



NIKO SILLANPÄÄ

Multimodal Computed Tomography  
in the Evaluation of Acute Ischemic Stroke



ACADEMIC DISSERTATION

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the board of the School of Medicine of the University of Tampere,  
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UNIVERSITY OF TAMPERE

## ACADEMIC DISSERTATION

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# ABSTRACT

Stroke is one of the leading causes of mortality and the loss of quality life years worldwide. Ischemic stroke is a vascular disease that is characterized by insufficient flow of blood to brain tissue. In general, stroke results from the occlusion of an intracranial artery by a thrombus. Therapeutic interventions are aimed at restoring the normal circulation and limiting the extent of irreversible damage. Thus, therapies that elicit reperfusion, such as intravenous thrombolysis (IVT) and intra-arterial interventions, are of special interest. Imaging has a central role in the evaluation of acute-stroke patients. It enables the detection of intracranial hemorrhage, the approximation of the volume of reversible and irreversible ischemic changes and provides information on cerebral vasculature. These data can be used to predict the clinical outcome and the risk of hemorrhagic complications and to triage the patients to different therapeutic approaches. Multimodal computed tomography CT, especially parameters derived from CT angiography (CTA) and CT perfusion (CTP) studies, holds promise for achieving these goals with increased precision.

This thesis examined, in a retrospective, observational cohort, the utility and the predictive performance of imaging parameters derived from CTA and CTP scans obtained upon admission in the evaluation of acute (less than 3 h from the onset of the symptoms) ischemic stroke patients who received IVT during the years 2004 to 2007. The 3-month functional outcome was the main prognostic end point. The parameters studied included the Alberta Stroke Program Early CT Score (ASPECTS) that was assigned to different CTP maps and the CTP ASPECTS mismatch, the Boston Acute Stroke Imaging Scale (BASIS), the Clot Burden Score (CBS), and the location of the clot. In addition, two modified imaging parameters (M1-BASIS and CBSV) were introduced. The quality of CTP scans using scanners with detector widths of either 16 or 64 rows was also investigated.

The CTP ASPECTS parameters were found to detect reversible ischemia and to correlate with the clinical outcome. The CTP ASPECTS mismatch adequately identified the amount of potentially salvageable tissue. CBS, BASIS and the cerebral blood volume (CBV) ASPECTS scores were statistically robust and sensitive but unspecific predictors of a favorable clinical outcome. The two modified imaging parameters, CBSV and M1-BASIS, shared these same properties and appeared to provide slightly improved prognostic accuracy. The functional outcomes of an acute internal carotid artery (ICA) occlusion and/or a proximal M1 segment of the middle cerebral artery (MCA) occlusion were typically found to be poor even if treated with IVT. A cut-point between the proximal and the distal M1 segments showed the highest accuracy in discerning favorable from poor clinical outcome. CTP scans performed using a 16-row scanner were significantly less sensitive in the detection of perfusion defects in the cranial parts of the MCA region compared with a 64-row scanner. The 16-row scans showed more uncorrected motion artifacts that resulted from periodic small-scale patient movements.

Overall, the parameters derived from the multimodal CT provided added value in the evaluation of acute ischemic stroke.

*Keywords:* ASPECTS, Boston Acute Stroke Imaging Scale, Clot Burden Score, computed tomography perfusion, computed tomography angiography, stroke, thrombolytic therapy.

# TIIVISTELMÄ

Aivoverenkiertohäiriö (AVH) on eräs merkittävimpiä kuolemaan johtavia tai elämän laatua heikentäviä kansansairauksia. Iskeeminen AVH eli aivoinfarkti aiheutuu riittämättömästä veren virtauksesta aivokudoksessa. Yleisimmin tämä johtuu kallon sisäisen valtimon tukkeutumisesta verihyytymän vuoksi. Aivoinfarktin hoito tähtää normaalin verenkierron palauttamiseen ja palautumattoman kudosaaurion rajoittamiseen. Näin ollen tukkeutuneen verisuonen avaamiseen perustuvat hoidot, kuten laskimonsisäinen liuotushoito ja valtimonsisäiset toimenpiteet, ovat avainasemassa. Lääketieteellisellä kuvantamisella on keskeinen rooli akuutin aivoverenkiertohäiriön diagnostisessa selvittelyssä. Kuvantaminen mahdollistaa aivoverenvuodon toteamisen, palautuvien ja palautumattomien iskeemisten muutosten laajuuden arvioimisen sekä verisuonen tukoksen paikantamisen. Näitä tietoja käytetään ennusteen määrittämiseen, komplikaatioiden todennäköisyyden arviointiin ja hoidon valintaan. Multimodaalisen tietokonetomografiatutkimuksen erityisesti angiografia- ja perfuusio-osatutkimuksiin (CTA ja CTP) perustuvat tunnusluvut mahdollisesti helpottavat näiden tavoitteiden saavuttamista.

Tässä väitöstutkimuksessa tarkasteltiin retrospektiivisessä asetelmassa akuutisti (oireiden alkamisesta alle kolme tuntia) aivoinfarktioireistoon sairastuneiden, laskimonsisäisen liuotushoidon saaneiden potilaiden kohorttia vuosilta 2004–2007. Tutkimuksen tavoitteena oli selvittää akuutin vaiheen CTA- ja CTP-kuvauksista saatujen muuttujien ominaisuuksia ja hyödyllisyyttä aivoinfarktin ennusteen arvioinnissa. Näitä muuttujia olivat CTP-karttoihin sovellettu Alberta Stroke Program Early CT Score (ASPECTS) -pisteitys, CTP ASPECTS -poikkeama, Boston Acute Stroke Imaging Scale (BASIS) -pisteitys, Clot Burden Score (CBS) -pisteitys ja verisuonen tukoksen sijainti. Pisteytyksistä muokattiin kaksi uutta muuttujaa vastaavaa tarkastelua varten. Ennustemuuttujana käytettiin kolmen



kuukauden kohdalla arvioitua potilaan funktionaalista tilaa. Lisäksi vertailtiin 16- ja 64-leikelaitteilla tehtyjen CTP-tutkimusten laatua.

CTP ASPECTS -muuttujat mahdollistivat palautuvien ja palautumattomien iskeemisten muutosten määrällisen arvioinnin ja korreloivat funktionaalisen lopputuloksen kanssa. CBS, BASIS ja aivojen veritilavuuskartan (CBV) ASPECTS-pisteitys olivat tilastollisesti merkitseviä ja herkkiä, mutta epätarkkoja hyvän funktionaalisen lopputuloksen ennustamisessa. Kahdella muokatulla pisteityksellä, joille annettiin nimet CBSV ja M1-BASIS, oli vastaavat ominaisuudet, mutta hieman parempi ennustearvo. Sisemmän kaulavaltimon distaaliosien ja keskimmäisen aivovaltimon M1-segmentin proksimaalipuoliskon tukosten todettiin johtavan huonoon lopputulokseen laskimonsisäisestä liuotushoidosta huolimatta; M1-segmentin puoliväli erotteli tarkimmin hyvän ja huonon funktionaalisen lopputuloksen. 16-leikelaitteella tehtyjen CTP-tutkimusten herkkyys havaita perfuusiohäiriö oli merkitsevästi huonompi 64-leikelaitteella tehtyihin tutkimuksiin verrattuna erityisesti keskimmäisen aivovaltimon suonitusalueen yläosissa. Lisäksi 16-leikelaitteella tehdyissä tutkimuksissa oli enemmän potilaan vähäisistä liikkeistä johtuvia, tulkintaa vaikeuttavia häiriöitä.

Yhteenvetona, multimodaalisen tietokonetomografiatutkimuksen avulla saatavilla muuttujilla on lisäarvoa akuutin aivoverenkiertohäiriön diagnostisessa arvioinnissa.

# ABBREVIATIONS

2D	two-dimensional
3D	three-dimensional
A1	A1 segment of the anterior cerebral artery
ACA	anterior cerebral artery
AComm	anterior communicating artery
ADC	apparent diffusion coefficient
AFL	activities of daily living
AHA	American Heart Association
AIF	arterial input function
AIS	acute ischemic stroke
ASPECTS	Alberta Stroke Program Early CT Score
ATLANTIS	Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke
AUC	area under the curve
AVH	aivoverenkiertohäiriö
BASIS	Boston Acute Stroke Imaging Scale
CBF	cerebral blood flow
CBS	clot burden score
CBV	cerebral blood volume
CCS	causative classification system for ischemic stroke
CECT	contrast-enhanced computed tomography
CI	confidence interval
CT	computed tomography
CTA	computed tomography angiography
CTA-SI	CTA source images
CTP	computed tomography perfusion
DEFUSE	Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution

$\Delta$ mRS	delta-mRS, change in mRS (postictal vs. preictal)
DIAS	Desmoteplase in Acute Ischemic Stroke
DSA	digital subtraction angiography
DWI	diffusion-weighted imaging
ECASS	European Cooperative Acute Stroke Study
EIC	early ischemic change
EMS	Emergency Management of Stroke
EPITHET	Echoplanar Imaging Thrombolytic Evaluation
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient echo
H-L	Hosmer-Lemeshow
IAT	intra-arterial thrombolysis
ICA	internal carotid artery
IMS	Interventional Management of Stroke
IS	ischemic stroke
IST-3	the Third International Stroke Trial
IVT	intravenous thrombolysis
HMCAS	the hyperdense MCA sign
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
MCA	middle cerebral artery
MERCI	Mechanical Embolus Removal in Cerebral Ischemia
MIP	maximum intensity projection
MRI	magnetic resonance imaging
MTT	mean transit time
NCCT	non-contrast (enhanced) computed tomography
NIHSS	National Institutes of Health stroke scale
NINDS	National Institute of Neurological Disorders and Stroke
NNT	number needed to treat
mRS	modified Rankin Scale

MRS	Merci Retrieval System
OR	odds ratio
PCA	posterior cerebral artery
PComm	posterior communicating artery
PET	positron emission tomography
PROACT	Prolyse in Acute Cerebral Thromboembolism
PS	Penumbra System
PWI	perfusion-weighted imaging
ROC	receiver-operating characteristic curve
r-proUK	recombinant prourokinase
RR	risk ratio
r-tPA	recombinant tissue plasminogen activator
SARIS	Stent-Assisted Recanalization in Acute Ischemic Stroke
sICH	symptomatic intracranial hemorrhage
SITS-ISTR	Safe Implementation of Thrombolysis in Stroke–International Stroke Treatment Registry
SSS	Scandinavian stroke scale
TOAST	trial of org 10172 acute stroke treatment
tPA	tissue plasminogen activator
TTP	time to peak
VOF	venous output function

# LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original research reports that are referred to as I-IV in the text:

- I) Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, Elovaara I, Dastidar P, Soimakallio S: CT Perfusion ASPECTS in the Evaluation of Acute Ischemic Stroke: Thrombolytic Therapy Perspective. *Cerebrovasc Dis Extra*. 2011;1:6-16. DOI: 10.1159/000324324
- II) Sillanpaa N, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, Elovaara I, Dastidar P, Soimakallio S: The Clot Burden Score, the Boston Acute Stroke Imaging Scale, the Cerebral Blood Volume ASPECTS and Two Novel Imaging Parameters in the Prediction of Clinical Outcome of Ischemic Stroke Patients Receiving Intravenous Thrombolytic Therapy. *Neuroradiology*. 2011 Sep 9 [Epub ahead of print]. DOI: 10.1007/s00234-011-0954-z
- III) Saarinen JT, Sillanpää N, Rusanen H, Hakomaki J, Huhtala H, Lähteelä A, Dastidar P, Soimakallio S, Numminen H, Elovaara I: The Mid-M1 Segment of the Middle Cerebral Artery Is a Cut-Off Clot Location for Good Outcome in Intravenous Thrombolysis. *Eur J Neurol*. 2012 Mar 15 [Epub ahead of print]. DOI: 10.1111/j.1468-1331.2012.03689.x
- IV) Sillanpaa N, Rusanen H, Saarinen JT, Dastidar P, Soimakallio S: Comparison of 64-row and 16-row Multidetector CT in the Perfusion CT Evaluation of Acute Ischemic Stroke Patients Receiving Intravenous Thrombolytic Therapy. *Neuroradiology*. 2012 Feb 10 [Epub ahead of print]. DOI: 10.1007/s00234-012-1015-y

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# 1. INTRODUCTION

Stroke is the second-leading cause of death in adults aged 15 years and over worldwide, the fourth-leading cause of disease burden as measured in disability-adjusted life years, and the leading cause of acquired disability in adults in most regions <sup>1,2</sup>. Globally, an estimated 5.7 million people died as a result of a stroke in 2005 <sup>2</sup>. The estimated direct medical cost of stroke in the United States was \$25 billion in 2007 <sup>3</sup>. In Finland, the yearly medical expenses caused by stroke care are estimated to be \$1.6 billion, which is 7% of all healthcare expenditures <sup>4</sup>.

Ischemic stroke is a vascular disease that is caused by insufficient flow of blood to the brain tissue. In general, stroke results from a thrombotic occlusion of an intracranial artery. Reperfusion following recanalization or bypass of the occlusion, or improved collateral flow is a necessary but not sufficient condition for a favorable clinical outcome with the time from the onset of ischemia to the reperfusion being a pivotal determinant <sup>5</sup>. Thus, therapies that target the prerequisites of reperfusion, such as intravenous thrombolysis (IVT) and intra-arterial interventions, are of special interest.

Imaging has a central role in the evaluation of patients with acute stroke. Typically, a multimodal CT or stroke MRI is performed. Both methods enable the detection of intracranial hemorrhage, allow the approximation of the extent of reversible and irreversible ischemic changes and provide anatomical information on the cerebral and cervical vasculature <sup>6,7</sup>. These data can be used to predict the clinical outcome and the risk of hemorrhagic complications and to triage the patients to different therapeutic approaches. Multimodal CT, especially parameters derived from CT angiography (CTA) and CT perfusion (CTP) studies, holds promise in achieving these goals with increased accuracy <sup>8,9</sup>.

This thesis examines, in a retrospective, observational cohort, the utility and the prognostic performance of imaging parameters derived from CTA and CTP studies in the evaluation of acute ( $< 3$  h) ischemic stroke patients receiving IVT. These parameters include ASPECTS assigned to different CTP maps, the Boston Acute Stroke Imaging Scale (BASIS), the Clot Burden Score (CBS) and the location of the clot. Two modified imaging parameters are introduced. The quality of CTP studies with scanners of different detector widths is also investigated.

## 2. REVIEW OF THE LITERATURE

### 2.1 Acute ischemic stroke

#### 2.1.1 Pathophysiology and etiology

The symptoms and the imaging and histopathologic findings following ischemic stroke result from insufficient flow of blood to the brain parenchyma. Most commonly, this reduction in blood flow is caused by an occlusion of an arterial branch supplying a part of the brain in the absence of adequate collateral circulation. Systemic factors, such as hypoperfusion because of sustained severe hypotension, can also lead to irreversible ischemic damage in the brain tissue. An occlusion of a blood vessel is typically due to arterial or paradoxical embolism, due to a local thrombotic event that is triggered by rupture of an atherosclerotic plaque or due to prothrombotic conditions (Figure 1). The Trial of Org 10172 Acute Stroke Treatment (TOAST) classification and its variants (SSS-TOAST, CCS) define five major etiological subtypes of ischemic stroke <sup>10-12</sup>:

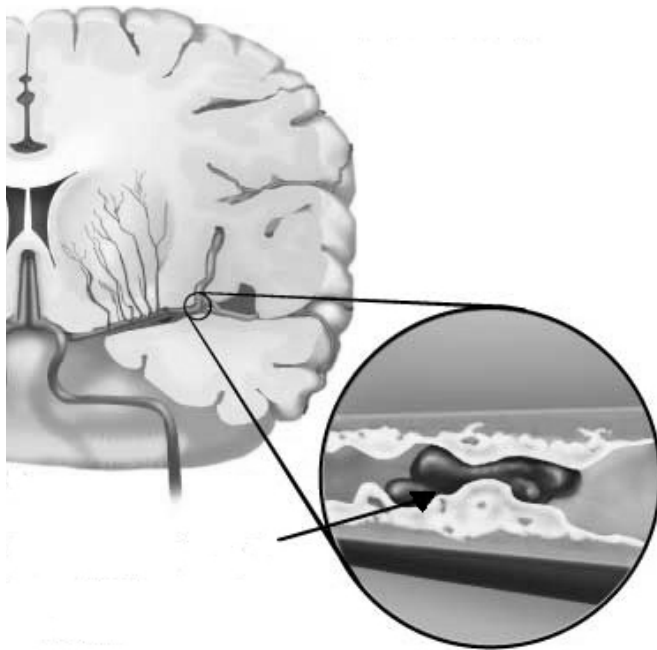
1. large-artery atherosclerosis (19%)
2. cardioembolism (9%)
3. small-vessel occlusion (44%)
4. stroke of another determined etiology (5%)
5. stroke of an undetermined etiology (22%)

The proportion of patients in each etiological category varies greatly between different reports and depends on the population studied and the sophistication of the diagnostic procedures. The above percentages are averages based on a large, worldwide study <sup>13</sup>. When only high-income countries are considered, the proportion of cardioembolism is higher (26%), whereas that of small-vessel disease is lower (30%). Overall there is a trend toward a higher incidence of



cardioembolism and large-artery atherosclerosis (including arterio-arterial embolism) in Western countries.

If the reduction in blood flow is of sufficient severity and duration, a series of events occurs at the cellular level that leads to irreversible changes. These events include the release of excitatory neurotransmitters and inflammatory mediators, influx of calcium to the cells, the generation of free-oxygen radicals, the depolarization of the cellular membrane, and the loss of the membrane integrity<sup>14, 15</sup>. A concept of the neurovascular unit comprising neurons, astrocytes, microglial cells, and microvascular structures has emerged recently in the study of ischemic injury<sup>15</sup>. The interactions and signaling between these components appears to play a pivotal role in the response of the tissue to the ischemic insult<sup>16</sup>. If adequate blood supply is not restored in the appropriate time, the affected tissue becomes infarcted, undergoes necrosis and shows scarring with accompanying, potentially permanent neurological deficits<sup>17</sup>.



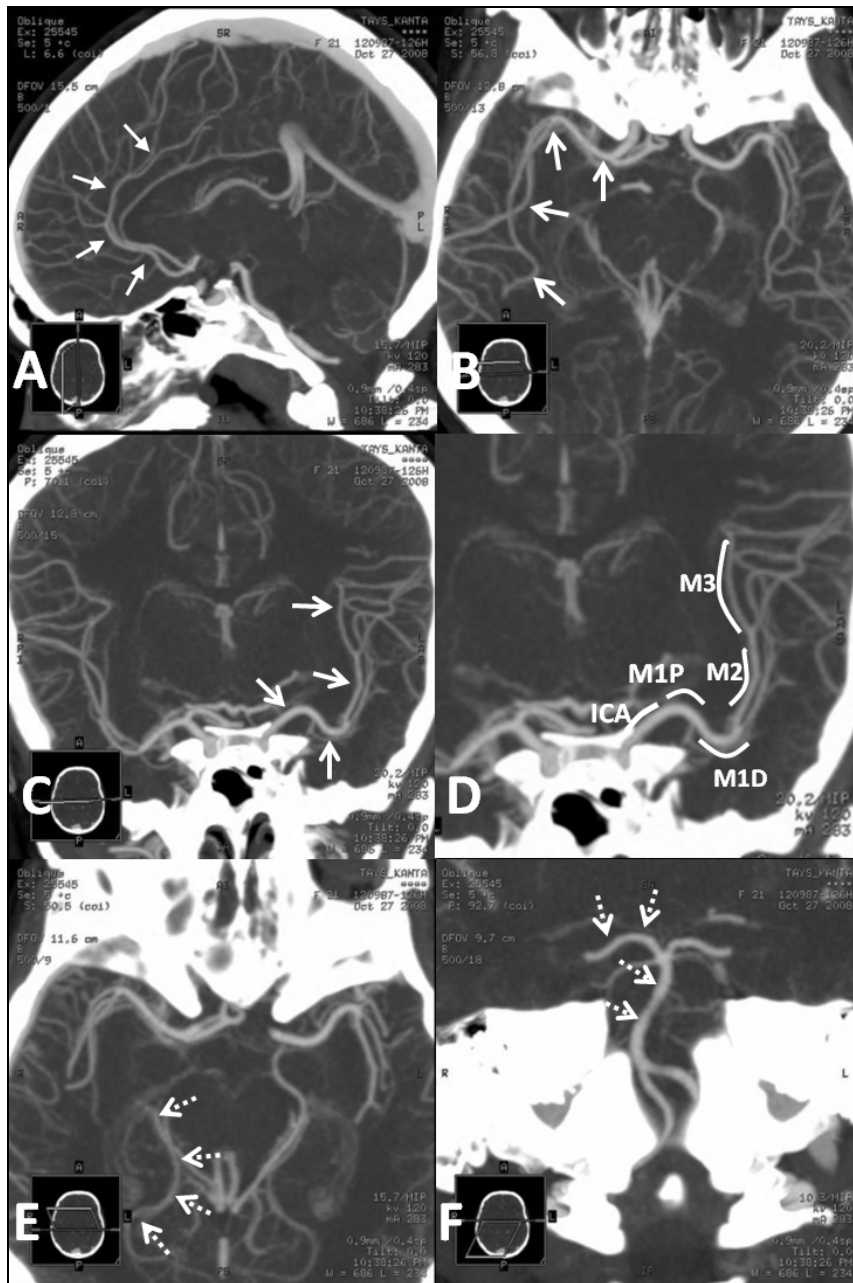
**Figure 1:** A thrombotic mass (black arrow) occluding the distal M1 segment of the middle cerebral artery. Adapted from the Heart and Stroke Foundation of Canada, [www.heartandstroke.ca](http://www.heartandstroke.ca).

## 2.1.2 Risk factors

Numerous risk factors for stroke have been identified. The main risk factor is age with each year of age after the age of 19 showing an increased risk of stroke of 9% for men and 10% for women, on average <sup>18</sup>. Other key non-preventable risk factors include the male gender, a family history of strokes and a previous stroke. In a large worldwide study, ten preventable risk factors—hypertension, current smoking, high waist-to-hip ratio, poor diet, lack of physical activity, diabetes mellitus, high alcohol intake, psychosocial stress and depression, cardiac disease (especially atrial fibrillation) and an unfavorable lipid profile—contributed 90.3% of the total risk in a multivariate model <sup>13</sup>. In general, risk factors tend to have a greater impact at younger ages <sup>18</sup>.

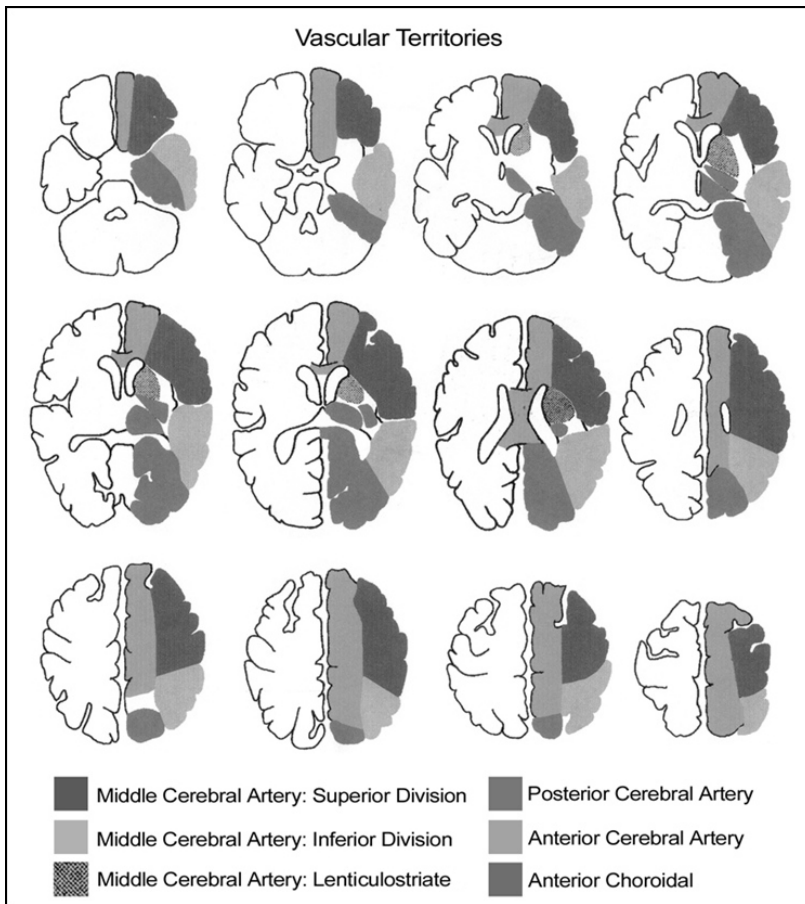
## 2.1.3 Vascular anatomy and vascular territories

The cerebral vasculature is divided into the anterior circulation, which is formed intracranially by the middle cerebral arteries (MCA) and the anterior cerebral arteries (ACA), and the posterior circulation that comprises the basilar artery, its end-arteries in the posterior fossa and the posterior cerebral arteries (PCA) in the supratentorial space (Figure 2). The vessels are often divided into numbered segments on the basis of their branching pattern, as demonstrated for MCA in Figure 2D. The anterior circulation is supplied by the internal carotid arteries (ICA), and the posterior circulation is supplied by the vertebral arteries (VA). Typically, there are several interconnecting vessels that allow collateral flow between the anterior and the posterior circulation, most notably the anterior and the posterior communicating arteries (AComm and PComm) that form the circle of Willis together with parts of the ACA, ICA and PCA vessels <sup>19</sup>. The vascular anatomy gives rise to vascular territories, i.e., volumes of brain tissue supplied by a certain vascular trunk in near end-artery fashion (Figure 3). Stroke symptoms correlate with the vascular territories affected by the stroke <sup>20-23</sup>.



**Figure 2:** CT angiography maximum-intensity projection (MIP) images of the main blood vessels of the brain. The anterior circulation is demonstrated in panels A through D. Panel A depicts the anterior cerebral arteries (small arrows); Panels B and C, the middle cerebral arteries (large arrows). Panel D is an inset to Panel C featuring the left middle cerebral artery (MCA). The posterior circulation is demonstrated in Panels E and F with Panel E depicting the distal parts of the right distal posterior cerebral artery and Panel F, the proximal parts along with the basilar artery (dashed arrows). In panel D, the left MCA is divided into segments comprising the proximal M1 segment (M1P), the distal M1 segment (M1D), the M2

segment (M2) and the M3 segment (M3). The supraclinoid portion of the internal carotid artery (ICA) is also marked.



**Figure 3:** The supratentorial vascular territories of the brain. Image adapted from [www.eMedicine.com](http://www.eMedicine.com).

