (32)	29 (43)	0.24
CAD, n (%)	35 (33)	19 (40)	16 (28)	0.17	12 (22)	23 (46)	0.01	16 (42)	19 (28)	0.15

*Abbreviations: AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CAD, coronary artery disease; CS, collateral score; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; M1D, distal M1 segment of the middle cerebral artery; M1P, proximal M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; M3, M3 segment of the middle cerebral artery; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Score; OTT, onset-to-treatment time; SD, standard deviation.*

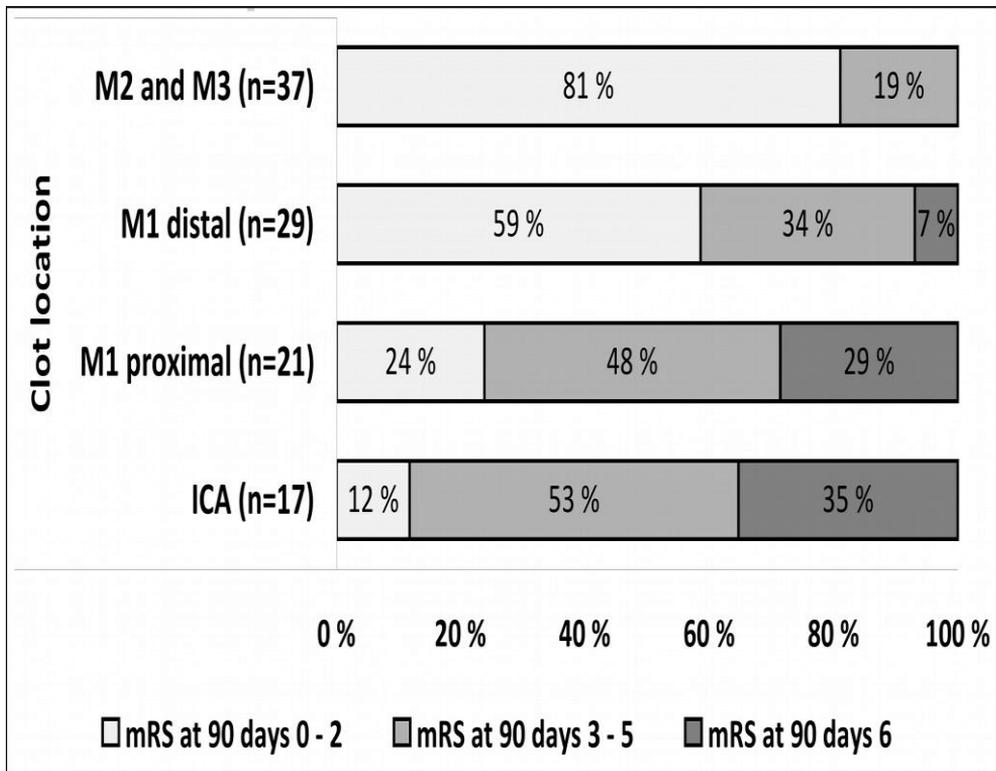


Figure 7

*Clinical outcomes (3-month mRS) for different clot locations.* Abbreviations: ICA, internal carotid artery; mRS, modified Rankin Scale.

### 5.2.1 The location of the clot predicts the clinical outcome at discharge and at three months

There was a significant increase in mortality (32% vs. 3%,  $p < 0.001$ ) and functional dependency (82% vs. 29%,  $p < 0.001$ ) in patients with an ICA or M1P occlusion compared to those with a more distal occlusion (Fig.7). When adjoining clot locations (ICA-M1P, M1P-M1D, M1D-M2, M2-M3) were compared in pairs to identify differences in the rate of favorable clinical outcomes, the largest difference in prognosis (2.5-fold) between adjoining clot locations was discovered between

M1P and M1D with favorable clinical outcomes in 24% and 59%, respectively. This was the only difference that was statistically significant ( $p=0.01$ ).

At the time of discharge from the neurology ward, seven (7%) patients who had either an ICA or a M1P occlusion died during the primary hospitalization. Sixty-three (60%) patients were discharged to a skilled nursing facility or to a rehabilitation facility. Thirty-five (33%) patients were discharged to their homes.

Only one patient (6%) in the ICA group and one patient (5%) in the M1P group were discharged to their homes. However, 13 (45%) patients in the M1D group, 15 (48%) patients in the M2 group and 5 (71%) patients in the M3 group had favorable outcomes at discharge. The results for the pairwise comparisons between adjoining clot locations were similar to the 3-month outcomes, with a significant difference in favorable outcomes only detected between M1P (5%) and M1D (45%) ( $p=0.003$ ).

To assess further the prognostic value of the clot location, we performed binary logistic regression analysis using 3-month mRS dichotomized with a threshold  $\leq 2$  and the outcome at the time of discharge (dichotomous) as the dependent variables (Table 5). When the clot location was included in the model, OTT, sex, diabetes, hypertension, atrial fibrillation, and CAD, tested one at a time, were not statistically significant covariates. Age, NIHSS, sex and OTT were maintained in the final multivariate regression model and were treated as potential confounders. The latter two variables were selected for theoretical reasons. The clot location was a highly significant ( $p=0.001$ ) predictor of a favorable clinical outcome even when the model was adjusted for NIHSS. Interestingly, when tested in the absence of the other variables, the clot location resulted in a model fit that was better than that of NIHSS, based on the Nagelkerke  $R^2$  measurement (0.47 vs. 0.40). Using ICA as a reference of the clot location, the OR for a favorable clinical outcome at 3 months exhibited a dose-response relationship when moving from a proximal vessel position to a more distal vessel (Table 5). The largest difference (6.5-fold) in the ORs of adjoining vessel positions was detected between M1P and M1D.

Table 5.

Logistic regression analysis of a favorable clinical outcome. Odds ratios are determined per minute for onset-to-treatment time, per year for age and per one point for NIHSS. *Abbreviations: CI, confidence interval; C, C-statistic; H-L, Hosmer-Lemeshow significance; ICA, internal carotid artery; M1D, distal M1 segment of the middle cerebral artery; M1P, proximal M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; M3, M3 segment of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score; OTT, onset-to-treatment time, ref, reference location.*

	mRS at three months $\leq 2$ (H-L = 0.57, C = 0.90)			Discharge to home (H-L = 0.71, C = 0.86)		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
<b>Clot location</b>	-	-	0.001	-	-	0.007
<b>ICA</b>	ref	ref	-	ref	ref	-
<b>M1 Proximal</b>	4.2	0.45 - 38.2	0.21	0.8	0.04 - 18.6	0.89
<b>M1 Distal</b>	27.4	2.9 - 257.9	0.004	31.1	2.3 - 417.8	0.009
<b>M2 and M3</b>	57.3	6.0 - 549.0	0.001	26.2	3.3 - 340.2	0.01
<b>OTT</b>	1.0	0.98 - 1.02	0.81	1.0	0.99 - 1.03	0.52
<b>Sex</b>	0.49	0.15 - 1.6	0.23	0.86	0.29 - 2.5	0.77
<b>Age</b>	0.94	0.90 - 0.98	0.005	0.93	0.89 - 0.97	0.002
<b>Admission NIHSS</b>	0.82	0.74 - 0.92	0.001	0.91	0.82 - 0.99	0.03

To study the context of the location-based decision-making, the clot location was dichotomized using three cut-offs: ICA-M1P, M1P-M1D, M1D-M2 and M3 combined. These dichotomized variables were entered into the regression model one at a time (Table 6). In the case of the 3-month outcome, ICA-M1P and M1P-M1D displayed near equal ORs. When the discharge status was the dependent variable, the cut-off M1P-M1D yielded the largest OR.

Table 6.

Logistic regression analysis of a favorable clinical outcome for different dichotomization clot location cut-offs. The model was adjusted for age, onset-to-treatment time, sex and NIHSS. The proximal vessel location is indicated in the reference. *Abbreviations: CI, confidence interval; C, C-statistic; H-L, Hosmer-Lemeshow significance; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score;*

Cut-off	mRS at 3 months $\leq 2$					Discharge to home				
	Odds ratio	95 % CI	p-value	H-L	C	Odds ratio	95 % CI	p-value	H-L	C
<b>ICA / M1 Proximal</b>	17.1	2.3-129.5	0.006	0.59	0.87	11.2	1.1-118.8	0.04	0.84	0.80
<b>M1 Proximal / M1 Distal</b>	16.0	3.9-66.2	<0.001	0.68	0.89	31.0	4.5-215.3	0.001	0.47	0.87
<b>M1 Distal / M2 and M3</b>	5.5	1.8-16.8	0.003	0.87	0.86	2.5	0.93-6.7	0.07	0.82	0.79

Next, the sensitivities and specificities for the detection of a favorable clinical outcome were calculated. The cut-off M1P-M1D demonstrated the highest diagnostic accuracy (0.75) in predicting a favorable clinical outcome at 3 months (Table 7). When the outcome at the time of discharge was analyzed, the M1D-M2 and M3 cut-offs combined performed slightly better (0.69 vs. 0.66). This result was due to 34 patients (51%) with an M1D or a more distal clot group that were discharged into a rehabilitation facility, while only 19 (29%) of these patients had an mRS  $\leq 2$  after three months. When the cut-offs were tested in pairs, the overall diagnostic performance was significantly different in every pair ( $p < 0.001$  for each pair). The differences between the sensitivities and the specificities were all statistically significant ( $p < 0.01$  for each pair) for both outcome measurements.

Table 7.

Diagnostic accuracies of different dichotomization cut-offs for the clot location in predicting a favorable clinical outcome. *Abbreviations: Acc, accuracy; CI, confidence interval; ICA, internal carotid artery; mRS, modified Rankin Scale; Se, sensitivity; Sp, specificity.*

Cut-off	mRS at 3 months $\leq 2$					Discharge to home				
	Se	95% CI	Sp	95% CI	Acc	Se	95% CI	Sp	95% CI	Acc
<b>ICA / M1 Proximal</b>	0.96	0.86 - 0.99	0.30	0.18 - 0.45	0.64	0.97	0.83 - 1.00	0.23	0.14 - 0.35	0.48
<b>M1 Proximal / M1 Distal</b>	0.87	0.74 - 0.94	0.62	0.47 - 0.75	0.75	0.94	0.79 - 0.99	0.51	0.39 - 0.63	0.66
<b>M1 Distal / M2 and M3</b>	0.56	0.41 - 0.62	0.86	0.73 - 0.94	0.70	0.57	0.40 - 0.73	0.74	0.62 - 0.84	0.69

## 5.2.2 Collateral scores and clinical outcomes in different clot locations

The distribution of CSs in different clot locations is depicted in Fig. 8, in which CS 3-4 has been pooled into 1 group. In the 2 most proximal clot locations (ICA and M1P), approximately two-thirds of the patients (59% and 66%, respectively) displayed poor (CS 0-1) collateral filling. In contrast, in the 2 more distal clot locations (M1D and M2), only approximately one-third of the patients (35% and 42%, respectively) had poor collaterals. In the most distant clot location studied (M3), all of the patients had a good collateral status. The distribution of the CS was significantly different across the studied clot locations ( $P = 0.04$ ). When adjoining clot locations (ICA-M1P, M1P-M1D, M1D-M2, M2-M3) were compared in pairs, only the distribution of CS between M1P and M1D yielded statistically significant differences ( $p = 0.05$ ).

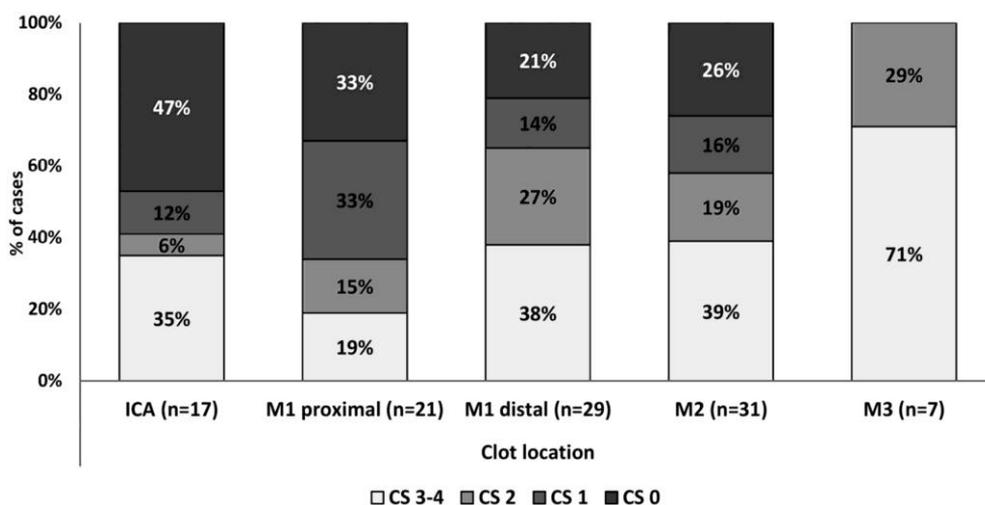


Figure 8

*The distribution of collateral scores in different clot locations. Collateral scores 3 and 4 are pooled into one group.* Abbreviations: CS, collateral score; ICA, internal carotid artery.

To assess the prognostic value of CS in different clot locations, we dichotomized the CS as described above and cross-tabulated it with the dichotomized 3-month mRS score in different clot locations. Overall, a poor collateral status was associated with an unfavorable clinical outcome, especially in proximal clot locations: none of the patients with a symptomatic occlusion of the ICA and poor collaterals experienced a favorable clinical outcome. However, the association between good collaterals and a favorable clinical outcome was less pronounced in the proximal locations (29% in ICA and 43% in M1P). When individual clot locations were considered, only M1D showed statistically significant differences; 70% and 74% of those with poor and good collaterals experienced unfavorable and favorable outcomes, respectively ( $p = 0.05$ ).

Based on these results, the location was dichotomized using M1P-M1D as the dividing point, and cross-tabulation was repeated. A proximal clot was more

strongly associated with an unfavorable outcome than poor collateral status (Fig. 9). However, good collaterals were associated with an improved outcome in both proximal and distal clot locations ( $p = 0.08$  and  $p = 0.004$ , respectively).

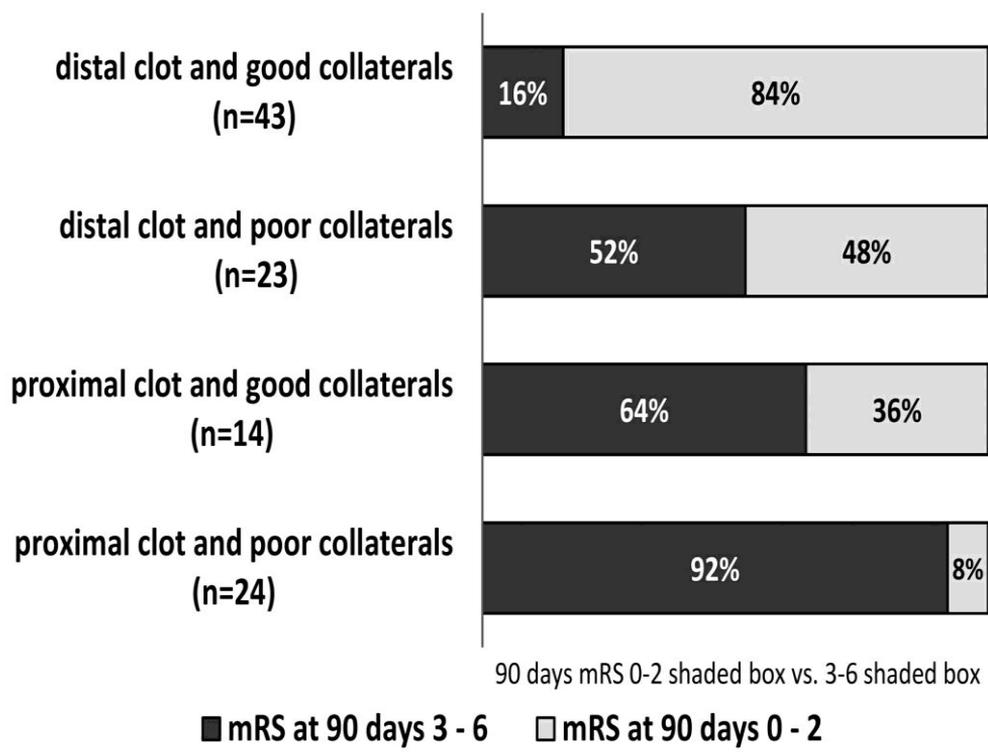


Figure 9

*Collateral score and the site of the occlusion predict the clinical outcome. A proximal clot (internal carotid artery or proximal M1 segment of the middle cerebral artery) is more strongly associated with unfavorable outcome than poor collateral status (collateral score 0–1). mRS, modified Rankin Scale.*

To further assess the prognostic value of CS and its interplay with the clot location, we performed a binary logistic regression analysis using the dichotomized 3-month mRS score as the dependent variable. The CS was analyzed using the

model described in our previous article [II]. When the site of the occlusion was included in the model as a covariate, the OTTs, sex, diabetes, hypertension, atrial fibrillation, and CAD, tested one at a time, were not statistically significant covariates. Age, NIHSS score, CS, sex, and OTTs were maintained in the final multivariate regression model. The latter 2 variables were included for theoretical reasons. The resulting model (Table 8) displayed a satisfying fit and calibration (Hosmer-Lemeshow test,  $P = 0.95$ ; C-statistic = 0.92). The model was also tested with an interaction term (CS\* clot location) that was not statistically significant. Both the clot location and the CS were highly significant ( $p = 0.003$  and  $p = 0.001$ , respectively) independent predictors of a favorable clinical outcome in the presence of the NIHSS score (Table 8). A good collateral status increased the odds of a favorable clinical outcome approximately 9-fold (OR = 9.3; 95% CI, 2.4-35.8). The OR for a favorable clinical outcome increased in a graded fashion when moving from a proximal vessel position to a more distal position. A higher NIHSS score and advanced age were significantly associated with a worse outcome. Finally, the clot location was dichotomized similarly to that shown in Fig. 9 (off value at M1P/M1D), and the model was recalculated. A distal clot location had a larger OR (OR = 13.3; 95% CI, 3.0-60.0) compared with a good collateral status (OR = 5.9; 95% CI, 1.8-19.0).