### 2.1.4 Epidemiology and socioeconomic impact

Epidemiological and health economics data often do not differentiate ischemic from hemorrhagic stroke. According to a recent global study, 87% of strokes are ischemic in origin<sup>3</sup>. In the following text, both stroke subtypes are addressed together unless stated otherwise.

As stated above, stroke is the second-leading cause of death (10% of all deaths) in adults aged 15 years and over worldwide, the fourth-leading cause of disease burden as measured in disability-adjusted life years, and the leading cause of acquired disability in adults in most regions<sup>1, 2</sup>. An estimated 5.7 million people died as a

result of a stroke in 2005 <sup>2</sup>. Stroke accounts for approximately 6% of deaths in the United States and 8% of male and 12% of female deaths in Finland <sup>3, 24</sup>. The mean early (one month) case fatality was 14.3% in developed countries in the years 2000 through 2008 <sup>25</sup>. During extended follow-up, other causes of death then begin to take precedence <sup>26</sup>.

In a meta-analysis by *Feigin et al.*, the age-standardized prevalence of stroke for people aged 65 years or older ranged from 46 to 73 per 1000 (men: 59 to 93 per 1000; women: 32 to 62 per 1000) <sup>25</sup>. The authors reported that the incidence increased progressively with each decade of life. The age-standardized incidence for people aged 55 years or older was in the range of 4.2 to 6.5 per 1000 person-years. In Finland, the incidences in the year 2002 were 2 per 1000 person-years for people aged 25 to 74 years, 16 per 1000 person-years for people aged 75 to 84 years, and 30 per 1000 person-years for people aged 85 years and over <sup>24</sup>. In developed countries, the incidence has declined in recent decades, whereas developing countries are experiencing a stroke epidemic <sup>25</sup>.

The estimated direct medical cost of stroke in the United States was \$25 billion in 2007 <sup>3</sup>. In Finland, every fourth stroke patient belongs to the labor force, which incurs an annual loss of 16500 labor-years <sup>27</sup>. The yearly medical expenses caused by stroke care are estimated to be \$1.6 billion, which is 7% of all healthcare expenditures <sup>4</sup>. The estimated mean lifetime costs of ischemic stroke are \$130000 <sup>4</sup>.

### 2.1.5 Functional outcome measures

The majority (64%) of the contemporary stroke trials use modified Rankin scale (mRS) evaluations at different time points (1-, 3-, or 6-month mRS) as the functional outcome measure <sup>28</sup>. This scoring system is depicted in Table 1. The score is often dichotomized using the threshold  $\leq 2$  (“good clinical outcome”) or  $\leq 1$  (“excellent clinical outcome”) to facilitate statistical analyses. Another commonly used (41%) outcome measure is the Barthel activities of daily living (ADL) index <sup>28</sup>. The dichotomization cut-off for the Barthel index is typically  $\geq 90$  points.

Score	Description
0	No symptoms at all
1	No significant disability despite having symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

**Table 1:** The modified Rankin scale (mRS). mRS is a 6-point scale, with higher scores indicating a worse functional outcome.

### 2.1.6 Symptoms, signs and diagnosis

A diagnosis of acute ischemic stroke is based on history, general physical and neurological examination and imaging findings<sup>24, 29</sup>. Laboratory and cardiac tests have a minor role in diagnostics and are typically used to rule out stroke mimics, to detect comorbid conditions and in part to determine eligibility for revascularization therapies. The symptoms and findings of the neurological examination are best evaluated, quantified and communicated when using a standardized, formal stroke scale<sup>30-32</sup>. The National Institutes of Health Stroke Scale (NIHSS) is the most widely used formal scoring system<sup>33</sup>. NIHSS essentially captures and quantifies the stroke symptoms and the neurological signs and findings (Table 2). The role of CT imaging in the diagnosis of acute stroke is detailed in section 2.2.

Category	Score/Description
1a. Level of Consciousness (LOC)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma
1b. LOC Questions (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect
1c. LOC Commands (Open/close eyes, make fist/let go)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect
2. Best Gaze (Eyes open – patient follows examiner’s finger or face)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual Fields (Introduce visual stimulus/threat to patient’s visual field quadrants)	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind)
4. Facial Paresis (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete
5a. Motor Arm – Left 5b. Motor Arm – Right (Elevate arm to 90 degrees if patient is sitting, 45 degrees if supine)	0 = No drift 1 = Drift 2 = Can’t resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (limb amputation etc.)
6a. Motor Leg – Left 6b. Motor Leg – Right (Elevate leg to 30 degrees with patient supine)	0 = No drift 1 = Drift 2 = Can’t resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (limb amputation etc.)
7. Limb Ataxia (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs
8. Sensory (Pin prick to face, arm, trunk, and leg – compare side to side)	0 = Normal 1 = Partial loss 2 = Severe loss
9. Best Language (Name item, describe a picture and read sentences)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute
10. Dysarthria (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near unintelligible or worse X = Intubated or other physical barrier
11. Extinction and Inattention (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect

**Table 2:** The National Institutes of Health Stroke Scale (NIHSS). NIHSS is a 42-point scale that quantifies neurological deficits in 11 categories. Higher scores indicate more severe deficits. Adapted from *Richardson et al.*<sup>34</sup>

## 2.1.7 Acute management and therapies

The aims of acute stroke therapy are 1) to restore the perfusion of the ischemic brain tissue as rapidly as possible, 2) to limit the amount of damage to the ischemic tissue whether caused by primary (hypoperfusion) or secondary (for example, hyperglycemia or hyperthermia) mechanisms, and 3) to decrease the probability of complications (such as hemorrhagic transformation, aspiration). Both in experimental models and clinical trials, the duration and severity of ischemia determines the extent of irreversible damage<sup>17, 35</sup>. However, potentially viable ischemic tissue (penumbra) has been demonstrated to exist for at least 24 h after symptom onset<sup>36, 37</sup>. Overall, the time elapsed from the onset of the symptoms to treatment is a critical determinant of the outcome that guides decision making and pre- and in-hospital management<sup>38</sup>.

Four interventions have been unanimously proven to improve the outcome of ischemic stroke: 1) the management of patients in a stroke unit, 2) the use of aspirin within 48 h of stroke onset, 3) decompressive surgery (hemicraniectomy) for supratentorial malignant hemispheric cerebral infarction, and 4) the use of an intravenous thrombolytic within 4.5 h of symptom onset<sup>39-43</sup>. Therapeutic interventions that directly address *revascularization*—the reperfusion of the ischemic tissue by recanalization of the occluded vessel or by other means—are of particular importance because they could reverse the disease process. Currently available revascularization therapies include intravenous thrombolysis (IVT), sonothrombolysis, intra-arterial thrombolysis (IAT) possibly assisted with balloon angioplasty, IVT followed by an intra-arterial intervention, mechanical thrombectomy using aspiration, stent retrievers, other specific retrieval devices or a combination of these therapies, and bypass stenting<sup>44-47</sup>.

For a comprehensive review of the early management of adults with ischemic stroke, see the current United States and Finnish guidelines<sup>24, 29</sup>.



### 2.1.7.1 Intravenous thrombolytic therapy

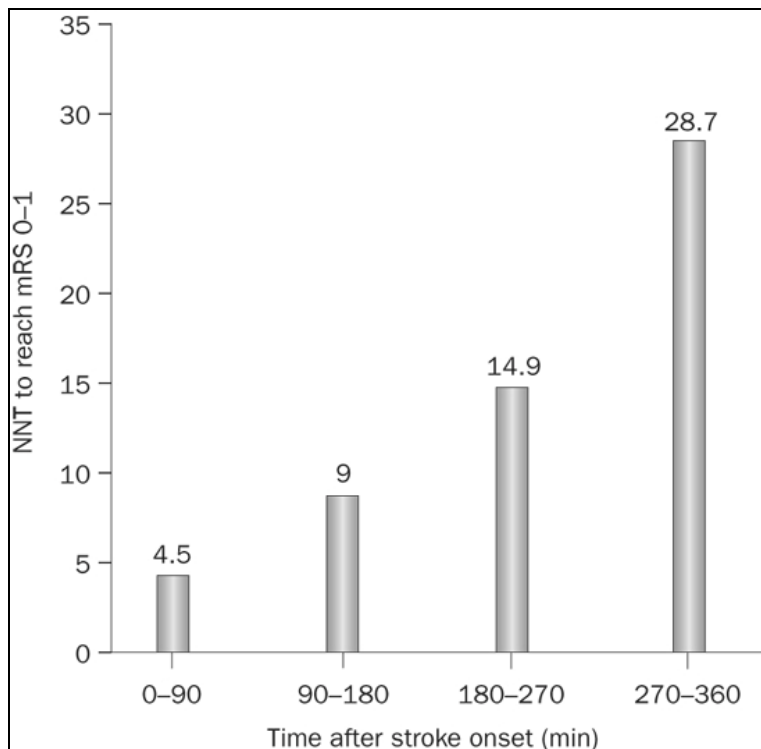
Tissue plasminogen activator (tPA) is a serine protease that enhances the conversion of plasminogen to active plasmin that acts on fibrin clots to dissolve the clot<sup>48</sup>. This interaction has been targeted for pharmacotherapy. First-generation therapeutic plasminogen activators—streptokinase and urokinase—have been gradually replaced by different recombinant tissue plasminogen activators (r-tPAs) that preferentially activate fibrin-bound plasminogen and thus have better spatial specificity<sup>49</sup>. r-tPA can be administered intravenously or intra-arterially, but only the intravenous administration route has been approved by the Food and Drug Administration (FDA). An obvious systemic and local adverse side effect is the increased risk of bleeding.

In 1996, the FDA approved the use of intravenous r-tPA for the treatment of acute ischemic stroke. The approval was based on the results of the National Institute of Neurological Disorders and Stroke trial (NINDS)<sup>43</sup>. This trial established a time window for the therapy to within 3 h from symptom onset. This time limit was supported by a meta-analysis of all trials up to 2004<sup>50</sup>. The other relevant trials included the European Cooperative Acute Stroke Study (ECASS), ECASS II and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study<sup>51-53</sup>. These trials allowed patients to be enrolled for up to 6 h after the stroke onset and, in this setting, showed no benefit of the intravenous r-tPA compared to placebo. However, in 2008, the ECASS III trial and evaluation of the Safe Implementation of Thrombolysis in Stroke–International Stroke Treatment Registry (SITS-ISTR) provided evidence that a time window of 4.5 h was safe and effective<sup>54, 55</sup>. This time window has since been adopted into most current treatment guidelines<sup>24, 56</sup>.

Recently, three trials have studied the IVT beyond the 4.5 h window. These trials utilized MRI to measure the mismatch between diffusion-weighted imaging and perfusion-weighted imaging findings (DWI-PWI mismatch, see section 2.2.4), which can be used to approximate the ischemic penumbra<sup>57, 58</sup>. In the Desmoteplase in Acute Ischemic Stroke (DIAS) series of trials, the decision to treat with r-tPA was based on non-quantitatively defined mismatch criteria, and the time window was

extended to 9 h<sup>59-61</sup>. The phase III trial failed to show a benefit of r-tPA treatment. In the open-label, non-randomized Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study, patients received r-tPA at up to 6 h after symptom onset<sup>62</sup>. A close relationship between a favorable clinical response, and the DWI-PWI mismatch was observed. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) investigators conducted a double-blinded, randomized, controlled trial using intravenous tPA from 3 to 6 h after stroke onset<sup>63, 64</sup>. They found a significant trend toward attenuation of infarct growth on DWI and a significant increase in reperfusion that was detected with PWI. Further trials addressing a treatment time window of beyond 4.5 h are being conducted. The largest of these trials is the Third International Stroke Trial (IST-3)<sup>65</sup>.

According to a meta-analysis of intravenous r-tPA trials by *Lees et al.*, the odds ratio (OR) of an excellent outcome ( $mRS \leq 1$ ) was 2.4 if the treatment was administered during the first 90 min and declined steadily to 1.4 during the 3.0-4.5 h time epoch<sup>35</sup>. These data are reflected in the number needed to treat (NNT) figures that increased proportionally with time (Figure 4). Symptomatic intracranial hemorrhage (sICH), which has potentially deleterious effects on the short- and long-term clinical outcome, occurs in 1.7-8.0% of patients receiving intravenous r-tPA<sup>43, 54, 66-68</sup>. Numerous risk factors for sICH have been identified. Patients with severe stroke ( $NIHSS \geq 20$ ) have a greater likelihood of hemorrhage<sup>69</sup>. Advanced age alone does not increase the probability of hemorrhagic complication, but the outcomes are worse<sup>70</sup>. Hyperglycemia and sustained hypertension have been linked with an increased risk of sICH<sup>71-75</sup>. The numerous CT imaging findings that are associated with an increased risk of hemorrhage are described in section 2.2. MRI findings that predict hemorrhagic complications include a profound reduction of cerebral blood volume, large diffusion or perfusion abnormalities upon baseline imaging ( $\geq 100$  ml), low apparent diffusion coefficient (ADC) values, signs of early blood-brain barrier disruption, and leukoaraiosis of the deep white matter<sup>75-81</sup>. Some of the absolute and relative contraindications to intravenous r-tPA are due to the increased probability of hemorrhage. The exact inclusion and exclusion criteria for intravenous r-tPA vary somewhat between institutions and countries. For a typical treatment protocol, see *Wechsler*<sup>49</sup>.



**Figure 4:** NNT to reach a mRS score of 0-1 for all trials of intravenous r-tPA in acute ischemic stroke prior to 2010. NNT is almost doubled with each additional 90 min after stroke onset. Adapted from *Donnan et al.*<sup>39</sup>

### 2.1.7.2 Intra-arterial interventions

The two largest trials that have studied intra-arterial administration of a thrombolytic agent are the phase II Prolyse in Acute Cerebral Thromboembolism (PROACT) and the PROACT II trials<sup>82, 83</sup>. In both studies, the pharmacological intervention was intra-arterial recombinant prourokinase (r-proUK) with intravenous heparin, which were both administered within 6 h of symptom onset. Patients receiving IAT had increased vessel recanalization rates (58-66% vs. 14-18%) and better clinical outcomes although the probability of intracranial hemorrhage was increased. The Emergency Management of Stroke (EMS) trial and the Interventional Management of Stroke (IMS) trials I and II studied a combined intra-arterial and intravenous thrombolysis with r-tPA administered within a 3 h time window<sup>30, 84, 85</sup>. Combined IV-IA strategies are collectively called *bridging therapies*. The investigators reported that there was a significantly improved 3-month outcome compared with the NINDS placebo arm, whereas there was only a trend toward improved outcomes when compared with the NINDS r-tPA arm. Other studies with

more heterogeneous setups have shown better functional outcomes in combined IV-IA treatment groups <sup>47</sup>. IAT can be assisted with balloon angioplasty.

During the last decade, different methods and devices have been introduced to perform mechanical thrombectomy. Two of these devices, the Merci Retrieval System (MRS) and the Penumbra System (PS), have been approved by the FDA for the treatment of acute ischemic stroke. The Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial was a single-arm study that included patients presenting between 3-8 h from symptom onset or within 3 h if there was a contraindication to IVT or if the treatment failed <sup>86</sup>. This trial was extended in the Multi MERCi study <sup>87</sup>. In a pooled analysis, recanalization, which was achieved in 65% of patients, significantly predicted improved 3-month outcome <sup>88</sup>. Higher degrees of recanalization were associated with improved outcome and decreased mortality <sup>89</sup>. In the Phase II Penumbra Pivotal Stroke Trial, the time window for treatment was 8 h. Eighty-one percent of the patients showed recanalization, 42% showed an improvement of at least 4 points in NIHSS scores and a 1-month mRS score  $\leq 2$  <sup>90</sup>. There are several case reports and retrospective study series showing high recanalization rates when using intracranial stents as an emergency revascularization strategy <sup>47</sup>. However, the Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial is the only high-quality prospective study <sup>91</sup>. In this study, following intervention, 100% of occlusions were recanalized. At one-month follow-up, 65% of patients showed an improvement of at least 4 points in NIHSS scores, and 62% had mRS  $\leq 3$ . Recanalization with retrievable, unfolded stents (stent retrievers) and temporary stent placement is currently being investigated and has shown promising preliminary results <sup>92-95</sup>.

## 2.2 Multimodal computed tomography

Traditionally CT examinations of the brain have been performed by imaging sequential axial slices with or without intravenously administered iodinated contrast-agent. These imaging modalities are called contrast-enhanced computed tomography (CECT) and non-contrast (enhanced) computed tomography (NCCT). Both of these modalities provide anatomical and structural information on the

intracranial space. CECT is not typically included in the acute ischemic stroke imaging protocols. The introduction of multidetector technology in the past two decades has enabled the use of thinner section-widths and rapid coverage of large imaging volumes. This technology has resulted in the development of computed tomography angiography (CTA) and computed tomography perfusion (CTP). CTA provides detailed anatomical information on the cerebral vasculature. CTP conveys functional information on the hemodynamic status of the vasculature at the tissue (capillary) level and allows the detection and characterization of ischemic brain parenchyma. Together, the three modalities—NCCT, CTA and CTP—are referred to as *multimodal computed tomography*.

### 2.2.1 Non-contrast computed tomography

The first scan obtained when using a multimodal CT imaging protocol is NCCT. It is used to exclude etiologies that cause symptoms mimicking those of ischemic stroke, the most important of which are intracranial hemorrhage and neoplasms, to detect possible early or irreversible ischemic changes in the brain parenchyma and to assess the risk of post-treatment bleeding complications, especially in the context of revascularization therapy <sup>7, 43, 50, 71</sup>.

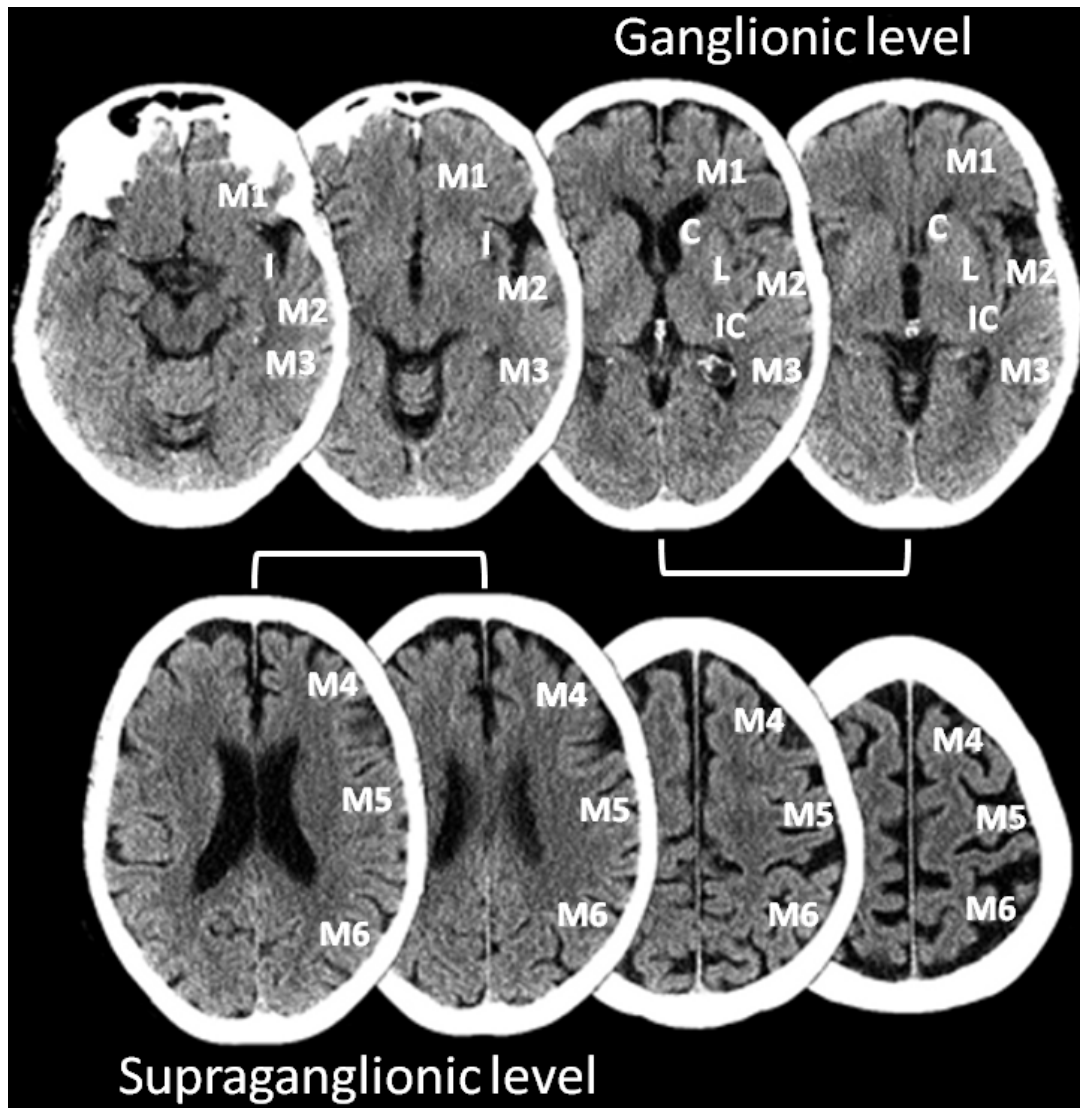
Early ischemic changes (EICs) observed using NCCT within 6 h of symptom onset include 1) subtle parenchymal hypoattenuation with or without swelling that often manifests as a loss of visualization of the gray-white matter interface and 2) isolated parenchymal swelling without hypoattenuation. Focal hyperattenuation of an arterial trunk is an additional sign that can be considered a surrogate for ongoing parenchymal ischemia. In some specific locations, these findings have been given names including the insular ribbon sign, obscuration of the lentiform nucleus, the MCA dot sign, and the dense media sign or the hyperdense MCA sign (HMCAS). The EICs are insensitive for detecting acute ischemic processes and show, at best, moderate interobserver agreement and reproducibility. In general, they indicate an increased risk of poor clinical and imaging outcomes. The presence of HMCAS is associated with a major neurologic deficit, and it predicts poor clinical and radiologic outcomes after IVT <sup>96</sup>. For a review, see <sup>7, 97</sup>.

The duration and degree of hypoperfusion determines the presence of EICs <sup>98</sup>. Although the presence or absence of different types of EICs cannot reliably differentiate between irreversibly damaged brain tissue and penumbra, the isolated focal swelling is associated with the penumbra and the parenchymal hypoattenuation with the infarct core and a poor functional outcome <sup>99-103</sup>. Frank parenchymal hypoattenuation indicates irreversible ischemic damage <sup>101</sup>. The extent of these changes is predictive of the risk of hemorrhagic transformation <sup>71, 73, 104, 105</sup>. Evaluation of this risk is especially important when deciding whether a patient is eligible for revascularization therapies. In the ECASS I and II trials, the involvement of more than one-third of the MCA territory with EICs and/or frank hypoattenuation was considered a contraindication for reperfusion therapy due to an increased risk of hemorrhagic transformation <sup>51</sup>. This rather arbitrary criterion that is challenging to interpret has been widely adopted <sup>106-108</sup>. However, the relationship between EICs and adverse outcomes following IVT is not straightforward. It appears that IVT administered in the presence of early infarction signs does not induce a poorer outcome than that predicted by the early signs alone <sup>97</sup>.

#### *2.2.1.1 Alberta Stroke Program Early CT Score*

To overcome the issues associated with the “one-third of the MCA territory” criterion, an algorithmic, topographic system called the Alberta Stroke Program Early CT Score (ASPECTS) was developed <sup>104, 109, 110</sup>. ASPECTS is a weighted scoring scheme that allows quantitative assessment of the extent of acute ischemic changes in the anterior circulation. Only parenchymal hypoattenuation is considered a finding in the scoring process. Each hemisphere is divided into 10 regions (Figure 5) comprising the caudate nucleus, lenticular nucleus, insula, internal capsule, inferior anterior MCA territory, inferior middle MCA territory, inferior posterior MCA territory, superior anterior MCA territory, superior middle MCA territory, and the superior posterior MCA territory in two axial sections at the level of the basal ganglia (the ganglionic level) and the corona radiata (the supraganglionic level). Each of these regions is given a score of 1 point. This point is deducted if the region shows acute ischemic changes. Thus, negative findings yield a score of 10, and

extensive ischemia covering the entire MCA region yields a score of 0. On the basis of a volumetric assessment, if the ASPECTS score is  $\leq 6$ , then more than one-third of the MCA territory is affected, on average. When 3 or more of the ASPECTS regions show ischemic changes (ASPECTS  $\leq 7$ ), the patient is unlikely to achieve an independent functional outcome. Overall, ASPECTS applied to NCCT images is predictive of the clinical outcome, the effectiveness of IVT and IAT and the rate of hemorrhagic complications but is not sufficiently accurate for triaging IVT candidates <sup>110-115</sup>. The ASPECTS paradigm has also been adapted to the posterior circulation <sup>116</sup>. However, when applied to NCCT, this score did not predict functional independence <sup>116</sup>.



**Figure 5:** Axial NCCT images showing the MCA territory regions as defined by ASPECTS. The ganglionic and the supraganglionic levels are indicated using white

brackets. C- Caudate, 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, rostral to the basal ganglia. Subcortical structures are allotted 3 points (C, L, and IC). The MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5 and M6). The image is adapted from [www.aspectsinstroke.com](http://www.aspectsinstroke.com).

### 2.2.2 Computed tomography angiography

The second modality acquired in a multimodal protocol is typically the CTA. In general, a volume from the aortic arch up to the vertex of the skull is covered, and thin-section slices of isotropic spatial resolution are calculated<sup>117</sup>. This method enables the reconstruction of two-dimensional (2D) reformatted images in arbitrary planes, maximum intensity projection (MIP) images and three-dimensional (3D) images and provides detailed information on the cerebral vasculature that is comparable with that obtained using digital-subtraction angiography (DSA)<sup>118-122</sup>. Both intracranial and extracranial vessels can be evaluated in a single study. Thus, the vascular anatomy and the collateral circulation can be visualized, the pathology of the vessel wall that alters the diameter of the vessel lumen can be evaluated, and intravascular thrombi can be identified<sup>117, 123</sup>. CTA can detect large- and small-vessel occlusions and stenoses highly accurately (95-99%) both intracranially and extracranially<sup>123-126</sup>. The location and the volume of the thrombi are independent prognostic factors in acute ischemic stroke with proximal, high-volume clots predicting poor clinical outcomes compared with distal, low-volume clots. This finding is related to the rate of recanalization, which is lower in proximal-vessel positions. In addition, the location and volume of the clot limits the effectiveness of IVT in dissolving the occluding thrombus<sup>127-138</sup>. This information can be used to guide therapeutic decision making and the choice between IVT, intra-arterial interventions or refraining from revascularization therapy.