### 5.2.3 Collateral score and radiological outcome

When cross-tabulated with the dichotomized CS, 79% of the patients with minor infarcts ( $\leq 10$  ml) in the 24-hour follow-up NCCT had good collaterals at admission NCCT, whereas 61% of the patients with larger-than-minor infarcts ( $>10$  ml) presented poor collateral circulation ( $p < 0.001$ ). Good collateral circulation was associated with minor infarcts, especially in the distal clot positions: 92% of patients with a clot in the M1D and a minor infarct had good collaterals ( $p = 0.02$ ) and 72% of patients with a M2 occlusion and a minor infarct had good

collaterals ( $p = 0.08$ ). Some patients (17%, 18 of 105) had an extensive infarct ( $\geq 100$  ml). Among these patients, two-thirds (12 of 18) had a proximal (ICA/M1P) occlusion. Most of the patients (89%, 16 of 18) with an extensive infarct had poor collaterals according to the CS ( $p < 0.001$ ).

Table 8.

Logistic regression analysis of a favorable clinical outcome. Odds ratios are presented per minute for onset-to-treatment time, per year for age and per one point for NIHSS. *Abbreviations: CI, confidence interval; C, C-statistic; CS, collateral score H-L, Hosmer-Lemeshow significance; ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score; OTT, onset-to-treatment time, ref, reference location.*

	<b>mRS at three months <math>\leq 2</math></b> <b>(H-L = 0.95, C = 0.92)</b>		
	<b>Odds ratio</b>	<b>95% CI</b>	<b>p value</b>
<b>Clot location</b>	-	-	0.003
<b>ICA</b>	ref	ref	-
<b>M1 Proximal</b>	10.1	0.74 – 140	0.08
<b>M1 Distal</b>	33.8	2.9 – 428	0.007
<b>M2 and M3</b>	115.8	7.7 – 1737	0.001
<b>OTT</b>	0.99	0.97 - 1.02	0.44
<b>Sex</b>	0.34	0.09 - 1.3	0.11
<b>Age</b>	0.95	0.90 - 0.99	0.02
<b>Admission NIHSS</b>	0.81	0.71 - 0.92	0.001
<b>Good CS (2-4)</b>	9.3	2.4 - 35.8	0.001

### 5.3 COMPUTED TOMOGRAPHY PERFUSION FEATURES AND CLINICAL OUTCOME (IV)

CTP was successfully completed in 58 of the 105 patients (55%) with an anterior circulation clot. Eleven patients were not imaged with CTP; 9 image sets were excluded due to poor technical quality and 27 image sets were excluded because an ASPECTS level was not covered, thus precluding scoring. A perfusion defect was detected in 57 (98%) cases. The median age of the patients was 72 years old (IQR, 63–81 years; 52% men). The median NIHSS score at admission was 12 (interquartile range, 6-17), and 24 hours later, the median NIHSS score was 5. The median mRS score was 1 preictally and 2 three months later. At 24 hours, a local hemorrhagic complication was detected in 2 patients (3.4%), and 1 patient (1.7%) had a parenchymal hemorrhage that was distant from the site of the infarct. The differences in age, sex, prestroke mRS scores, and the number of hemorrhagic complications were not statistically significant between the different vessel positions (Table 9). The admission NIHSS score decreased proportionately in more distal sites of occlusion. There were no statistically significant differences among the OTTs, onset-to-imaging times, or the ASPECTS for NCCT at admission.

Thirty-four patients (59%) experienced favorable 3-month clinical outcomes. The differences in favorable outcomes between the 2 most proximal clot locations (ICA and M1P segment) and between the 2 most distal (M1D segment and combined M2 and M3 segments) were not statistically significant, whereas the difference between these 2 groups was highly significant ( $p < 0.001$ , Fig. 10A). The mid-M1 segment was a determinant for a favorable clinical outcome, with the more distal clot locations predicting a favorable clinical outcome. This finding was reflected in the imaging outcomes. A clot in the ICA or M1P segment of the MCA resulted in a significantly larger infarct at 24 hours NCCT, than an occlusion of the M1D segment or the combined M2 and M3 segments (Fig. 10B, -C).

Table 9.

Baseline characteristics in different clot locations. All values are means  $\pm$  SDs or numbers of patients (percentages).

	<b>ICA (n = 9)</b>	<b>M1P (n = 9)</b>	<b>M1D (n = 11)</b>	<b>M2+M3 (n = 29)</b>	<b>P</b>
Age	70.2 $\pm$ 9.7	68.2 $\pm$ 16.2	70.5 $\pm$ 15.3	69.4 $\pm$ 11.7	.98
Female sex	3 (33)	3 (33)	8 (72)	14 (48)	.24
Admission NIHSS	18.2 $\pm$ 3.5	14.0 $\pm$ 4.5	12.3 $\pm$ 5.4	8.7 $\pm$ 5.3	<.001
mRS, prestroke	0.7 $\pm$ 0.5	0.7 $\pm$ 0.7	0.6 $\pm$ 0.7	0.8 $\pm$ 0.6	.93
Onset to treatment (minutes)	138 $\pm$ 30	133 $\pm$ 43	117 $\pm$ 16	133 $\pm$ 28	.35
Onset to imaging (minutes)	99 $\pm$ 25	90 $\pm$ 31	82 $\pm$ 17	100 $\pm$ 31	.33
Admission NCCT ASPECTS	8.2 $\pm$ 1.7	7.8 $\pm$ 2.2	9.5 $\pm$ 0.9	9.0 $\pm$ 1.8	.12
Hemorrhagic complication	1 (11)	0 (0)	0 (0)	1 (3)	.37

*Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; NCCT, noncontrast computed tomography; M1P, the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score, SD, standard deviation.*

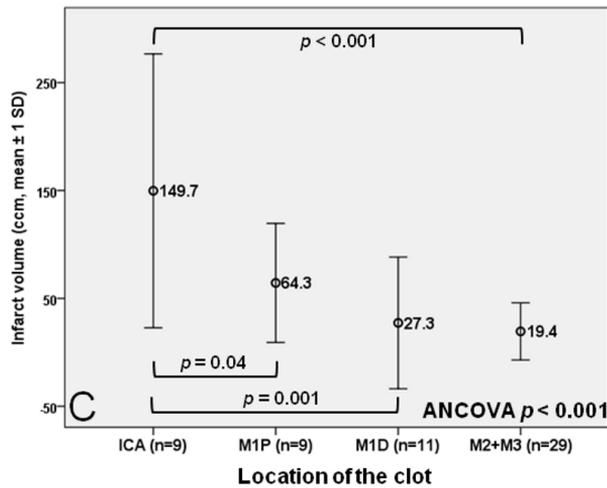
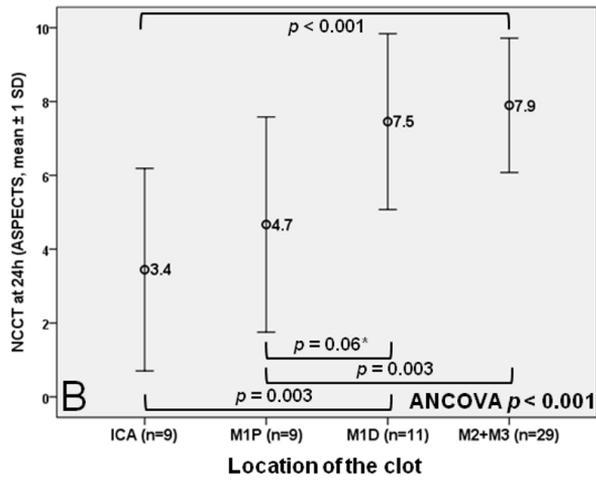
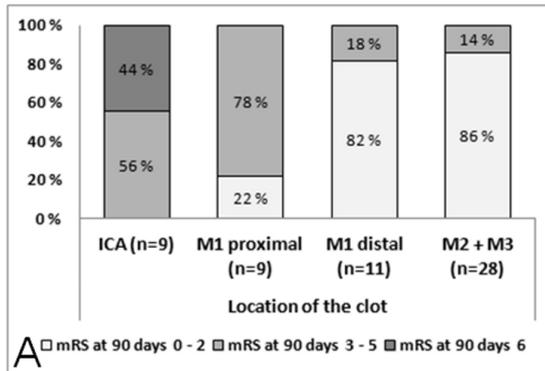


Figure 10 A,-B,-C.

The 3-month clinical outcome and the 24-hour NCCT imaging outcome. Mean values. Error bars indicate 1 SD. The  $p$  value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and  $p$  values indicate differences between individual groups. *Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; NCCT, noncontrast computed tomography; M1P, the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score; SD, standard deviation.*

A clot located in the M2 or M3 segment of the MCA produced a significantly smaller perfusion defect than all 3 of the more proximal vessel positions, which were not significantly different from one another (Fig. 11A). Occlusion of the M1D segment resulted in a slightly smaller MTT defect, compared with the ICA or the M1P segment, but the difference was not statistically significant. A clot in the ICA caused a significantly larger lesion in the CBV map than a clot in the M1D segment or the combined M2 and M3 segments (Fig. 11B). In general, a more proximal clot was associated with a larger CBV defect on the admission CTP.

The CBS and CBSV increased nearly linearly from the proximal-to-distal vessel positions, which is, in part, to be expected because the CBS contains information about the location of the clot (Fig. 11C, -D).

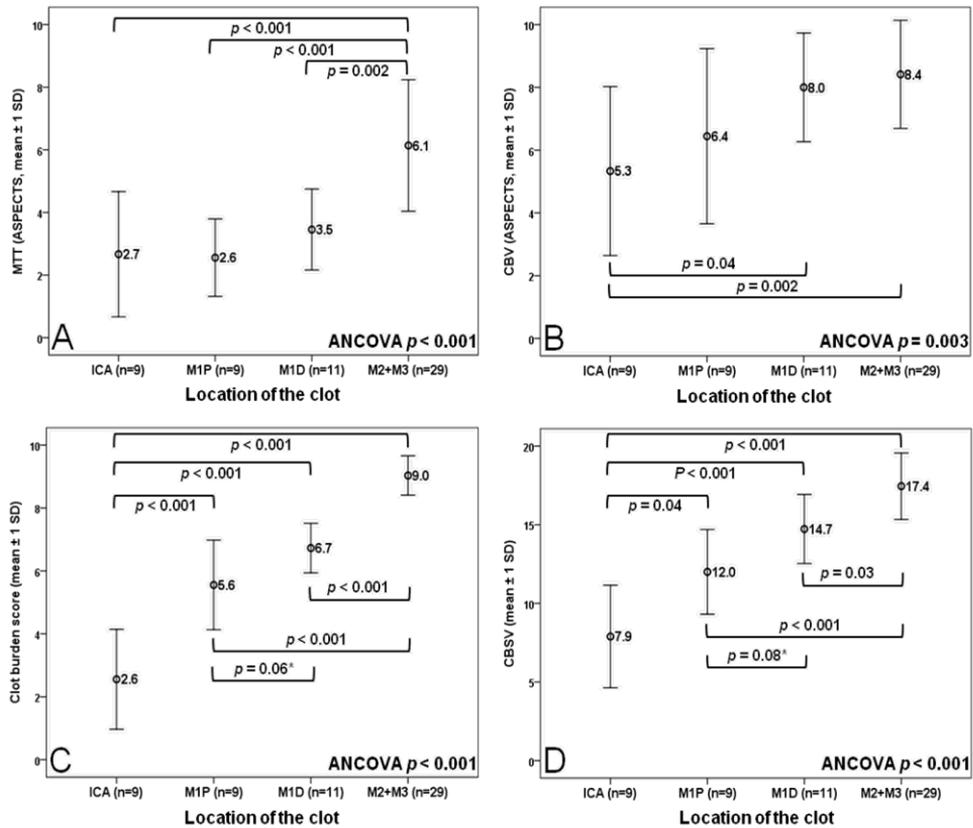


Figure 11 A,-B,-C,-D.

The admission CTP and CTA features in different clot locations. Mean values. Error bars indicate 1 SD. The  $p$  value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and  $p$  values indicate differences between individual groups. The asterisk indicates not significant. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CBV, cerebral blood volume; CBSV, the sum of clot burden score and CBV ASPECTS; ICA, internal carotid artery; M1P, the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments; MTT, mean transit time; SD, standard deviation.

A clot in the M2 or M3 segment of the MCA produced a significantly smaller MTT-CBV mismatch (penumbra) and a smaller amount of salvaged brain tissue, which essentially reflects the vascular anatomy (Figs. 12*A*, -*B* and 13*A*). However, there was a nonsignificant trend toward a larger proportion of salvageable brain tissue when moving from proximal to distal vessel positions (Fig. 12*C*). In addition, the fraction of the penumbra that was salvaged at 24 hours based on the NCCT findings was higher in the more distal vessel positions (Fig. 13*B*, -*C*).

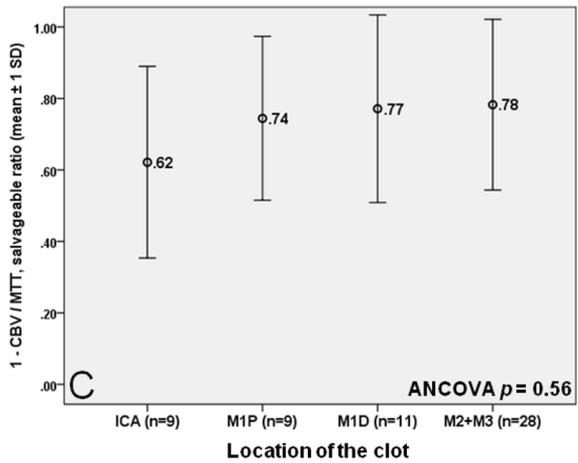
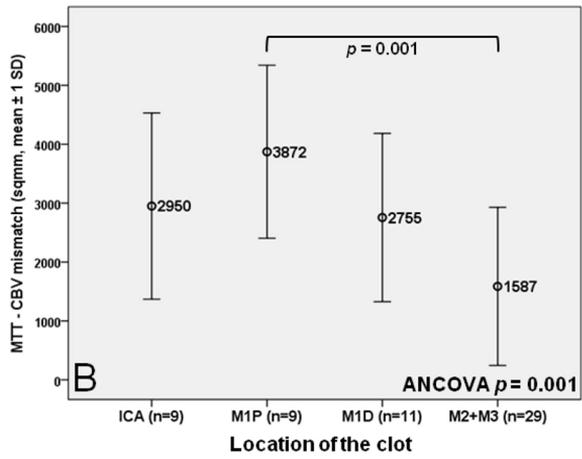
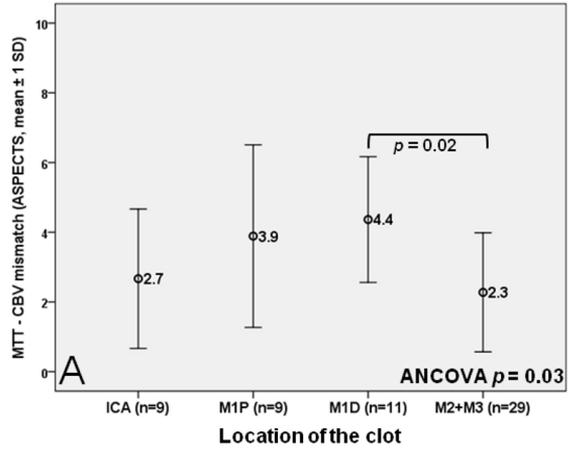


Figure 12 A-,B-,C.

*Analysis of the perfusion mismatches. Mean values. Error bars indicate 1 SD. The P value for ANCOVA (adjusted for onset-to-imaging time) is provided in the lower right-hand corner of each panel. Brackets and P values indicate differences between individual groups. A, Calculations were performed using ASPECTS. B and C, Calculations were performed by using area measurements in the ASPECTS sections. An asterisk indicates not significant. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CBV, cerebral blood volume; ICA, internal carotid artery; M1P, the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments; MTT, mean transit time; SD, standard deviation.*

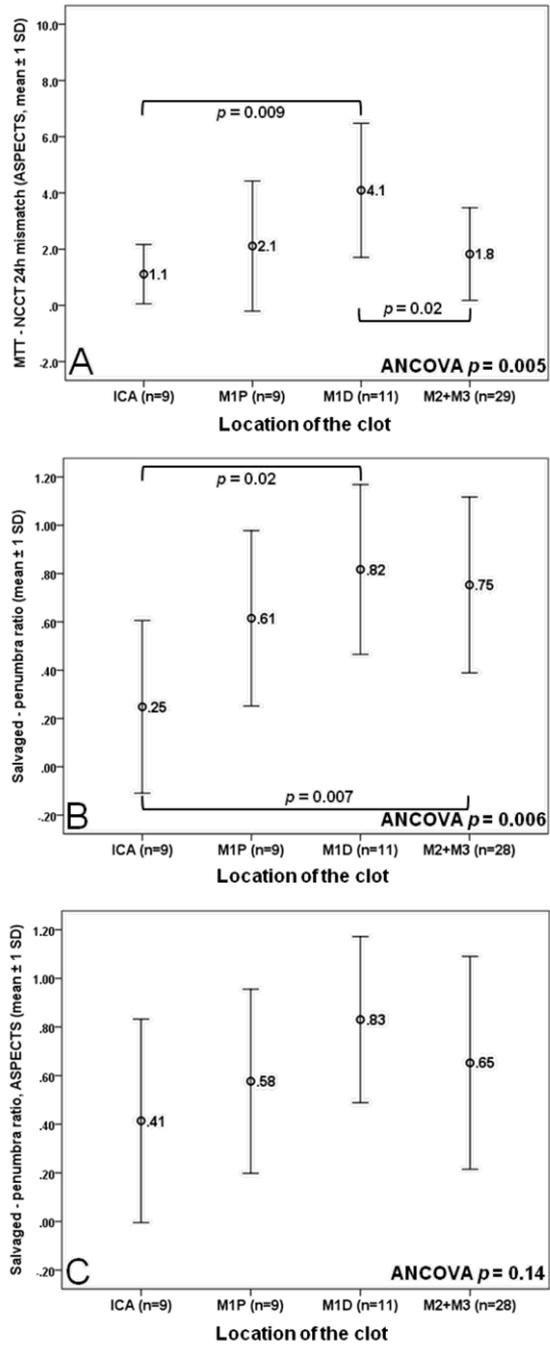


Figure 13 A-,B-,C.

*Analysis of the perfusion-NCCT 24-hour mismatches and the fate of the penumbra. Mean values. Error bars indicate 1 SD. The P-value for ANCOVA (adjusted for onset-to-imaging time) is provided in the lower right-hand corner of each panel. Brackets and P values indicate differences between individual groups. A and C, Calculations were performed using ASPECTS. B, Calculations were performed by using area measurements in the ASPECTS sections. An asterisk indicates not significant. Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; NCCT, noncontrast computed tomography; M1P, the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments; MTT, mean transit time; SD, standard deviation.*

## 6. DISCUSSION

### 6.1 GENERAL DISCUSSION

Our cohorts consisted of HIS patients being treated with thrombolytic therapy, and there was a high proportion of cardioembolism (57%) as an etiology. Patients with milder or less abrupt symptoms, typically caused by small-artery occlusion, are less likely to be treated at specialized centers within 3 hours of symptom onset than patients with cardio-embolic or large-artery atherosclerosis-related etiologies for IS. Risk factors that increase the probability of a cardiac source of embolism should be targeted in both primary and secondary prevention of IS.