### 2.2.2.1 Clot Burden Score

The Clot Burden Score (CBS) is an imaging score based on the location and the extent of the thrombus detected using CTA<sup>135, 139</sup>. In this scoring scheme, a score of 0 to 10 is assigned on the basis of the number and location of arterial segments affected in the anterior circulation (Figure 6). Similar to ASPECTS, the absence of an occlusion is scored with 10 points and points are deducted if non-opaque arterial segments are shown by the contrast agent. CBS is correlated with the clinical and radiological outcomes<sup>134, 135, 139</sup>. Patients with higher CBS values are more likely to experience independent functional outcomes and less likely to die. Correspondingly, the final infarct volumes are smaller and the rates of hemorrhagic transformation lower.



**Figure 6:** Schematic representation of the Clot Burden Score (CBS). One or two points each are subtracted from a total score of 10 when no contrast opacity is detected using CTA in the infraclinoid ICA (1 point), supraclinoid ICA (2 points), proximal M1 segment (2 points), distal M1 segment (2 points), M2 segment branches (1 point each) and the A1 segment (1 point), as indicated by the numbers next to the corresponding vessel segments. CBS applies only to the symptomatic hemisphere. From *Puetz et al.*<sup>135</sup>

#### 2.2.2.2 *Boston Acute Stroke Imaging Scale*

The Boston Acute Stroke Imaging Scale (BASIS) is an imaging score that combines arterial and parenchymal imaging findings<sup>140</sup>. BASIS is a binary, 2-step classification scheme where patients are designated as having either a major or minor stroke. If the distal ICA, the proximal MCA (segments M1 and M2) or the basilar artery is occluded or if there is a significant ischemic lesion either in NCCT or DWI based on the one-third of the MCA rule, ASPECTS or bilateral pons or bithalamic involvement, the stroke is considered major. Otherwise, the stroke is designated as minor. BASIS is correlated with mortality, short-term clinical outcome evaluated at discharge from the hospital, and the length and costs of hospitalization with major stroke predicting poor outcomes and higher costs<sup>133, 140</sup>.

#### 2.2.2.3 *Evaluation of the leptomeningeal collateral circulation*

Leptomeningeal collateral circulation occurs due to the arterio-arterial connections between the major cerebral artery systems that enable the filling of pial arteries distal to the site of vessel occlusion. Sufficient flow through the collaterals allows the brain tissue to remain viable even if the normal antegrade flow supplying the tissue volume is diminished or interrupted<sup>141-143</sup>. This additional blood flow reduces the baseline infarct core and the expansion of the core, decreases the risk of hemorrhagic transformation and increases the odds of a good clinical outcome in-hospital, at discharge and six months after the stroke<sup>123, 144-152</sup>. A multitude of heterogeneous methods have been used to identify and score collateral circulation including classification schemes utilizing CTA<sup>123, 138, 148, 152, 153</sup>. However, currently, a systematic evaluation of the extent of the collateral pathways is seldom performed in the acute-stroke imaging workup.

#### 2.2.2.4 *Computed tomography angiography source images*

Unprocessed CTA source images (CTA-SI) can be used to predict whether the tissue volume will infarct regardless of whether recanalization is achieved<sup>154</sup>. CTA-SI is clearly superior to NCCT in the detection of the infarct core and in the prediction of infarct extension, symptomatic hemorrhagic complications and clinical

outcomes<sup>60, 112, 126, 155-159</sup>. CTA-SI obtained using a 16-row or shorter detector-length scanners essentially capture the steady state of the contrast agent, which approximates the cerebral blood volume and irreversible ischemic changes<sup>160, 161</sup>. Wider detector lengths and faster image-acquisition times make CTA-SI more blood-flow weighted, and thus, it increasingly reflects the at-risk tissue rather than only the tissue that will undergo necrosis<sup>112, 162-164</sup>.

### 2.2.3 Computed tomography perfusion

The final imaging modality obtained in a typical multimodal protocol is CTP. A perfusion study enables the quantification of capillary, tissue-level blood flow. CTP is a dynamic imaging modality where the first pass of a bolus of iodinated contrast-agent is traced through the brain parenchyma by repeated scanning of the volume of interest immediately following the injection<sup>165</sup>. This method provides insight into the physiology and pathophysiology of cerebral hemodynamics. Based on a multi-compartmental tracer kinetic model, CTP allows the calculation of a variety of parameters that reflect different aspects of the hemodynamic state<sup>7, 166, 167</sup>:

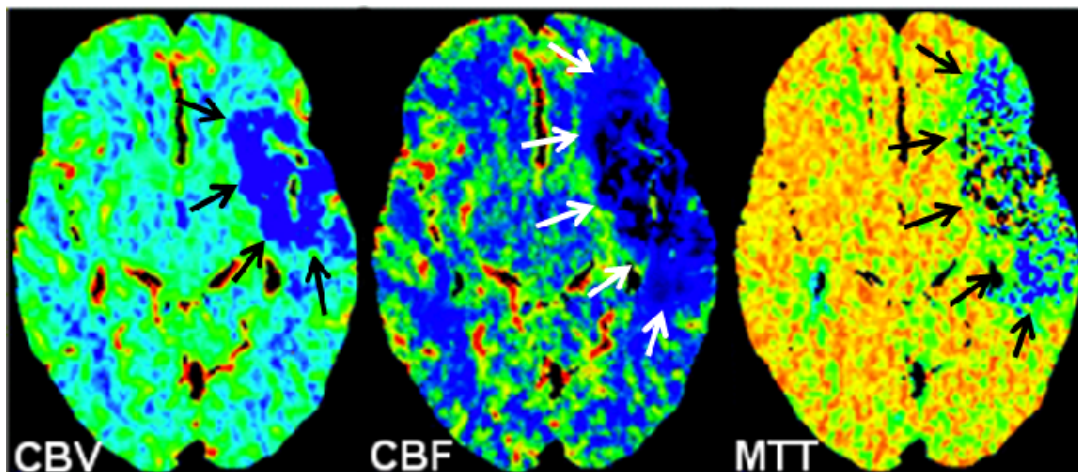
1. **Cerebral Blood Flow (CBF)** indicates the volume of blood moving through a brain volume (mass) of interest per unit time ( $[CBF] = \text{ml}/100 \text{ g}/\text{min}$ ).
2. **Cerebral Blood Volume (CBV)** describes the total volume of blood in a given brain volume (mass) of interest ( $[CBV] = \text{ml}/100 \text{ g}$ ). This volume includes the intracellular, intravascular and extravascular interstitial spaces.
3. **Mean Transit Time (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. MTT can be calculated from the CBF and CBV with the central volume principle<sup>168</sup>:  $MTT = CBV/CBF$ .
4. **Time to Peak (TTP)** is defined as the time from the beginning of the arterial enhancement to the peak of the enhancement curve ( $[TTP] = \text{s}$ ).

In essence, two mathematical approaches have been applied in calculating the CBF and MTT from raw measurement data obtained using a CT scanner: the

deconvolution and non-deconvolution methods<sup>166</sup>. Non-deconvolution methods are based on the application of Fick's principle of conservation of mass to a given region of interest. The CBF can be calculated using the maximum slope technique. Non-deconvolution methods make use of simplifying assumptions that decrease the accuracy of the results. Deconvolution methods attempt to correct the effect of contrast delay and dispersion. There are multiple deconvolution techniques, and the singular value decomposition (SVD) has gained widespread acceptance. Deconvolution methods enable the creation of accurate, quantitative perfusion parametric maps. The concept and calculations have been validated in humans using xenon-CT, positron emission tomography (PET) and MRI and in animals, using microsphere studies. For a comprehensive theoretical and technical analysis, see the series of reviews by *Konstas et al.*<sup>166, 167, 169</sup>.

The main goal of a stroke perfusion study is to provide an assessment of the viability of the ischemic tissue, i.e., to identify the irreversibly damaged tissue (the infarct core), the tissue that is at risk for progression to infarction if reperfusion is not achieved (the penumbra) and the normally perfused or hyperemic tissue<sup>167, 170, 171</sup>. This classification stems from experimental studies that characterized two functional thresholds for CBF: 1) below which cortical function ceases without an increase in extracellular potassium or reduction in pH (the penumbra) and 2) below which there is disruption of cellular integrity (the core)<sup>172</sup>. These thresholds have been correlated with advanced neuroimaging findings—the perfusion parametric maps—to define a more clinically relevant *operational penumbra*, which identifies hypoperfused but potentially salvageable tissue<sup>170, 173, 174</sup>. In the simplest terms, the operational penumbra is the mismatch (subtraction) volume between the CBF or MTT (or TTP) and the CBV (or DWI), in which the CBV (or DWI) lesion reflects the infarct core and the CBF or MTT (or TTP) lesion reflects the boundaries of the hypoperfused penumbral tissue (Figure 7)<sup>167</sup>. This concept was initially validated for MRI, and later MRI and CT results were correlated (see section 2.2.4 for a discussion of the DWI-PWI mismatch in MRI)<sup>154, 175</sup>. However, standardization or validation of the quantitative perfusion parameter map values has not been achieved for acquisition and postprocessing across different vendor platforms or even across different platforms from the same vendor<sup>176, 177</sup>. Thus, numerous absolute threshold values have been proposed for different perfusion parameters in multiple studies.

The use of relative values obtained by comparing to the contralateral, uninvolved side can, in part, circumvent this problem<sup>178-180</sup>. However, even the relative values vary with postprocessing technique, and the interpreter must be familiar with the software and hardware used<sup>179, 180</sup>. The perfusion parameters that best define the core and the penumbra remain under discussion. This task is challenging, as both regions are dynamic in character because of the nature of the disease process. Recent reports suggest that appropriately thresholded relative and absolute MTT values optimally distinguish the at-risk penumbra and that thresholded CBF values may assess the core more accurately than CBV cut-offs<sup>176, 179, 180</sup>. Depending on the postprocessing technique used, relative MTT thresholds ranged between 150 and 249% and relative CBF values were between 16 and 44%. Relative CBVs ranged between 56 and 60%<sup>179</sup>. ASPECTS has been validated for CTP parametric maps, which provides another method for quantifying CTP findings in the anterior circulation including calculation of the perfusion mismatch<sup>113, 181, 182</sup>.



**Figure 7:** A patient suffering from an acute stroke of the left MCA region who displays both MTT and CBF–CBV mismatch. The CBV lesion is obviously smaller than the MTT or the CBF lesion. Arrows mark the boundaries of the perfusion defect in the three parametric maps.

CTP has the potential to serve as a surrogate marker for stroke severity and as an independent predictor of clinical outcome. Multiple studies utilizing a variety of imaging methods have established a strong correlation between the size of the core upon admission and the clinical outcome<sup>167, 183</sup>. Patients with a core lesion volume  $\geq 70$ -100 ml show poor outcomes regardless of therapy or recanalization status<sup>184-</sup>

<sup>186</sup>. It is unclear how large a clinically significant penumbra should be. An arbitrary mismatch ratio (for example, defined as  $\text{Volume}_{\text{MTT}}/\text{Volume}_{\text{CBV}}$ ) –cut-off of 1.2 or 2.0 has been used in most studies <sup>167</sup>. The degree of early reduction in CBF and CBV and, interestingly, the size and severity of the DWI lesion are correlated with the risk of a hemorrhagic complication <sup>76, 77, 187-189</sup>. CTP can identify potentially salvageable brain tissue in the context of IVT <sup>190</sup>.

A major disadvantage of CTP in most currently used scanners is the limited z-axis coverage. According to a recent report, 75 mm of z-axis coverage was required to reliably detect a perfusion mismatch ratio of 2.0 in the anterior circulation, whereas 50 mm was sufficient when a ratio of 1.2 was used <sup>191</sup>. Newer 256- and 320-row scanners can achieve whole-brain coverage <sup>192, 193</sup>. CTP is insensitive to acute lacunar and small, deep white-matter lesions <sup>194, 195</sup>. CTP may overestimate the size of the CBV lesion <sup>190, 196</sup>. In contrast, CBV and CBF may underestimate the core due to post-ischemic hyperperfusion <sup>197</sup>. If not properly thresholded, the MTT and CBF defects include a region of reactive benign oligemia that is not at risk of progressing to infarction <sup>180, 198-200</sup>. CTP involves an intravenous injection of 35-60 ml of iodinated contrast material. However, this procedure does not appear to increase the incidence of contrast-induced nephropathy <sup>201</sup>. The patient also receives a dose of ionizing radiation. If the CTP protocol has been set-up correctly, the dose is slightly higher than that used for NCCT <sup>167</sup>. The complex post-processing may be prone to operator errors <sup>202</sup>, which can be counteracted with training and quality control <sup>203</sup>.

#### 2.2.4 Comparison of multimodal CT and stroke MRI

Multimodal MRI offers an alternative method to study acute stroke. A typical stroke MRI protocol includes diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), MR angiography (MRA), gradient-echo (GRE) and fluid-attenuated inversion recovery (FLAIR) imaging <sup>204, 205</sup>. GRE and FLAIR are used to detect intracranial hemorrhage, and MRA provides information on major-vessel patency. DWI is used to detect the ischemic process and to characterize the extent of the infarct core <sup>206, 207</sup>. PWI allows the assessment of cerebral hemodynamics using the

perfusion parameters described in section 2.2.3<sup>208, 209</sup>. The DWI-PWI mismatch estimates the size of the operational penumbra<sup>209-211</sup>.

MRI is superior to NCCT in sensitivity and accuracy of detection of acute ischemia and hemorrhage<sup>212, 213</sup>. The anatomical and pathophysiological information obtained with CTA and CTP and the clinical utility of these data are comparable to MRI<sup>160, 175, 214-217</sup>. Theoretically, CTP provides better approximation of the true quantitative perfusion values<sup>117, 205</sup>. As with CTP parameters, DWI can overestimate the size of the infarct core but appears superior to any CT option<sup>205, 218</sup>. Multimodal CT is readily available, is faster and cheaper to perform, is less sensitive to motion artifacts and has fewer contraindications<sup>7, 117, 205</sup>. However, MRI typically has better z-axis coverage and does not involve exposure to ionizing radiation or iodinated contrast-agents<sup>117, 205</sup>.

## 2.2.5 The role of multimodal CT in acute ischemic stroke

Imaging plays a central role in the evaluation of patients with acute stroke. The current American Heart Association (AHA) guidelines for imaging of acute ischemic stroke recommend the use of NCCT or MRI to detect ICH and frank ischemic changes<sup>219</sup>. However, the guidelines state that in patients presenting within 3 h of symptom onset, NCCT alone shows suboptimal detection rates of ischemic changes and that more definitive diagnoses can be obtained using DWI or CTA-SI if they do not unduly delay the timely administration of r-tPA. A multimodal protocol takes 2 to 10 min to complete and does not significantly delay the administration of IVT<sup>220, 221</sup>. In addition, the authors of the guidelines reported that a vascular study—CTA, MR angiography (MRA) or DSA—is “probably indicated” and that patients who are more than 3 h from symptom onset should be examined using a DWI or a CTA-SI and also using vascular imaging and perfusion studies, particularly if an intra-arterial intervention is contemplated. Furthermore, an incremental protocol that includes CTP enhances stroke diagnostics and inter- and intraobserver agreement<sup>8</sup>. Overall, the guidelines assert that progress in the treatment of the acute-stroke patient has been modest, and it is apparent that the use of NCCT alone is insufficient to properly triage patients to different treatments.

A multimodal protocol enables diagnostics beyond excluding intracranial hemorrhage and provides information that allows more diverse clinical decision making with the intention of selecting patients for different revascularization therapies<sup>7, 45, 117, 166, 167, 219</sup>. A multimodal protocol enables questions, such as whether there are intravascular thrombi that can be targeted for thrombolysis, whether there is a sizable core of critically ischemic tissue that is irreversibly infarcted, whether there is adequate collateral circulation, and whether there is a penumbra of severely ischemic but potentially salvageable tissue, to be answered. Patients outside the currently accepted therapeutic time window for revascularization therapies or who have an unknown duration of symptoms can potentially be treated. The risk of a hemorrhagic complication can be evaluated more accurately. Patients can be more sensibly triaged in trials of experimental therapies, such as sonothrombolysis, mechanical thrombectomy using new devices, induced hypertension therapy and different neuroprotective strategies. One report suggests that it may be possible to increase the proportion of good functional outcomes among IVT patients by using multimodal CT upon admission<sup>222</sup>. Multimodal imaging is an essential component in the shift from time window-based decision making to management based on the characterization of the ischemic tissue. The steps to reach this paradigm change have been traced in a recent multidisciplinary consensus statement<sup>223</sup>.



### 3. AIMS OF THE STUDY

The aims of this study are as follows:

- 1) To study the potential of ASPECTS as applied to CTP parametric maps in the characterization of acute ischemic stroke and the prediction of clinical and imaging outcomes. In particular, to test the hypothesis that the CTP ASPECTS mismatch, which is the difference between MTT and CBV ASPECTS scores, may be useful for identifying patients that could benefit from IVT [I].
- 2) To correlate the anatomical information conveyed by BASIS and CBS to the dynamic information of the CTP parameters in order to determine how these variables predict the clinical outcome and whether a derived parameter combining both CTA and CTP data could provide increased value for the prediction of the clinical outcome of acute ischemic stroke in the context of IVT [II].
- 3) To analyze in depth the impact of the location of the clot, visualized in the anterior circulation using CTA, on the clinical outcome in acute ischemic-stroke patients treated with IVT [III].
- 4) To compare the technical quality of the CTP studies performed using a 64-row or a 16-row scanner and to analyze the differences in the ability to detect perfusion defects between the two scanners in the context of acute ischemic stroke [IV].

# 4. SUBJECTS, MATERIALS AND METHODS

## 4.1 Overview

All studies [I-IV] had retrospective observational cohort design. The clinical and imaging data of consecutive patients, who were admitted to Tampere University Hospital between January 2004 and December 2007 because of acute (duration < 3 h) stroke symptoms and who after evaluation received IVT to treat acute ischemic stroke, were collected and analyzed.

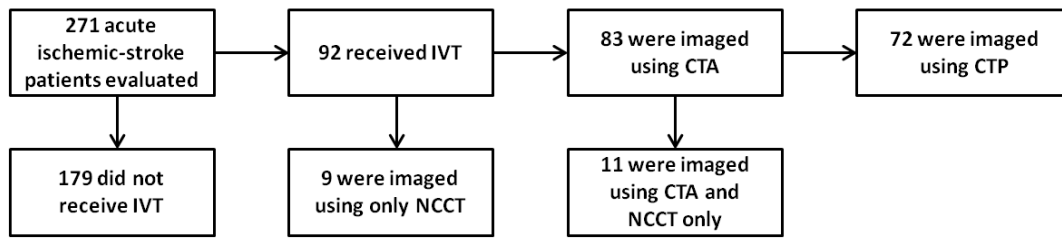
The initial imaging evaluation consisted of NCCT, CTA and CTP. The selection of patients to receive thrombolytic therapy was based on institutional guidelines, which did not have CTP or CTA parameters as exclusion or inclusion criteria. To rule out possible selection bias caused by CTA and CTP studies, a sample population of 179 acute-stroke patients who did not receive IVT in 2007 was reviewed. The indication to exclude a patient from IVT was documented carefully. In one case, the decision to exclude a patient was based on the results of a CTP study (extremely poor technical quality of the admission NCCT and over one-third MCA lesion in the CBV map). In addition, we discovered three cases in which the admission NCCT was initially erroneously interpreted as negative, the results reported orally to the stroke neurologist, a review and a correction was conducted after the CTP maps had been calculated and analyzed some minutes later, and the decision to administer thrombolytic therapy was withdrawn. A follow-up NCCT was performed for all patients at 24 h after the administration of the thrombolytic agent.

IVT was administered according to guidelines from the American Heart Association (AHA) <sup>224</sup>: Actilyse (Boehringer-Ingelheim, Ingelheim, Germany), total dose 0.9 mg/kg, was administered in a 10% bolus with the remaining 90% administered as a continuous infusion over 1 h.

## 4.2 Subjects, study population and baseline characteristics

### 4.2.1 Patients who received IVT to treat acute ischemic stroke in 2007 [I and II]

The clinical and imaging data from 92 consecutive patients, who were admitted to Tampere University Hospital between January 2007 and December 2007 due to acute (duration < 3 h) stroke symptoms and who received intravenous r-tPA to treat acute ischemic stroke after evaluation, were collected. In total, 271 patients suffering from acute ischemic stroke were evaluated as candidates for thrombolytic therapy during this period. A full multimodal imaging evaluation was successfully completed in 72 of the 92 patients (78%) who received thrombolytic therapy. Nine patients (10%) were evaluated using NCCT alone, and 11 patients (12%) were evaluated using NCCT and CTA due to a previously known hypersensitivity to the contrast agent, chronic renal failure, imminent closure of the three-hour time window or movement artifacts that rendered some of the imaging data uninterpretable (Figure 8). Altogether, 83 patients (90%) were imaged using CTA. The median age of the patients was 71 years (interquartile range 58-80 years, 42 female). Based on the clinical features and the imaging studies, in 11 of the 92 patients evaluated, the ischemic episode involved the posterior circulation (8 cases of thrombosis of the basilar artery). The other episodes were considered to involve the anterior circulation. The thrombosis was demonstrated with CTA in 37 cases (45% of the CTA studies and 40% of all patients). In 40 cases (56%) of the 72 evaluated using CTP, a perfusion defect was detected in the ASPECTS levels. An additional 6 perfusion defects were found outside the ASPECTS levels. A perfusion pattern implying acute ischemia was detected in half of the cases involving the posterior circulation when CTP was conducted. In total, a perfusion defect was demonstrated in 64% of the CTP scans (50% of all patients). The median NIHSS upon admission was 7 points (56.0% < 8, 18.7% > 15; interquartile range 4-12). The median mRS was 1 point preictally.



**Figure 8:** The population and subpopulations of studies I and II.

#### 4.2.2 Patients who received IVT to treat acute ischemic stroke from 2004 to 2007 [III]

Altogether, 313 anterior- or posterior-circulation ischemic-stroke patients from January 2004 to December 2007 were treated with IVT and had a 3-month follow-up after thrombolysis. CTA was performed on 283 patients (90%). The inclusion criteria were acute anterior-circulation vessel occlusion confirmed with CTA and IVT treatment. There were 105 (37%) patients who met the inclusion criteria. Thrombi were not detected in 140 (50%) cases, and 38 (13%) patients showed a posterior-circulation clot. The median age of the patients was 69 years (interquartile range 54-83 years; 45 female). The median NIHSS upon admission was 13 points (interquartile range 4-12) and 6 points (interquartile range 0-20) at 24 h after IVT administration. The median NCCT ASPECTS upon admission was 10 points (interquartile range 8-10). The median time from imaging to the initiation of IVT was 35 minutes. The median preictal mRS was 1. A 3-month mRS was missing from one patient who was discharged to another district and was not contacted for phone interview. At 24 h, a local hemorrhagic complication or parenchymal hemorrhage distant to the site of the infarct was detected in 7 cases (7%). According to the 5-subtype Causative Classification of Stroke (CCS) scheme<sup>12</sup>, large-artery atherosclerosis was the etiology in 23 (22%) cases; cardiac embolism in 55 (52%) cases; and other uncommon cause in 6 (6%) patients. There were no cases of small-artery occlusion, and 21 (20%) patients had an ischemic stroke of undetermined cause. Sixty-nine percent of the patients had hypertension, 17% suffered from diabetes, 41% had atrial fibrillation, and 33% had coronary artery disease.

### 4.2.3 Patients who received IVT to treat acute ischemic stroke from 2006 to 2007 [IV]

Clinical and imaging data were analyzed of 140 consecutive patients who were admitted to Tampere Hospital between January 2006 and December 2007 due to acute (duration < 3 h) stroke symptoms, who were imaged with NCCT and CTP and who subsequently received intravenous r-tPA. The patients were scanned using either a 64-row or a 16-row scanner located in neighboring rooms. Although the patients were not explicitly randomized for imaging with either scanner, the selection of the scanner was effectively random. The median age of the patients was 71 years (interquartile range 58–80 years; 45% female). Based on the clinical features and the imaging data, in 16 of the 140 patients evaluated (11%), the ischemic episode involved the posterior circulation. The median NIHSS score upon admission was 7 (interquartile range 4–12; 54% < 8, 13% > 15). The median mRS was 1 preictally. There were no significant differences in age, admission NIHSS, prestroke mRS or onset-to-treatment times between the patients imaged with the 64-row and those examined with the 16-row scanner. There were significantly fewer females in the 16-row group (36% vs. 55%).

## 4.3 Clinical variables

Baseline characteristics included antiplatelet therapy (aspirin, dipyridamole or clopidogrel) prior to stroke, age, gender, prestroke functional status, time from both symptom onset and imaging to the initiation of IVT and the stroke clinical risk factors hypertension, diabetes, coronary heart disease, and atrial fibrillation. These data were collected from patient records. Admission clinical evaluation results had been prospectively stored according to a specific protocol and comprised blood pressure, the NIHSS score at the time of initiation of IVT and whether an intravenous antihypertensive was used. The admission hemoglobin, 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. A follow-up NIHSS score was determined for all patients at 24 h after the administration of the

thrombolytic agent. The CCS scheme was used by a certified CCS-rater to assess stroke etiology.

A Modified Rankin Scale (mRS) score, which was scored three months after the stroke, was the primary clinical outcome measure in all studies. In the years from 2004 to 2005, the three-month mRS score was prospectively recorded by a neurologist experienced in stroke management during a follow-up visit, and from 2006 to 2007, the three-month mRS score was prospectively recorded by a stroke neurologist during a phone interview. Death during the primary hospitalization and discharge from the neurology ward to a rehabilitation facility were both considered to signify unfavorable clinical outcomes upon discharge. These data were used as secondary clinical outcome measures in study III.

#### 4.4 Imaging parameters

NCCT scans were obtained using two different multidetector scanners: a General Electric LightSpeed 16-slice scanner (GE Healthcare, Milwaukee, WI) and a Philips Brilliance 64-slice scanner (Philips, Cleveland, OH). Brain NCCT was performed using the following parameters: 64-row, 120 kV, 430 mAs, collimation 12 x 1.25 mm, rotation 1.5 s and 16-row, 120 kV, 320 mAs, collimation 16 x 1.25 mm, rotation 1s. Contiguous slices were reconstructed to the thickness of 5 mm over the entire scanning range (64-row) or to the 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 mAs (using dynamic tube current modulation), collimation 64 x 0.625 mm, rotation 0.75 s, pitch factor 0.923 (64-row) or 120 kV, 160 mAs, collimation 16 x 0.625 mm, rotation 0.8 s, pitch factor 0.938 (16-row). Contiguous slices were reconstructed to the thickness of 0.9 mm with a 0.45 mm overlap (64-row) or to the thickness of 1.25 mm (16-row). The contrast agent (iobitridol, Xenetix, 350 mgI/ml, Aulnay-sous-Bois, France) was administered via an antecubital 18G cannula using a double-piston power injector at

a flow rate of 4 ml/s using 70 ml of contrast agent followed by a 50-ml saline flush. Manual bolus triggering was used.