Despite adequate and evidence-based treatments among the two studied cohorts, the radiological and clinical outcomes emphasized the severity of IS: the median ASPECTS on the follow-up MRI was less than 5, and half of the patients were dependent at 3 months after IS. However, the 3-month mortality of 13% in the Tampere cohort was lower than that reported among patients with a natural history of CTA-confirmed anterior circulation IS (22%) [102].

Currently, there is increasing evidence that with the aid of contemporary endovascular techniques in imaging selected patients, endovascular treatment within 6 hours of symptom onset is superior to standard optimal medical management (including IVT) alone in improving neurological outcomes in patients with a hyperacute occlusion of the proximal anterior circulation [130-134]. However, it is of primary importance to focus on as many candidates for IVT as possible receiving treatment without delay, thus emphasizing the hyperacute management of IS. In Finland, this treatment goal could be optimized by offering telemedicine at all times to all acute-care hospitals without full-time neurological and/or radiological services.

## 6.2 THE EFFECT OF WINDOW SETTING OPTIMIZATION ON THE ACCURACY OF THE ASPECTS (I)

The presence and extent of EICs on the admission NCCT provide important information regarding the volume of the ischemic territory, the potential for hemorrhagic complications after thrombolysis, and long-term functional outcomes [112, 143]. Recently, in both the ESCAPE and SWIFT PRIME trials, patients with a moderate/large core defined as extensive EICs with a an ASPECTS of 0-5 on baseline NCCT (ESCAPE and SWIFT PRIME) or MRI DWI (SWIFT PRIME) were excluded from the trials [131,133]. In the REVASCAT trial imaging exclusion criteria were an ASPECTS of <7 on NCCT, or <6 on DWI MRI. Patients 81-85 years old with an ASPECTS of <9 on NCCT or DWI MRI were also excluded. In addition, ASPECTS was evaluated based on the CBV maps of CTP, CTA-SI or DWI-MRI in patients whose vascular occlusion examination confirmed qualifying occlusion event and these measurements were performed beyond 4.5 hours after last seen well. [134]. In ESCAPE trial nine subjects (3%) exhibited an ASPECTS of 0-5 on NCCT (protocol violators) and in REVASCAT trial discrepancies between central and investigator-adjudicated ASPECTS were also observed: Centrally adjudicated imaging analysis showed that 25% of the patients exhibited an ASPECTS of <7. However, inclusion according to investigator-based interpretation of imaging may represent a more accurate reflection of real-world clinical practice [131, 134]. Automated, standardized, computer-aided, image interpretation could provide complementary information to measurements of the extent of EICs on brain CT scans [157].

In a study by Coutts et al., it was shown that the accuracy of ASPECTS could be improved by the application of the grading system to CTA-SI [79]. Our study not only confirmed this observation but also emphasized the importance of optimizing the window width and center settings for the detection of EICs by using ASPECTS on NCCT and CTA-SI. The application of narrow window settings on CT images is well known to improve the detection rate of lesions

localized within soft tissues, especially those showing subtle differences in density from the surrounding tissues [158]. This difference also applies to HIS, during which the density of the ischemic area only decreases at a rate of 0.4 HU per hour within the initial six hours of symptom onset [159]. In NCCT, the use of window width and center level settings of 8 HU and 32 HU, compared with the standard settings of 80 HU and 20 HU, respectively, improved the sensitivity for detecting EICs from 57% to 71% with no changes in specificity [78]. However, previous study comparing the sensitivity and accuracy of ASPECTS on NCCT and CTA-SI using variable window width and center level settings did not evaluate the roles of different settings [160]. As expected, our findings showed that when users were allowed to adjust the window width and center level settings rather than use standard display settings, they assigned more accurate ASPECTS to both NCCT and CTA-SI images. The use of interactive, soft copy narrow window and level settings does not significantly increase the time required for scan interpretation compared to the time using standard settings.

We assessed the accuracy of CT-based ratings by comparing their difference with respect to the MRI-based ASPECTS, which is considered the gold standard imaging modality. However, the MRI images were obtained after a median delay of approximately 24 hours after the CT examinations and thus might not reflect the extent of actual tissue injury at the time of the CT examinations.

In conclusion, our findings suggested that the accuracy of ASPECTS was improved by optimizing the window display settings. This improvement occurred irrespective of the background of the rater performing the assessment. Future studies testing the accuracy of a variety of window settings in large patient cohorts with MRI obtained immediately after NCCT and CTA could facilitate the identification of a standardized window width and center level setting that could be used to evaluate HIS. Furthermore, as CTA-ASPECTS, compared with NCCT-ASPECTS, further improves the prediction of clinical outcome at the time of

admission [161], this information could better guide clinicians in the selection of patients for acute endovascular treatment.

### 6.3 CLINICAL SIGNIFICANCE OF THE CLOT LOCATION (II)

We studied the impact of the location of the clot in predicting the clinical outcomes of patients suffering from HHS treated with IVT. The results showed that the outcomes improved, and the mortality decreased consistently when moving from a proximal to a more distal vessel position. After the dichotomization of the clot location, a cut-off point between M1P and M1D was associated with the largest increase in the odds of a favorable outcome compared to neighboring cut-points and it had the highest diagnostic accuracy in predicting a favorable outcome.

Certain anatomic and pathophysiological factors conceivably contributed to the last finding: the lenticulostriate arteries, which supply blood to the basal ganglia, mainly originate from the M1P segment of the MCA. An infarction in this region affects gait, which is an important component of functional independence. As the diameter of the MCA vessel increases towards the proximal segment, the volume of the clot increases substantially, decreasing the effectiveness of IVT [148]. Moreover, a proximal clot has the tendency to propagate distally, which also increases the total volume of the clot.

We found that CBS was an independent predictor of a favorable clinical outcome, and it performed comparably to the clot location. Few studies have previously addressed the effects of the clot location on recanalization and the clinical outcomes in the context of thrombolytic therapy: Del Zoppo et al. [162] used angiogram to show that the M2 and M3 segments were more likely to undergo recanalization than the M1 segment or the ICA and Bhatia et al. [163], in a retrospectively collected data, showed that in patients treated with IVT or endovascular revascularization and recanalization assessed with transcranial Doppler (TCD) or angiogram, the rate of acute recanalization was low and was

lower for those with distal ICA. However, early recanalization was associated with favorable clinical outcome and reduced mortality and the outcomes improved with a proximal to a distal gradient. In contrast, in the IMS III trial, there was a lack of relationship between higher 24-hour recanalization rates and better rates of favorable outcomes. The 25% higher rate of recanalization with endovascular therapy translated into only a 3% higher rate of favorable clinical outcome [164]. However, in the IVT alone-treated subgroup of the IMS III trial, carotid T- or carotid T with M1 and/or A1 segment anterior cerebral artery involvement (carotid L-type occlusion) or tandem ICA and M1 occlusions, which represent the largest clot volumes, 4% of the patients had a favorable outcome at 90 days. Based on other individual sites of occlusions, proximal M1 (M1P) and distal M1 (M1D) had favorable outcomes of 42%, 64%, respectively [164].

The rates of favorable outcomes in our study, is comparable to that of the above mentioned studies. The overall better outcome in M1 subgroup in IMS III cohort compared to Tampere cohort can be partly explained by shorter OTT (123min vs. 132min). In contrast, in the MR CLEAN study at the usual care alone group (91% of the patients received IVT) only 19% had favorable functional outcome at 90 days despite very early OTT (median 87min) and in our study the OTT was not a significant determinant of the clinical outcome (Table 4). The worse outcome in MR CLEAN study compared to Tampere cohort can be partly explained by a higher proportion of tandem ICA and M1 or carotid T occlusions [130]. The subgroup analyses from the MR CLEAN, ESCAPE and the REVASCAT trials regarding extracranial ICA involvement and benefit from endovascular treatment produced conflicting results and in EXTEND-IA trial, only 10 patients in endovascular arm had an ICA occlusion [130-132, 134]. In SWIFT PRIME trial complete cervical carotid occlusion requiring stenting was an imaging exclusion criterion [133]. Furthermore, subgroup analysis from ESCAPE revealed that subjects with occlusion in M1 or in both M2 segments were independent in 57% of cases in intervention group and 30% of cases were in

control group [131]. In SWIFT PRIME trial subjects with M1 occlusion were independent in 66% of cases in intervention group and 38% in control group [133]. However, in REVASCAT trial subjects with M1 occlusion were independent in 46% of cases in intervention group and 37% of cases in control group. OR of 1.2 for favorable outcome in favor of thrombectomy was accompanied by a wide CI [134]. MCA subgroup analyses from the MR CLEAN and meta-analysis according to specific clot locations (M1P, M1D) are not currently available [130].

To summarize, there is no clear correlation between recanalization and reperfusion to the observed clinical benefit in all patients with HIS due to the interactive variables such as the collateral circulation, extent of irreversible ischemic damage, time from symptom onset to IVT and/or endovascular treatment, sICHs, rehabilitation or withdrawal of care after severe stroke are all related to outcome.

Due to the retrospective design of this study, selection bias was a potential limitation of our study. In practice, in years 2004-2007 nearly all HIS cases underwent acute CTA at our institution. However, data for extracranial ICA occlusion at admission or data for the vessel recanalization were not available but a low ASPECTS on 24-hour NCCT and unfavorable clinical outcomes are intimately related to a delayed or failed recanalization/reperfusion and could be used as a surrogates.

Our results support the notion that alternative treatment strategies should be considered if the clot is located in the intracranial ICA or in the M1P. Vascular imaging at the time of admission is required to guide this decision.

## 6.4 CLINICAL SIGNIFICANCE OF THE COLLATERAL CIRCULATION (III)

We studied the interplay between the location of the clot and the collateral status with regard to the 3-month clinical and 24-hour imaging outcomes in an HIS cohort treated with IVT. The tendency of patients with more proximal clot and a

larger clot burden to experience a poorer collateral status was recently observed [165]. In our study, the proportion of patients with good collateral status doubled when the location of the occlusion moved from the proximal to the distal half of the M1 segment. When the clot was found in the M3 segment, the collateral status was always good; this outcome could be expected, based on the definition of CS for vascular territories supplied by the M2 segment arteries. The differential distribution of the CS in different clot locations might be due to proximal clot and poor collaterals sharing common risk factors, such as advanced atherosclerosis, old age, and hypertension [166, 167]. However, an obvious mechanism explaining this observation is that the more proximal the occlusion is, the more extensive the volume of the ischemic brain parenchyma is and the more profound the reduction of cerebral blood flow in the ischemic core is, the easier it is to overwhelm the collateral vessels, resulting in a lower CS.

In a study by Calleja et al. [168], patients with a good leptomeningeal collateral status responded better to IVT. In another study, a poor collateral pattern had a high specificity for poor tissue and clinical outcomes, despite endovascular treatment [169]. In our study, both the clot location and the CS proved to be highly significant and independent predictors of a favorable clinical outcome, a finding that is consistent with previous studies [105, 168]. Using a multivariate model, Lima et al. [170] found that both the site of the intracranial occlusion and the pattern of leptomeningeal collateral circulation predicted the functional outcome when all treatment modalities were considered. In a recent study, there was a good correlation between MRI-based and DSA-based collateral grades. In addition to infarct growth, collateral status and achievement of early reperfusion were the 2 main determinants of favorable functional outcomes and neurological improvement. However, regardless of the achievement of early reperfusion, better collaterals were significantly associated with a lower modified Rankin scores at day 90. Most symptomatic intracranial hemorrhages occurred in patients with a poor collateral grade and early reperfusion, whereas none of the patient with excellent

collaterals suffered symptomatic intracranial hemorrhage or died [171]. In ESCAPE trial on conventional or dynamic CTA, no or minimal collaterals in a region greater than 50% of the MCA territory relative to the pial filling on the contralateral side (collateral score of 1) was an exclusion criteria [131]. Thus, it is unknown whether patients with poor collateral circulation benefit from endovascular therapy compared to standard treatment alone or if recanalization is futile and increases risk for sICH.

In our cohort, the addition of the CS to a model that already contained the location of the clot and NIHSS score resulted in a better model fit (C-statistic, 0.92 versus 0.90). A good collateral status increased the odds of a favorable clinical outcome by approximately 9-fold, and the odds of a favorable clinical outcome increased substantially with a more distal clot location (Table 8). The site of the occlusion proved to be a stronger determinant of the outcome; good collaterals combined with IVT managed to save only approximately one-third (36%) of the patients with a proximal clot from functional dependence or death at 3 months.

Poor collateral circulation is a major risk factor for already having developed an extensive infarct volume at the time of admission. The combination of a proximal clot and poor collaterals is referred to as a “malignant profile” [105]. However, it is recommended that the term malignant be reserved for malignant edema, rather than for imaging features predictive of an unfavorable outcome or a low probability of a favorable response to therapy [93]. Nevertheless, in our study, 89% of the patients who experienced an extensive (>100 ml) infarct on 24-hour follow-up NCCT had poor collateral filling.

A single phase CTA, used in our study, has limitations in the evaluation of collateral circulation: it provides a snapshot of the filling of collaterals at the time of image acquisition. It has been shown that a snapshot could lead to underestimating the collateral circulation due to late vessel filling [172]. The use of dynamic CTA within the arteriovenous phase by quantifying of the volume of hypoattenuation is the superior technique for assessment of collateralization [173].

## 6.5 CLINICAL SIGNIFICANCE OF COMPUTED TOMOGRAPHY PERFUSION (IV)

We studied the impact of the location of the clot on the CTP maps, the derived variables describing the penumbra and the salvaged brain tissue, and the clinical and imaging outcomes. The 24-hour NCCT ASPECTS behaved in a manner consistent with the functional outcome, demonstrating a clear grouping in the 2 proximal (the ICA and M1P segment) and the 2 distal (the M1D segment and the combined M2 and M3 segments) vessel positions. The scenario was statistically less clear when the total infarct volume was considered, with only the differences between the ICA and the other vessel positions providing statistically significant results. However, there was a 2.4-fold difference between the means of the proximal and the distal M1 segments. Furthermore, a previous study suggested that an infarct volume of  $>70 \text{ cm}^3$  lead to a poor clinical outcome [174]. This threshold is close to the mean infarct volume determined in the proximal M1 segment ( $64.3 \text{ cm}^3$ ) at 24-hour NCCT in our study.

Occlusion in the 3 most proximal vessel positions produced a significantly larger defect on the MTT map than an M2 or M3 occlusion, which was to be expected based on the anatomy of the blood vessel and vascular territory. Correspondingly, the absolute size of the penumbra was significantly smaller in the combined M2 and M3 group. The relative size of the penumbra in comparison to the size of the total perfusion defect was larger in the 3 distal vessel positions, although the difference was not statistically significant, because the patients with an occlusion of the ICA had significantly larger lesions on the CBV maps compared with the M1P segment and the combined M2 and M3 groups. In general, there was a significant trend toward larger defects in the CBV map when moving from a distal to a more proximal vessel position. Considering that there were no significant differences in baseline variables, it appeared that irreversible ischemic changes developed at a faster pace with a larger perfusion defect. This finding could be attributed to more profound ischemia in the core region of a large

perfusion defect. This finding was consistent with that reported by Gasparotti et al. [175], who observed that patients with acute stroke with a carotid T occlusion had larger lesions on the admission CBV maps than patients with occlusion of the M1 segment. In a study by Yoo et al. [170], patients with a large lesion on DWI on the admission MRI invariably had an acute occlusion of the ICA.

A significantly larger proportion of the penumbra is, on average, saved by the IVT or by spontaneous recanalization in the more distal vessel positions. This effect seemed to reach its maximum in the M1D segment. This outcome was likely a result of reperfusion by the emerging collateral circulation and a decreased clot burden in the more distal vessel positions, as reflected by the significantly smaller clot-burden scores, which potentially increased the rate and the pace of recanalization.

A prognostic variable CBSV combining the CBV ASPECTS and the clot-burden scores was recently introduced [156]. A threshold value of 15 in the prediction of a favorable clinical outcome was derived for CBSV. This threshold value of 15 was compatible with our findings showing a mean score for the ICA, M1P, M1D and, combined M2 and M3 groups, of 7.9, 12.0, 14.7 and 17.4, respectively (Fig. 11D).

In ESCAPE trial on CTP (>8 cm coverage) a low CBV and very low CBF ASPECTS <6 or on CTP (<8cm coverage) a region of low CBV and very low CBF >1/3 of CTP, were exclusion criteria [131]. In addition, EXTEND-IA trial relied on penumbral imaging (RAPID software) for patient selection using CTP, PWI or DWI with a Tmax >6 second delay perfusion volume and either CBF or DWI ischemic core volume, and inclusion criteria were a mismatch ratio of >1.2, and absolute mismatch volume of > 10 ml, and ischemic core lesion volume of < 70ml. Approximately 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria [132]. Additionally, in SWIFT PRIME trial, absence of target mismatch (RAPID software) was an exclusion criteria in the early phase of patient enrollment [133].

Our study was limited by its retrospective design and sample size. The distribution of the patients to the different clot locations was uneven, with half of the patients in the combined M2 and M3 group. However, there were no significant differences in the baseline variables that could represent potential confounders between the groups. The craniocaudal coverage of the CTP was 20 mm at a minimum. Volumetric data are not available as the size of the perfusion defect was estimated by using ASPECTS and area measurements in the ASPECTS sections. MTT maps potentially overestimated the size of the perfusion defects, while CBV maps could overestimate or underestimate the volume of the irreversibly damaged brain parenchyma [93].

## 7. SUMMARY AND CONCLUSIONS

The use of computed tomography source images and window setting optimization facilitates the detection of early ischemic changes irrespective of the background of the rater performing the assessment. A proximal site of occlusion in the intracranial anterior circulation on computed tomography angiography was associated with a poor collateral status compared with a more distal occlusion site. Both the location of the clot, the mid-M1 segment of the middle cerebral artery as the cut-off, and the collateral score were important, independent predictors of the 3-month clinical outcome in the context of hyperacute ischemic stroke treated with intravenous thrombolysis. The location of the clot was a more powerful determinant of clinical outcome than the poor collateral pattern. Clots that are more proximal in location produce larger perfusion defects in the admission computed tomography perfusion imaging and larger infarct volumes at 24-hour computed tomography imaging. More of the penumbra was salvaged if the occlusion was located more distally. This effect reached a plateau in the distal M1 segment of the middle cerebral artery.