CTP was performed using the parameters 80 kV, 200 mAs (effective), collimation 32 x 1.25 mm, rotation 0.4 s (64-row) or 80 kV, 200 mAs, collimation 8 x 2.5 mm, and rotation 1s (16-row). A total of 120 slices covering 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 covering a range of 20 mm were generated in 50 s in a stationary table position (16-row). Contiguous slices were reconstructed to the thickness of 10 mm (64-row) or to the thickness of 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 cranial and caudal 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 18G cannula using a double-piston power injector at a flow rate of 5 ml/s using 60 ml of contrast agent followed by a 40 ml saline flush.

## 4.5 Image analysis

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). CTA images were reviewed by examining both the raw data and the MIP images. Parametric perfusion maps were generated using the CT Perfusion 3 software, 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 a phenomenon caused by noise sources, was not recorded as noise in this context. 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 2.2.1.1. The location of the image section closest to an ASPECTS level was considered suboptimal if the location did not exactly correspond with the reference level described in the literature<sup>109</sup> but did allow 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 ASPECTS scored for the maps. When characterizing a perfusion defect, we used a semiquantitative approach where the presence of a perfusion defect was determined visually from color-coded maps by comparing the appearance of the affected location to that of the healthy tissue on the contralateral hemisphere. On the basis of theoretical considerations and to increase 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 > 7s (or mean CBV < 2.5 mL/100 g; adapted from *Wintermark et al.*<sup>225</sup>). Further validation was performed by requiring the mean relative MTT > 249% for the penumbra and the mean relative CBF < 31% and the mean relative CBV < 58% for the infarct core compared with the contralateral side<sup>179, 180</sup>.

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 two parts of equal length: the proximal and the distal half. The principles of the Clot Burden Score (CBS) scoring system and the assignment of BASIS are described in sections 2.2.2.1 and 2.2.2.2.

The examinations were reviewed in the order NCCT, CTA and finally CTP, which parallels 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 BASIS, NCCT and CTP ASPECTS were assigned by two radiologists (N.S. and A.L. or J.H., see study I). In cases where the scoring differed, a consensus score was agreed 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 (N.S.). The boundaries of the affected areas were determined visually, and absolute- and relative-value thresholds described above were applied. Volumes were calculated by multiplying the measured area by the slice thickness.

Intraclass correlation coefficients (ICC) between a staff radiologist (N.S.) and an experienced neuroradiologist (J.H.) 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%. The interobserver agreement index for BASIS was 95%. Cohen's kappa for the location of the clot was 0.94.

## 4.6 Statistical analyses

Data were analyzed using SPSS versions 17 and 18 (SPSS Inc., Chicago, IL). A biostatistician was consulted where deemed necessary. Patients with  $mRS \leq 2$  (primary clinical outcome measure) at the 3-month follow-up or those discharged to home from the neurology ward (secondary clinical outcome measure) were considered to have experienced favorable clinical outcomes. P-values of less than 0.05 were considered statistically significant. In study I, the difference between the 3-month postictal and the preictal mRS was used as an indicator of a good clinical outcome, as it more accurately reflects the disease load inflicted by the current episode. As expected from the definitions,  $\Delta mRS$  and mRS were highly correlated ( $r = 0.85$ ), and the offset between  $\Delta mRS$  and mRS was generally very small or nonexistent. The median preictal mRS in the research population was 1. The threshold for a good clinical outcome was deemed to be  $\Delta mRS \leq 1$  to enable comparison with the  $mRS \leq 2$  threshold.

Group comparisons were performed using Fisher's exact test [I]; the Mann-Whitney U test and Fisher's exact test [II]; Student's t-test, the Chi-squared test, the Kruskal-

Wallis, and Fisher's exact test [III]; and Student's t-test, the Mann-Whitney U test, the Chi-squared test and Fisher's exact test [IV].

Binary logistic regression modeling using either the primary or secondary clinical outcome measures as the dependent variable was repeated for different variables of interest. In study II, age and gender were treated as potential confounders and were controlled for by treating them as covariates. One variable of interest was included in the model at a time. In study III, NIHSS, age, gender, time from onset to treatment and clinical risk-factors were examined as potential confounders and were tested both in univariate models and with the location of clot in the model. The final regression model retained the statistically significant and theoretically relevant confounders. The calibration of the models was evaluated using the Hosmer-Lemeshow test and the discrimination using the C statistic. The odds ratio (OR) at a 95% confidence interval (CI) was calculated for each covariate.

Pearson correlation coefficients and 2-tailed significance levels were calculated in all correlation analyses. Differences between correlation coefficients were examined using Steiger's Z-test.

After excluding cases of thrombosis of the basilar artery, receiver-operating characteristic curves (ROC) were computed and Youden indices were evaluated to select optimal threshold values for imaging parameters in predicting the dichotomized good clinical outcome [I, II]. Differences between areas under the curves (AUCs) of ROCs were tested using the Hanley-McNeil procedure.

Diagnostic sensitivities and specificities and confidence intervals were calculated according to their textbook definitions. Normal and extended McNemar tests were used to compare the overall diagnostic performance, the sensitivities and the specificities.

Where necessary, the Bonferroni correction was applied to adjust for multiple comparisons.

## 5. RESULTS

### 5.1 CTP ASPECTS, CBS, and BASIS in the evaluation of acute ischemic stroke [I, II]

The diagnostic performances of ASPECTS applied to CTP parametric maps, BASIS and CBS were studied in the context of IVT. It was further hypothesized that CTP ASPECTS mismatch may be useful in identifying patients that potentially benefit from thrombolytic therapy and that a derived parameter combining both CTA and CTP data may best predict clinical outcomes.

#### 5.1.1 CTP ASPECTS parameters predict the final infarct volume and the clinical outcome [I]

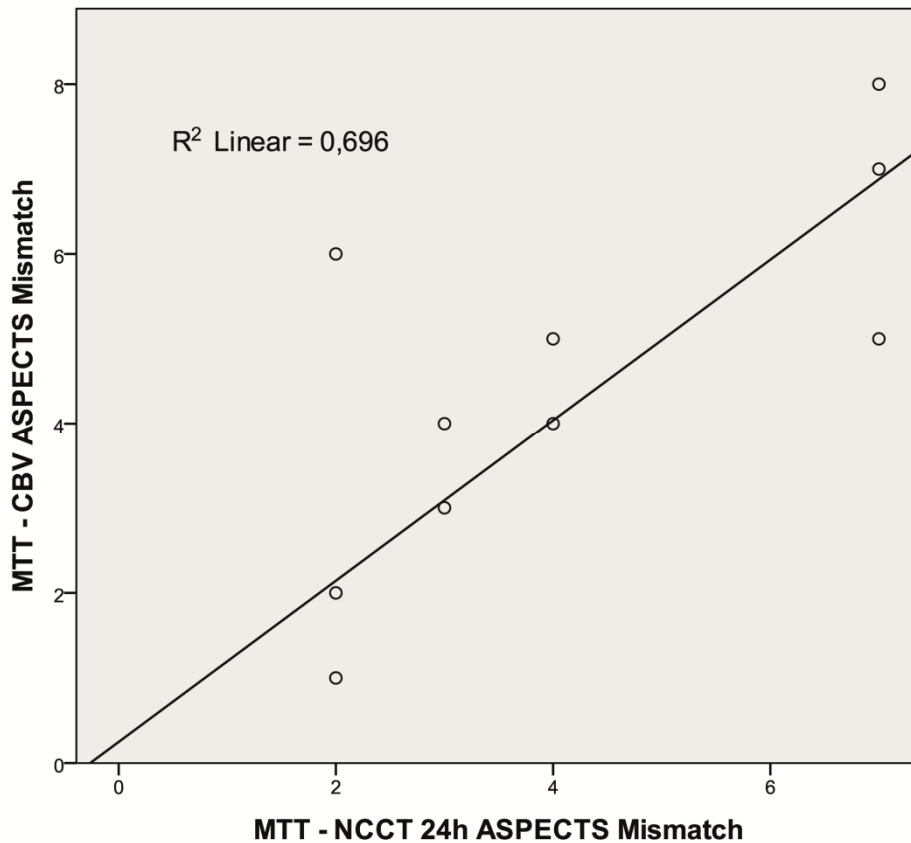
To assess the prognostic performance, the correlations between different ASPECTS parameters, the final infarct volume and the clinical outcome (measured by the  $\Delta$ mRS, which is the difference between the postictal and preictal mRS scores) were studied. When both anterior- and posterior-circulation strokes were included in the analysis ( $n = 92$  for NCCT and  $n = 72$  for CTP), the final infarct volume correlated inversely with all ASPECTS scores, and the absolute values of the correlation coefficients having the order 24 h follow-up NCCT (NCCT 24 h) > CBV > admission NCCT (NCCT 0 h) > MTT. In the case of the clinical outcome, the correlations were ordered NCCT 24 h > CBV > MTT > NCCT 0 h. When the anterior-circulation ischemic events were included in the analysis ( $n = 81$  for NCCT and  $n = 66$  for CTP), correlations between the ASPECTS scores and the clinical outcome were strengthened, although a similar order was maintained. This change is due primarily to the generally poor prognosis of the posterior-circulation events that were excluded and the definition of ASPECTS addressing only the anterior circulation. In the CTP ASPECTS mismatch subgroup ( $n = 36$ ), the correlation coefficients between the ASPECTS scores and the clinical outcome were higher,

whereas the correlations between the ASPECTS scores and infarct volume remained essentially unchanged. All correlations described were statistically significant. Overall, the correlations between the MTT and CBV scores and the clinical outcome were stronger than that of the admission NCCT score and the clinical outcome, suggesting that the CTP parameters may classify the patients more accurately. However, only the CBV score displayed a statistically significant difference from the admission NCCT score in all subgroups studied ( $p = 0.01-0.02$ ).

The dichotomized thresholds for a good clinical outcome ( $\Delta mRS \leq 1$ ) in anterior-circulation stroke were calculated for the CTP and NCCT ASPECTS scores using ROC curves.  $CBV \geq 7$  (AUC = 0.72) was the most accurate in identifying patients with a good clinical outcome and thus those who potentially benefited from IVT. This parameter showed 100% sensitivity and 44% specificity, and no patients with a good clinical outcome were in the  $CBV < 7$  group. Although statistically robust, the  $MTT \geq 4$  (AUC = 0.68) and  $NCCT\ 0\ h \geq 10$  (AUC = 0.66) thresholds were outperformed. However, the differences between the AUCs were not statistically significant.

### 5.1.2 CTP ASPECTS mismatch identifies potentially salvageable ischemic tissue [I]

A mismatch between the NCCT 24 h and the MTT ASPECTS scores may be used to estimate the amount of tissue salvaged because MTT approximates the extent of at-risk tissue and the NCCT 24 h depicts the infarct volume. Going upstream in the pathophysiological chain of events, this mismatch parameter is related to reperfusion and vessel recanalization. Dichotomizing  $\Delta mRS$  using the threshold  $\Delta mRS \leq 1$  to signify a good clinical outcome, the lowest statistically significant threshold for the MTT–NCCT 24 h ASPECTS mismatch that was related with a favorable clinical outcome was 2 ( $p = 0.04$ ). Using this threshold as an indicator for total or partial timely tissue reperfusion, in the subgroup of patients showing MTT–NCCT 24 h ASPECTS mismatch  $\geq 2$  ( $n = 17$ ), this parameter and the CTP ASPECTS mismatch were highly correlated ( $r = 0.83$ ) and showed a strong linear relationship ( $R^2 = 0.70$ , Figure 9). These data suggest that the CTP ASPECTS mismatch adequately predicts the amount of potentially salvageable tissue.



**Figure 9:** The relationship between the MTT–CBV ASPECTS and the MTT–NCCT 24 h ASPECTS mismatches.

### 5.1.3 CBS, BASIS and CBV ASPECTS as prognostic classifiers [II]

CBS and CBV ASPECTS were dichotomized using the thresholds (CBS > 6 and CBV ASPECTS  $\geq$  7) that most accurately differentiated favorable from poor clinical outcomes in study I and previous studies<sup>111, 113, 114, 139, 182</sup>. By definition, BASIS is a dichotomous variable. When the subgroups, which were defined by the dichotomizations, were compared separately for each variable, patients with low CBS or CBV ASPECTS scores or with major strokes had significantly higher admission-NIHSS scores, larger perfusion defects in the CBV and MTT maps and more findings of acute ischemic processes in the admission NCCT. A low CBS score correlated with a low CBV ASPECTS score and major stroke. All these properties significantly predicted poor clinical outcomes and larger infarct volume. The accuracy of CBS and CBV ASPECTS in the prediction of the clinical outcome

was enhanced when only anterior circulation strokes were included in the analysis, whereas the predictive power of BASIS improved when all vascular territories were included in the analysis. The performance of BASIS also improved if patients with occlusion of the M2 segment were classified as having a minor stroke. This modification was named M1-BASIS. An imaging parameter that combines CBS and CBV ASPECTS was also devised by calculating an unweighted sum of the scores. This parameter was named CBSV. An optimal threshold for dichotomization was calculated for CBSV using ROC analysis where the 3-month clinical outcome was used as the state variable ( $> 15$ , AUC = 0.72).

The prognostic value of these dichotomous imaging parameters was further assessed using binary logistic regression analyses having functional independence (mRS  $\leq 2$ ) at three months after the stroke as the dependent variable. Age and gender were considered potential confounders and were controlled for by treating them as covariates. When all vascular territories were included in the analysis, CBV ASPECTS, CBS, CBSV, BASIS and M1-BASIS were all significant predictors of good clinical outcome. CBV ASPECTS displayed the largest OR (13.3, CI 95% = 2.2-79.7). NCCT 0 h ASPECTS was not significantly associated with the clinical outcome. When only anterior-circulation strokes were considered, CBSV was the most robust predictor (OR = 16.3, CI 95% = 2.7-98.8,  $p = 0.002$ ), whereas BASIS did not reach statistical significance.

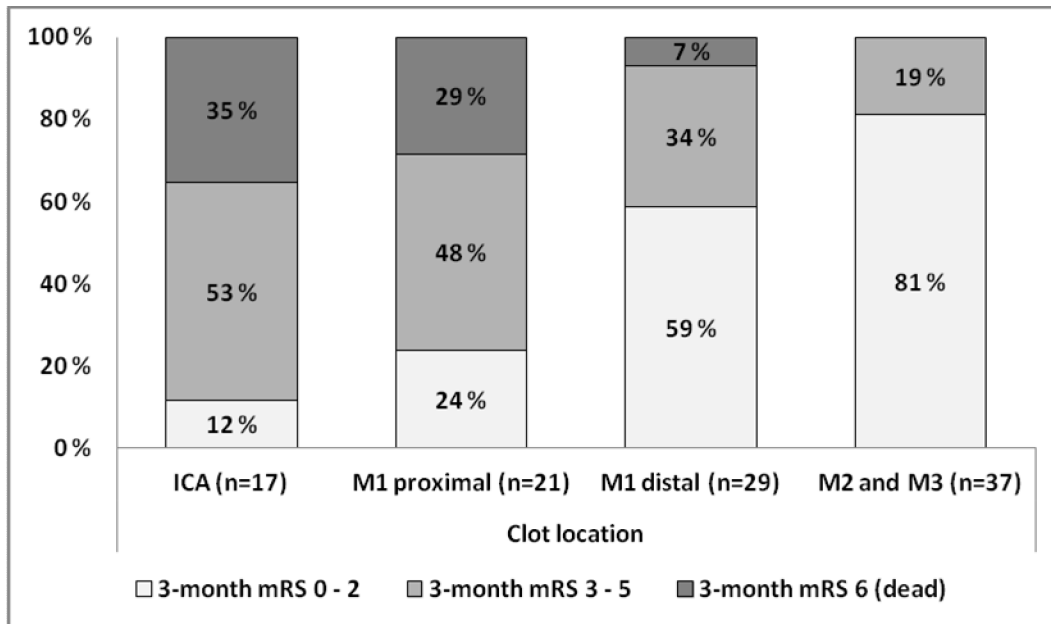
Sensitivities and specificities for detecting good clinical outcome (mRS  $\leq 2$ ) were calculated for the dichotomized imaging parameters. When all vascular territories were included in the analysis, CBV ASPECTS was the most sensitive predictor of good clinical outcome (0.96, CI 95% = 0.86-0.99), whereas BASIS showed the most accurate specificity (0.57, CI 95% = 0.34-0.77). BASIS was significantly less sensitive than any of the other parameters. When only the anterior circulation was considered, CBV ASPECTS was the most sensitive (0.96, CI 95% = 0.86-0.99) predictor, and CBSV was the most specific (0.47, CI 95% = 0.22-0.73) predictor, and again, BASIS was significantly less sensitive when compared to all other parameters. CBV ASPECTS showed the best overall diagnostic accuracy in both setups (0.82 for all vascular territories and 0.83 for the anterior circulation).

## 5.2 The location of the thrombus in the prediction of the clinical outcome [III]

The location of the clot is one of the components used in the calculation of the CBS. The impact of the location of the clot only on the clinical outcome of anterior-circulation stroke patients treated with IVT was studied. An assumption was made that dividing the M1 segment of the MCA into proximal (M1P) and distal (M1D) parts would provide increased accuracy in predicting the clinical outcome.

### 5.2.1 The location of the clot predicts the clinical outcome in a dose-response manner

Patients with more proximal clots showed a poorer functional outcome at three months after their stroke (Figure 10). When adjoining clot locations (ICA-M1P, M1P-M1D, M1D-M2, M2-M3) were compared in pairs to determine differences in the rate of good clinical outcome, the largest difference in prognosis (2.5-fold) between adjoining clot locations was found between M1P and M1D where 24% and 59% showed a good clinical outcome, respectively. This measurement was the only difference that was statistically significant ( $p = 0.01$ ). 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 with patients with a more distal occlusion.



**Figure 10:** Clinical outcome (3-month mRS) for different clot locations. A favorable clinical outcome was defined as mRS  $\leq 2$  (functional independence).

Only one patient (6%) with an ICA and one patient (5%) with a M1P occlusion were discharged to home, whereas 13 (45%) patients with an M1D clot, 15 (48%) patients with an M2 clot and 5 (71%) patients with an M3 clot returned to home from the primary hospital episode. Similar to the 3-month outcome, in a pairwise comparison between the adjoining clot locations, the difference in favorable outcomes between M1P (5%) and M1D (45%) was the only statistically significant difference ( $p = 0.003$ ).

Binary logistic regression analysis was performed using functional independence (mRS  $\leq 2$ ) at three months after the stroke as the dependent variable. When the clot location was included in the model, the onset-to-treatment time (OTT), the gender, presence of diabetes or hypertension or atrial fibrillation or coronary heart disease, tested one at a time, were not statistically significant covariates. Age, NIHSS, gender and OTT were retained in the final multivariate regression model as potential confounders. Gender and OTT were selected for theoretical reasons, although they did not reach statistical significance. The clot location was a highly significant independent predictor of good clinical outcome in this model that was adjusted for NIHSS (Table 3). When the ICA was set as the reference for the clot location, the OR for a good clinical outcome at three months increased when moving from a



proximal vessel position to a more distal one. The difference between ICA and M1P was not statistically significant, whereas the differences to more distal locations were highly significant, implying that the two proximal and the two distal vessel positions form separate groups. The largest difference in the ORs of adjoining vessel positions was between M1P and M1D (6.5-fold). A higher NIHSS score and advanced age were both significantly associated with poorer outcome.

	<b>Odds ratio</b>	<b>CI 95%</b>	<b>p value</b>
<b>Clot location</b>	-	-	0.001
<b>ICA</b>	Ref	Ref	-
<b>M1 Proximal</b>	4.2	0.45 - 38.2	0.21
<b>M1 Distal</b>	27.4	2.9 - 257.9	0.004
<b>M2 and M3 (combined)</b>	57.3	6.0 - 549.0	0.001
<b>Onset-to-treatment time</b>	1.0	0.98 - 1.02	0.81
<b>Gender</b>	0.49	0.15 - 1.6	0.23
<b>Age</b>	0.94	0.90 - 0.98	0.005
<b>Admission NIHSS</b>	0.82	0.74 - 0.92	0.001

**Table 3:** Binary logistic regression analysis for 3-month favorable clinical outcome (mRS  $\leq$  2). Odds ratios are per minute for onset-to-treatment time, per year for age and per one point for NIHSS. Ref = reference location.

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

On the basis of the above analyses, the clot location was dichotomized using three cut-offs: ICA-M1P, M1P-M1D, M1D-M2 and M3 combined to simulate location-based decision making. These dichotomized variables were entered into the regression model one at a time instead of the clot-location variable. When the 3-month outcome was the dependent variable, ICA-M1P and M1P-M1D showed almost equal ORs (17.1 vs. 16.0), with the latter having a narrower 95% CI (2.3-129.5 vs. 3.9-66.2). The most distal cut-off clearly showed a smaller OR (5.5, 95% CI 1.8-16.8). When using the discharge status as the dependent variable, the cut-off M1P-M1D yielded the largest OR (31.0, 95% CI 4.5-215.3). Overall, the increase in the odds of a favorable outcome was clearly dampened when distal to M1P-M1D.

Sensitivities and specificities for detecting good clinical outcomes were calculated for these cut-offs. A clot distal to the cut-off location constituted a positive test result. The cut-off MIP-M1D showed the highest diagnostic accuracy (0.75) in predicting good clinical outcome at three months after the stroke. When the cut-offs were tested in pairs, the overall diagnostic performance was significantly different in every pair ( $p < 0.001$  for each pair).

### 5.3 The technical quality and perfusion-defect detection properties of CTP studies performed using a 16-row or a 64-row multidetector CT scanner [IV]

The technical quality of the perfusion studies performed using 16-row or 64-row scanners were compared and the differences in the ability to detect perfusion defects were analyzed. The hypothesis was that the 16-row scanner would miss information that is potentially critical for clinical decision making when compared with the 64-row scanner.

The 64-row scanner was used to perform a perfusion study with 67 of the 140 patients (48%). A perfusion defect was demonstrated in 56% of the CTP studies. Seventy-seven percent of the patients experienced a favorable clinical outcome at 3 months ( $mRS \leq 2$ ). The clinical outcome was not significantly different between patients evaluated using different scanners.

#### 5.3.1 The 16-row CTP scans show poorer technical quality

There were more motion artifacts in the 16-row group (Table 4). The artifacts appeared to be due to the capture of small-scale periodic patient movements, such as tremor, swallowing, nodding and minor swinging of the head. Correspondingly, the AIF and the VOF curves were significantly noisier when calculated from the 16-row scans. The analysis software completely corrected significantly fewer of these artifacts. Both ASPECTS levels were optimally covered in only 29% of the 16-row scans, whereas in the 64-row scans, both levels were optimally included in the imaging volume in every case. In 46 of the 16-row scans (63%), only the lower level

was optimally covered. Because of this lack of coverage, ASPECTS could not be reliably assigned for the upper level in 26 cases (34%). Furthermore, because of its larger z-axis coverage, the 64-row scanner fully or partially visualized the subtentorial compartment significantly more often.

	64-row (n = 67)	16-row (n = 73)	<i>p</i>
Both ASPECTS levels optimally covered	67 (100%)	21 (29%)	< 0.001
Motion artifacts	36 (54%)	52 (71%)	0.04
Incompletely corrected motion artifacts	8 (12%)	33 (42%)	0.001
Noisy AIF and/or VOF	1 (1%)	28 (38%)	< 0.001
Subtentorial parenchyma not visualized	1 (1%)	31 (42%)	< 0.001
ASPECTS score uninterpretable	0 (0%)	31 (42%)	< 0.001
Scan not reliably interpretable	0 (0%)	6 (8%)	0.03

**Table 4:** Comparison of the technical quality of the 64-row and 16-row perfusion scans.

### 5.3.2 The 16-row CTP studies suffer from decreased sensitivity in the detection of perfusion defects in the cranial parts of the middle cerebral artery region

The overall ASPECTS scores for MTT and CBV maps and the ASPECTS mismatch scores were not significantly different between scanners. When the ASPECTS regions that were missed by the 16-row scanner because of limited anatomic coverage were scored as normal and were included in the analysis, the average number of regions affected in the upper ASPECTS level was reduced. This reduction reflects the decreased sensitivity for detecting perfusion defects. In the case of MTT, this difference between the scanners became statistically significant (Table 5). However, there were no significant differences in the total MTT and CBV scores or the mean and number of ASPECTS mismatches. There were 9 patients (6%) who showed perfusion defects that were located entirely outside the regions covered by the ASPECTS levels and the volume between these levels. Eight were detected by the 64-row scanner ( $p = 0.03$ ).

ASPECTS regions affected	64-row (n = 67)	16-row (n = 42)	$p_1$	16-row (n = 67)	$p_2$
MTT lower ASPECTS level	1.4 ± 2.0	1.1 ± 1.6	0.74	1.5 ± 2.0	0.74
MTT upper ASPECTS level	0.9 ± 1.1	0.7 ± 1.1	0.54	0.5 ± 1.0	0.02
CBV lower ASPECTS level	0.7 ± 1.4	0.5 ± 1.2	0.35	0.6 ± 1.2	0.77
CBV upper ASPECTS level	0.3 ± 0.7	0.3 ± 0.7	0.87	0.2 ± 0.6	0.25

**Table 5:** Comparison of the perfusion-defect detection properties at different ASPECTS levels. The 16-row (n = 67) column heading refers to the inclusion of patients with ASPECTS regions that were missed by the 16-row scanner due to its limited anatomic coverage. These regions were scored as normal. In the n = 42 population, these patients were excluded.  $p_1$ : 64-row (n = 67) vs. 16-row (n = 42),  $p_2$ : 64-row (n = 67) vs. 16-row (n = 67). All values are of the mean ± SD.

## 6. DISCUSSION

### 6.1 Predicting the outcome of acute ischemic stroke using CTA and CTP

Predicting the clinical outcome is perilous. Ischemic stroke is a highly dynamic condition comprising interplay between multiple different pathophysiological and possibly also interventional processes that influence the eventual outcome. Some of the most important of these factors include the coagulation cascade, the endogenous fibrinolytic system, the exogenous drug effects, re-embolization, tissue susceptibility to ischemic damage, the processes that modify the infarct threshold, the collateral circulation, and the duration and the severity of the ischemia. The clot may undergo complete or partial dissolution resulting in vessel recanalization, undergo stabilization resulting in persistent occlusion, or progress to a more extensive thrombosis. No single clinical or imaging variable sampled at the time of admission to the hospital can capture these phenomena sufficiently to enable deterministic prediction of the outcome. However, parameters derived from CTA and CTP imaging potentially provide improved accuracy in the evaluation of the prognosis and enable more precise risk stratification and decision making for treatment<sup>8,9</sup>.

In **study I**, the ASPECTS scoring scheme was applied to CTP maps and the association of these scores with the clinical and the imaging outcomes was examined. The limited z-axis coverage of the majority of CT scanners that are currently in use means that CTP images cannot cover the entire brain volume with a single contrast bolus. Furthermore, exact volumetric analysis of the perfusion maps requires user supervision and is too slow to be used in the context of acute stroke imaging. Thus, applying the ASPECTS scoring scheme to the perfusion images becomes an appealing alternative. This method has been validated by previous investigators<sup>111-114</sup>.

The initial analyses in study I included all patients who received IVT within a period of one year regardless of the vascular territory affected to provide a realistic estimate of the overall performance in a clinical setting. A perfusion defect was detected in 50% of these patients implying that with limited z-axis coverage, a CTP study could affect approximately half of the positive thrombolytic treatment decisions. Correlation analyses including all patients, patients with an anterior-circulation stroke, and patients with a CTP ASPECTS mismatch revealed that the CTP ASPECTS scores correlated more closely with the clinical outcome than the findings from the admission NCCT. However, only CBV displayed a statistically significant difference from the NCCT, whereas the MTT did not reach statistical significance. This result appears to be due to the heterogeneity introduced by cases where timely reperfusion occurred and the MTT defect was completely or partially reversed. These findings are similar to previous reports in which the CTP ASPECTS scores, especially the CBV ASPECTS, better predicted the clinical outcome of IVT patients compared with the admission NCCT and CTA-SI <sup>111-114, 181</sup>. Using ROC analysis, *Kloska et al.* suggested that an optimal threshold value for CBV ASPECTS that best differentiated between good and poor clinical outcomes was  $\geq 7$ , whereas *Aviv et al.* found that no patients with CBV ASPECTS  $\leq 7$  achieved a good clinical outcome <sup>113, 114</sup>. In study I, the threshold that performed best in ROC analyses was CBV ASPECTS  $\geq 7$ , which agrees closely with these reports.

The perfusion mismatch concept has also been adapted to CTP ASPECTS <sup>182</sup>. CTP ASPECTS mismatch has been used as a criterion to extend the time window of IVT to 6 h <sup>226</sup>. In study I, 39% of patients presented with such a mismatch. It was demonstrated that the CTP ASPECTS mismatch identified the amount of potentially salvageable tissue adequately and described the spectrum of possible imaging outcomes. Small mismatches ( $\leq 1$  ASPECTS points) were difficult to assess because of noise introduced by the dynamic stroke pathophysiology and interpretation issues during image analysis. A threshold of  $\geq 2$  salvaged ASPECTS regions was correlated with a favorable clinical outcome, suggesting that reversal of smaller perfusion defects are unlikely to benefit the patient. This threshold corresponds approximately to a mismatch ratio of 2.0 <sup>182</sup>. This result prompted *Sztriha et al.* to use this CTP ASPECTS threshold in the classification of patients who presented

between 3 and 6 h from symptom onset <sup>226</sup>. They reported that this threshold performed adequately in identifying patients who could benefit from IVT.

Building on and expanding these concepts, in **study II**, we examined the performance of two CTA-based classification schemes, BASIS and CBS, and one perfusion parameter, CBV ASPECTS, and a combination of these variables in the prediction of clinical outcomes in the same IVT cohort as in study I. Both BASIS and CBS address the location of the clot, whereas CBS also takes the volume of the clot into account. CBV ASPECTS provides an approximation of the size of the infarct core. Thus, these parameters provide information on markedly different aspects of the stroke pathophysiology.

Patients with low CBS and CBV ASPECTS scores and with major strokes according to BASIS experienced poor clinical outcomes more often, which is consistent with recent studies <sup>111-114, 134, 135, 139, 181, 227</sup>. As expected from their definition, which does not address the posterior circulation, CBS and CBV ASPECTS predicted the clinical outcome with greater accuracy when only anterior-circulation strokes were analyzed. In contrast, BASIS encompasses both the anterior and posterior circulation and correspondingly performed better when all vascular territories were included in the analysis. However, BASIS did not reach statistical significance when only patients with anterior-circulation strokes were analyzed ( $p = 0.23$ ). This finding was reversed if patients with thrombosis of the M2 segment were classified as having a minor stroke ( $p = 0.002$ ). This modified BASIS performed better than the original and was named M1-BASIS. This finding is likely due to the effect of IVT and supports the notion that patients with a clot in the M2 segment often benefit from IVT, whereas when the clot is more proximal, a limited response is more likely <sup>131, 134, 136, 228</sup>. Only a minority of patients (8%) received IVT in the cohort that was originally used to validate BASIS <sup>140</sup>. In the logistic regression analysis, BASIS, M1-BASIS and dichotomized CBV ASPECTS and CBS were all significant predictors of the clinical outcome.

A new, derived imaging parameter was created by calculating the sum of a parameter from the CTA and one from the CTP, the CBS and CBV ASPECTS. This variable was named CBSV. When only anterior-circulation strokes were considered,

CBSV proved to be, statistically, the most robust predictor of favorable clinical outcome (OR = 16.3, CI 95% = 2.7-98.8,  $p = 0.002$ ). In view of the fact that the CBSV combines two independent predictors of the clinical outcome that both reflect different pathophysiological aspects of stroke, in theory, the CBSV should have better predictive power than either of its components, which is supported by the results of study II. An imaging score resembling CBSV but utilizing CTA-SI instead of CBV was introduced recently<sup>134</sup>. This scoring scheme improved the identification of patients with high mortality rates or poor functional outcomes despite early IVT.

CBV ASPECTS, CBS, CBSV and M1-BASIS all had high sensitivity (85-96%) but moderate to poor specificity (24-52%) for predicting good clinical outcome. BASIS was only moderately sensitive (70-71%). This rather low specificity is to be expected because not all patients experience reperfusion, and although strategic infarcts may cause a serious functional deficit, they may show minimal imaging findings. *Tan et al.* found CBS to be less sensitive but more specific when compared with our results<sup>139</sup>. This inconsistency is likely due to the higher median NIHSS score and lower proportion of patients treated with r-tPA (71%) in their study population.

The location of the clot is one of the main components of CBS and BASIS. **Study III** examined the ability of the location of the clot *alone* in predicting the clinical outcome. The results revealed that the location was an independent predictor of the clinical outcome even when the NIHSS score was controlled for. The odds ratios for a good clinical outcome increased and the mortality decreased consistently when moving from a proximal to a more distal vessel position. When adjoining vessel positions were tested in pairs, only the difference between M1P and M1D was statistically significant. Following dichotomization of the clot location, a cut-point between the M1P and M1D was associated with the largest increase in the odds of a favorable outcome and showed the highest diagnostic accuracy. This cut-point is likely due to specific anatomic and pathophysiological factors. The lenticulostriate arteries, which supply blood to the basal ganglia, originate primarily from the proximal M1 segment. A lesion in this region affects gait and other motor functions and has direct consequences for functional independence. The mean diameter of the



vessel, and thus the volume of the clot, is larger in the proximal segment, which potentially decreases the effectiveness of IVT. Moreover, proximal thrombi tend to propagate distally, which can also increase the total volume of the clot.

Some studies have previously addressed the effect of the clot location on recanalization and clinical outcomes in the context of IVT. *Del Zoppo et al.* used DSA to reveal that thrombi situated in the M2 and M3 segments are more likely to undergo recanalization than those in the M1 segment and the ICA <sup>127</sup>. Consistent with these results, in a more recent study, *Saqqur et al.* utilized repeated transcranial Doppler ultrasonography to detect recanalization where the main end-point was the clinical outcome at 3 months <sup>129</sup>. Different subareas of the M1 segment were not addressed in either of these studies. However, the rate of good outcomes at M1P in study III was comparable to that of the proximal MCA and the M1D to that of the distal MCA in these published reports. Furthermore, other studies with more heterogeneous setups have corroborated that large-vessel occlusions are less likely to recanalize and that they predict unfavorable clinical outcomes <sup>128, 131, 132</sup>.

Overall, the findings of study III and the previously published research support the notion that alternatives to IVT, which are chiefly primary intra-arterial or bridging therapy, should be considered if the thrombus is located in the ICA or in the proximal M1 segment.

## 6.2 The 16-row scanner is inferior to the 64-row scanner in the CTP evaluation of acute ischemic stroke

The differences in the technical quality and the perfusion-defect detection properties between CTP studies performed using a 16-row or a 64-row scanner were compared in a clinically managed IVT cohort. The 64-row scanner covered 80 mm of the z-axis, whereas the 16-row scanner covered 20 mm. The coverage of the 64-row scanner was increased by alternating the table between two positions. This procedure can also be utilized with 16-row scanners. Typically, 40-mm coverage is achieved. Another method to double the imaging range is to use two contrast

injections and to image adjoining 20 mm slabs separately. Although these techniques increase the number of perfusion defects detected, the results remain inferior compared with z-axis ranges larger than 40 mm<sup>191, 193</sup>.

Some studies have addressed the impact of different z-axis ranges in the detection of perfusion defects. Using a 320-row scanner, *Page et al.* reported that 160-mm coverage better defined the extent of the infarct core and the penumbra compared with 40-mm coverage<sup>193</sup>. *Morhard et al.* observed that 20-mm coverage missed 24% of pathological findings when compared with 96-mm coverage<sup>229</sup>. *Furtado et al.* noted that 75 mm of z-axis coverage was required to reliably detect a perfusion mismatch ratio of 2.0, whereas 50 mm was sufficient when a ratio of 1.2 was used<sup>191</sup>. Fifty-five millimeters must be covered to provide sufficiently accurate estimations whether more than one-third of the MCA region is irreversibly damaged. Interestingly, rules based on ASPECTS provide potential alternatives for excluding patients from thrombolytic therapy and require less extensive coverage<sup>109, 112</sup>. *Youn et al.* reported that 80-mm coverage was associated with a significantly higher lesion-detection rate compared with 20-mm coverage<sup>230</sup>. The results presented in this thesis are consistent with these findings. All previous studies contained somewhat heterogeneous populations and simulated narrower coverage by selecting ranges of larger volumes that were imaged using one scanner, whereas in study IV, all patients received IVT and two scanners with different detection widths were used.

In study IV, the 16-row examinations suffered from limited anatomic coverage that often resulted in inadequate visualization of the cranial MCA region. ASPECTS could not be assigned to the upper, supraganglionic level in one-third (34%) of these scans, which significantly decreased the detection sensitivity of perfusion defects in the upper level (Table 5). The impact on the overall ASPECTS score was limited because the lower ganglionic level is given considerably heavier weight (7 vs. 3 regions). However, in study I, the threshold for salvaged ASPECTS regions (and hence the CTP ASPECTS mismatch) that was associated with a favorable outcome was 2 points. Thus, the supraganglionic level alone is potentially critical in the evaluation of the mismatch. Furthermore, the 64-row scanner was capable of

discovering a significantly larger number of perfusion defects entirely outside the volume limited by the ASPECTS levels.

The number of movement artifacts was significantly greater in the 16-row group. This increase may be due to the higher sampling frequency (1/s vs. 0.27/s) and the smaller slice thickness (5 mm vs. 10 mm), which appeared to capture small-scale periodic patient movements more frequently. This type of movement was poorly corrected by the analysis software. Although this feature does not typically render the scan uninterpretable, it introduces inaccuracies to the measurement of absolute values of the perfusion parameters. However, a lower sampling frequency could result in the same effect and a larger slice thickness may decrease the sensitivity in detecting small perfusion defects due to averaging.

Overall, the 16-row scanner was inferior to the 64-row scanner in the CTP evaluation of acute ischemic stroke. However, there was no significant difference in the clinical outcome between the study groups. This finding is to be expected because the institutional guidelines on stroke management did not define any specific role for the CTP findings at the time; thus, stroke management was essentially similar between the both groups.

### 6.3 Limitations

All studies were limited methodologically by the retrospective single center design. The sample size is a potential limitation in particular for the subgroup analyses. Because of the design of the studies, direct data on vessel recanalization or reperfusion were not available for the majority of patients. However, a low ASPECTS score at the 24 h NCCT and poor clinical outcomes are closely correlated with delayed or failed reperfusion and can be used as a surrogate. The craniocaudal coverage of the CTP was, at a minimum, 20 mm. Thus, the size of the perfusion defect was estimated using ASPECTS scoring and area measurements in the ASPECTS levels. It should be noted that MTT maps potentially overestimate the size of the perfusion defect, whereas CBV maps may overestimate or underestimate the volume of the irreversibly damaged parenchyma, and CTP results may vary with

machine<sup>177</sup>. Interobserver agreement in some imaging parameters was not perfect, although this finding is consistent with previous reports<sup>113</sup>. M1-BASIS was created based on a *post hoc* analysis of the data set and should be further validated in other thrombolytic therapy cohorts. In study III, the distribution of patients based on clot locations was uneven because 63% of patients showed a clot distal to the mid M1 segment. The only confounding variable between these two groups (proximal and distal to the mid M1 segment) that was significantly different was gender. However, gender was not a significant predictor of the clinical outcome. The Pearson correlation coefficient for gender and the clot location was 0.18. The Kruskal-Wallis test for gender did not reveal significant differences between clot locations. The disparity in gender distribution could be attributed to chance because no selection process was identified that would potentially produce this result.

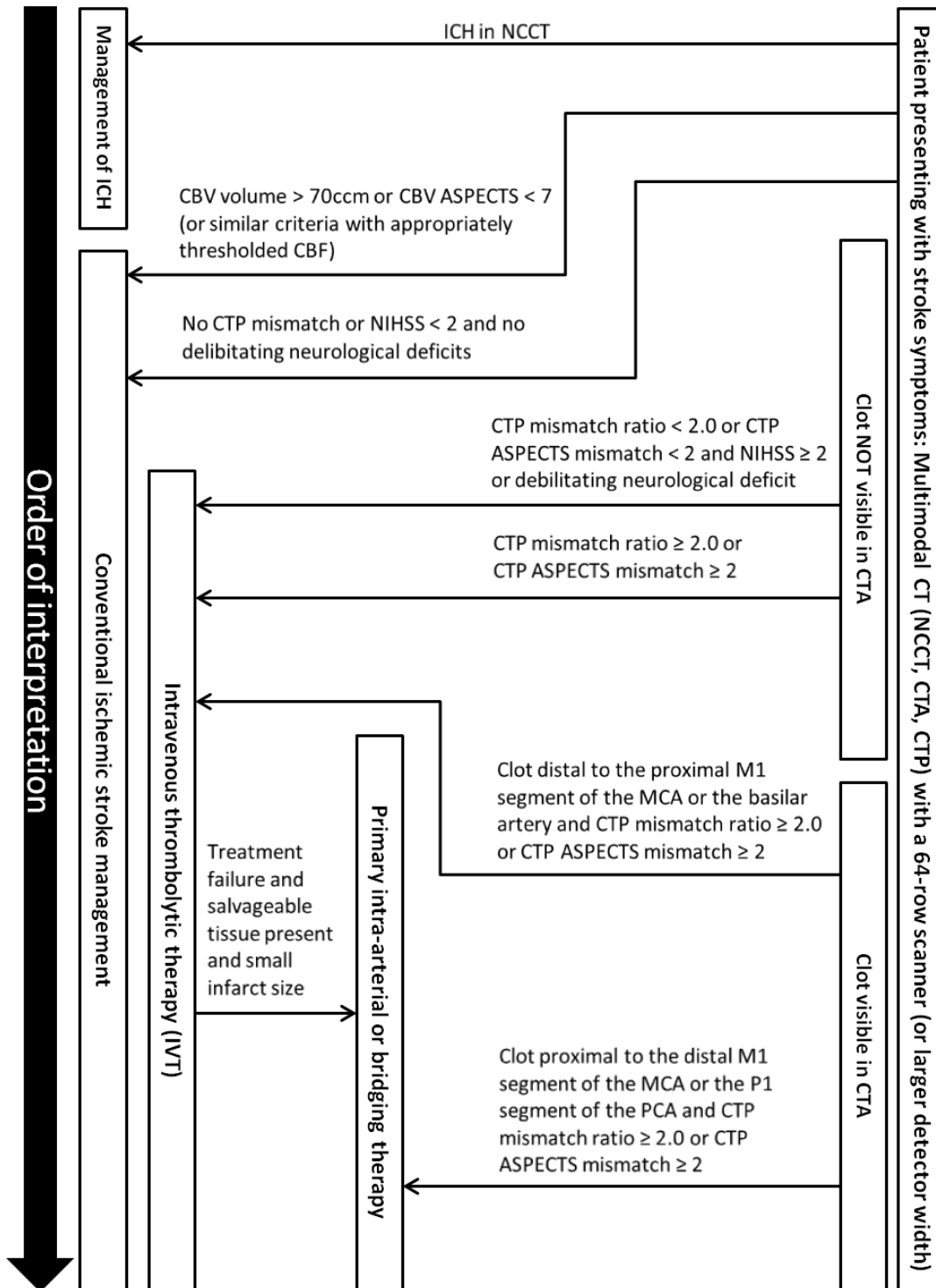
## 6.4 Multimodal CT-based evaluation protocol for acute stroke

Multimodal CT is fast, increasingly available, safe when performed correctly, and affordable<sup>167</sup>. There is an accumulating body of evidence that multimodal CT can provide diagnostic information comparable to that of MRI, which can aid in clinical decision making, in particular in the selection of different revascularization therapies. Thus, CT-only imaging protocols in the evaluation of acute stroke have been proposed<sup>167</sup>.

Distal ICA occlusions, proximal MCA-branch occlusions or a considerable thrombi burden may be poor candidates for IVT and may be better candidates for intra-arterial thrombolysis or mechanical interventions<sup>137, 231, 232</sup>. An observational study by *Mattle* et al. compared IAT to IVT in patients with hyperdense MCA sign and noted that IAT was more beneficial<sup>233</sup>. The findings of study III are consistent with these reports, and the results provide improved spatial resolution in the M1 segment. In a recent study, multimodal intra-arterial therapy resulted in the highest recanalization rates of anterior-circulation clots<sup>233, 234</sup>. Furthermore, intra-arterial therapies have a potential role when IVT fails, if there is contraindication to IVT, in

the extension of the treatment time window and in the treatment of wake-up strokes  
47.

Drawing from the previously published research and the results of studies I-IV, a multimodal CT-based evaluation and treatment triage protocol for acute stroke is proposed (Figure 11)<sup>49, 167, 235</sup>. This protocol demonstrates how the findings of this thesis can be integrated to the emerging, imaging-oriented, time-independent concept of acute stroke evaluation and management outlined in section 2.2.4. The overall level of evidence on the use of intra-arterial stroke interventions remains suboptimal and does not permit definitive recommendations. The recanalization strategy for thrombosis of the basilar artery remains an open issue, and the cut-off location for intra-arterial or bridging therapy suggested in Figure 11 is largely speculative<sup>236</sup>. Although the time from the onset of the symptoms has no explicit role in the proposed protocol, when a perfusion defect is undetected in the presence of significant symptoms and more than 4.5 h has elapsed from the symptom onset, DWI imaging may detect a possible acute lacunar ischemic event.



**Figure 11:** An imaging-oriented evaluation protocol for acute stroke based on the use of multimodal CT.

## 7. SUMMARY AND CONCLUSIONS

This thesis investigated the utility and the prognostic performance of imaging parameters derived from CTA and CTP scans in the evaluation of acute ischemic-stroke patients receiving intravenous thrombolytic therapy and the quality of CTP studies with scanners of different detector widths.

The main findings and conclusions are as follows:

1. Parameters derived using ASPECTS scores of CTP maps obtained upon admission to the hospital can detect reversible ischemia and are correlated with the clinical outcome. CBV ASPECTS best differentiates between good and poor outcomes in anterior-circulation strokes and is superior to NCCT ASPECTS. CTP ASPECTS mismatch adequately identifies the amount of potentially salvageable tissue and describes the spectrum of possible imaging outcomes.
2. CBS, BASIS and CBV ASPECTS are statistically robust and sensitive but unspecific predictors of good clinical outcomes among patients receiving IVT. Two derived imaging parameters, CBSV and M1-BASIS, essentially share these same properties but appear to provide slightly better prognostic accuracy.
3. The functional outcome of acute ICA or proximal M1 segment occlusion is generally poor even if treated with intravenous thrombolytic therapy. A cut-point between the proximal and the distal M1 segment best differentiates between good and poor clinical outcomes and provides the highest accuracy in predicting favorable clinical outcomes.

4. CTP studies performed using a 16-row scanner suffer from limited z-axis coverage that significantly decreases the sensitivity for detecting perfusion defects in the cranial parts of the MCA region compared with a 64-row scanner. The 16-row scans show more motion artifacts that result from small-scale periodic patient movements.



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# ORIGINAL COMMUNICATIONS



Original Paper

# CT Perfusion ASPECTS in the Evaluation of Acute Ischemic Stroke: Thrombolytic Therapy Perspective

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## Key Words

ASPECTS · Computed tomography · Perfusion · Stroke · Thrombolytic therapy

## Abstract

**Background and Purpose:** Advances in the management of acute ischemic stroke and medical imaging are creating pressure to replace the rigid one-third middle cerebral artery (MCA) and non-contrast-enhanced CT (NCCT) Alberta Stroke Program Early CT Score (ASPECTS) thresholds used for the selection of patients eligible for intravenous thrombolytic therapy. The identification of potentially salvageable ischemic brain tissue lies at the core of this issue. In this study, the role of CT perfusion ASPECTS in the detection of reversible ischemia was analyzed. **Materials and Methods:** We retrospectively reviewed the clinical and imaging data of 92 consecutive patients who received intravenous thrombolytic therapy for acute (duration <3 h) ischemic stroke. Most of the patients underwent admission multimodal CT, and all patients had follow-up NCCT at 24 h. ASPECTS was assigned to all modalities and correlated with clinical and imaging parameters. Receiver-operating characteristic curve analysis was performed to determine optimal thresholds for different parameters to predict clinical outcome. **Results:** A perfusion defect could be detected in 50% of the patients. ASPECTS correlated inversely with the clinical outcome in the following order: follow-up NCCT > cerebral blood volume (CBV) > mean transit time (MTT) > admission NCCT. The follow-up NCCT and the CBV displayed a statistically significant difference from the admission NCCT, while the MTT did not reach statistical significance. The threshold that best differentiated between good and bad clinical outcome on admission was CBV ASPECTS  $\geq 7$ . In patients with CT perfusion ASPECTS mismatch, MTT and CBV ASPECTS

essentially provided the lower and upper limits for the follow-up NCCT ASPECTS, thus defining the spectrum of possible outcomes. Furthermore, CT perfusion ASPECTS mismatch strongly correlated ( $r = 0.83$ ) with the mismatch between the tissue at risk and the final infarct, i.e. the amount of salvaged tissue. This finding suggests that the CT perfusion ASPECTS mismatch adequately identifies the amount of potentially salvageable ischemic brain tissue. **Conclusions:** Parameters derived from the use of CT perfusion ASPECTS can detect reversible ischemia and are correlated with clinical outcome.

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## Introduction

The role of CT perfusion (CTP) in the decision to administer thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rtPA) remains controversial. Research initiatives have been proposed to establish a sufficient body of evidence that would allow formal clinical guidelines to be composed [1]. At the core of this dilemma lie the detection of the ischemic penumbra and the infarct core and the implications this information should have for clinical decision making. Previous studies suggest that CTP can provide an estimate of the amount of potentially salvageable, acutely ischemic brain tissue and that the resulting CTP parameters provide an independent prognostic factor of the clinical outcome [2–6]. CTP also seems to increase diagnostic performance in stroke diagnosis and inter- and intraobserver agreement [7].

The Alberta Stroke Program Early CT Score (ASPECTS) is a semiquantitative, weighted scoring system that was developed to overcome the difficulties in the application of the non-contrast-enhanced CT (NCCT) one-third middle cerebral artery (MCA) rule that is used to select patients eligible for intravenous thrombolytic therapy [8]. ASPECTS is predictive of clinical outcome and hemorrhagic complications but is not sufficiently accurate in the triage of thrombolysis candidates [9–11]. Applying ASPECTS to CTP parametric maps has been suggested to be more reliable in both detecting reversible ischemia and predicting clinical outcome [12–15].

We retrospectively reviewed the clinical and imaging data of 92 consecutive patients who received intravenous thrombolytic therapy for acute (duration <3 h) ischemic stroke in order to study the potential of CTP ASPECTS in the detection of reversible ischemia. We hypothesized that CTP ASPECTS mismatch [16], the difference between the mean transit time (MTT) and cerebral blood volume (CBV) map scores, might be useful in identifying patients who potentially benefit from thrombolytic therapy.

## Materials and Methods

### Overview

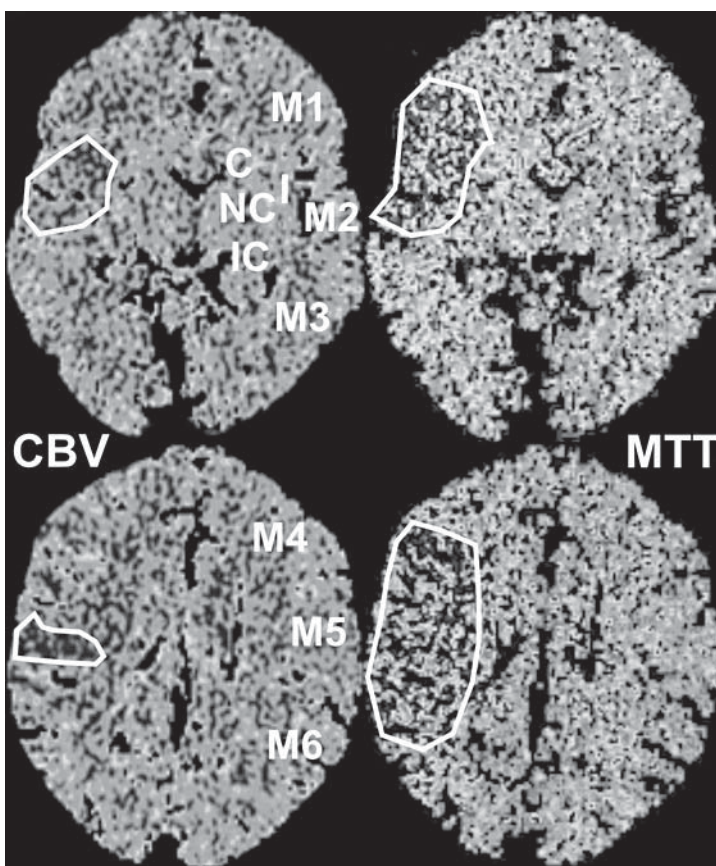
We retrospectively analyzed the clinical and imaging data of 92 consecutive patients who were admitted to Tampere University Hospital between January 2007 and December 2007 because of acute (duration <3 h) stroke symptoms and who received intravenous rtPA for the treatment of acute ischemic stroke after evaluation. In total, 271 patients suffering from acute ischemic stroke were evaluated as candidates for thrombolytic therapy during this period of time. The initial imaging evaluation of stroke patients consisted of NCCT, CT angiography (CTA) and CTP. The selection of patients eligible for thrombolytic therapy was based on institutional guidelines that did not have CTP or CTA parameters as exclusion or inclusion criteria. Still, we reviewed patient records of 179 patients who did not receive thrombolytic ther-

apy in order to detect possible selection bias caused by CTP studies. The indications to exclude a patient from thrombolytic therapy had been carefully documented. In 1 case, the decision to exclude the patient was based on the results of a CTP study (extremely poor technical quality of the admission NCCT and over one third MCA lesions in the CBV map). In addition, we discovered 3 cases in which the admission NCCT was initially erroneously interpreted as negative and the results were reported orally to the stroke neurologist, followed by a review and a correction after the CTP maps had been calculated and analyzed some minutes later, with the result that the decision to administer thrombolytic therapy was withdrawn.