In future meta-analyses and revascularization trials, particular attention should be paid to the subgroups of occlusion in the extracranial carotid artery, the distal M1 segment or the M2 segment of the middle cerebral artery, the basilar artery and the vertebral artery, as patients in these subgroups may have favorable prognosis even when intravenous thrombolysis treatment is provided by community hospital. Furthermore, the role of the collateral circulation, computed tomography source images in infarct core assessment and fully automated image interpretation of core and penumbra should be of interest in future trials focused on the management of hyperacute ischemic stroke.

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## ORIGINAL PUBLICATIONS



# Impact of Window Setting Optimization on Accuracy of Computed Tomography and Computed Tomography Angiography Source Image-based Alberta Stroke Program Early Computed Tomography Score

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The use of narrower window width settings on computed tomography (CT) improves sensitivity for detection of early ischemic changes in acute ischemic stroke. This study analyzed the effect of optimization of window settings on the accuracy of Alberta Stroke Program Early Computed Tomography Score (ASPECTS) performed on non-contrast CT (NCCT) and CT angiography source images (CTA-SI). ASPECTS was calculated on NCCT and CTA-SI with standard and optimized window width/center settings in a consecutive series of patients with acute ischemic stroke. The difference between CT-based ASPECTS and ASPECTS performed on follow-up magnetic resonance imaging (MRI) were calculated to determine the disparity between initial estimates of the extent of ischemia on CT and follow-up lesion imaging by MRI. Forty-four patients were included into the study. The mean difference with respect to follow-up MRI-ASPECTS was  $4.1 \pm 2.2$  for standard NCCT-ASPECTS,  $3.7 \pm 2.3$  for optimized NCCT-ASPECTS,  $3.0 \pm 2.2$  for standard CTA-SI-ASPECTS, and  $2.7 \pm 2.1$  for optimized CTA-SI-ASPECTS. The improvement introduced by the optimization of window settings and use of CTA-SI was statistically significant ( $P < .01$ ). Our data indicate that the accuracy of ASPECTS is improved with optimized window display settings. This improvement is irrespective of experience or specialty of the rater performing the assessment. **Key Words:** Early ischemic changes—window width and center.

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The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a semiquantitative grading system developed to quantify the extent of early ischemic

changes (EIC) in the middle cerebral artery territory.<sup>1</sup> ASPECTS performed on noncontrast computed tomography (NCCT) obtained within the initial hours of symptom onset correlate with, yet underestimate, the final lesion volume on follow-up images.<sup>2</sup> Performing ASPECTS on computed tomography angiography source images (CTA-SI) increases the sensitivity and accuracy for the detection of EIC and thereby improves predictions for final infarct size.<sup>2-4</sup> The aim of this study was to determine whether the use of optimized window settings had an effect on the accuracy of ASPECTS performed on admission NCCT and CTA-SI.

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## Methods

We retrospectively analyzed a consecutive series of ischemic stroke patients who received intravenous

(IV) or intra-arterial thrombolysis over a 4-year period in our institution. All patients presenting with symptoms consistent with acute ischemic stroke routinely undergo NCCT and CTA in our center. The present study was restricted to patients who sustained a stroke within the middle cerebral artery territory and underwent magnetic resonance imaging (MRI) within 14 days after receiving thrombolytic treatment. The study protocol was approved by the local Institutional Review Board.

NCCT and CTA were performed using a commercially available multidetector row scanner (SOMATOM Emotion Duo or Sensation 16; Siemens, Erlangen, Germany). Image acquisition parameters of NCCT were sequential mode, 5-mm slice thickness, 120-130 kV, and 200 mAs. CTA was obtained with a helical scanning technique after a single bolus injection of 100-130 mL of nonionic contrast medium into an antecubital vein at a rate of 3-4 mL/second with a dynamic contrast bolus detection technique used for timing of acquisition (CareBolus; Siemens Medical Systems). CTA parameters were as follows: SOMATOM Emotion Duo: 130 kV foramen magnum to vertex, 50 mAs, slice thickness 2 mm, reconstruction increment 0.7 mm; Sensation 16: 120 kV aortic arch to vertex, 100 mAs, slice width 1 mm, slice collimation 0.75 mm, reconstruction increment 0.7 mm. MRI was performed with a 1.5-T scanner (Magnetom TIM; Siemens). The protocol included axial T2-weighted turbo spin echo (repetition time [TR]/echo time [TE], 3800/90 ms; matrix, 256 × 256), fluid-attenuated inversion-recovery (FLAIR) (TR/TE/inversion time [TI]: 9000/100/2100 ms; matrix, 224 × 256), and diffusion-weighted imaging (DWI) (single-shot echo planar, applied 3 b values with a maximum of 1000 s/mm<sup>2</sup> and a TR/TE of 4800/120 ms; matrix, 96 × 256) sequences all with a slice thickness of 5 mm, a 10% interslice distance, and a 220- to 240-mm field of view.

Three stroke neurologists, 1 neurology resident, and 1 radiologist retrospectively assigned 4 separate ASPECTS to CT examinations of the patients obtained at the time of admission in the following order: (1) NCCT with standard window width (W)/center (C) settings (W: 80; C: 20), (2) NCCT with optimized window width/center settings, (3) CTA-SI with standard window width/center settings (W: 80; C: 40), and (4) CTA-SI with optimized window width/center settings. Optimization of window width/center settings was left to the discretion of the rater and thus showed a certain amount of variability among raters and patients. The raters were aware of the patients' neurologic deficits, but were blinded to their previous ASPECTS ratings and MRI data. The patient order was random and different for each set of CT-based evaluations. Follow-up ASPECTS was graded on MRI DWI or FLAIR images by a neuroradiologist (K.K.O.) who was blinded to clinical and CT data and had not performed any of the CT-based ASPECTS ratings described above. In addition to stroke patients, raters

have performed the same 4 sets of CT-based ASPECTS assessments in a set of 20 age- and sex-matched controls who had undergone NCCT, CTA, and MRI during the study period and were found to have no abnormalities on their imaging studies.

Intraclass correlation coefficients were used to assess the interexaminer agreement of CT-based ASPECTS ratings. The absolute value of the difference between MRI-based ASPECTS and CT-based ASPECTS were calculated for all ratings to determine the degree of disparity between initial estimates of EIC on CT and the follow-up lesion on MRI. The Friedman test was used to analyze the effect of window setting optimization on the amount of difference between initial and follow-up images. All numerical variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate. A 2-tailed *P* value of <.05 was considered significant. Statistical analyses were performed using SPSS version 16.0 (IBM, Armonk, NY).

## Results

A total of 44 patients met the inclusion criteria. Table 1 summarizes the clinical characteristics of the study cohort. The mean age of the study population was 62 ± 13 years. Thirty-two patients (73%) were treated with IV thrombolysis, 5 (11%) with intra-arterial thrombolysis, and 7 (16%) with combined IV and intra-arterial thrombolysis. The mean time from symptom onset to CT was 81 ± 33 minutes, and that to CTA was 90 ± 38 minutes. MRI was performed after a median delay of 1.2 days (IQR, 0.5-3.0 days).

Table 2 summarizes the interexaminer agreement of CT-based ASPECTS ratings and pooled results of all examiners with respect to differences between CT- and MRI-based ASPECTS. The mean and median ASPECTS on follow-up MRI was 4.6 ± 2.4 and 5 (IQR, 3-7). The greatest difference was evident when ASPECTS was determined on NCCT with standard window settings. This difference sequentially decreased when scores were assessed on NCCT after window setting optimization, CTA-SI without optimization and CTA-SI with optimization (*P* < .01). Pairwise comparisons, corrected for multiple comparisons, revealed statistically significant improvement between each pair of ratings (*P* < .005) (Figs 1 and 2). The improvement introduced by window setting optimization and use of CTA-SI was consistent among all raters, irrespective of experience or specialty (Fig 2). The raters adjusted the window settings to mean values of W: 22 ± 12 C: 37 ± 3 for NCCT and W: 43 ± 14 C: 45 ± 4 for CTA-SI during evaluation of ASPECTS at optimized window settings.

The median and mean ASPECTS were 10 (10-10) and 10.0 ± 0.0 for NCCT, 10 (10-10) and 9.8 ± 0.4 for NCCT-optimized, 10 (10-10) and 9.8 ± 0.5 for CTA-SI, and 10

**Table 1.** Baseline characteristics of the study population ( $n = 44$ )

Age, years, mean $\pm$ SD	62 $\pm$ 13
Sex, n (%)	21 (48%) females; 23 (52%) males
Admission NIHSS score, median (IQR)	16 (12-19)
Time from onset of stroke to initiation of thrombolysis, minutes, mean $\pm$ SD	138 $\pm$ 37
Type of thrombolytic treatment, n (%)	
IV rtPA	32 (73)
Intra-arterial thrombolysis	5 (11)
Combined IV and intra-arterial treatment	7 (16)
Time from stroke onset to noncontrast CT, minutes, mean $\pm$ SD	81 $\pm$ 33
Time from stroke onset to CTA, minutes, mean $\pm$ SD	90 $\pm$ 38
Time from stroke onset to MRI, days, median (IQR)	1.2 (0.5-3.0)
Stroke subtype, n (%)	
Large-artery atherosclerosis	8 (18)
Cardioembolic	30 (68)
Small-artery occlusion	0 (0)
Other	1 (2)
Undetermined	5 (11)

Abbreviations: CT, computed tomography; CTA, computed tomography angiography; IQR, interquartile range; IV, intravenous; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Score; rtPA, recombinant tissue plasminogen activator; SD, standard deviation.

(10-10) and  $9.8 \pm 0.5$  for CTA-SI—optimized in the control group.

## Discussion

The presence and extent of EIC on admission CT provide important information on the volume of ischemic territory, potential for hemorrhagic complications after thrombolysis, and long-term functional outcome.<sup>5-7</sup> ASPECTS performed on NCCT is a reliable and valid grading system for assessing the extent of the ischemic injury.<sup>1</sup> Recent publications have shown that accuracy of ASPECTS can be improved by application of the grading system to CTA-SI.<sup>2-4</sup> Our study, not only confirms this observation, but also highlights the importance of optimization of window width and center settings in detection of EIC by using ASPECTS on NCCT and CTA-SI.

The application of narrow window settings on CT images is well known to improve the detection rate of lesions localized within soft tissues, especially those

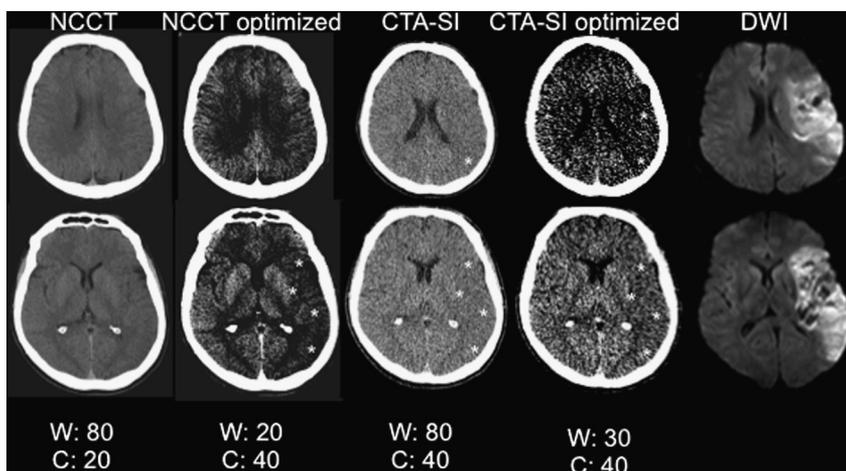
showing subtle difference in density with respect to surrounding tissues.<sup>8</sup> This also applies to acute ischemic stroke, during which the density of ischemic area decreases only at a rate of 0.4 HU per hour within the initial six hours of symptom onset.<sup>9</sup> Lev et al<sup>10</sup> have shown that the use of window center and width settings of 32 HU and 8 HU, compared with the standard settings of 20 HU and 80 HU, improved the sensitivity for detecting EIC from 57% to 71% with no changes in specificity. However, the effect of changing window settings has not been formally analyzed for ASPECTS. Previous studies analyzing the sensitivity and accuracy of ASPECTS used predetermined window settings and did not evaluate the roles of different settings.<sup>1-4,11-13</sup> As expected, our findings show that when users were allowed to adjust window center and width rather than use standard display settings, they were more accurate in assigning ASPECTS on CT images. This effect was evident for assessments on both NCCT and CTA-SI, but yielded a greater improvement for the former.

**Table 2.** Interrater agreement and accuracy of CT-based ASPECTS

	Intraclass correlation coefficient (95% confidence intervals)	CT-based ASPECTS		Difference of CT-based ASPECTS with respect to MRI-ASPECTS	
		Median (IQR)	Mean $\pm$ SD	Median (IQR)	Mean $\pm$ SD
NCCT, standard settings	0.79 (0.66-0.88)	9 (8-10)	8.7 $\pm$ 1.6	4 (2-6)	4.1 $\pm$ 2.2
NCCT, optimized settings	0.81 (0.70-0.89)	9 (7-10)	8.3 $\pm$ 1.8	3 (2-5)	3.7 $\pm$ 2.3
CTA-SI, standard settings	0.81 (0.68-0.89)	8 (7-9)	7.5 $\pm$ 2.3	3 (1-4)	3.0 $\pm$ 2.2
CTA-SI, optimized settings	0.85 (0.76-0.91)	8 (6-9)	7.2 $\pm$ 2.3	2 (1-4)	2.7 $\pm$ 2.1

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CCT, noncontrast computed tomography; CT, computed tomography; CTA-SI, computed tomography angiography source images; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation.

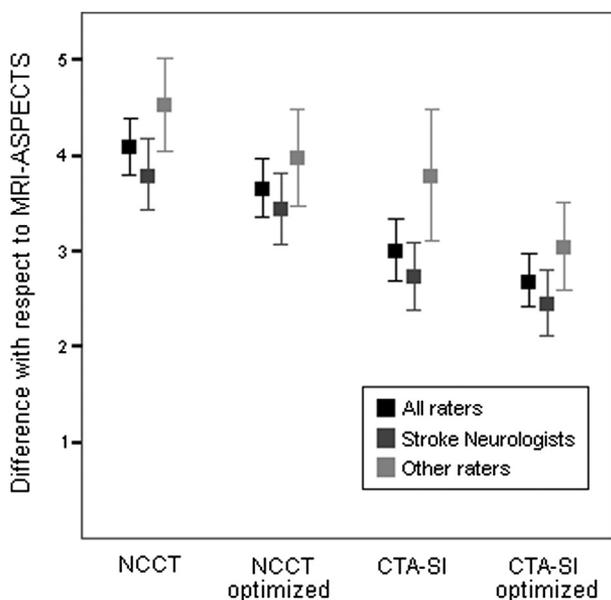
**Figure 1.** NCCT and CTA-SI of a 44-year-old male patient with acute-onset right hemiparesis and aphasia, obtained 1 hour after symptom onset. ASPECTS was 10 on NCCT, 6 on NCCT with window setting optimization, 5 on CTA-SI, and 4 on CTA-SI with window setting optimization. ASPECTS on follow-up MRI was 4. ASPECTS regions judged to be abnormal on CT are marked with with an asterisk.



We assessed the accuracy of CT-based ratings by comparing their difference with respect to the MRI-based ASPECTS, which was considered the gold standard imaging modality. However, MRI was obtained after a median delay of approximately 24 hours after the CT examinations and thus might not reflect the extent of actual tissue injury at the time of CT examinations. Despite this limitation, we compared all 4 sets of CT ratings with the same imaging endpoint, and considering the difference between the extent of tissue injury on CT and MRI as a marker of accuracy of the imaging modality in detecting EIC remains plausible.

In conclusion, our findings suggest that the accuracy of ASPECTS is improved by optimization of window

display settings. This improvement occurs irrespective of the background of the rater performing the assessment. Because we did not use a predefined window setting and left the optimization to the discretion of the raters, there was a certain amount of variability in the settings used by the raters in this study. Future studies testing the accuracy of a variety of window settings in large patient cohorts with MRI obtained immediately after NCCT and CTA could aid the identification of a standardized window center and width setting that can be used in evaluation of acute ischemic stroke. These studies also should assess the impact of using such a “stroke window” in therapeutic decision algorithms and patient outcome analyses. Recent studies have shown better accuracy in predicting clinical and tissue outcome with CTA-ASPECTS compared with CT-ASPECTS.<sup>14</sup> Optimization of window settings might further improve these predictions for tissue and clinical outcome predictions at the time of admission and guide clinicians in the selection of patients for acute stroke treatments.



**Figure 2.** Mean difference between CT- and MRI-based ASPECTS ratings. The improved accuracy with the use of CTA-SI and window optimization showed a similar trend among stroke neurologists and other raters. Error bars represent 95% confidence intervals.

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# The mid-M1 segment of the middle cerebral artery is a cutoff clot location for good outcome in intravenous thrombolysis

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**Background and purpose:** We studied the impact of the location of the thrombus (internal carotid artery, proximal M1 segment, distal M1 segment, M2 segment, and M3 segment of the middle cerebral artery) in predicting the clinical outcome of patients treated with intravenous thrombolytic therapy (< 3 h) in a retrospective cohort. **Methods:** Anterior circulation thrombus was detected with computed tomography angiography in 105 patients. Baseline clinical and radiological information was collected and entered into logistic regression analysis to predict favorable clinical outcome (3-month modified Rankin Scale from 0 to 2 was a primary outcome measure). **Results:** Three months after stroke, there was a significant increase in mortality (32% vs. 3%,  $P < 0.001$ ) and functional dependency (82% vs. 29%,  $P < 0.001$ ) in patients with internal carotid artery or proximal M1 segment of the middle cerebral artery thrombus compared to a more distal occlusion. In the regression analysis, after adjusting for National Institutes of Health Stroke Scale, age, sex, and onset-to-treatment time, the clot location was an independent predictor of good clinical outcome ( $P = 0.001$ ) and exhibited dose-response type behavior when moving from a proximal vessel position to a more distal one. When the location was dichotomized, a cutoff between the proximal and the distal M1 segments best differentiated between good and poor clinical outcome (OR = 16.0, 95% CI 3.9–66.2). **Conclusions:** The outcome of acute internal carotid artery or proximal M1 segment of the middle cerebral artery occlusion is generally poor even if treated with intravenous thrombolysis. Alternative revascularization strategies should be considered. Vascular imaging at the admission is required to guide this decision.

## Introduction

The location and the volume of the thrombus are independent prognostic factors in acute ischemic stroke (AIS) with proximal, high-volume clots predicting poor clinical outcome when compared to distal, low-volume clots [1–11]. In addition, the location and the volume of the clot induce limitations to the effectiveness of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) in dissolving the occluding thrombus [1–11].

The purpose of our study was to analyze in more depth the impact of the location of the clot, visualized in the anterior circulation using computed tomography angiography (CTA), to the clinical outcome in AIS

patients treated with IVT. We assumed that separating the M1 segment of the middle cerebral artery (MCA) to proximal (M1P) and distal (M1D) parts could provide increased accuracy in predicting the clinical outcome. We discuss the implications of the anterior clot location and clinical baseline information in evaluating the outcomes in an IVT cohort.

## Methods

### Study population

Our retrospective observational cohort study was approved by Tampere University Hospital ethics committee. Altogether, 315 anterior or posterior circulation AIS patients from January 2004 to December 2007 were treated with thrombolytic therapy and had a 3-month follow-up after thrombolysis at the department of neurology of the Tampere University Hospital. CTA

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had been performed to 285 patients (90%). The thrombolytic therapy protocol used was similar to the American Heart Association (AHA) guidelines [12]. Inclusion criteria for the study were acute anterior circulation vessel occlusion confirmed with CTA and treatment with standard IVT administration scheme. From 2004 to 2007, intra-arterial interventions were not performed to anterior circulation occlusions at our institution.

### Participants and variables

Baseline clinical characteristics included age, sex, time from both symptom onset and imaging to the initiation of IVT, and stroke clinical risk factors (hypertension, diabetes, coronary heart disease, atrial fibrillation). These data were collected from the patient records. National Institutes of Health Stroke Scale (NIHSS) score at the time of initiation of the rtPA had been prospectively stored according to a specific protocol. A follow-up non-contrast-enhanced computed tomography (NCCT) and NIHSS scoring were performed for all patients 24 h after the administration of the thrombolytic agent. A hemorrhagic complication was considered symptomatic if there was no notable (>4 points) improvement in 24 h NIHSS compared to admission NIHSS. Causative Classification of Stroke (CCS) system was used by certified CCS-rater (J.T.S.) to assess stroke etiology [13]. Modified Rankin Scale (mRS), scored 3 months after the stroke, was the primary outcome measure. In the years from 2004 to 2005, the 3-month mRS score was prospectively recorded based on a follow-up visit to neurologist and from 2006 to 2007 on a phone interview by neurologist. One patient had not been reached with telephone or by other means. Death during the primary university hospital episode or discharge from neurology ward to a rehabilitation facility was considered to signify unfavorable clinical outcome at discharge. This status was used as the secondary outcome measure. The seven (7%) patients who were discharged temporarily to primary health care centers only because of adjustment of the warfarin dose were included to the favorable discharge group along with patients discharged directly to their homes. All the prospectively stored clinical data were carefully evaluated (J.T.S.) for possible errors.

### Imaging parameters

Computed tomography scans were obtained using two different multidetector scanners: General Electrics LightSpeed 16-slice (GE Healthcare, Milwaukee, WI, USA) and Philips Brilliance 64-slice (Philips, Cleveland, OH, USA). The imaging procedures and the parameters

used are described in our previous study available online as an open-access article at the website of the publisher [14].

### Image analysis

Non-contrast-enhanced computed tomography (NCCT) examinations were reviewed using dedicated medical imaging workstations. The Alberta Stroke Program Early CT Score (ASPECTS) was assessed from admission and follow-up NCCT images as described in our previous article [14]. CTA images were analyzed with Advantage Workstation version 3.2 (GE Healthcare). The examinations were reviewed in the order NCCT and CTA paralleling that of the clinical work flow. The reviewers were blinded to the clinical data apart from the side and nature of the acute symptoms. CTA images were studied by examining the raw data and maximum intensity projection images.

The location of the clot was recorded based on the most proximal position of the occlusion. The M1 segment of the MCA was divided into two parts of equal length: the proximal and the distal half.

The principles of the Clot Burden Score (CBS) scoring system have been described in recent studies [8,9]. The location of the clot was determined, and CBS was scored independently by two radiologists (N.S. and A.L.). In cases where the scoring or the assignment differed, a consensus opinion was agreed on. Intraclass correlation coefficient (ICC) between a staff radiologist (N.S) and an experienced neuroradiologist (J.H.) for a test sample ( $n = 20$ ) for CBS was 0.87. Cohen's kappa for the location of the clot was 0.94.

### Statistics

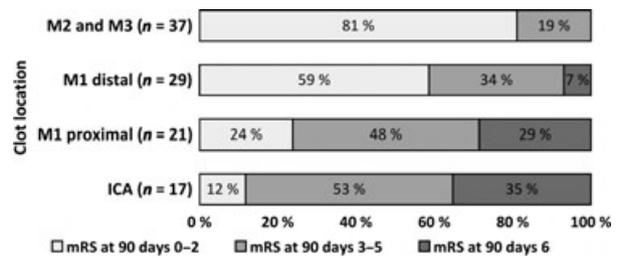
A biostatistician was consulted (H.H.). The data were analyzed with spss version 18 (SPSS Inc., Chicago, IL, USA). Group comparisons were performed using the Student *t*-test, the Chi-squared test, the Fisher exact test, and the Kruskal–Wallis test. The Bonferroni correction for multiple comparisons was applied where necessary. Patients who had 3-month mRS  $\leq 2$  or who were discharged to home from neurology ward were considered to have experienced favorable clinical outcome. Binary logistic regression modeling using these outcome measures as the dependent variable was repeated for different variables of interest. NIHSS, age, sex, time from onset to treatment, and clinical risk factors were examined as potential confounders and were tested both in univariate models and with clot location. The calibration of the models was evaluated with the Hosmer–Lemeshow test and the discrimination with the *C* statistic. Odds ratio (OR) with 95% CI was

calculated for each covariate. Sensitivity, specificity, and CI calculations were performed using standard procedures. The normal and extended McNemar tests were used to compare the overall diagnostic performance, the sensitivities, and the specificities.

## Results

### Baseline characteristics

Of the 285 patients, 105 (37%) met the inclusion criteria: acute anterior circulation vessel occlusion followed by IVT. A thrombus was not detected in 142 (50%) cases, and 38 (13%) patients had a posterior circulation clot. The first data column of Table 1 summarizes the baseline characteristics of the study cohort, and the number of patients with different clot locations is described in Fig. 1. The mean onset-to-treatment time (OTT) was 132 min (SD = 27). There was one patient (1%) with OTT > 180 min (217 min). The median time from imaging to the initiation of IVT was 35 min. The median preictal mRS was 1, and the median 3-month mRS was 2. There were no patients with preictal mRS > 2 in the study population. At 24 h, a local hemorrhagic complication or parenchymal hemorrhage distant to the site of the infarct was detected in seven



**Figure 1** Clinical outcome (3-month mRS) for different clot locations. Good clinical outcome was defined as mRS ≤ 2 at 3 months.

out of 105 cases (7%) in NCCT. The hemorrhage was symptomatic in 5 (5%) cases. According to the 5-subtype CCS, large artery atherosclerosis was the etiology in 23 (22%), cardiac embolism in 55 (52%), and other uncommon cause in 6 (6%) patients. Twenty-one (20%) patients had AIS of undetermined cause.

### The location of the clot predicts the clinical outcome at discharge and at 3 months and exhibits a dose-response type relationship

Three months after stroke (primary outcome), patients with more proximal clots had worse functional outcome

**Table 1** Demographic and baseline characteristics of all patients and by the locus of the thrombus and outcome (mRS) at 3 months after intravenous thrombolysis

Characteristic	All patients (n = 105)	mRS ≤ 2 at day 90 (n = 54)	mRS 3–6 at day 90 (n = 50)	$P_1$	Proximal thrombus (ICA + M1P, n = 38)	Distal thrombus (M1D + M2 + M3, n = 67)	$P_2$
Age (y), mean (SD)	68.8 (13.5)	66.4 (13.1)	71.3 (13.6)	0.06	66.0 (15.1)	70.4 (12.3)	0.11
Male sex (%)	60 (57)	32 (59)	28 (56)	0.74	27 (71)	33 (49)	0.03
National Institutes of Health Stroke Scale (NIHSS) before treatment, median (IQR)	13 (10)	9 (10)	17 (7)	<0.001	18 (7)	11 (10)	<0.001
NIHSS 24 h after thrombolysis, median (IQR)	6 (14)	2 (4)	16 (11)	<0.001	15 (10)	3 (7)	<0.001
ASPECTS score at admission CT, median (IQR)	10 (2)	10 (1)	9 (2)	0.20	9 (3)	10 (2)	0.07
ASPECTS score at 24 h CT, median (IQR)	7 (5)	9 (3)	5 (4)	<0.001	4 (5)	8 (4)	<0.001
Onset-to-treatment time (min), mean (SD)	132 (27)	133 (26)	129 (29)	0.46	131 (31)	132 (25)	0.85
Hypertension n (%)	69 (65.7)	36 (66.7)	33 (66.0)	0.94	22 (57.9)	47 (70.1)	0.20
Diabetes n (%)	17 (16.2)	6 (11.1)	11 (22.0)	0.13	8 (21.1)	9 (13.4)	0.31
Atrial fibrillation n (%)	41 (39.0)	23 (42.6)	18 (36.0)	0.49	12 (31.6)	29 (43.3)	0.24
Coronary artery disease n (%)	35 (33.3)	12 (22.2)	23 (46.0)	0.01	16 (42.1)	19 (28.4)	0.15

$P_1$ ,  $P$  value between mRS ≤ 2 and mRS 3–6 groups;  $P_2$ ,  $P$ -value between proximal and distal thrombus groups.

(Fig. 1). There was a significant increase in mortality (32% vs. 3%,  $P < 0.001$ ) and functional dependency (82% vs. 29%,  $P < 0.001$ ) in patients with an ICA or M1P occlusion compared to a more distal occlusion. When adjoining clot locations (ICA-M1P, M1P-M1D, M1D-M2, M2-M3) were compared in pairs to find differences in the rate of favorable clinical outcome, the largest difference in prognosis (2.5 fold) between adjoining clot locations was found between M1P and M1D with 24% and 59% having good clinical outcome, respectively. This was the only difference that proved to be statistically significant ( $P = 0.01$ ).

Evaluated at the time of discharge from the neurology ward (secondary outcome), seven (7%) patients, who all had either ICA or M1P occlusion, had died during the primary hospitalization. Sixty-three (60%) patients were discharged to a skilled nursing facility or to a rehabilitation facility. Thirty-five (33%) patients were discharged to their homes.

Only one patient (6%) within an ICA group and one patient (5%) within a M1P group were discharged to home. On the other hand, 13 (45%) patients within a M1D group, 15 (48%) patients within a M2 group, and 5 (71%) patients within a M3 group had favorable outcome at discharge. The results for pairwise comparisons between adjoining clot locations were similar to the 3-month outcome with the difference in favorable outcome between M1P (5%) and M1D (45%) being the only statistically significant one ( $P = 0.003$ ).

To further assess the prognostic value of the clot location, we performed binary logistic regression analysis using 3-month mRS dichotomized with the threshold  $\leq 2$  and outcome at discharge (dichotomous) as the dependent variables (Table 2). When the clot location was included in the model, OTT, sex, diabetes, hypertension, atrial fibrillation, and coronary heart disease, tested one at a time, were not statistically sig-

nificant covariates. Age, NIHSS, sex, and OTT were kept in the final multivariate regression model and treated as potential confounders. The latter two variables were selected only because of theoretical reasons.

The clot location was a highly significant ( $P = 0.001$ ) predictor of good clinical outcome even when the model was adjusted for NIHSS (Table 2). Interestingly, when tested in the absence of the other, the clot location resulted in a model fit that was better than that of NIHSS based on Nagelkerke  $R^2$  measure (0.47 vs. 0.40). Setting ICA as the reference for the clot location, the odds ratio for good clinical outcome at 3 months exhibited dose-response type behavior when moving from a proximal vessel position to a more distal one. The difference between ICA and M1P was not statistically significant ( $P = 0.21$ ) whilst the differences to more distal locations were highly significant ( $P = 0.004$  for M1D and  $P = 0.001$  for M2 and M3) implying that the two proximal and the two distal vessel positions behave differently. The largest difference (6.5 fold) in the odds ratios of adjoining vessel positions was between M1P and M1D. The admission NIHSS score and age significantly predicted the clinical outcome.

The model was also tested using CBS instead of the clot location. CBS was an independent predictor ( $P < 0.001$ ) having an odds ratio of 1.7 per one point (95% CI 1.3–2.2). When CBS and the clot location were added to the model at the same time, both variables were rendered non-significant.

#### A cut-off between M1P and M1D best differentiates between good and poor clinical outcome

To study the context of location-based decision making, the clot location was dichotomized using three cutoffs: ICA-M1P, M1P-M1D, and M1D-M2 and M3 com-

**Table 2** Logistic regression analysis for favorable clinical outcome

	mRS at 3 months $\leq 2$ (H–L = 0.57, C = 0.90)			Discharge to home (H–L = 0.71, C = 0.86)		
	Odds ratio	CI 95%	P value	Odds ratio	CI 95%	P value
Clot location		–	0.001	–	–	0.007
ICA	ref	ref	–	ref	ref	–
M1 Proximal	4.2	0.45–38.2	0.21	0.8	0.04–18.6	0.89
M1 Distal	27.4	2.9–257.9	0.004	31.1	2.3–417.8	0.009
M2 and M3	57.3	6.0–549.0	0.001	26.2	3.3–340.2	0.01
Onset-to-treatment time	1.0	0.98–1.02	0.81	1.0	0.99–1.03	0.52
Sex	0.49	0.15–1.6	0.23	0.86	0.29–2.5	0.77
Age	0.94	0.90–0.98	0.005	0.93	0.89–0.97	0.002
Admission National Institutes of Health Stroke Scale (NIHSS)	0.82	0.74–0.92	0.001	0.91	0.82–0.99	0.03

H–L, Hosmer–Lemeshow significance; C, C statistic; ref, reference location.

Odds ratios are per minute for onset-to-treatment time, per year for age, and per one point for NIHSS.

bined. These dichotomized variables were entered into the regression model one at a time (Table 3). In the case of the 3-month outcome, ICA-M1P and M1P-M1D had near equal odds ratios (17.1 vs. 16.0) with the latter having a narrower 95% CI (2.3–129.5 vs. 3.9–66.2) whilst the most distal cutoff had a considerably smaller odds ratio (5.5, 95% CI 1.8–16.8). When the discharge status was the dependent variable, the cutoff M1P-M1D yielded the largest odds ratio (31.0, 95% CI 4.5–215.3) whilst again the most distal cutoff had the smallest odds ratio (2.5, 95% CI 0.98–6.7,  $P = 0.07$ ).

Next, sensitivities and specificities for detecting good clinical outcome were calculated. A clot distal to the cutoff location constituted a positive test result. The cutoff M1P-M1D had the highest diagnostic accuracy (0.75) in predicting good clinical outcome at 3 months (Table 4). When outcome at the discharge was analyzed, the cutoff M1D-M2 and M3 combined performed slightly better (0.69 vs. 0.66). This was attributed to 34 patients (51%) having a M1D or a more distal thrombus that were discharged into a rehabilitation facility, whilst 3 months later only 19 (29%) of these patients had mRS  $\leq 2$ . When the cutoffs were tested in pairs, the overall diagnostic performance was significantly different in every pair ( $P < 0.001$  for each pair). The differences between the sensitivities and the specificities were all statistically significant ( $P < 0.01$  for each pair) for both outcome measures apart from the differences in the sensitivities between the cutoffs ICA-M1P and M1P-M1D. The differences in baseline characteristics between groups defined by the cutoff M1P-M1D are depicted in Table 1.

## Discussion

We studied the impact of the location of the clot in predicting the clinical outcome of patients suffering from AIS treated with intravenous thrombolytic therapy. The results showed that the outcome improved and the mortality decreased consistently when moving from a proximal to a more distal vessel position. The odds ratios for good clinical outcome (3-month mRS  $\leq 2$ ) exhibited corresponding dose-response type relationship in the logistic regression analysis with ICA as the reference for the clot location. When individual adjoining vessel locations were tested in pairs, only the difference between M1P and M1D proved to be statistically significant. After dichotomization of the clot location, a cut-point between M1P and M1D was associated with the largest increase in the odds of favorable outcome compared to neighboring cut-points and had the highest diagnostic accuracy in predicting favorable outcome.

Certain anatomic and pathophysiological factors conceivably contribute to the last finding. First, the lenticulostriate arteries, which supply blood to the basal ganglia, mainly originate from the proximal M1 segment of MCA. An infarction in this region affects gait, an important component of functional independence. Secondly, as the diameter of the MCA vessel increases toward the proximal segment, the volume of the clot increases substantially decreasing the effectiveness of IVT. Moreover, a proximal thrombus has the tendency to propagate distally, which also increases the total volume of the clot.

**Table 3** Logistic regression analysis for favorable clinical outcome for different dichotomization cutoffs of clot location

Cutoff	mRS at 3 months $\leq 2$					Discharge to home				
	Odds ratio	CI 95 %	<i>P</i> value	H-L	<i>C</i>	Odds ratio	CI 95 %	<i>P</i> value	H-L	<i>C</i>
ICA/M1 Proximal	17.1	2.3–129.5	0.006	0.59	0.87	11.2	1.1–118.8	0.04	0.84	0.80
M1 Proximal/M1 Distal	16.0	3.9–66.2	<0.001	0.68	0.89	31.0	4.5–215.3	0.001	0.47	0.87
M1 Distal/M2 and M3	5.5	1.8–16.8	0.003	0.87	0.86	2.5	0.93–6.7	0.07	0.82	0.79

H-L, Hosmer–Lemeshow significance; *C*, *C* statistic.

The model was adjusted for age, onset-to-treatment time, sex, and National Institutes of Health Stroke Scale. The proximal vessel location is the reference.

**Table 4** Diagnostic accuracies of different dichotomization cutoffs for clot location in predicting favorable clinical outcome

Cutoff	mRS at 3 months $\leq 2$					Discharge to home				
	Se	CI 95%	Sp	CI 95%	Acc	Se	CI 95%	Sp	CI 95%	Acc
ICA/M1 Proximal	0.96	0.86–0.99	0.30	0.18–0.45	0.64	0.97	0.83–1.00	0.23	0.14–0.35	0.48
M1 Proximal/M1 Distal	0.87	0.74–0.94	0.62	0.47–0.75	0.75	0.94	0.79–0.99	0.51	0.39–0.63	0.66
M1 Distal/M2 and M3	0.56	0.41–0.62	0.86	0.73–0.94	0.70	0.57	0.40–0.73	0.74	0.62–0.84	0.69

Se, sensitivity; Sp, specificity; Acc, accuracy.