A full multimodal imaging evaluation was successfully completed in 72 of the 92 patients who received thrombolytic therapy. Nine patients were evaluated with NCCT alone and 11 patients with NCCT and CTA because of previously known contrast agent hypersensitivity, chronic renal failure, imminent closure of the 3-hour time window, or movement artifacts that rendered some of the imaging data not evaluable. A standard rtPA administration scheme was used: a total dose of 0.9 mg/kg Actilyse (Boehringer-Ingelheim, Ingelheim, Germany) was administered, with 10% given as a bolus and the remaining 90% as a continuous infusion for 1 h. A follow-up NCCT was performed for all patients 24 h after the administration of the thrombolytic agent. National Institutes of Health Stroke Scale (NIHSS) scores were assessed on admission and 24 h after the thrombolytic therapy. The modified Rankin Scale (mRS) was evaluated preictally and on day 90. The clinical data were stored (prospectively) in the patient records during the hospital stay and on day 90 after the ictus, the latter following a phone interview. These data were collected from the patient records and critically reviewed for errors using the data available from all medical and related disciplines (J.T.S.). The study was approved by the Tampere University Hospital Ethics Committee.

#### *Imaging Parameters*

CT scans were obtained using two different multidetector scanners: the General Electrics LightSpeed 16-slice scanner (GE Healthcare, Milwaukee, Wisc., USA) and the Philips Brilliance 64-slice scanner (Philips, Cleveland, Ohio, USA). Brain NCCT was performed using the parameters 120 kV, 430 mA, collimation  $12 \times 1.25$  mm, and rotation 1.5 s (64-slice scanner), or 120 kV, 320 mA, collimation  $16 \times 1.25$  mm, and rotation 1 s (16-slice scanner). Contiguous slices were reconstructed to the thickness of 5 mm in the whole scanning range (64-slice scanner) or to the thickness of 5 mm in the skull base and 7.5 mm in the supratentorial region (16-slice scanner). 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  $64 \times 0.625$  mm, rotation 0.75 s, and pitch factor 0.923 (64-slice scanner), or 120 kV, 160 mA, collimation  $16 \times 0.625$  mm, rotation 0.8 s, and pitch factor 0.938 (16-slice scanner). Contiguous slices were reconstructed to the thickness of 0.9 mm with a 0.45-mm overlap (64-slice scanner) or to the thickness of 1.25 mm (16-slice scanner). The contrast agent (iobitridol 350 mg I/ml; Xenetix, Aulnay-sous-Bois, France) was administered via an antecubital vein with an 18-gauge cannula using a double-piston power injector with a flow rate of 4 ml/s and 70 ml of contrast agent followed by a 50-ml saline flush. Manual bolus triggering was used. CTP was performed using the parameters 80 kV, 200 mA (effective), collimation  $32 \times 1.25$  mm, and rotation 0.4 s (64-slice scanner), or 80 kV, 200 mA, collimation  $8 \times 2.5$  mm, and rotation 1 s (16-slice scanner). 120 slices covering a range of 80 mm were generated in 55 s using an alternating jog protocol, i.e. shuttle mode (64-slice scanner), or 200 slices covering a range of 20 mm were generated in 50 s with a stationary gantry position (16-slice scanner). Contiguous slices were reconstructed to a thickness of 10 mm (64-slice scanner) or 5 mm (16-slice scanner) at even time intervals. The imaging range was positioned so that the ASPECTS planes [8] were always covered. The rest of the 80-mm range (64-slice scanner) was positioned both cranial and caudal to the ASPECTS planes with the exact balancing



**Fig. 1.** CTP ASPECTS mismatch in a patient suffering from acute ischemia in the right MCA territory. In the CBV maps, ASPECTS areas I, M2, and M5 are affected (CBV ASPECTS = 7), whereas in the MTT maps areas I, M1, M2, M4, M5, and M6 display a perfusion defect (MTT ASPECTS = 4). Thus, CTP ASPECTS mismatch = 3.

depending on the clinical presentation. The contrast agent (Xenetix 350 mg I/ml) was administered via an antecubital vein with an 18-gauge cannula using a double-piston power injector with a flow rate of 5 ml/s and 60 ml of contrast agent followed by a 40-ml saline flush.

#### Image Analysis

NCCT examinations were reviewed using dedicated medical imaging workstations. CTA and CTP images were analyzed, and areas and volumes were measured with Advantage Workstation version 3.2 (GE Healthcare). Parametric perfusion maps – MTT, cerebral blood flow, and CBV – were generated with the CT Perfusion 3 software that uses a deconvolution-based algorithm. CTA images were reviewed by examining both the raw data and maximum intensity projection images.

The principles of ASPECTS scoring in NCCT and CTP maps and the evaluation of CTP ASPECTS mismatch have been described in previous studies [8, 12, 15]. In short, each hemisphere is divided into 10 regions in 2 axial planes at the level of the basal ganglia and corona radiata (fig. 1). Each of these regions has a score of 1 point. This point is deducted if that region has ischemic changes. Thus, a negative finding yields a score of 10, and extensive ischemia covering the whole MCA region yields a score of 0.

MTT maps were used to detect tissue at risk, and CBV maps were used to approximate the infarct core [4]. The calculation of CTP ASPECTS mismatch is described in figure 1. We adopted a semiquantitative approach where the presence of a perfusion defect was determined visually from color-coded maps by comparing the appearance of the affected location with that of the healthy tissue on the contralateral side. In order to increase measurement

accuracy and based on theoretical considerations, the area in the visually identified location was required to measure  $>25 \text{ mm}^2$  with a mean MTT  $>7 \text{ s}$  (or mean CBV  $<2.5 \text{ ml}/100 \text{ g}$ , correspondingly). NCCT and CTP ASPECTS were assigned by two radiologists (N.S. and A.L.). In cases where the scoring differed, a consensus score was agreed on. This score was correlated with the original findings of an experienced neuroradiologist, and if significant discrepancies were present, this neuroradiologist was further consulted. The examinations were reviewed in the order NCCT, CTA, and finally CTP, 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. Perfusion defect areas and final infarct volumes were measured by one radiologist (N.S.). The boundaries of the affected areas were determined visually, and absolute value thresholds described above were applied. Volume was calculated by multiplying the measured area with the slice thickness. Intraclass correlation coefficients (ICC) between a staff radiologist (N.S.) and an experienced neuroradiologist (J.H.) were calculated for ASPECTS assignments in a test sample ( $n = 20$ ):  $\text{ICC}_{\text{NCCT}} = 0.86$ ,  $\text{ICC}_{\text{MTT}} = 0.79$ ,  $\text{ICC}_{\text{CBV}} = 0.73$ , and  $\text{ICC}_{\text{NCCT } 24 \text{ h}} = 0.93$ . Median interobserver agreement indices for areas and volumes were  $\text{Area}_{\text{MTT}}$ : 68%,  $\text{Area}_{\text{CBV}}$ : 90%, and  $\text{Volume}_{\text{INFARCT}}$ : 80%.

### Statistics

Data were analyzed with SPSS version 17 (SPSS Inc., Chicago, Ill., USA). Pearson correlation coefficients and 2-tailed significance levels were calculated in all correlation analyses. Receiver-operating characteristic curves (ROC) were computed and Youden indices were evaluated to select optimal threshold values for imaging parameters to predict dichotomized good clinical outcome. After the dichotomization of the imaging parameters based on the threshold values, the data were cross tabulated and significance levels were calculated using Fisher's exact test. Differences between correlation coefficients and ROC area under the curves (AUCs) were studied with Steiger's Z test and the Hanley-McNeil procedure, respectively. Sensitivity, specificity, and confidence interval calculations were performed using standard procedures. In the text and the illustrations, the following notation is used to denote the level of statistical significance: \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$ . If  $p \geq 0.01$ , the precise p value is given.

## Results

### Baseline Characteristics and Validation of the Scoring System

The median age of the patients was 71 years (interquartile range 58–80 years, 42 female). Based on the clinical features and the imaging studies, in 11 of the 92 patients evaluated, the ischemic episode involved the posterior circulation (8 cases of thrombosis of the basilar artery). The rest of the episodes were considered to involve the anterior circulation. The thrombosis could be demonstrated with CTA in 37 cases (45% of the CTA studies and 40% of all patients). In 40 (56%) of the 72 patients evaluated with CTP, a perfusion defect could be detected in the ASPECTS planes. An additional 6 perfusion defects were found outside the ASPECTS planes. A perfusion pattern implying acute ischemia could be detected in half of the cases involving the posterior circulation when CTP was performed. In total, a perfusion defect could be demonstrated in 64% of the CTP studies (50% of all patients). The median NIHSS on admission was 7 points (56.0% had NIHSS  $<8$ , 18.7% had NIHSS  $>15$ , interquartile range 4–12), and 24 h later the median NIHSS was 2 points. The median mRS was 1 point preictally and 2 points 3 months later. The median change in mRS ( $\Delta\text{mRS}$ ) was 1 point. 74.4% of the patients experienced a favorable clinical outcome at 3 months ( $\text{mRS} \leq 2$ ). At 24 h, a local hemorrhagic complication (HI1, HI2, PH1, or PH2) was detected in 6 cases (6.5%), and 4 patients (4.4%) had parenchymal hemorrhage distant to the site of the infarct (PHr1 or PHr2). In order

**Table 1.** Correlations between the NCCT and CTP ASPECTS scores and the final infarct volume and the clinical outcome ( $\Delta$ mRS) for all patients, patients with anterior circulation ischemia, and patients with CTP ASPECTS mismatch

	Infarct volume		$\Delta$ mRS	
	corr. coeff.	vs. NCCT <sub>0h</sub>	corr. coeff.	vs. NCCT <sub>0h</sub>
All patients (n = 92 for NCCT and n = 72 for CTP)				
NCCT <sub>0h</sub>	r = -0.56***	–	r = -0.25*	–
MTT	r = -0.56***	p = 1.0	r = -0.34**	p = 0.40
CBV	r = -0.69***	p = 0.07	r = -0.48***	p = 0.01*
NCCT <sub>24h</sub>	r = -0.82***	p < 0.001***	r = -0.49***	p = 0.01*
Anterior circulation (n = 81 for NCCT and n = 66 for CTP)				
NCCT <sub>0h</sub>	r = -0.57***	–	r = -0.34**	–
MTT	r = -0.58***	p = 0.91	r = -0.43***	p = 0.41
CBV	r = -0.70***	p = 0.08	r = -0.55***	p = 0.02*
NCCT <sub>24h</sub>	r = -0.85***	p < 0.001***	r = -0.65***	p < 0.001***
Patients with CTP ASPECTS mismatch (n = 36)				
NCCT <sub>0h</sub>	r = -0.55**	–	r = -0.39*	–
MTT	r = -0.48**	p = 0.63	r = -0.57***	p = 0.12
CBV	r = -0.66***	p = 0.33	r = -0.69***	p = 0.01*
NCCT <sub>24h</sub>	r = -0.84***	p = 0.003**	r = -0.85***	p < 0.001***

The final infarct volume and the clinical outcome correlated inversely with all ASPECTS scores, with the 24-hour follow-up NCCT having the highest correlation. All the correlation coefficients (corr. coeff.) were statistically significant. The correlations between the MTT and CBV ASPECTS scores and the clinical outcome are stronger than the correlation of the admission NCCT score and the clinical outcome, suggesting that CTP parameters may better classify reversible and non-reversible ischemia. However, only the CBV score displayed a statistically significant difference ( $p < 0.05$ ) from the admission NCCT score in all the subgroups (vs. the NCCT<sub>0h</sub> columns). \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

to validate the ASPECTS scoring method, we studied the correlations between CTP and NCCT ASPECTS, and the area and the volumetric data acquired from the perfusion maps and the NCCT images. ASPECTS for CBV and MTT were inversely correlated with the perfusion defect areas with  $r = -0.87***$  and  $r = -0.91***$ , respectively. The correlation between the CTP ASPECTS mismatch and the measured mismatch area was  $r = 0.77***$ . As expected, the infarct volume correlated with  $\Delta$ mRS ( $r = 0.54***$ ) as did NIHSS on admission ( $r = 0.35**$ ).

#### *CTP ASPECTS Parameters Correlate with Final Infarct Volume and Clinical Outcome*

In order to assess the prognostic performance, we studied the correlations between different ASPECTS parameters, the final infarct volume, and the clinical outcome, which we measured with  $\Delta$ mRS. First, we studied the overall performance of the ASPECTS scoring method systematically applied to all patients identified as candidates for thrombolytic therapy based on clinical features, including patients with a subsequently diagnosed posterior circulation stroke (table 1, ‘all patients’). The final infarct volume correlated inversely with all ASPECTS, with the 24-hour follow-up NCCT having the highest correlation, as expected. Also the other scores displayed statistically significant correlations in the order CBV > NCCT<sub>0h</sub> > MTT, with NCCT<sub>0h</sub> and MTT having close to equal correlation coefficients. This pattern is reflected in the clinical outcome, where the correlations were ordered NCCT<sub>24h</sub> > CBV > MTT > NCCT<sub>0h</sub>, with CBV having a correlation coefficient almost equal to that of NCCT<sub>24h</sub>. In general, the correlations between ASPECTS and  $\Delta$ mRS were weaker than those between ASPECTS and the infarct volume but still highly statistically significant. This pat-

tern is mostly due to the inclusion of the ischemic events of the posterior circulation in the analysis, as the prognosis of these events is generally worse and ASPECTS is designed to detect disturbances in the anterior circulation. When only anterior circulation events are included in the analysis, the correlations between ASPECTS and  $\Delta mRS$  are strengthened, while the order remains unchanged (table 1, 'anterior circulation').

CTP ASPECTS mismatch gives a single-digit estimate of the extent of reversible ischemia (fig. 1). In our data, a mismatch was present in 36 cases (39%). In an additional 4 patients, a perfusion mismatch was present in the ASPECTS planes but not within any ASPECTS subterritory. In the ASPECTS mismatch subgroup, the correlations between ASPECTS and the clinical outcome were higher than in the case of all patients or all anterior circulation events, while the correlations between ASPECTS and infarct volume remained similar (table 1, 'patients with CTP ASPECTS mismatch').

Overall, the correlations between the MTT and CBV scores and the clinical outcome are stronger than the correlation of the admission NCCT score and the clinical outcome, suggesting that CTP parameters may better classify reversible and non-reversible ischemia. However, only the CBV score displayed a statistically significant difference ( $p < 0.05$ ) from the admission NCCT score in all the subgroups studied (table 1).

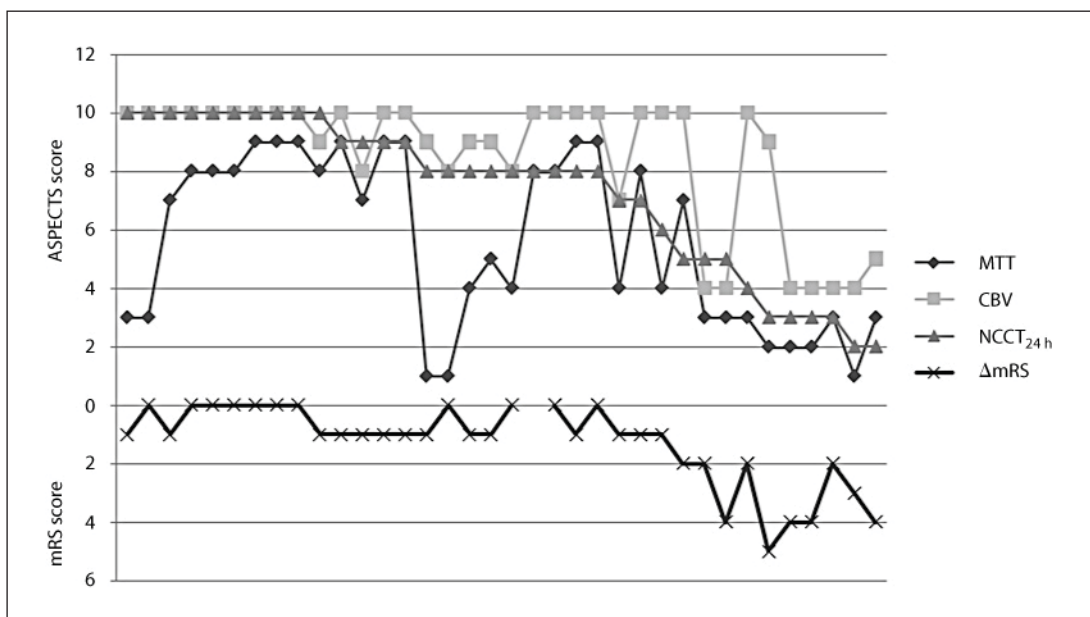
#### *CTP ASPECTS Mismatch Identifies Potentially Salvageable Ischemic Tissue*

In figure 2, the MTT, CBV, and NCCT<sub>24h</sub> ASPECTS scores and  $\Delta mRS$  are plotted for each of the 36 patients with a CTP ASPECTS mismatch and sorted according to the NCCT<sub>24h</sub> ASPECTS in descending order along the x-axis. Essentially, MTT and CBV provide the lower and upper limits for NCCT<sub>24h</sub>, thus defining the spectrum of possible outcomes. The  $\Delta mRS$  curve traces the contour of all the other curves; it lies most closely to the NCCT<sub>24h</sub> curve, which can be expected considering the results of the correlation analysis.

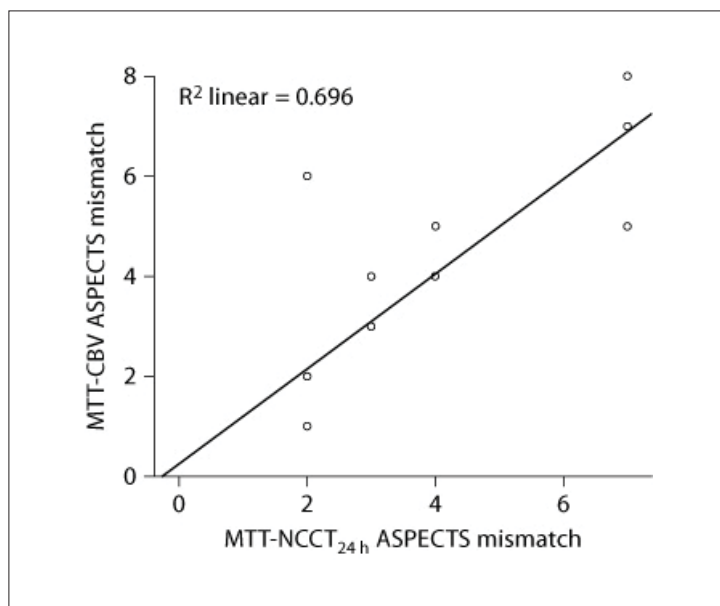
A mismatch between the NCCT<sub>24h</sub> and the MTT ASPECTS scores can be used to estimate the amount of tissue salvaged, as MTT gives an estimate on the amount of tissue at risk and NCCT<sub>24h</sub> depicts the size of the actual infarct. Thus, this mismatch parameter can be used as a surrogate for vessel recanalization. Dichotomizing  $\Delta mRS$  with the condition  $\Delta mRS \leq 1$  to signify good clinical outcome, the lowest statistically significant threshold for the MTT-NCCT<sub>24h</sub> ASPECTS mismatch that predicted good clinical outcome was 2 ( $p = 0.04$ ). Using this threshold as an indicator for total or partial vessel recanalization, in the subgroup of patients with MTT-NCCT<sub>24h</sub> ASPECTS mismatch  $\geq 2$  ( $n = 17$ ), this parameter and CTP ASPECTS mismatch are highly correlated ( $r = 0.83^{***}$ ) and have a strong linear relationship ( $R^2 = 0.70$ , fig. 3). Overall, these findings suggest that the CTP ASPECTS mismatch adequately predicts the amount of potentially salvageable ischemic brain tissue.

#### *CBV ASPECTS $\geq 7$ Identifies Patients with Good Clinical Outcome*

Table 2 demonstrates the thresholds for good clinical outcome ( $\Delta mRS \leq 1$ ) for the CTP and NCCT ASPECTS scores derived from ROC. Overall, the most robust predictor of a good clinical outcome was the 24-hour follow-up NCCT score  $\geq 8$ , which had 94% sensitivity and 65% specificity. However, CBV  $\geq 7$  performed well in identifying patients who had good clinical outcome and who potentially benefited from thrombolytic therapy. This threshold had 100% sensitivity, 44% specificity, and no patients with good clinical outcome in the CBV  $< 7$  partition. The thresholds MTT  $\geq 4$  (AUC = 0.68) and NCCT<sub>0h</sub>  $\geq 10$  (AUC = 0.66), although statistically robust, were outperformed by CBV  $\geq 7$  (AUC = 0.72). The differences between AUCs did not yield statistical significance. However, in the case of MTT and NCCT<sub>0h</sub>, the AUCs were below the 0.70 threshold, which is often considered as a cutoff value for an adequately performing diagnostic test. Patients with thrombosis of the basilar artery in the admission CTA were excluded from the analysis.



**Fig. 2.** The MTT, CBV, and NCCT<sub>24h</sub> ASPECTS scores and  $\Delta$ mRS are plotted for each of the 36 patients with a CTP ASPECTS mismatch  $>0$  according to the NCCT<sub>24h</sub> ASPECTS in descending order along the x-axis. The  $\Delta$ mRS curve traces the contour of all the other curves; it lies most closely to the NCCT<sub>24h</sub> curve. Essentially, MTT and CBV provide the lower and upper limits for NCCT<sub>24h</sub>, thus defining the spectrum of possible outcomes.



**Fig. 3.** The lowest statistically significant threshold for the MTT-NCCT<sub>24h</sub> ASPECTS mismatch that predicted good clinical outcome was 2. Using this threshold as a marker indicating total or partial vessel recanalization, in the subgroup of patients with MTT-NCCT<sub>24h</sub> ASPECTS mismatch  $\geq 2$  ( $n = 17$ ), this mismatch and CTP ASPECTS mismatch are highly correlated ( $r = 0.83^{***}$ ) and have a strong linear relationship ( $R^2 = 0.70$ ). In the case of the outlier in the top left corner of the graph, the recanalization was partial or too late, allowing part of the tissue at risk to become infarcted, while the rest of the tissue at risk was salvaged.



**Table 2.** Threshold values for dichotomized NCCT and CTP ASPECTS parameters that best differentiate between good ( $\Delta mRS \leq 1$ ) and bad clinical outcome

Threshold	Good outcome	p value	RR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUC
CBV $\geq 7$ vs. $< 7$	74 vs. 0%	$< 0.001$	n/a	1.00 (0.93–1.00)	0.44 (0.25–0.66)	0.72
MTT $\geq 4$ vs. $< 4$	68 vs. 6%	$< 0.001$	11.5 (2.9–45.6)	0.92 (0.81–0.97)	0.5 (0.29–0.71)	0.68
NCCT <sub>0h</sub> $\geq 10$ vs. $< 10$	65 vs. 11%	0.01	6.0 (3.2–11.3)	0.86 (0.75–0.92)	0.45 (0.26–0.66)	0.66
NCCT <sub>0h</sub> $\geq 7$ vs. $< 7$	75 vs. 1%	0.04	62.0 (8.8–436.7)	0.98 (0.92–1.00)	0.15 (0.05–0.36)	0.66
NCCT <sub>24h</sub> $\geq 8$ vs. $< 8$	71 vs. 5%	$< 0.001$	27.4 (7.0–107.5)	0.94 (0.85–0.98)	0.65 (0.43–0.82)	0.83

ROC were devised to find the optimal threshold values. Overall, the most robust predictor of good clinical outcome was the 24-hour follow-up NCCT score  $\geq 8$ . CBV  $\geq 7$  performed well in identifying patients who had good clinical outcome and who potentially benefited from thrombolytic therapy. The differences between the AUCs did not yield statistical significance for the admission imaging studies (CBV, MTT, and NCCT<sub>0h</sub>). Patients with thrombosis of the basilar artery were excluded from the analysis. RR = Risk ratio; CI = confidence interval; n/a = not available.

## Discussion

We set off to study the performance of different quantitative parameters obtained using CTP ASPECTS that potentially have an impact on the choice of treatment in acute stroke. With 16- and 64-slice scanners, the axial dimension of the imaging volume is limited to 20–80 mm depending on the protocol used. This is not enough to cover the whole brain. Further, exact volumetric analysis of the perfusion maps requires user supervision, especially in the case of CBV, and is too slow a procedure to be used in the context of acute stroke imaging, which requires rapid online interpretation of the images. Thus, applying the ASPECTS scoring system to the perfusion images becomes an attractive option [12].

We decided to use the difference between the postictal and the preictal mRS as the indicator of good clinical outcome, as this better reflects the disease load inflicted by the current episode. As expected from the definitions,  $\Delta mRS$  and 3-month mRS are highly correlated ( $r = 0.85^{***}$ ). Since poor preictal functional status is essentially a contraindication to thrombolytic therapy, the offset between  $\Delta mRS$  and 3-month mRS is generally very small or non-existent. The median preictal mRS in our research population was 1. The threshold for good clinical outcome was chosen to be  $\Delta mRS \leq 1$  in order to maintain comparability to the traditional 3-month mRS  $\leq 2$  threshold.