Two classification methods based in part on the location of the clot have been introduced recently [7–10]. These scoring schemes are correlated with the clinical outcome. We found that CBS was an independent predictor of good clinical outcome and that performed comparably to the clot location. Some studies have previously addressed the effect of the clot location on recanalization and the clinical outcome in the anterior circulation AIS in the context of IVT. *Del Zoppo et al.* [1] used DSA to find that the M2 and M3 segments are more likely to undergo recanalization than the M1 segment and ICA. *Saqqur et al.* [3] arrived at similar results in a more recent work utilizing repeated transcranial Doppler ultrasonography in studying recanalization and its effect on clinical outcome at 3 months. Different parts of the M1 segment were not addressed. However, the rate of good outcome at M1P in our study was comparable to that of the proximal MCA and M1D to that of the distal MCA in these studies. Still other studies with more heterogeneous setups have reported that large vessel occlusions are less likely to recanalize and predict poor clinical outcome [2, 5, 6].

An observational study by *Mattle et al.* [15] compared intra-arterial thrombolysis to IVT in patients with hyperdense middle cerebral artery sign, a sign of proximal occlusion of the MCA, and found intra-arterial thrombolysis to be more beneficial. In a recent report, multimodal therapy resulted in the highest recanalization rates of anterior circulation clots [16]. Moreover, according to a scientific statement from the American Heart Association, it would be ideal to obtain vascular imaging studies such as CTA to potentially triage patient to primary intra-arterial therapies if an endovascular team is available and undue delay is not caused [17]. CTA can also be used to guide bridging therapy even if immediate IVT is preferred as the therapy of choice [18]. In our study population, the rate-limiting step was waiting for the results of the mandatory laboratory parameters, not the multimodal CT imaging. Interestingly, the onset-to-treatment time was not a significant determinant of clinical outcome (Table 2).

Owing to the retrospective study design, selection bias is a potential limitation of this study, and data on vessel recanalization were not available. Even so, a low ASPECTS score at 24 h NCCT and poor clinical outcomes are intimately related to delayed or failed recanalization and can be used as a surrogate.

The results of this study show that the outcome of acute ICA and proximal M1 segment occlusion is generally poor even if treated with intravenous thrombolysis and that a cut-point between proximal and distal M1 segment best differentiates between good and

poor clinical outcome and has the highest accuracy in predicting good clinical outcome. These findings support the notion that alternative treatment strategies, primary intra-arterial, or bridging therapy, should be taken into consideration if the thrombus is located in the ICA or in the proximal M1 segment. Vascular imaging at the admission is required to guide this decision. Verification of these results with prospective studies is necessary, optimally in a randomized setup.

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## Disclosure of conflict of interest

None.

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# Collateral Score Complements Clot Location in Predicting the Outcome of Intravenous Thrombolysis

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Collateral circulation is an important determinant of stroke outcome. We studied the impact of leptomeningeal collateral circulation with respect to the location of the thrombus in predicting the clinical outcome of patients treated with intravenous thrombolytic therapy (<3 hours) in a retrospective cohort.

**MATERIALS AND METHODS:** Anterior circulation thrombus was detected with CT angiography in 105 patients. Baseline clinical and imaging information was collected, and the site of the occlusion was recorded. Collaterals were assessed by using a 5-grade collateral score and were entered into logistic regression analysis to predict favorable clinical outcome (3-month modified Rankin Scale score of 0–2).

**RESULTS:** Two-thirds of patients with a proximal occlusion displayed poor collateral filling (collateral score 0–1), whereas in more distal clot locations, approximately one-third had poor collaterals. Only 36% of patients with a proximal occlusion and good collaterals experienced favorable clinical outcome. In multivariate analysis, both clot location and collateral score were highly significant ( $P = .003$  and  $P = .001$ ) and independent predictors of favorable clinical outcome. Good collateral status increased the odds of favorable clinical outcome about 9-fold (OR = 9.3; 95% CI, 2.4–35.8). After dichotomization, a distal clot location had a larger odds ratio (OR = 13.3; 95% CI, 3.0–60.0) compared with the odds ratio of good collaterals (OR = 5.9; 95% CI, 1.8–19.0).

**CONCLUSIONS:** A proximal occlusion in the anterior circulation is associated with poorer collateral status compared with a more distal occlusion. Both the clot location and collateral score are important and independent predictors of favorable clinical outcome of hyperacute stroke treated with intravenous thrombolysis. The location of the clot is a stronger determinant of the outcome than the collateral score.

**ABBREVIATIONS:** CS = collateral score; HIS = hyperacute ischemic stroke; IVT = intravenous thrombolytic therapy; MID = distal MI segment of the MCA; MIP = proximal MI segment of the MCA

Ischemic stroke results from occlusion of an artery, with subsequent reduction in regional cerebral blood flow. The ischemic penumbra can remain viable for hours because some degree of blood flow is sustained through the leptomeningeal collateral supply. An important aspect of the work-up of patients with acute neurovascular syndrome is imaging of cervical and intracranial vasculature to detect the location of the occluding clot and evaluate the integrity of the collateral circulation. Both of these potentially influence decision-making for revascularization thera-

pies. Patients with proximal occlusions have a poor prognosis, even if treated with intravenous thrombolytic therapy (IVT).<sup>1</sup> Patients with good collateral status have larger penumbra<sup>2</sup> and respond better to both IVT and intra-arterial interventions,<sup>2–5</sup> whereas diminished or absent collaterals are associated with increased stroke severity, faster progression, and worse outcome.<sup>6–8</sup> Unfortunately, it appears that patients with a more proximal clot more frequently have worse collateral status.<sup>9</sup>

The purpose of our study was to analyze the impact of leptomeningeal collateral circulation with respect to the location of the clot in predicting 24-hour imaging findings and the 3-month clinical outcome of hyperacute ischemic stroke (HIS) in patients treated with IVT (<3 hours). We discuss the interplay between the location of the clot and the collateral circulation.

## MATERIALS AND METHODS

### Study Population

Our retrospective observational cohort study was approved by the Tampere University Hospital ethics committee. Altogether 315

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patients with anterior or posterior circulation HIS were treated with IVT from January 2004 to December 2007 and had a 3-month follow-up after thrombolysis at the department of neurology of the Tampere University Hospital. CT angiography had been performed at admission in 285 (90%) of these patients. CTA was not performed because of previously known contrast agent hypersensitivity, chronic renal failure, or imminent closure of the 3-hour time window. Inclusion criteria for the study were acute anterior circulation vessel occlusion confirmed with CTA and treatment with a standard IVT administration protocol. The thrombolytic therapy protocol used was in line with the American Heart Association guidelines.<sup>10</sup>

### **Participants and Variables**

Baseline clinical characteristics were collected from patient records. The National Institutes of Health Stroke Scale score at the time of administration of rtPA had been prospectively stored. Follow-up noncontrast-enhanced CT and NIHSS scoring were performed for all patients 24 hours after the administration of the thrombolytic agent. The modified Rankin Scale score 3 months after the stroke was the primary outcome measure. The 3-month mRS score was prospectively recorded on the basis of a follow-up visit to a neurologist or a phone interview by a neurologist.

### **Imaging Parameters**

CT scans were obtained by using 2 different multidetector scanners: LightSpeed 16-detector row (GE Healthcare, Milwaukee, Wisconsin) and Brilliance 64-detector row (Philips Healthcare, Best, the Netherlands). CTA was performed from the C2 vertebra to the vertex. The imaging parameters were the following: 120 kV; 212 mAs (dynamic tube-current modulation); collimation, 64 × 0.625 mm; rotation, 0.75 seconds; pitch factor, 0.923 (64-detector row); or 120 kV; 160 mAs; collimation, 16 × 0.625 mm; rotation, 0.8 seconds; pitch factor, 0.938 (16-detector row). Contiguous sections were reconstructed to 0.9-mm thickness by using 0.45-mm overlap (64-detector row) or 1.25-mm thickness (16-detector row). The contrast agent (iobitridol, Xenetix, 350 mg I/mL; Guerbet, Aulnay-sous-Bois, France) was administered through an antecubital 18-ga cannula by using a double-piston power injector with a flow rate of 4 mL/s by using 70 mL of contrast agent followed by a 50-mL saline flush. Manual bolus triggering was used. NCCT was performed as described in our previous report.<sup>11</sup>

### **Image Analysis**

The Alberta Stroke Program Early CT Score was assessed from admission and follow-up NCCT images, and CTA studies were interpreted as described in our previous article.<sup>11</sup> Infarcts with a volume of ≤10 mL in the 24-hour NCCT were defined as minor infarcts and those ≥100 mL were considered extensive infarcts. The location of the clot was recorded on the basis of the most proximal position of the occlusion. The M1 segment of the middle cerebral artery was divided into 2 parts of equal length: the proximal and the distal halves (designated as M1P and M1D). The status of the leptomeningeal collateral circulation was evaluated by using the scoring system devised by Souza et al.<sup>8</sup> In short, the collateral score (CS) was determined from MIP images according to the following rules: 0 = absent collaterals in >50% of an M2

branch territory; 1 = diminished collaterals in >50% of an M2 branch territory; 2 = diminished collaterals in <50% of an M2 branch territory; 3 = collaterals equal to the contralateral hemisphere; and 4 = increased collaterals.

The clot location was determined and CS was scored independently by 2 radiologists. In cases in which the scoring or the assignment differed, a consensus opinion was agreed on. The intraclass correlation coefficient between a staff radiologist and an experienced neuroradiologist for a test sample ( $n = 20$ ) for CS was 0.87. Cohen  $\kappa$  was 0.94 for the location of the clot and 0.68 for the CS (0.90 after dichotomization).

### **Statistics**

The data were analyzed with the Statistical Package for the Social Sciences, Version 19 (IBM, Armonk, New York). Group comparisons were performed by using the Student  $t$  test, the  $\chi^2$  test, the Fisher exact test, the Mann-Whitney  $U$  test, and the Kruskal-Wallis test. Patients with collateral scores from 2 to 4 had good collateral vessel filling. Patients who had 3-month mRS ≤ 2 had favorable clinical outcome. Binary logistic regression modeling by using this outcome measure as the dependent variable was repeated for single covariates of interest and their combinations. An odds ratio with a 95% CI was calculated for each covariate. The calibration of the models was evaluated with the Hosmer-Lemeshow test, and the discrimination, with the C statistic.

## **RESULTS**

### **Baseline Characteristics**

We studied 105 consecutive patients who met the inclusion criteria: acute anterior circulation vessel occlusion followed by IVT. The demographic and baseline characteristics of the study population have been described in depth in our previously published work.<sup>1</sup> The main baseline and other characteristics are summarized in Table 1. Fifty-four (52%) patients experienced favorable clinical outcome (mRS ≤ 2) at 3 months. One patient could not be reached with telephone or by other means for evaluation of mRS. Thirty-eight (36%) patients had a proximally located (distal ICA and/or proximal half of the M1 segment of MCA) occlusion, and 58 (55%) patients had good collateral status (CS 2–4). Overall, 29 (28%), 18 (17%), 20 (19%), 36 (34%), and 2 (2%) patients had CSs of 0, 1, 2, 3, and 4, respectively. The differences in baseline characteristics between patients with good and poor collateral status, proximal and distal occlusions, and favorable and unfavorable clinical outcome are given in Table 1. Poor collateral circulation was associated with more severe strokes according to admission NIHSS (15 versus 11,  $P = .02$ ), more extensive ischemic changes in the admission NCCT ( $P < .001$ ), worse clinical and imaging outcomes 24 hours after the treatment ( $P < .001$ ), and somewhat shorter onset-to-treatment times (124 minutes versus 138 minutes,  $P = .008$ ).

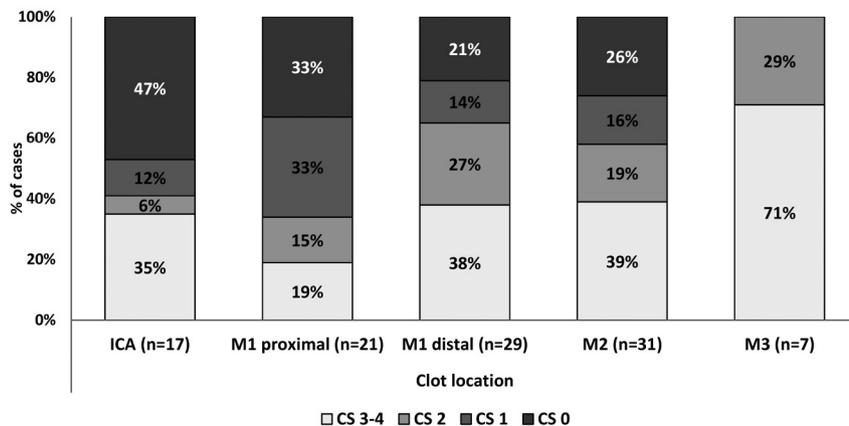
### **Collateral Score and Clinical Outcome in Different Clot Locations**

The distribution of CSs in different clot locations is depicted in Fig 1, where CS 3–4 has been pooled into 1 group. In the 2 most proximal clot locations (ICA and M1P), approximately two-thirds of the patients (59% and 66%, respectively) displayed poor

**Table 1: Demographic and baseline characteristics of all patients and by good collateral status, the locus of the thrombus, and 3-month outcome**

Characteristic	All Patients (n = 105)	Collateral Score 0–1 (n = 47)	Collateral Score 2–4 (n = 58)	P <sub>1</sub>	mRS ≤2 at Day 90 (n = 54)	mRS 3–6 at Day 90 (n = 50)	P <sub>2</sub>	Proximal Thrombus (ICA+M1P, n = 38)	Distal Thrombus (M1D+M2+M3, n = 67)	P <sub>3</sub>
								n	n	
Age (yr) (mean) (SD)	68.8 (13.5)	70.1 (14.4)	67.8 (12.7)	.38	66.4 (13.1)	71.3 (13.6)	.06	66.0 (15.1)	70.4 (12.3)	.11
Male (%)	60 (57)	29 (62)	31 (53)	.40	32 (59)	28 (56)	.74	27 (71)	33 (49)	.03
NIHSS score before treatment (median) (IQR)	13 (10)	15 (7)	11 (12)	.02	9 (10)	17 (7)	<.001	18 (7)	11 (10)	<.001
NIHSS score 24 hours after thrombolysis (median) (IQR)	6 (14)	14 (14)	3 (7)	<.001	2 (4)	16 (11)	<.001	15 (10)	3 (7)	<.001
ASPECTS at admission CT (median) (IQR)	10 (2)	8 (3)	10 (0)	<.001	10 (1)	9 (2)	.20	9 (3)	10 (2)	.07
ASPECTS at 24 hours after CT (median) (IQR)	7 (5)	5 (4)	8.5 (3)	<.001	9 (3)	5 (4)	<.001	4 (5)	8 (4)	<.001
Collateral score (median) (IQR)	2 (3)	0 (1)	3 (1)	<.001	3 (1)	1 (2)	<.001	1 (3)	2 (2)	.01
Onset-to-treatment time (min) (mean) (SD)	132 (27)	124 (26)	138 (27)	.008	133 (26)	129 (29)	.46	131 (31)	132 (25)	.85
Hypertension (No.) (%)	69 (65.7)	31 (66)	38 (66)	.96	36 (66.7)	33 (66.0)	.94	22 (57.9)	47 (70.1)	.20
Diabetes (No.) (%)	17 (16.2)	9 (19)	8 (14)	.46	6 (11.1)	11 (22.0)	.13	8 (21.1)	9 (13.4)	.31
Atrial fibrillation (No.) (%)	41 (39.0)	19 (40)	22 (38)	.79	23 (42.6)	18 (36.0)	.49	12 (31.6)	29 (43.3)	.24
Coronary artery disease (No.) (%)	35 (33.3)	19 (40)	16 (28)	.17	12 (22.2)	23 (46.0)	.01	16 (42.1)	19 (28.4)	.15

**Note:**—P<sub>1</sub> indicates a P value between poor and good collateral status; P<sub>2</sub>, P value between mRS ≤ 2 and mRS > 2 groups; P<sub>3</sub>, P value between the proximal and distal thrombus groups; IQR, interquartile range; min, minutes.



**FIG 1.** The distribution of collateral scores in different clot locations. Collateral scores 3 and 4 are pooled into same group.

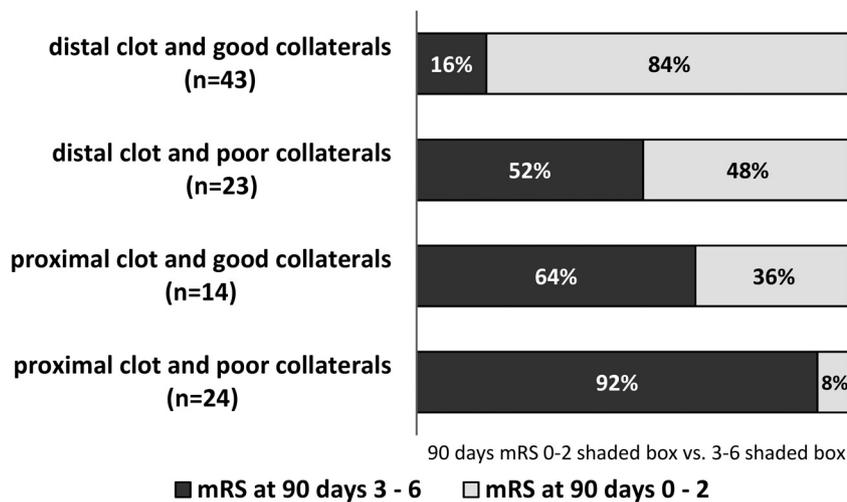
(CS 0–1) collateral filling, whereas in the 2 more distal clot locations (M1D and M2), only about one-third (35% and 42%, respectively) had poor collaterals. In the most distant clot location studied (M3), all patients had good collateral status. The distribution of the CS was significantly different across the studied clot locations ( $P = .04$ ). When adjoining clot locations (ICA-M1P, M1P-M1D, M1D-M2, M2-M3) were compared in pairs, only the difference in the distribution of CS between M1P and M1D yielded statistical significance ( $P = .05$ ).