All patients who received intravenous thrombolytic therapy in a period of 1 year were included in the baseline analysis regardless of the vascular territory affected in order to gain a realistic idea of the performance of the multimodal CT evaluation of stroke in a clinical setting. A perfusion defect could be detected in 50% of these patients, implying that with the technology used, a CT perfusion study could have an impact on half of the positive thrombolytic treatment decisions at the maximum. In total, 87% of the perfusion defects were present in either or both of the two ASPECTS planes. Those located outside the ASPECTS planes were detected by the 64-slice scanner in all but 1 case. The acute ischemic lesions that escape detection by CTP are mostly lacunar processes or are localized infratentorially or cranially to the perfusion study volume [17].

We hypothesized that CTP ASPECTS parameters predict the clinical outcome of patients who receive intravenous thrombolytic therapy better than the traditional admission NCCT. Correlation analyses with all patients and relevant subgroups support this hypothesis, as the CTP parameters correlate more closely with the clinical outcome when compared

to the NCCT findings (table 1). However, only CBV displayed a statistically significant difference from NCCT, while MTT did not reach statistical significance. This is probably due to the heterogeneity introduced by cases in which thrombolytic therapy was effective and the MTT defect was totally or partially reversed. There was no statistically significant difference in the correlations between the admission CTP and NCCT parameters and the total infarct volume. This finding can be expected as the strength of the correlation between the infarct volume and the clinical outcome was only moderate ( $r = 0.54^{***}$ ), which probably reflects the presence of strategic infarcts that have a relatively small volume but have a considerable impact on the clinical outcome and often escape detection by the follow-up NCCT.

Optimally, the decision of administering thrombolytic therapy is based on the amount of salvageable brain tissue present. In the MCA region, this tissue volume is correlated with CTP ASPECTS mismatch [16]. In total, 39% of the patients presented with such a mismatch. We demonstrated that in patients who received thrombolytic therapy CTP ASPECTS mismatch adequately identifies the amount of potentially salvageable tissue (fig. 2, 3). However, small mismatches are difficult to interpret because of noise introduced by biological heterogeneity and errors in image analysis. In our data, a mismatch  $\geq 2$  was linked with good clinical outcome. A larger sample size is needed for a more accurate analysis.

Other notable limitations of this study are its retrospective design and non-excellent interobserver agreement in some imaging parameters, which, however, is comparable to that previously reported [13].

Finally, in the footsteps of previous investigators, we identified threshold values for dichotomized NCCT and CTP ASPECTS parameters that would best differentiate between good and bad clinical outcome. Our approach emphasized the sensitivity of identifying patients with potentially good outcome. While a statistically robust threshold could be devised for all the parameters studied, the threshold that performed best at presentation was  $CBV \geq 7$ , which is in accordance with previous findings [12–15]. However, thresholds 6 and 8 performed almost equally well, implying that relying on a single threshold value in decision making is probably ill advised. We also tested the established admission NCCT ASPECTS  $\geq 7$  threshold. This threshold proved to be very unspecific (Specificity 15%), which is to be expected as there were only patients who received thrombolytic therapy in our study population.

In conclusion, advances in the management of acute ischemic stroke and medical imaging and the extension of the time window for thrombolytic therapy are creating pressure to replace the rigid one-third MCA rule and non-contrast-enhanced CT ASPECTS thresholds in selecting patients to receive thrombolytic therapy with a shift toward identifying patients with potentially salvageable ischemic brain tissue. Our data suggest that parameters derived using ASPECTS scoring of CT perfusion images, especially the CTP ASPECTS mismatch, can in part answer these demands. Further, on admission, the ASPECTS of the CBV map correlates more strongly with clinical outcome than the NCCT ASPECTS.

### Disclosure Statement

The authors have no conflict of interest.

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# **The Clot Burden Score, the Boston Acute Stroke Imaging Scale, the Cerebral Blood Volume ASPECTS and Two Novel Imaging Parameters in the Prediction of Clinical Outcome of Ischemic Stroke Patients Receiving Intravenous Thrombolytic Therapy**

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## ***Running title:***

**CBS, BASIS and CBV ASPECTS in the Classification of Stroke Patients**

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## **Abstract**

**Purpose:** Recently two classification methods based on the location and the extent of thrombosis detected with CT angiography have been introduced: the Boston Acute Stroke Imaging Scale (BASIS) and the clot burden score (CBS). We studied the performance of BASIS and CBS in predicting good clinical outcome (mRS  $\leq 2$  at 90 days) in an acute (<3h) stroke cohort treated with intravenous thrombolytic therapy.

**Methods:** 83 consecutive patients who underwent multimodal CT were analyzed. Binary logistic regression model was used to assess how BASIS, CBS and cerebral blood volume (CBV) ASPECTS predict favorable clinical outcome. Diagnostic sensitivities and specificities were calculated and compared.

**Results:** Patients with low CBS and CBV ASPECTS scores and major strokes according to BASIS had significantly higher admission NIHSS scores, larger perfusion defects and more often poor clinical outcome. In logistic regression analysis CBV ASPECTS, CBS and BASIS were significantly associated with the clinical outcome. The performance of BASIS improved when patients with thrombosis of the M2 segment of the middle cerebral artery were classified as having minor stroke (M1-BASIS). In the anterior circulation the sum of CBS and CBV ASPECTS (CBSV) proved to be the most robust predictor of favorable outcome. CBV ASPECTS and CBS had high sensitivity but moderate to poor specificity while BASIS was only moderately sensitive and specific.

**Conclusions:** CBS, BASIS and CBV ASPECTS are statistically robust and sensitive but unspecific predictors of good clinical outcome. Two new derived imaging parameters, CBSV and M1-BASIS, share these properties and may have increased prognostic value.

**Abbreviation key:** ASPECTS = Alberta Stroke Program Early CT Score, AUC = area under the curve, BASIS = Boston Acute Stroke Imaging Scale, CBV = cerebral blood volume, C = C statistic, CBS = clot burden score, CI = confidence interval, CTA = computed tomography angiography, CTP = computed tomography perfusion, H-L = Hosmer-Lemeshow , MTT = mean transit time, MCA = middle cerebral artery, NCCT = non-contrast-enhanced computed tomography, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale, ROC = receiver-operating characteristic, RR = risk ratio, rtPA = recombinant tissue plasminogen activator

**Key words:** computed tomography angiography, Boston Acute Stroke Imaging Scale, clot burden score, computed tomography perfusion, thrombolytic therapy, stroke, ASPECTS

## Introduction

Computed tomography angiography (CTA) of the intracranial vessels is increasingly being performed either separately or as part of multimodal CT evaluation of acute ischemic stroke to detect intravascular occlusion by clots, hemodynamically significant stenotic atherosclerotic lesions, arterial dissection and other arteriopathies. CTA provides an independent prognostic factor with proximal, high volume clots predicting poor clinical outcome when compared to distal, low volume clots [1-9].

Recently two classification methods based on the location and the extent of the thrombus detected with CTA have been introduced. BASIS (Boston Acute Stroke Imaging Scale) is a binary classification scheme where patients are designated to have either major or minor stroke [5]. In short, if the distal internal carotid artery (ICA), the proximal (segments M1 and M2) middle cerebral artery (MCA) or the basilar artery is occluded or if there is a significant ischemic lesion either in non-contrast CT (NCCT) or diffusion weighted MRI, the stroke is considered major, otherwise the stroke is considered minor [5]. BASIS is correlated to short-term clinical outcome evaluated at discharge from the hospital and the length and the costs of hospitalization [5, 6]. Clot burden score (CBS) is a more elaborate scheme in which a score from 0 to 10 is given based on the extent of arterial segments affected in the anterior circulation [7, 8]. The scoring system has been pictorially demonstrated by Puetz et al. [8]. CBS is correlated to the clinical and radiological outcomes [7-9].

We reviewed retrospectively the clinical and imaging data of 83 consecutive patients who underwent multimodal CT assessment and received intravenous thrombolytic therapy to treat acute (<3h) ischemic stroke in order to study the performance of BASIS and CBS in predicting the clinical outcome. Further, we correlated the anatomical information conveyed by BASIS and CBS

with CT perfusion (CTP) parameters that reflect the hemodynamic state in the cerebral vasculature and hypothesized that a derived parameter combining both CTA and CTP data might best predict the clinical outcome.

## **Materials and Methods**

### *Overview*

We analyzed retrospectively the clinical and imaging data of 380 consecutive patients who were admitted to Tampere University Hospital between January 2007 and December 2007 because of acute (duration <3h) strokelike symptoms. After clinical and imaging evaluation 92 patients received intravenous rtPA to treat acute ischemic stroke. Among these patients full admission multimodal (NCCT, CTA and CTP) imaging evaluation was successfully completed with 72 patients while an additional 11 patients were evaluated with just NCCT and CTA because of chronic renal failure, imminent closure of the 3h time window or movement artifacts that rendered some of the imaging data uninterpretable. These 83 patients were selected to this study. The selection of patients to receive thrombolytic therapy was based on institutional guidelines that did not have CTP or CTA derived parameters as exclusion or inclusion criteria. Standard intravenous rtPA administration scheme was used: Actilyse (Boehringer-Ingelheim, Ingelheim, Germany), total dose 0.9 mg/kg from which 10% given as a bolus and the remaining 90% as a continuous infusion for 1h. Stable access to an emergency angiography suite was not available at the time so intra-arterial interventions were not included in the treatment protocol. A follow-up NCCT was performed for all patients 24h after the administration of the thrombolytic agent. National Institutes of Health Stroke Scale (NIHSS) was assessed at the admission and 24h after the thrombolytic therapy. Modified Rankin Scale (mRS) was evaluated preictally and on day 90. The clinical data was stored



prospectively to the patient records during the hospital stay and on day 90 after the ictus, the latter following a phone interview. This data was collected from the patient records and critically reviewed for errors using the data available from all medical and related disciplines (J.T.S.). The study was approved by Tampere University Hospital ethics committee.

### *Imaging parameters*

Computed tomography scans were obtained using two different multidetector scanners: General Electrics LightSpeed 16-slice (GE Healthcare, Milwaukee, Wis) and Philips Brilliance 64-slice (Philips, Cleveland, Oh). The imaging procedures and the parameters used are described thoroughly in our previous study available online as an open-access article at the website of the publisher [10].

### *Image analysis*

NCCT examinations were reviewed using dedicated medical imaging workstations. CTA and CTP images were analyzed with Advantage Workstation version 3.2 (GE Healthcare). The examinations were reviewed in the order NCCT, CTA and finally CTP 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. The analysis of the NCCT and the CTP images is detailed in our previous article [10]. CTA images were studied by examining the raw data and maximum intensity projection images. The principles of the CBS scoring system and the assignment of BASIS have been described in recent studies [5, 7]. CBS was scored and BASIS was assigned independently by two radiologists (N.S. and A.L.). In cases where the scoring or the assignment differed, a consensus opinion was agreed on. These

results were correlated with the original neuroradiological report. If significant discrepancies were present the neuroradiologist that had issued the report was further consulted. 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. The interobserver agreement index for BASIS was 95%. The interobserver variability statistics for the other imaging parameters used are described in our previous article [10].

### *Statistics*

The data was analyzed with SPSS version 18 (SPSS Inc., Chicago, Ill). Group comparisons were performed by using the Mann-Whitney U test and the Fisher exact test. Patients with mRS  $\leq 2$  at 90 days were considered to have experienced good clinical outcome. After excluding cases with thrombosis of the basilar artery Receiver-operating characteristic curves (ROC) were computed for the imaging parameters studied using dichotomized clinical outcome as the state variable. Youden index was evaluated to select for optimal threshold value. A binary logistic regression model using the clinical outcome as the dependent variable was repeated for different variables of interest. Age and gender were treated as potential confounders and were controlled for by treating them as covariates. One variable of interest was included in the model at a time. The calibration of the models was evaluated with the Hosmer-Lemeshow test and the discrimination with the C statistic. Odds ratio (OR) with 95% confidence interval (CI) was calculated for each covariate. Sensitivity, specificity and confidence interval calculations were performed using standard procedures. The McNemar test was used to compare the sensitivities and specificities calculated. The Bonferoni correction was applied to adjust for multiple comparisons.

## Results

### *Baseline characteristics*

The median age of the patients was 71 years (interquartile range 62-80 years, 40 female). Based on the clinical features and the imaging studies, in 11 of the 83 patients evaluated (13%) the ischemic episode involved the posterior circulation. The rest of the episodes were considered to involve the anterior circulation. Thrombosis could be demonstrated with CTA in 37 cases (45%). The locations of the thrombi are described in Table 1. In 40 cases (56%) of the 72 evaluated with CTP a perfusion defect could be detected in the ASPECTS planes. An additional 6 perfusion defects were found outside the ASPECTS planes. In total, a perfusion defect could be demonstrated in 64% of the CTP studies (50% of all patients). The median NIHSS score at the admission was 7 (interquartile range 4-12, 54% had NIHSS <8, 18% had NIHSS >15) and 24h later the score was 2. The median time from symptom onset to treatment was 138 minutes (interquartile range 114-162). The median mRS was 1 preictally and 2 90 days later. The median change in mRS ( $\Delta$ mRS) was 1 point. 74% of the patients experienced favorable clinical outcome at 90 days (mRS  $\leq$ 2). At 24h a local hemorrhagic complication (HI1, HI2, PH1 or PH2) was detected in 5 cases (6.0%) and 4 patients (4.8%) had parenchymal hemorrhage distant to the site of the infarct (PHr1 or PHr2). The validation of the ASPECTS scoring method for CTP is depicted in our previous study [10].

### *CBS, BASIS and CBV ASPECTS as prognostic classifiers*

CBS and CBV ASPECTS were dichotomized using the thresholds (CBS >6 and CBV ASPECTS >6) that best differentiated good from poor clinical outcome in the previous studies [7, 10-14]. BASIS is by definition a dichotomous variable that classifies strokes as either major or minor. Table 2

summarizes the comparison of patients in the subgroups so formed for all intracranial vascular territories (n=83) whereas in Table 3 only patients suffering from anterior circulation stroke were included in the analysis (n=72). There was no significant difference in age between the patients in the different subgroups. There were more female patients with major strokes and more male patients with minor strokes according to the BASIS classification ( $p=0.01$ ). As expected, patients with low CBS and CBV ASPECTS scores and patients with major strokes had significantly higher admission NIHSS scores, significantly larger perfusion defects in the CBV and MTT maps and more findings related to acute ischemic process in the admission NCCT. Patients in the low CBS and low CBV ASPECTS subgroups invariably had major stroke according to BASIS. Patients with low CBV ASPECTS and major stroke had more proximal and higher volume thrombi shown by significantly lower CBS. Low CBS and CBV ASPECTS and major stroke significantly predicted poor clinical outcome and larger infarct volume 24 hours after the administration of thrombolytic therapy. The ability of CBS and CBV ASPECTS to predict the clinical outcome was enhanced when only anterior circulation strokes were included in the analysis, whereas the predictive power of BASIS improved when all vascular territories were included in the analysis. BASIS did not reach statistical significance when only patients with anterior circulation strokes were analyzed ( $p=0.23$ ). This is because patients with thrombosis in the M2 segment of the MCA are classified as having major stroke and yet in the study population 83% of these patients had good clinical outcome. If these patients were classified as having minor stroke, BASIS performed considerably better (Table 4). This modification is referred to as *M1-BASIS* in Tables 4, 5 and 6 and in the following paragraphs.

There were eight cases of local and/or peripheral hemorrhagic complications in the study population. In four patients the hemorrhages were mild and did not produce any symptoms. In the other four patients a notable space occupying effect was present. When cross-tabulated with the

dichotomized imaging parameters, none of the parameters predicted hemorrhagic transformation statistically significantly.

In order to further assess the prognostic value of these dichotomous imaging parameters we performed binary logistic regression analysis using the mRS at 90 days dichotomized with the threshold  $\leq 2$  as the dependent variable (Table 5). We also devised a novel parameter which combines CBS and CBV ASPECTS by calculating an unweighted sum of the scores for each patient. This parameter was named *CBSV*. Using ROC analysis with clinical outcome as the state variable, an optimal threshold for dichotomization was calculated for *CBSV* ( $>15$ , AUC=0.72, Figure 1) and this dichotomized variable was entered into the regression analysis. Figure 1 also shows ROC curves for CBS (AUC=0.69) and CBV ASPECTS (AUC=0.70). Age and gender were treated as potential confounders and were controlled for by treating them as covariates. When all vascular territories were included in the analysis, CBV ASPECTS, CBS, *CBSV*, BASIS and M1-BASIS were all significantly associated with the clinical outcome. CBV ASPECTS displayed the largest odds ratio for good clinical outcome ( $p=0.005$ , OR=13.3). NCCT ASPECTS and gender were not significantly associated with the clinical outcome whereas a low NIHSS score at presentation significantly predicted good clinical outcome ( $p=0.007$ ). Age had a modest effect with old age being a risk factor for poor outcome ( $p=0.02$ ). When only anterior circulation strokes were considered, CBV ASPECTS, CBS, *CBSV* and M1-BASIS were significantly associated with the clinical outcome with *CBSV* having the best statistical confidence level ( $p=0.002$ , OR=16.3). CBS displayed the largest odds ratio ( $p=0.005$ , OR=25.1). BASIS did not reach statistical significance.

Sensitivities and specificities for detecting good clinical outcome were calculated for all the imaging parameters that achieved statistical significance in the regression analysis (Table 6). When all vascular territories were included in the analysis, CBV ASPECTS was the most sensitive predictor

of good clinical outcome (0.96, CI 95% = 0.86-0.99) while BASIS had the best specificity (0.57, CI 95% = 0.34-0.77). In the case of sensitivity, the differences between CBV ASPECTS, CBS and CBSV were not statistically significant while BASIS was significantly less sensitive than any of the other parameters. M1-BASIS was less sensitive than CBV ASPECTS ( $p=0.03$ ). In the case of specificity, BASIS and M1-BASIS were significantly more specific when compared to CBS ( $p=0.02$  and  $p=0.04$ , respectively). Otherwise there were no statistically significant differences. When only the anterior circulation was considered, CBV ASPECTS was the most sensitive (0.96, CI 95% = 0.86-0.99) and CBSV the most specific (0.47, CI 95% = 0.22-0.73) predictor. BASIS proved to be significantly less sensitive when compared to all the other parameters ( $p=0.001-0.008$ ). There were no statistically significant differences between specificities. When the Bonferoni correction was applied to adjust for multiple comparisons, BASIS remained to be significantly less sensitive than other parameters both in the case of all vascular territories and the anterior circulation while all other differences were rendered statistically non-significant.

## **Discussion**

Recently a number of imaging parameters have been introduced that may be useful in the risk stratification and the treatment decision making in acute ischemic stroke. We studied the performance of two CTA-based classification schemes, BASIS and CBS, and one perfusion parameter, CBV ASPECTS, in a thrombolytic therapy cohort.

In the absence of adequate collateral circulation vessel recanalization is a necessary condition to favorable clinical outcome. The location, the volume and the composition of the clot essentially determine the effectiveness of intravenous rtPA in dissolving the occluding thrombus [1-9, 15]. The time from the onset of the symptoms to the possible recanalization largely determines the

functional outcome as the duration of parenchymal ischemia dictates the progression of the irreversible changes, i.e. the size of the infarct core [16]. Both BASIS and CBS address the location of the clot while CBS also takes into account the volume. CBV ASPECTS estimates the size of the infarct core.

Patients with low CBS and CBV ASPECTS scores and with major strokes according to BASIS had significantly higher admission NIHSS scores, larger perfusion defects, larger infarct volumes, more findings related to acute ischemic process in the admission NCCT and more often poor clinical outcome. CBS and CBV ASPECTS predicted the clinical outcome more accurately when only anterior circulation strokes were analyzed which is to be expected as these scoring schemes do not include data from the posterior circulation. BASIS, on the other hand, also takes into account the posterior circulation. Thus it performs better when all vascular territories are included in the analysis as patients with occlusion of the basilar artery are correctly classified as having major stroke. However, BASIS did not reach statistical significance when only patients with anterior circulation stroke were analyzed. This is remedied if patients with thrombosis of the M2 segment are classified as having minor stroke ( $p=0.23$  vs.  $p=0.002$ ). This modified BASIS, which we named M1-BASIS, seems to perform slightly better than BASIS also when all vascular territories are included in the analysis. These findings probably reflect the effect of the thrombolytic therapy and support the notion that patients with thrombosis of the M2 segment of the MCA benefit from intravenous thrombolytic therapy whereas a more proximal clot location predicts limited response [1, 3, 9, 17]. Only a minority of patients (8%) received thrombolytic therapy in the study population that was originally used to validate BASIS [5].

In the logistic regression analysis dichotomized M1-BASIS, CBV ASPECTS, CBS and BASIS were all significantly associated with the clinical outcome ( $p=0.001$ ,  $p=0.005$ ,  $p=0.02$  and  $p=0.01$ ,

respectively). When only anterior circulation strokes were considered, the sum of CBS and CBV ASPECTS, a novel variable which we named CBSV, proved to be the most robust predictor of favorable outcome ( $p=0.002$ , OR=16.3). CBSV combines two independent predictors of clinical outcome that reflect different pathophysiological processes: CBV ASPECTS that approximates the volume of already irreversibly damaged brain tissue and CBS that provides information about clot extent and location [7, 8, 10]. Thus, theoretically CBSV should have better predictive power than either of its components. This is supported by our results.

CBV ASPECTS, CBS, CBSV and M1-BASIS all had high sensitivity (85-96%) but moderate to poor specificity (24-52%) in predicting good clinical outcome. The rather modest specificity is to be expected as not all patients with potentially favorable profile experience recanalization and as strategic infarcts may cause serious functional deficit with minimal imaging findings. Further, there were 4 patients (2 with anterior circulation strokes) with prestroke mRS >2 that were classified as low risk patients by CBS, CBV ASPECTS and CBSV, which decreases the specificity of these parameters somewhat. BASIS was only moderately sensitive (70-71%). There were no statistically significant differences between specificities after the Bonferoni correction was applied to adjust for multiple comparisons. Tan et al. found CBS to be less sensitive but more specific when compared to our findings [7]. This is probably due to considerably higher median NIHSS score (16) and lower proportion of patients treated with rtPA (70.5%) in their study population.

Our study is limited by retrospective design and sample size. There was some heterogeneity in the details of treatment and variation in onset-to-needle times which are to be expected in a clinically managed population. Because of the study design data on vessel recanalization was not available for the majority of the patients. However, a large final infarct volume is intimately related to delayed or failed recanalization and can be used as a surrogate. M1-BASIS was created based on a



post hoc analysis of the data set and should be further validated in other thrombolytic therapy cohorts.

In conclusion, novel imaging parameters that lie upstream to clinical parameters (NIHSS) in the pathophysiological chain of ischemic stroke potentially allow higher resolution in the risk stratification and the treatment decision making. Optimally a selection of markers portraying different aspects of the disease state and having independent prognostic value would be utilized. These markers include anatomical angiographic data revealing the location and the extent of the clot (CBS and BASIS) and dynamic perfusion data enabling the detection of irreversibly damaged and potentially salvageable brain tissue (CBV ASPECTS and CTP ASPECTS mismatch) [10]. We demonstrated that CBS, BASIS and CBV ASPECTS are statistically robust and sensitive but unspecific predictors of good clinical outcome among patients receiving intravenous thrombolytic therapy. We introduced two derived imaging parameters, CBSV and M1-BASIS, that essentially share these same properties but seem to have slightly better prognostic accuracy. BASIS was significantly less sensitive than the other parameters studied.

## **Disclosures**

Conflict of interest statement: We declare that we have no conflict of interest.

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**Table 1. The location of the clot in CT angiography.** A thrombus could be detected in 44.6% of the studies. The most common locations were the M2 and the M1 segments of the MCA. There were 8 cases of thrombosis of the basilar artery. The most distant thrombi detected were situated in the M3 segment.

<b>Thrombus location</b>	<b>n</b>	<b>%</b>
Basilar artery	8	9.6
PCA P2 segment	2	2.4
SCA	1	1.2
MCA M1 segment	10	12.0
MCA M2 segment	12	14.5
MCA M3 segment	3	3.6
ICA	1	1.2
<b>Total detected</b>	<b>37</b>	<b>44.6</b>
<b>Not detected</b>	<b>46</b>	<b>55.4</b>

**Table 2. All patients arranged into subgroups according to dichotomized CBS, CBV ASPECTS and BASIS.** Patients with low CBS and CBV ASPECTS scores and with major strokes according to BASIS had significantly higher admission NIHSS scores, larger perfusion defects, larger infarct volumes and more often poor clinical outcome. Patients in the low CBS and low CBV ASPECTS subgroups invariably had major stroke according to BASIS. Patients with low CBV ASPECTS and major stroke had more proximal and higher volume thrombi as reflected by significantly lower CBS. All values mean  $\pm$  1SD unless otherwise noted.  $\Delta$ mRS = mRS at 90 days – prestroke mRS.

	<b>All Vascular Territories</b>								
	<b>Clot Burden Score</b>			<b>CBV ASPECTS</b>			<b>BASIS</b>		
	CBS $\leq$ 6 n = 9	CBS > 6 n = 74	p value	CBV $\leq$ 6 n = 8	CBV > 6 n = 64	p value	major n = 32	minor n = 51	p value
<b>mRS at 90 days</b>	3.0 $\pm$ 2.0	2.0 $\pm$ 1.6	0.05	4.0 $\pm$ 1.3	1.8 $\pm$ 1.4	0.002	3.0 $\pm$ 1.9	1.7 $\pm$ 1.3	0.04
<b><math>\Delta</math>mRS</b>	2.6 $\pm$ 1.9	1.1 $\pm$ 1.4	0.01	3.3 $\pm$ 0.9	0.9 $\pm$ 1.3	< 0.001	2.1 $\pm$ 1.8	0.8 $\pm$ 1.1	0.004
<b>Infarct volume (cm<sup>3</sup>)</b>	60.1 $\pm$ 66.2	9.4 $\pm$ 21.5	0.001	87.5 $\pm$ 60.1	7.6 $\pm$ 16.3	< 0.001	33.1 $\pm$ 47.5	3.5 $\pm$ 7.8	< 0.001
<b>CBS</b>	5.2 $\pm$ 1.7	9.7 $\pm$ 0.6	-	6.9 $\pm$ 1.6	9.5 $\pm$ 1.4	< 0.001	8.0 $\pm$ 2.1	10.0 $\pm$ 0.0	< 0.001
<b>BASIS (major/minor)</b>	9 / 0	23 / 51	< 0.001	8 / 0	18 / 46	< 0.001	32 / 0	0 / 51	-
<b>CBV ASPECTS</b>	6.8 $\pm$ 2.8	9.4 $\pm$ 1.5	0.001	4.4 $\pm$ 0.7	9.7 $\pm$ 0.7	-	7.6 $\pm$ 2.4	10.0 $\pm$ 0.2	< 0.001
<b>MTT ASPECTS</b>	2.4 $\pm$ 1.1	8.3 $\pm$ 2.5	< 0.001	2.9 $\pm$ 1.5	8.3 $\pm$ 2.6	< 0.001	4.6 $\pm$ 2.7	9.4 $\pm$ 1.2	< 0.001
<b>NCCT ASPECTS</b>	8.6 $\pm$ 1.7	9.6 $\pm$ 1.2	0.04	7.4 $\pm$ 2.6	9.7 $\pm$ 0.9	0.001	8.8 $\pm$ 1.9	9.9 $\pm$ 0.5	< 0.001
<b>Admission NIHSS</b>	13.6 $\pm$ 4.4	8.2 $\pm$ 6.4	0.008	15.5 $\pm$ 3.2	7.6 $\pm$ 5.6	0.001	13.3 $\pm$ 7.0	6.1 $\pm$ 4.3	< 0.001
<b>Gender (female/male)</b>	7 / 2	33 / 41	0.08	5 / 3	30 / 34	0.47	21 / 11	19 / 32	0.01
<b>Age</b>	63.3 $\pm$ 17.8	69.4 $\pm$ 13.5	0.34	74.1 $\pm$ 11.4	68.0 $\pm$ 14.8	0.24	69.5 $\pm$ 13.2	68.3 $\pm$ 14.7	0.81

**Table 3. Patients with anterior circulation stroke arranged into subgroups according to dichotomized CBS, CBV ASPECTS and BASIS.** The ability of CBS and CBV ASPECTS to predict the clinical outcome improved when only anterior circulation strokes were included in the analysis. Interestingly, BASIS did not reach statistical significance when only patients with anterior circulation stroke were analyzed. All values mean  $\pm$  1SD unless otherwise noted.  $\Delta$ mRS = mRS at 90 days – prestroke mRS.