To assess the prognostic value of CS in different clot locations, we dichotomized the CS as described above and cross-tabulated it with the dichotomized 3-month mRS score ( $mRS \leq 2$ ) in different clot locations. Overall, poor collateral status was associated with unfavorable clinical outcome, especially in the proximal clot locations: Not a single patient with acute occlusion of the ICA and having poor collaterals experienced favorable clinical outcome ( $P < .001$ ). However, the association between good collaterals and favorable clinical outcome was less pronounced in the proximal locations, 29% in ICA and 43% in the M1P. When individual

clot locations were considered, only M1D showed statistically significant differences with 70% of those with poor collaterals experiencing unfavorable outcome and 74% of those with good collaterals experiencing favorable outcome ( $P = .05$ ).

On the basis of these results, location was dichotomized by using M1P-M1D as the dividing point and cross-tabulation was repeated. A proximal clot was more strongly associated with unfavorable outcome than poor collateral status (Fig 2). However, good collaterals were associated with improved outcome in both proximal and distal clot locations ( $P = .08$  and  $P = .004$ , respectively).

To further assess the prognostic value of CS and its interplay with the clot location, we performed binary logistic regression analysis by using the dichotomized 3-month mRS score as the dependent variable. The CS was analyzed with the model we used in our previous article.<sup>1</sup> When the site of the occlusion was included in the model as a covariate, onset-to-treatment times, sex, diabetes, hypertension, atrial fibrillation, and coronary heart disease, tested one at a time, were not statistically significant covariates. Age, NIHSS score, CS, sex, and onset-to-treatment times were kept in the final multivariate regression model. The latter 2 variables were included for theoretic reasons, though they did not reach statistical significance in the preliminary analysis. The resulting model (Table 2) displayed satisfying fit and calibration (Hosmer-Lemeshow test,  $P = .95$ ; C statistic = 0.92). The model was also tested with an interaction term (CS\*clot location) that proved not to be statistically significant. Both the clot location and the CS were highly significant ( $P = .003$  and  $P = .001$ , respectively) independent predictors of favorable clinical outcome in the presence of the NIHSS score (Table 2). Good collateral status increased the odds of favorable clinical out-



**FIG 2.** Collateral score and the site of the occlusion predict the clinical outcome. A proximal clot (ICA or M1P) is more strongly associated with unfavorable outcome than poor collateral status (CS 0–1).

**Table 2: Logistic regression analysis for favorable clinical outcome<sup>a</sup>**

	mRS ≤2 at 2 Months		
	Odds Ratio	95% CI	P Value
Clot location	–	–	.003
ICA	ref	ref	–
M1 proximal	10.1	0.74–140	.08
M1 distal	33.8	2.9–428	.007
M2 and M3	115.8	7.7–1737	.001
Onset-to-treatment time	0.99	0.97–1.02	.44
Sex	0.34	0.09–1.3	.11
Age	0.95	0.90–0.99	.02
Admission NIHSS score	0.81	0.71–0.92	.001
Favorable CS (2–4)	9.3	2.4–35.8	.001

**Note:**—ref indicates reference location; –, not applicable.

<sup>a</sup> Odds ratios are per minute for onset-to-treatment time, per year for age, and per 1 point for NIHSS.

come about 9-fold (OR = 9.3; 95% CI, 2.4–35.8). The OR for favorable clinical outcome increased in a graded fashion when moving from a proximal vessel position to a more distal one. A higher NIHSS score and advanced age were significantly associated with worse outcome. Finally, clot location was dichotomized similar to that in Fig 2 (cut-point at M1P/M1D), and the model was recalculated. A distal clot location had a larger odds ratio (OR = 13.3; 95% CI, 3.0–60.0) compared with that of good collateral status (OR = 5.9; 95% CI, 1.8–19.0).

### Collateral Score Identifies Patients at Risk of Developing an Extensive Infarct

When cross-tabulated with dichotomized CS, 79% of patients with minor infarcts (≤10 mL) in the 24-hour follow-up NCCT had good collaterals, whereas 61% of patients with larger-than-minor infarcts (>10 mL) had poor collateral circulation ( $P < .001$ ). Good collateral circulation was associated with minor infarcts, especially in the distal clot positions. Ninety-two percent of patients with a clot in the M1D and a minor infarct had good collaterals ( $P = .02$ ); 72% of patients with M2 occlusion and a minor infarct had good collaterals ( $P = .08$ ). Some patients (17%, 18 of 105) had an extensive infarct (≥100 mL). Two-thirds (12 of

18) of these had a proximal (ICA/M1P) occlusion. Most (89%, 16 of 18) patients with an extensive infarct had poor collaterals according to the CS ( $P < .001$ ).

### DISCUSSION

We studied the interplay between the location of the clot and the collateral status with regard to the 3-month clinical and the 24-hour imaging outcomes in a HIS cohort treated with IVT.

The tendency of patients with more proximal thrombi and larger clot burden to have poorer collateral status has been observed recently.<sup>9</sup> In our study, the proportion of patients with HIS with good collateral status doubled when the location of the occlusion moved from the proximal half of the M1 segment to the distal half. When the clot was found in

the M3 segment, the collateral status was always good; this outcome can be expected from the definition of CS based on vascular territories supplied by the M2 segment arteries. The differential distribution of the CS in different clot locations may be due to proximal thrombi and poor collaterals sharing common risk factors, such as advanced atherosclerosis, old age, and hypertension.<sup>12,13</sup> However, an obvious mechanism explaining this observation is that the more proximal the occlusion and the more extensive the volume of the ischemic brain parenchyma and the more profound the reduction of cerebral blood flow in the ischemic core, the more easily is the capacity of the collateral vessels overwhelmed, resulting in a lower CS.

In the multivariate analysis, both the clot location and the CS proved to be highly significant and independent predictors of favorable clinical outcome, a finding that is in line with previous studies.<sup>1-3,5-8,14-17</sup> The cohorts of these studies were heterogeneous as to the use and types of revascularization therapies and onset-to-treatment times. Two of these studies analyzed cohorts consisting exclusively of patients undergoing IVT and/or intra-arterial thrombolysis, and they found that a high degree of collateralization predicted a good response to IVT.<sup>3,5</sup> However, these studies did not include the location of the clot as a covariate in their multivariate models, or the location of the clot was not a statistically significant predictor. By using a multivariate model, Lima et al<sup>15</sup> found that both the site of the intracranial occlusion and the pattern of leptomeningeal collateral circulation predicted the functional outcome of patients with anterior circulation stroke when all treatment modalities were considered. When only patients without revascularization therapy were analyzed, the site of the occlusion was not a significant determinant. In our cohort, adding the CS to a model already containing the location of the clot and NIHSS score resulted in better model fit (C statistic, 0.92 versus 0.90). Good collateral status increased the odds of favorable clinical outcome about 9-fold, and the odds of favorable clinical outcome increased substantially when the clot location was more distal. The site of the occlusion proved to be a stronger determinant of the outcome; good collaterals combined with IVT

managed to save only about one-third (36%) of the patients with a proximal clot from functional dependence or death at 3 months.

Poor collateral circulation is a major risk factor for already having developed an extensive infarct volume at admission.<sup>8</sup> The combination of a proximal thrombus and poor collaterals is referred to as a “malignant profile.”<sup>8</sup> Supporting this concept, in our study, 89% of patients who had an extensive (>100 mL) infarct in the 24-hour follow-up NCCT had poor collateral filling. These findings emphasize the importance of timely and correct therapeutic decision-making in this patient subgroup and may have a role in avoiding futile recanalization.<sup>18</sup>

Selection bias related to the retrospective design is a potential limitation of this study. Direct data on vessel recanalization or reperfusion were not available. Even so, a low ASPECTS at 24-hour NCCT is intimately related to delayed or failed recanalization/reperfusion and can be used as a surrogate. CTA has limitations in the evaluation of collateral circulation. It provides a snapshot of the filling of collaterals at the time of image acquisition. It has been shown that this may lead to underestimation of the collateral circulation because of late vessel filling.<sup>19</sup> Finally, the impact of the CS or clot location on clinical outcome may vary according to treatment variables beyond consideration of this study, such as rehabilitation or withdrawal of care after severe stroke.

## CONCLUSIONS

The results of this study show that a proximal site of occlusion in the anterior circulation is associated with poorer collateral status compared with a more distal occlusion. Both the location of the clot and the CS are important, independent predictors of the 3-month clinical outcome in the context of HIS treated with IVT. The location of the clot is a more powerful determinant of clinical outcome than the CS. However, poor collateral circulation is closely associated with extensive infarct volumes.

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# Location of the Clot and Outcome of Perfusion Defects in Acute Anterior Circulation Stroke Treated with Intravenous Thrombolysis

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## ABSTRACT

**BACKGROUND AND PURPOSE:** The location of the clot is a major determinant of ischemic stroke outcome. We studied the impact of the location (ICA, proximal M1 segment of the MCA, distal M1 segment, and M2 segment and more distally) of the clot on the CT perfusion parametric maps, the mismatch ratio, the amount of salvaged brain tissue, and the imaging and clinical outcomes in a retrospective acute (<3 hours) stroke cohort treated with intravenous thrombolysis.

**MATERIALS AND METHODS:** We reviewed 105 patients who underwent admission multimodal CT that revealed an occluded vessel on CTA. CT perfusion was successfully performed in 58 patients (55%). Differences among the parameters in different vessel positions were studied with the ANCOVA by using onset-to-imaging time as a covariate followed by pair-wise testing.

**RESULTS:** There were no significant differences in potential confounding variables among the groups. A clot proximal to the M2 segment produced a significantly larger defect on the MTT map. A clot in the ICA resulted in a significantly larger CBV lesion compared with the distal M1 segment, the M2 segment, and the M3 segment. In general, a more proximal thrombus created a larger CBV defect. The fraction of penumbra that was salvaged at 24 hours was higher in the more distal vessel positions.

**CONCLUSIONS:** Admission CBV defects are larger in proximal vessel occlusions. More of the penumbra can be salvaged if the occlusion is located distally. This effect seems to reach a plateau in the distal M1 segment of the MCA.

**ABBREVIATIONS:** ANCOVA = analysis of covariance; ASPECTS = Alberta Stroke Program Early CT Score; CBS = clot-burden score; ICC = intraclass correlation coefficient; mRS = modified Rankin Scale

The time from the onset of stroke symptoms to possible reperfusion of ischemic brain tissue determines functional outcome because the duration of parenchymal ischemia dictates the progression of irreversible changes and the size of the infarct core.<sup>1,2</sup> In the absence of sufficient collateral circulation, recanalization is a necessary though not sufficient condition for good imaging and clinical outcome.<sup>2</sup> The location, volume, and composition of the clot determine the effectiveness of intravenous rtPA in dissolving the occluding thrombus.<sup>3-15</sup> The location and

volume of the thrombus provide independent prognostic factors, with proximal high-volume clots predicting poor clinical outcome compared with distal low-volume clots.<sup>3-12</sup>

Multimodal CT imaging may improve the prognosis of patients with acute stroke.<sup>16</sup> The heart of the multimodal approach is the perfusion study, which allows detection of the infarct core and the penumbra and the quantification of salvageable brain tissue. This can be accomplished with high accuracy and full anatomic coverage by using perfusion and diffusion-weighted MR imaging. CTP has emerged as an alternative to MR imaging.<sup>17,18</sup>

We reviewed retrospectively the clinical and imaging data of 105 patients with acute (<3 hours) anterior circulation stroke who underwent multimodal CT assessment that revealed an occluded vessel at CTA and subsequently received intravenous rtPA. Fifty-eight (55%) of these patients were adequately evaluated with CTP. We studied the impact of the location (ICA, proximal M1 segment of the MCA, distal M1 segment, and M2 segment and more distally) of the clot on the CTP parametric maps, the mismatch ratio, the proportion of salvaged brain tissue, the 24-hour imaging outcome, and the 3-month clinical outcome.

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## MATERIALS AND METHODS

### Study Population

Our retrospective observational cohort study was approved by Tampere University (Hospital) review board. Altogether 315 patients with anterior or posterior circulation ischemic stroke from January 2004 to December 2007 were treated with thrombolytic therapy and had a 3-month follow-up after the thrombolysis at the department of neurology of the Tampere University (Hospital). CTA had been performed in 285 patients (90%), and CTP, in 245 patients (78%). The thrombolytic therapy protocol used was similar to the American Heart Association guidelines.<sup>19</sup> Inclusion criteria for the study were acute anterior circulation ischemic stroke, vessel occlusion confirmed with CTA, a successfully performed CTP study, treatment with a standard intravenous rtPA administration regimen (Actilyse; Boehringer-Ingelheim, Ingelheim, Germany), and a total dose of 0.9 mg/kg, from which 10% was given as a bolus and the remaining 90%, as a continuous infusion for 1 hour. From 2004 to 2007, intra-arterial interventions were not performed for anterior circulation occlusions at our institution.

### Participants and Variables

Baseline characteristics included age, sex, prestroke mRS, times from symptom onset to the imaging and the initiation of intravenous rtPA, and stroke clinical risk factors (hypertension, diabetes, coronary heart disease, atrial fibrillation). These data were collected from the patient records. Clinical evaluation results had been prospectively stored according to a specific protocol. These data contained the NIHSS score at the time of initiation of the rtPA. Information from relatives, occupational therapists, and physiotherapists stored in medical records provided useful information for the assessment of a patient's health before stroke. Follow-up NCCT scans and NIHSS scores were obtained for all patients 24 hours after the administration of the thrombolytic agent. The 3-month mRS was the clinical outcome measure. In the years from 2004 to 2005, this score was prospectively recorded on the basis of a follow-up visit to neurologist and from 2006 to 2007 according to a phone interview by a neurologist. All these prospectively stored clinical data were carefully evaluated for possible errors.

### Imaging Parameters

CT scans were obtained by using 2 different multidetector scanners: LightSpeed 16-section (GE Healthcare, Milwaukee, Wisconsin) and Brilliance 64-section (Philips Healthcare, Best, the Netherlands). The imaging procedures and the parameters used are described extensively in our previous study available on-line as an open-access article at the Web site of the publisher.<sup>20</sup>

### Image Analysis

The NCCT examinations were reviewed by using dedicated medical imaging workstations. CTP and CTA images were analyzed, and areas and volumes were measured with Advantage workstation, Version 3.2 (GE Healthcare). MTT and CBV maps were generated with the CT Perfusion 3 software (GE Healthcare). The anterior cerebral artery was used as a source for the arterial input function, and the region of interest for the venous output func-

tion was positioned in the superior sagittal sinus. ASPECTS was assigned for NCCT and CTP maps. The principles of ASPECTS and the evaluation of CTP ASPECTS mismatch have been described in previous studies.<sup>20,21</sup> ASPECTS was considered not interpretable if either of the 2 reference levels was not covered. MTT maps were used to detect tissue at risk, and CBV maps were used to approximate the infarct core.

In the detection of a perfusion defect, we adopted a semiquantitative approach in which the presence of a defect was determined from color-coded maps visually, by comparing the appearance of the affected location with that of the healthy tissue on the contralateral side. The area of the defect was measured in the ASPECTS levels used in some analyses to increase accuracy and resolution. We required this area to have a mean MTT > 7 seconds (or mean CBV < 2.3 mL/100 g, correspondingly) in accordance with Wintermark et al.<sup>22</sup> Further validation was performed by requiring mean relative MTT > 249% for the penumbra and mean relative CBF < 31% and mean relative CBV < 58% for the infarct core compared with the contralateral side.<sup>23,24</sup>

CTA images were studied by examining the raw data and maximum-intensity-projection images. The location of the clot was recorded on the basis of the most proximal position of the occlusion. The M1 segment of the MCA was divided into 2 parts of equal length: the proximal and the distal half. The principles of the CBS system have been described in recent studies.<sup>9,10</sup>

The ASPECTSs were assigned, the location of the clot was determined, and the CBS was rated independently by 2 radiologists. In cases in which the findings differed, a consensus was reached. The examinations were reviewed in the order NCCT-CTA-CTP, paralleling that of the clinical workflow. The reviewers were blinded to the clinical data, apart from the side and nature of the acute symptoms. Perfusion defect areas and final infarct volumes were measured by 1 radiologist.

The ICC between a staff radiologist and an experienced neuro-radiologist were calculated for a test sample ( $n = 20$ ):  $ICC_{CBS} = 0.87$ ,  $ICC_{NCCT0\text{ hours}} = 0.86$ ,  $ICC_{MTT} = 0.79$ ,  $ICC_{CBV} = 0.73$ , and  $ICC_{NCCT24\text{ hours}} = 0.93$ . Median interobserver agreement indices for areas and volumes were  $AREA_{MTT} = 68\%$ ,  $AREA_{CBV} = 90\%$ , and  $VOLUME_{INFARCT} = 80\%$ . Cohen  $\kappa$  for the location of the clot was 0.94.

### Statistics

The data were analyzed with the Statistical Package for the Social Sciences, Version 18 (SPSS, Chicago, Illinois). Patients with mRS  $\leq 2$  at 90 days were considered to have experienced good clinical outcome. The threshold for statistical significance was .05. Group comparisons were performed for baseline variables by using 1-way ANOVA or the Fisher exact test. ANCOVA was used for the imaging parameters with onset-to-imaging time as a covariate. Pair-wise post hoc testing was done by using Šidák correction for multiple comparisons.

## RESULTS

### Baseline Characteristics

There were 105 (37% of all patients treated with intravenous rtPA during the study period) patients who had anterior circulation clots visible on CTA. Thrombus was not detected in 142 (50%)

### Baseline characteristics in different clot locations<sup>a</sup>

	ICA (n = 9)	M1P (n = 9)	M1D (n = 11)	M2+M3 (n = 29)	P
Age (yr)	70.2 ± 9.7	68.2 ± 16.2	70.5 ± 15.3	69.4 ± 11.7	.98
Female sex	3 (33)	3 (33)	8 (72)	14 (48)	.24
Admission NIHSS	18.2 ± 3.5	14.0 ± 4.5	12.3 ± 5.4	8.7 ± 5.3	<.001
mRS, prestroke	0.7 ± 0.5	0.7 ± 0.7	0.6 ± 0.7	0.8 ± 0.6	.93
Onset to treatment (min)	138 ± 30	133 ± 43	117 ± 16	133 ± 28	.35
Onset to imaging (min)	99 ± 25	90 ± 31	82 ± 17	100 ± 31	.33
Admission NCCT ASPECTS	8.2 ± 1.7	7.8 ± 2.2	9.5 ± 0.9	9.0 ± 1.8	.12
Hemorrhagic complication	1 (11)	0 (0)	0 (0)	1 (3)	.37

**Note:**—M1P indicates the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments.

<sup>a</sup>All values are mean ± SD or number of patients (percentage).

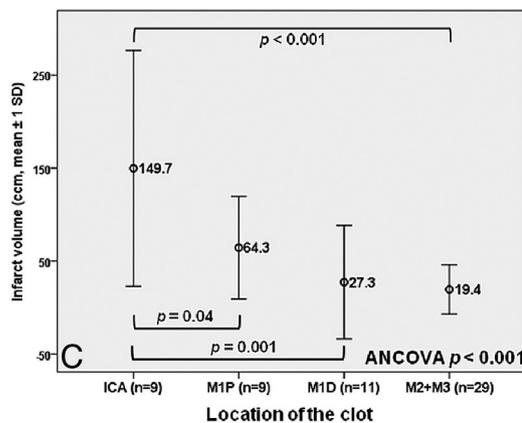
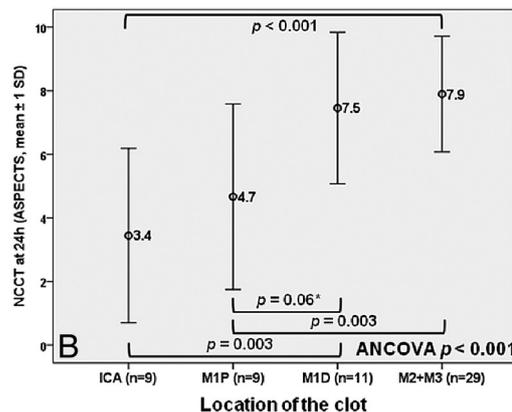
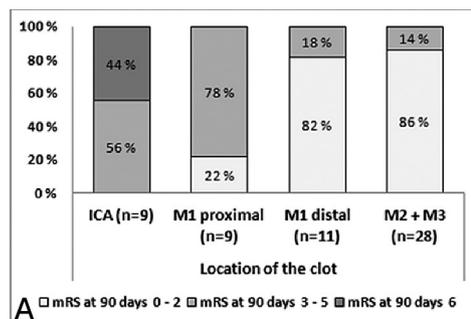
patients, and 38 (13%) patients had a posterior circulation clot. CTP was successfully completed in 58 of the 105 patients (55%) with an anterior circulation clot. These 58 patients constituted the study cohort. Eleven patients were not imaged with CTP; 9 studies were excluded because of poor technical quality; and 27 studies were excluded because either ASPECTS level was not covered, thus not permitting scoring. A perfusion defect was detected in 57 (98%) cases. The median age of the patients was 72 years (interquartile range, 63–81 years; 48% women). The median NIHSS score at admission was 12 (interquartile range, 6–17; 33% had an NIHSS score <8; 36% had an NIHSS score >15), and 24 hours later, the median NIHSS score was 5. The median mRS score was 1 preictally and 2 three months later. At 24 hours, a local hemorrhagic complication (hemorrhagic infarction1, hemorrhagic infarction2, parenchymal hemorrhage1, parenchymal hemorrhage2) was detected in 2 patients (3.4%), and 1 patient (1.7%) had parenchymal hemorrhage distant from the site of the infarct (remote parenchymal hemorrhage1, remote parenchymal hemorrhage2).

### Location of the Clot and Outcome of the Perfusion Defect

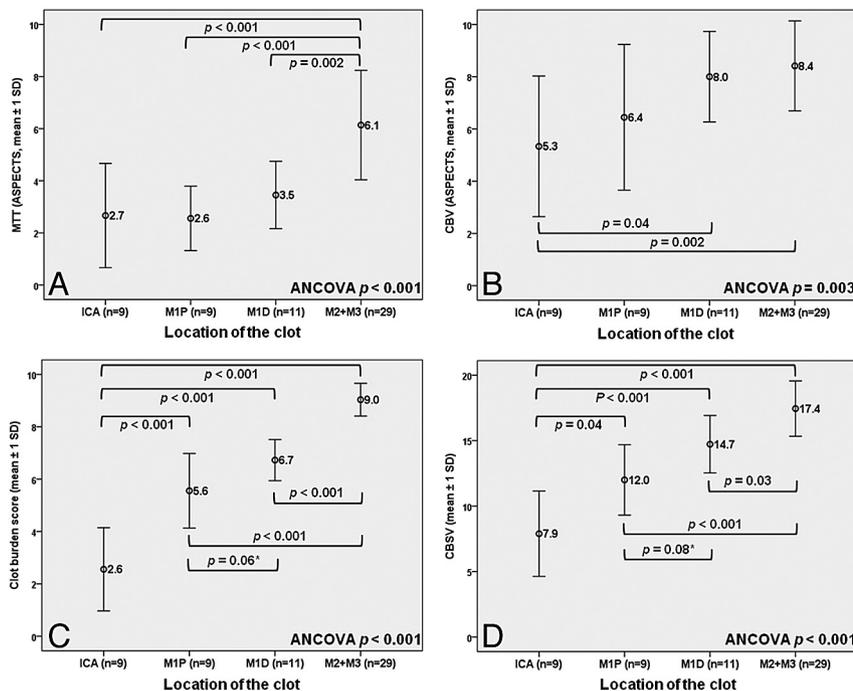
The differences in age, sex, prestroke mRS scores, and the number of hemorrhagic complications were not statistically significant between the different vessel positions (Table). The admission NIHSS score decreased proportionately in the more distal sites of occlusion. There were no statistically significant differences between the onset-to-treatment times, onset-to-imaging times, or the ASPECTS for NCCT at admission.

Thirty-four patients (59%) experienced favorable 3-month clinical outcomes (mRS ≤2). The difference in good outcome between the 2 most proximal clot locations (ICA and proximal M1 segment) and between the 2 most distal clot locations (distal M1 segment and combined M2 and M3) were not statistically significant, whereas the difference between these 2 groups was highly significant ( $P < .001$ , Fig 1A). The mid-M1 segment was a determinant for good clinical outcome, with the more distal clot locations predicting good clinical outcome. This is reflected in the imaging outcome. A clot in the ICA or the proximal M1 segment of the MCA resulted in a significantly larger infarct compared with an occluded distal M1 segment or the combined M2 and M3 segment group (Fig 1B, -C).

A thrombus located in the M2 or M3 segments of the MCA produced a significantly smaller perfusion defect compared with all of the 3 more proximal vessel positions, which did not have any



**FIG 1.** The 3-month clinical outcome and the 24-hour NCCT imaging outcome. Mean values. Error bars indicate 1 SD. The  $P$  value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and  $P$  values indicate differences between individual groups. M1P indicates the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments.



**FIG 2.** The admission CTP and CTA parameters in different clot locations. Mean values. Error bars indicate 1 SD. The *P* value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and *P* values indicate differences between individual groups. The asterisk indicates not significant. M1P indicates the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments.

statistically significant differences (Fig 2A). Occlusion of the distal M1 segment resulted in a slightly smaller MTT defect compared with the ICA or the proximal M1 segment, but the difference was not statistically significant. A clot in the ICA caused a significantly larger lesion in the CBV map compared with the distal M1 segment and the combined M2 and M3 segment group (Fig 2B). In general, a more proximal thrombus was associated with a larger CBV defect on the admission CTP. The CBS and the sum of CBS and CBV ASPECTS<sup>11</sup> increased almost linearly from proximal-to-distal vessel positions, which is, in part, to be expected because the CBS contains information about the location of the clot (Fig 2C, -D).

A clot in the M2 or M3 segment of the MCA produced a significantly smaller MTT-CBV mismatch (penumbra) and a smaller amount of salvaged brain tissue, which essentially reflects the vascular anatomy (Figs 3A, -B and 4A). However, there was a nonsignificant trend toward a larger proportion of salvageable brain tissue when moving from proximal to distal vessel positions (Fig 3C). In addition, the fraction of penumbra that was salvaged at 24 hours on the basis of the NCCT findings was higher in the more distal vessel positions (Fig 4B, -C). This is probably due to treatment effect, collateral circulation, and higher frequency of spontaneous recanalization, especially in the distal M1 segment (Fig 4A). However, most of the differences between individual vessel positions were not statistically significant.

## DISCUSSION

We studied the impact of the location of the clot on the CTP maps, the derived variables describing the penumbra and the salvaged

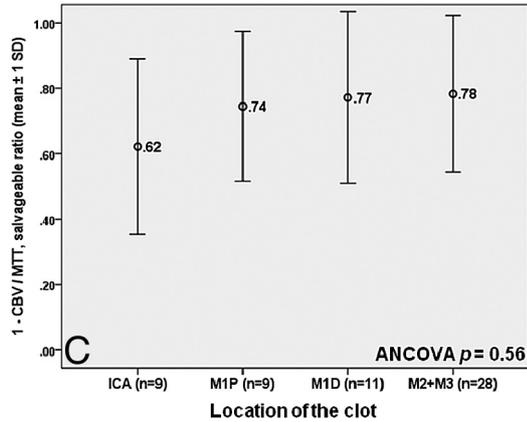
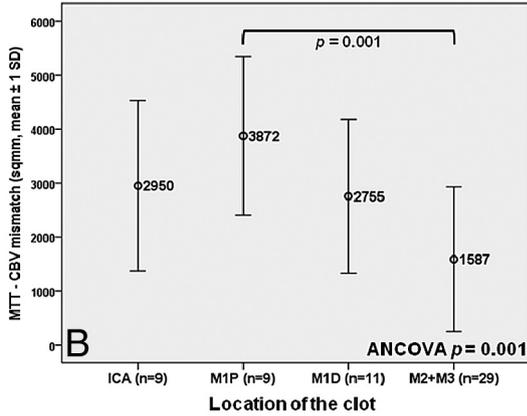
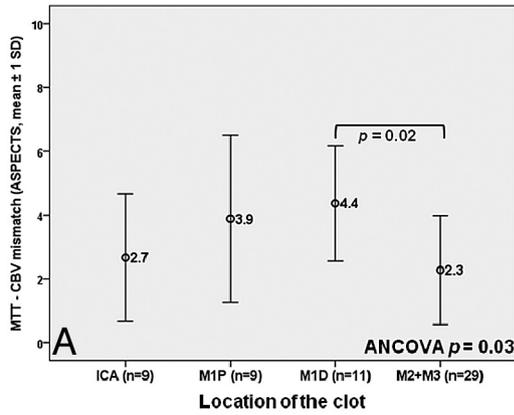
brain tissue, and the clinical and imaging outcome. There were no statistically significant differences between the various vessel locations in age, onset-to-imaging times, onset-to-treatment times, pre-stroke functional status, or acute ischemic changes on the admission NCCT.

The mid-M1 segment essentially acted as a divider between poor and good clinical outcome. The 24-hour NCCT ASPECTS behaved in a manner consistent with the functional outcome, with clear grouping in the 2 proximal (the ICA and proximal M1 segment) and the 2 distal (the distal M1 segment and the combined M2 and M3 segments) vessel positions. The picture was statistically less clear when the total infarct volume was considered, with only the differences between the ICA and the other vessel positions being statistically significant. However, the difference between the means of the proximal and the distal M1 segment was 2.4-fold. Furthermore, a previous study has suggested that an infarct volume of >70 cm<sup>3</sup> leads to poor clinical outcome.<sup>1</sup> This threshold is close to the mean infarct volume in the proximal M1 segment (64.3 cm<sup>3</sup>). The additional functional and anatomic imaging provided insight into clinical and imaging outcomes.

Occlusion in the 3 most proximal vessel positions produced a significantly larger defect in the MTT map than an M2 or M3 occlusion, which is to be expected from blood vessel and vascular territory anatomy. Correspondingly, the absolute size of the penumbra was significantly smaller in the combined M2 and M3 group. The relative size of the penumbra, compared with the size of the total perfusion defect, was larger in the 3 distal vessel positions, though the difference was not statistically significant, because patients with an occlusion of the ICA had significantly larger lesions in the CBV maps compared with the proximal M1 segment and the combined M2 and M3 group.

In general, there was a significant trend toward larger defects in the CBV map when moving from a distal to a more proximal vessel position. Considering that there were no significant differences in baseline variables, it appears that irreversible ischemic changes develop at a faster pace when the perfusion defect is larger. This can be conceivably attributed to more profound ischemia in the core region of a large perfusion defect. This is consistent with the finding by Gasparotti et al,<sup>25</sup> who observed that patients with acute stroke with a carotid T occlusion have larger lesions on the admission CBV maps compared with patients with occlusion of the M1 segment. In a study by Yoo et al,<sup>1</sup> patients with a large lesion in the diffusion-weighted images of admission MR imaging invariably had an acute occlusion of the ICA.

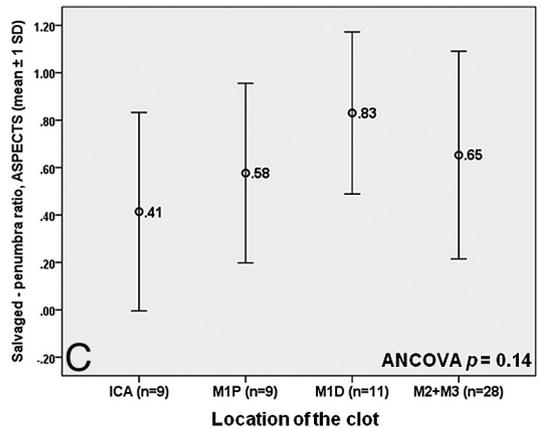
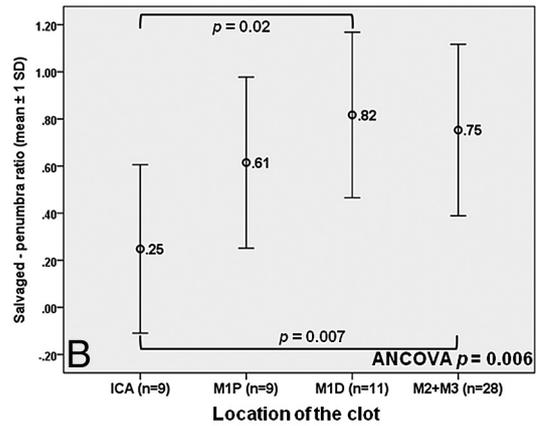
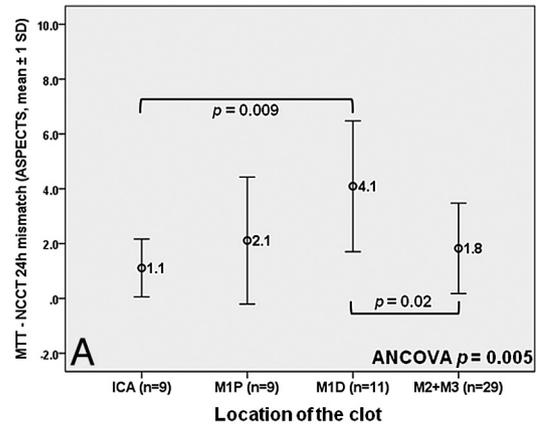
A significantly larger proportion of the penumbra is, on average, saved by the intravenous rtPA or spontaneous recanalization in the more distal vessel positions. This effect seems to reach its



**FIG 3.** Analysis of the perfusion mismatches. Mean values. Error bars indicate 1 SD. The *P* value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and *P* values indicate differences between individual groups. A, Calculations were made using ASPECTS scores. B and C, Calculations were made by using area measurements in the ASPECTS sections. The asterisk indicates not significant. M1P indicates the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments.

maximum in the distal M1 segment. This outcome is probably a result of reperfusion by the emerging collateral circulation and decreased clot burden in the more distal vessel positions as reflected by the significantly smaller clot-burden scores, which potentially increase the rate and the pace of recanalization.

Some studies have addressed the effect of clot location on recanalization and clinical and imaging outcome in the context of intravenous rtPA. None of these studies used CTP. Del Zoppo et al<sup>3</sup> used DSA to find that the M2 and M3 segments are more likely



**FIG 4.** Analysis of the perfusion-NCCT 24-hour mismatches and the fate of the penumbra. Mean values. Error bars indicate 1 SD. The *P* value for ANCOVA (adjusted for onset-to-imaging time) is given in the lower right-hand corner of each panel. Brackets and *P* values indicate differences between individual groups. A and C, Calculations were made using ASPECTS scores. B, Calculations were made by using area measurements in the ASPECTS sections. The asterisk indicates not significant. M1P indicates the proximal M1 segment; M1D, the distal M1 segment; M2+M3, M2 and M3 segments.

to undergo recanalization than the M1 segment and the ICA. Saqqur et al<sup>5</sup> arrived at similar results using repeated transcranial Doppler sonography in studying recanalization and its effect on 3-month clinical outcome. Still other studies with more heterogeneous setups have reported that large-vessel occlusions are less likely to recanalize and predict poor outcome.<sup>4,7,8</sup> These findings are in congruence with our results.

A prognostic variable that combines the CBV ASPECTS and

the clot-burden scores has been introduced recently.<sup>11</sup> A threshold value of 15 in the prediction of good clinical outcome was derived for this variable.<sup>11</sup> This result is compatible with our findings of the distal M1 segment having a mean score of 14.7 and the combined M2 and M3 group having a mean score of 17.4, and the 2 more proximal vessel positions having mean scores of 7.9 and 12.0.

Our study is limited by the retrospective design and sample size. The distribution of the patients as to different clot locations was uneven, with half of the patients in the combined M2 and M3 group. However, there were no significant differences in the baseline variables that could be potential confounders between the groups. Because of the study design, direct data on vessel recanalization or reperfusion were not available for most patients. The craniocaudal coverage of the CTP was 20 mm at minimum. Because of this, the size of the perfusion defect was estimated by using ASPECTS and area measurements in the ASPECTS sections. MTT maps potentially overestimate the size of the perfusion defect, while CBV maps may overestimate or underestimate the volume of the irreversibly damaged brain parenchyma, and there is vendor variability in CTP results.<sup>26</sup>

## CONCLUSIONS

The impact that location of the clot has on the findings of CTP examination of the anterior circulation has been seldom directly addressed in previous studies, especially in the context of early intravenous rtPA therapy. A clot proximal to the M2 segment led to a large defect in the admission MTT map with a nonsignificant trend of smaller perfusion defects distally in the 3 more proximal vessel positions. The admission CBV defect was larger in the case of more proximal vessel occlusions, though there were no significant differences in the onset-to-imaging time between the groups. A larger fraction of the penumbra could be salvaged if the occlusion was located more distally. This effect seems to reach a plateau in the distal M1 segment. This is reflected in the clinical outcome with the 2 proximal (the ICA and the proximal M1 segment) clot locations predicting poor outcome, whereas patients with more distal (the distal M1 segment and combined M2 and M3 segments) clots experienced significantly better outcomes.

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