### Anterior Circulation

	Clot Burden Score			CBV ASPECTS			BASIS		
	CBS $\leq$ 6	CBS $>$ 6	<i>p</i> value	CBV $\leq$ 6	CBV $>$ 6	<i>p</i> value	major	minor	<i>p</i> value
	n = 9	n = 63		n = 8	n = 58		n = 24	n = 48	
<b>mRS at 90 days</b>	3.0 $\pm$ 2.0	1.7 $\pm$ 1.4	0.02	4.0 $\pm$ 1.3	1.7 $\pm$ 1.4	0.001	2.5 $\pm$ 1.6	1.6 $\pm$ 1.4	0.23
<b><math>\Delta</math>mRS</b>	2.6 $\pm$ 1.9	0.9 $\pm$ 1.1	0.005	3.3 $\pm$ 0.9	0.8 $\pm$ 1.2	< 0.001	1.8 $\pm$ 1.5	0.7 $\pm$ 1.1	0.02
<b>Infarct volume (cm<sup>3</sup>)</b>	60.1 $\pm$ 66.2	8.9 $\pm$ 22.2	0.001	87.5 $\pm$ 60.1	6.8 $\pm$ 15.5	< 0.001	40.0 $\pm$ 52.1	3.2 $\pm$ 7.3	< 0.001
<b>CBS</b>	5.2 $\pm$ 1.7	9.7 $\pm$ 0.6	-	6.9 $\pm$ 1.6	9.4 $\pm$ 1.5	< 0.001	7.4 $\pm$ 2.0	10.0 $\pm$ 0.0	< 0.001
<b>BASIS (major/minor)</b>	9 / 0	15 / 48	< 0.001	8 / 0	15 / 43	< 0.001	24 / 0	0 / 48	-
<b>CBV ASPECTS</b>	6.8 $\pm$ 2.8	9.3 $\pm$ 1.5	0.001	4.4 $\pm$ 0.7	9.7 $\pm$ 0.7	-	7.3 $\pm$ 2.4	10.0 $\pm$ 0.2	< 0.001
<b>MTT ASPECTS</b>	2.4 $\pm$ 1.1	8.2 $\pm$ 2.5	< 0.001	2.9 $\pm$ 1.5	8.1 $\pm$ 2.7	< 0.001	4.0 $\pm$ 2.2	9.4 $\pm$ 1.3	< 0.001
<b>NCCT ASPECTS</b>	8.6 $\pm$ 1.7	9.5 $\pm$ 1.3	0.01	7.4 $\pm$ 2.6	9.7 $\pm$ 0.9	0.001	8.4 $\pm$ 2.0	9.9 $\pm$ 0.5	< 0.001
<b>Admission NIHSS</b>	13.6 $\pm$ 4.4	7.4 $\pm$ 5.1	0.003	15.5 $\pm$ 3.2	7.0 $\pm$ 4.7	< 0.001	11.7 $\pm$ 5.5	6.3 $\pm$ 4.4	< 0.001
<b>Gender (female/male)</b>	7 / 2	25 / 38	0.07	5 / 3	25 / 33	0.45	16 / 8	16 / 32	0.01
<b>Age</b>	63.3 $\pm$ 17.8	68.8 $\pm$ 13.9	0.41	74.1 $\pm$ 11.4	67.6 $\pm$ 15.0	0.20	68.3 $\pm$ 13.9	68.0 $\pm$ 14.8	0.98

**Table 4. Patients arranged into subgroups according to M1-BASIS, all vascular territories and the anterior circulation.** If patients with thrombosis in the M2 segment of the MCA were classified as having minor stroke, BASIS had considerably better prognostic value. This modification was named M1-BASIS. All values mean  $\pm$  1SD unless otherwise noted.  $\Delta$ mRS = mRS at 90 days – prestroke mRS.

	<b>M1-BASIS</b>					
	<b>All Vascular Territories</b>			<b>Anterior Circulation</b>		
	major n = 21	minor n = 62	p value	major n = 13	minor n = 59	p value
<b>mRS at 90 days</b>	2.9 $\pm$ 1.9	1.7 $\pm$ 1.3	0.02	3.5 $\pm$ 2.1	1.7 $\pm$ 1.3	0.002
<b><math>\Delta</math>mRS</b>	2.3 $\pm$ 1.8	0.8 $\pm$ 1.1	0.001	2.6 $\pm$ 2.0	0.8 $\pm$ 1.1	< 0.001
<b>Infarct volume (cm<sup>3</sup>)</b>	54.4 $\pm$ 59.3	6.6 $\pm$ 18.3	< 0.001	39.0 $\pm$ 51.9	6.8 $\pm$ 17.9	0.001
<b>CBS</b>	6.2 $\pm$ 2.2	9.8 $\pm$ 0.5	< 0.001	7.7 $\pm$ 2.5	9.8 $\pm$ 0.5	< 0.001
<b>BASIS (major/minor)</b>	13 / 0	9 / 50	< 0.001	21 / 0	11 / 51	< 0.001
<b>CBV ASPECTS</b>	6.6 $\pm$ 2.7	9.6 $\pm$ 1.1	< 0.001	7.3 $\pm$ 2.8	9.6 $\pm$ 1.1	< 0.001
<b>MTT ASPECTS</b>	2.8 $\pm$ 1.6	8.5 $\pm$ 2.3	< 0.001	4.1 $\pm$ 3.1	8.6 $\pm$ 2.2	< 0.001
<b>NCCT ASPECTS</b>	8.0 $\pm$ 2.2	9.7 $\pm$ 1.0	< 0.001	8.7 $\pm$ 2.0	9.7 $\pm$ 0.9	0.005
<b>Admission NIHSS</b>	13.5 $\pm$ 4.5	6.9 $\pm$ 4.8	< 0.001	15.4 $\pm$ 6.7	6.7 $\pm$ 4.7	< 0.001
<b>Gender (female/male)</b>	8 / 5	24 / 35	0.22	13 / 8	27 / 35	0.21
<b>Age</b>	66.3 $\pm$ 15.6	68.5 $\pm$ 14.2	0.71	68.8 $\pm$ 14.0	68.7 $\pm$ 14.2	0.97



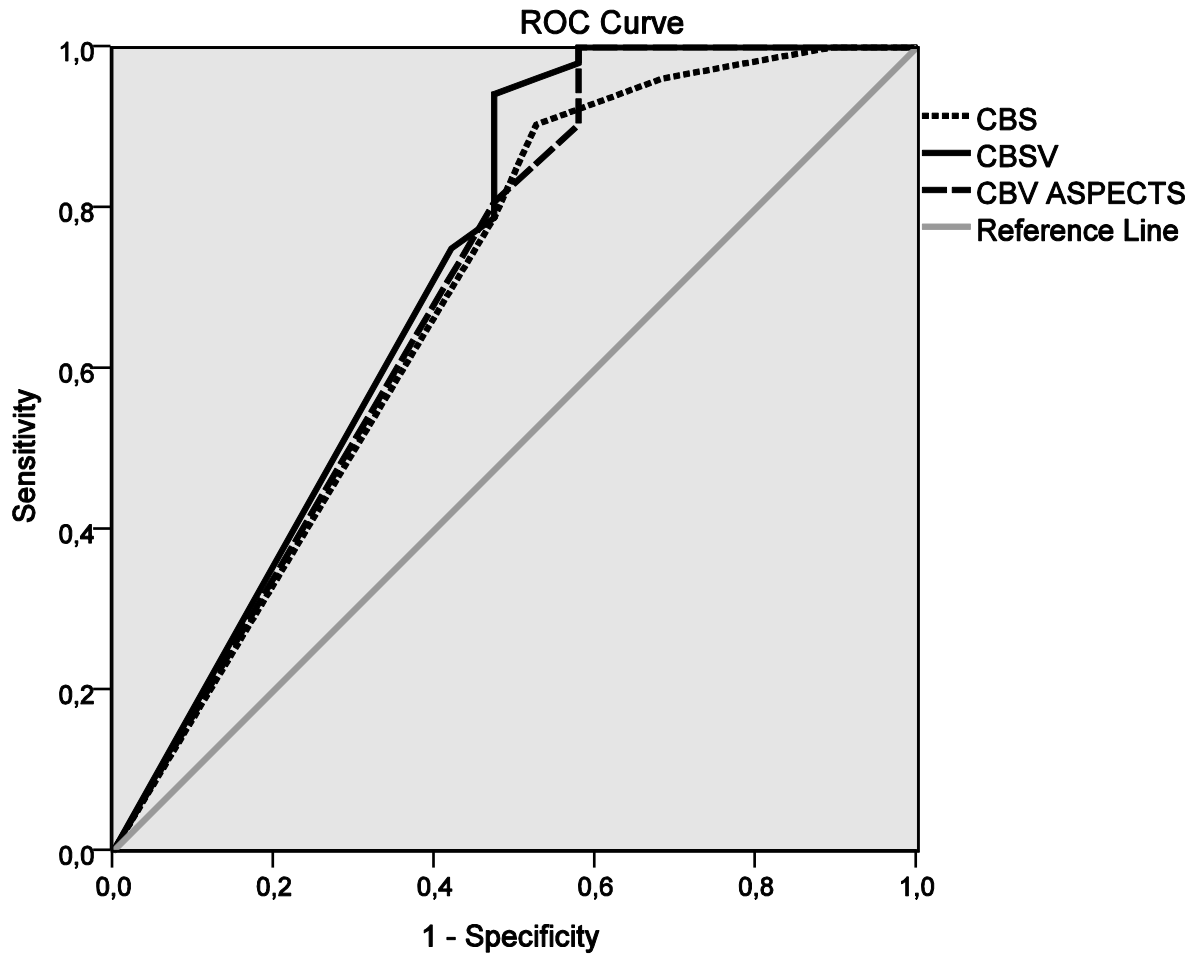
**Table 5. Binary logistic regression analysis for favorable clinical outcome (mRS  $\leq$  2 at 90 days), all vascular territories and the anterior circulation.** CBV ASPECTS, CBS and BASIS were all significantly associated with the clinical outcome with M1-BASIS having the best statistical confidence level in predicting of good clinical outcome when all vascular territories were included in the analysis. When only anterior circulation strokes were considered, the sum of CBS and CBV ASPECTS (CBSV) proved to be the most robust predictor. CI = Confidence Interval, H-L = Hosmer-Lemeshow significance, C = C statistic.

	All Vascular Territories					Anterior Circulation				
	Odds ratio	CI 95%	p value	H-L	C	Odds ratio	CI 95%	p value	H-L	C
<b>CBV ASPECTS &gt; 6</b>	13.3	2.2 - 79.7	0.005	0.51	0.75	15.3	2.4 - 98.8	0.004	0.88	0.79
<b>CBS &gt; 6</b>	11.6	1.7 - 77.1	0.01	0.36	0.74	25.1	2.6 - 240	0.005	0.16	0.80
<b>M1-BASIS (minor)</b>	8.7	2.4 - 31.6	0.001	0.92	0.80	7.3	1.5 - 34.0	0.01	0.70	0.78
<b>BASIS (minor)</b>	3.9	1.2 - 12.9	0.02	0.23	0.74	2.6	0.66 - 10.2	0.17	0.83	0.73
<b>CBSV &gt; 15</b>	12.1	2.4 - 60.8	0.003	0.48	0.76	16.3	2.7 - 98.8	0.002	0.71	0.80
<b>NCCT ASPECTS &gt; 7</b>	1.2	0.1 - 13.9	0.89	0.77	0.70	1.5	0.12 - 18.0	0.76	0.82	0.72
<b>Admission NIHSS</b>	0.87	0.79 - 0.96	0.007	0.86	0.79	0.82	0.71 - 0.94	0.004	0.54	0.85
<b>Onset-to-treatment time</b>	0.99	0.98 - 1.01	0.29	0.06	0.71	1.01	0.99 - 1.03	0.36	0.21	0.71
<b>Gender</b>	0.98	0.33 - 2.9	0.97	0.89	0.69	0.73	0.36 - 4.3	0.58	0.38	0.72
<b>Age</b>	0.95	0.90 - 0.99	0.02	0.89	0.69	0.94	0.89 - 0.99	0.03	0.38	0.72

**Table 6. Sensitivities and specificities for detecting good clinical outcome (mRS  $\leq 2$  at 90 days) for the imaging parameters that achieved statistical significance in the regression analysis.** When all vascular territories were included in the analysis, CBV ASPECTS was the most sensitive predictor of good clinical outcome while BASIS had the best specificity. When only the anterior circulation was considered, CBV ASPECTS was the most sensitive and CBSV the most specific predictor. In both settings BASIS was significantly less sensitive when compared to all the other parameters. CI = Confidence Interval, Se = Sensitivity, Sp = Specificity, Acc = Accuracy.

	<b>All Vascular Territories</b>					<b>Anterior Circulation</b>				
	<b>Se</b>	<b>CI 95%</b>	<b>Sp</b>	<b>CI 95%</b>	<b>Acc</b>	<b>Se</b>	<b>CI 95%</b>	<b>Sp</b>	<b>CI 95%</b>	<b>Acc</b>
<b>CBV ASPECTS &gt; 6</b>	0.96	0.86 - 0.99	0.35	0.15 - 0.61	0.82	0.96	0.85 - 0.99	0.40	0.17 - 0.67	0.83
<b>CBS &gt; 6</b>	0.93	0.83 - 0.98	0.24	0.09 - 0.48	0.77	0.93	0.82 - 0.98	0.35	0.13 - 0.61	0.76
<b>CBSV &gt; 15</b>	0.93	0.81 - 0.98	0.41	0.19 - 0.67	0.80	0.92	0.80 - 0.97	0.47	0.22 - 0.73	0.82
<b>M1-BASIS</b>	0.85	0.73 - 0.92	0.52	0.30 - 0.74	0.77	0.88	0.75 - 0.94	0.40	0.17 - 0.67	0.77
<b>BASIS</b>	0.70	0.57 - 0.81	0.57	0.34 - 0.77	0.67	0.71	0.58 - 0.82	0.41	0.19 - 0.67	0.66

**Figure 1. Receiver-operating characteristic curves for CBSV, CBS and CBV ASPECTS with clinical outcome as the state variable. Good clinical outcome was defined as mRS  $\leq 2$  at 90 days.  $AUC_{CBSV} = 0.72$ ,  $AUC_{CBV\ ASPECTS} = 0.70$  and  $AUC_{CBS} = 0.69$ .**



# 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

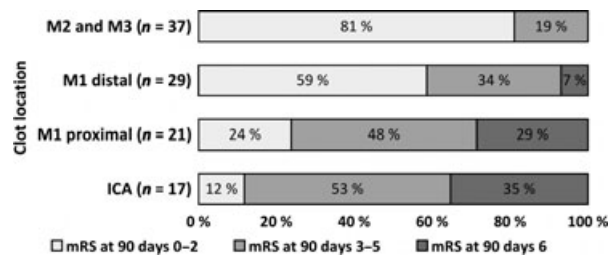
A biostatistician was consulted (H.H.). The data were analyzed with spss version 18 (SPSS Inc., Chicago, IL, USA). Group comparisons were performed using the Student *t*-test, the Chi-squared test, the Fisher exact test, and the Kruskal–Wallis test. The Bonferroni correction for multiple comparisons 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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# **Comparison of 64-row and 16-row Multidetector CT in the Perfusion CT Evaluation of Acute Ischemic Stroke Patients Receiving Intravenous Thrombolytic Therapy**

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## **Abstract**

**Purpose:** Perfusion computed tomography (PCT) is increasingly performed in multimodal CT evaluation of acute ischemic stroke. We compared the technical quality of perfusion studies performed with a 16-row and a 64-row scanner and analyzed the differences between the scanners in their ability to detect perfusion defects.

**Methods:** We analyzed retrospectively the clinical and imaging data of 140 consecutive acute (<3h) stroke patients who underwent multimodal CT evaluation and received intravenous rtPA. Alberta Stroke Program Early CT Score (ASPECTS) was assigned to PCT maps. Clinical and imaging parameters were compared between the two scanners.

**Results:** There were more motion artifacts in the 16-row studies ( $p=0.04$ ) and the analysis software was able to completely correct significantly fewer of these ( $p<0.001$ ). Both ASPECTS levels were optimally covered in only 29% of the 16-row studies whereas in the 64-row studies both levels were invariably optimally visualized ( $p<0.001$ ). This significantly decreased the sensitivity of the 16-row scanner to detect perfusion defects in the upper ASPECTS level ( $p=0.02$ ). The 64-row scanner was able to detect more perfusion defects that were located entirely outside the ASPECTS regions ( $p=0.03$ ). There was no significant difference in the 3-month functional outcome.

**Conclusions:** The 16-row scanner suffered from limited anatomic coverage that decreased the sensitivity to detect perfusion defects in the cranial parts of the middle cerebral artery region. The 16-row studies had poorer technical quality that was in part attributable to higher sampling frequency and smaller slice thickness making the imaging more sensitive to small scale movement of the patient.

**Abbreviation key:** AIF = arterial input function, ASPECTS = Alberta Stroke Program Early CT Score, CBV = cerebral blood volume, MCA = middle cerebral artery, MRI = magnetic resonance imaging, MTT = mean transit time, NCCT = non-contrast-enhanced computed tomography, NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin Scale, PCT = perfusion computed tomography, rtPA = recombinant tissue plasminogen activator, VOF = venous output function

**Key words:** computed tomography perfusion, thrombolytic therapy, stroke

## Introduction

Multimodal CT imaging may improve the prognosis of acute stroke patients especially in the context of revascularization therapy [1]. The heart of the multimodal approach is the perfusion study which allows the 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 MRI [2-4]. However, the availability of MRI in an acute setting is scarce and motion artifacts and length of the study induce limitations. Perfusion CT (PCT) has emerged as an alternative to MRI [5-8]. The pathophysiologic information obtained from PCT is comparable to that of MRI [9-10].

The main disadvantages of PCT are limited craniocaudal (z-axis) anatomic coverage, typically 20 to 80mm with 16- and 64-row scanners, and insensitivity in detecting lacunar ischemic events [11-12]. State-of-the-art scanners can achieve whole brain coverage [13], but the bulk of acute stroke imaging will be performed with 16- and 64-row scanners for several years to come.

The impact of using CT scanners of differing detector widths and acquisition protocols in the imaging evaluation of stroke has been little studied previously in the context of acute revascularization therapy. We reviewed retrospectively the clinical and imaging data of 140 consecutive acute (<3h) ischemic stroke patients who underwent full multimodal CT assessment with either a 64-row or a 16-row scanner and received intravenous thrombolytic therapy. We compared the technical quality of the perfusion studies and analyzed the differences in the ability to detect perfusion defects between the two scanners. We hypothesized that the 16-row scanner might miss information potentially critical to the clinical decision making when compared to the 64-row scanner.

## Materials and Methods

### *Overview*

We analyzed retrospectively the clinical and imaging data of 140 consecutive patients who were admitted to Tampere University Hospital between January 2006 and December 2007 because of acute (duration <3h) strokelike symptoms, imaged with non-contrast computed tomography (NCCT) and PCT and who subsequently received intravenous recombinant tissue plasminogen activator (rtPA) to treat acute ischemic stroke. The patients were scanned with either a 64-row or a 16-row scanner located in neighboring rooms. Although the patients were not explicitly randomized to be imaged with either scanner, the selection of the scanner was effectively random. The decision to administer thrombolytic therapy was based on institutional guidelines that did not have PCT derived parameters as exclusion or inclusion criteria at the time. Standard intravenous rtPA administration scheme was used: Actilyse (Boehringer-Ingelheim, Ingelheim, Germany), total dose 0.9 mg/kg from which 10% given as a bolus and the remaining 90% as a continuous infusion for 1h. A follow-up NCCT was performed for all patients 24h after the administration of the thrombolytic agent. National Institutes of Health Stroke Scale (NIHSS) was assessed at the admission and 24h after the thrombolytic therapy. Modified Rankin Scale (mRS) was evaluated preictally and on day 90. The clinical data was stored prospectively to the patient records during the hospital stay and on day 90 after the ictus, the latter following a phone interview. This data was collected from the patient records and critically reviewed for errors using the data available from all medical and related disciplines. The study was approved by (\*\*) Hospital ethics committee.

### *Imaging parameters*

CT scans were obtained using two different multidetector scanners: General Electrics LightSpeed 16-row (GE Healthcare, Milwaukee, Wis) and Philips Brilliance 64-row (Philips, Cleveland, Oh). Brain NCCT was performed using the parameters 120 kV, 430 mAs, collimation 12 x 1.25mm, rotation 1.5s (64-row) or 120kV, 320mAs, collimation 16 x 1.25mm, rotation 1s (16-row). Contiguous slices were reconstructed to the thickness of 5mm in the whole scanning range (64-row) or to the thickness of 5mm in the skull base and 7.5mm in the supratentorial region (16-row). PCT was performed using the parameters 80kV, 200mAs (effective), collimation 32 x 1.25mm, rotation 0.4s (64-row) or 80kV, 200mAs, collimation 8 x 2.5mm, rotation 1s (16-row). 120 slices covering a range of 80mm were generated in 55s using a protocol utilizing two alternating table positions to increase z-axis coverage, i.e. 'shuttle mode' (64-row), or 200 slices covering a range of 20mm were generated in 50s with a stationary table position (16-row). Contiguous slices were reconstructed to the thickness of 10mm (64-row) or to the thickness of 5mm (16-row) at even time intervals. The imaging range was positioned so that the Alberta Stroke Program Early CT Score (ASPECTS) levels [14] would be covered. The rest of the 80mm range (64-row) was positioned both cranial and caudal to the ASPECTS levels with the exact balancing depending on the clinical presentation. The contrast agent (Xenetix 350 mgI/ml, Aulnay-sous-Bois, France) was administered through an antecubital 18G cannula using a double piston power injector with a flow rate of 5ml/s using 60ml of contrast agent followed by a 40ml saline flush.

### *Image analysis*



The NCCT examinations were reviewed using dedicated medical imaging workstations. The PCT images were analyzed and areas and volumes were measured with Advantage Workstation version 3.2 (GE Healthcare). Parametric perfusion maps – mean transit time (MTT) and cerebral blood volume (CBV) – were generated with the CT Perfusion 3 software (GE Healthcare) that uses a deconvolution based algorithm. The anterior cerebral artery (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 potentially affecting the calculations. Minor rippling of the signal, although a phenomenon caused by noise sources, was not recorded as noise in this context. Persisting poor image quality was corrected when feasible by manually adjusting the parameters that control the motion artifact correction algorithm of the software.

The use of ASPECTS in reporting and quantifying the PCT findings was dictated by the limited anatomic coverage of the 16-row scanner and the differing slice thicknesses. ASPECTS offers an attracting measure of coverage as it has been designed to reflect most of the volume of the middle cerebral artery (MCA) territory. It also has clinical relevance. The principles of ASPECTS scoring in NCCT and PCT maps and the evaluation of PCT ASPECTS mismatch (core-penumbra mismatch) have been described in previous studies [11, 14-15]. In short, each hemisphere is divided to 10 regions in two axial sections at the level of the basal ganglia (the ganglionic level) and corona radiata (the supraganglionic level). Each of these regions has a score of one point. This point is deducted if the region has ischemic changes. Thus a negative finding yields a score of 10 and extensive ischemia covering the whole MCA region yields a score of 0. The location of the image section closest to a ASPECTS level was considered suboptimal if the location did not *exactly* correspond to the reference level described in the literature [14] but allowed reliable scoring.

ASPECTS was considered not interpretable if this section clearly represented a different anatomic region, for example the cranial parts of the basal ganglia when evaluating the upper level.

MTT maps were used to detect tissue at risk and CBV maps were used to approximate the infarct core. We adopted a semiquantitative approach where the presence of a perfusion defect was determined from color coded maps visually by comparing the appearance of the affected location to that of the healthy tissue on the contralateral side. In order to increase the accuracy of the measurements and based on theoretical considerations we required that the area measured in the visually identified location was larger than  $25\text{mm}^2$  with mean  $\text{MTT} > 7\text{s}$  (or mean  $\text{CBV} < 2.5\text{ mL}/100\text{g}$ , correspondingly). The technical quality of the study was assessed, the NCCT and PCT ASPECTS scores were assigned and the other imaging parameters were evaluated by two radiologists. In cases where the findings differed, a consensus was agreed on. These findings were correlated with the original report issued by an experienced neuroradiologist and if significant discrepancies were present that neuroradiologist was further consulted. The examinations were reviewed in the order NCCT first and then PCT 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. Perfusion defect areas and final infarct volumes were measured by one radiologist. The boundaries of the affected areas were determined visually and absolute value thresholds described above were applied. Volume was calculated by multiplying the measured area with the slice thickness. Intraclass correlation coefficients (ICC) between a staff radiologist and an experienced neuroradiologist were calculated for ASPECTS assignments in a test sample ( $n=20$ ):  $\text{ICC}_{\text{NCCT}}=0.86$ ,  $\text{ICC}_{\text{MTT}}=0.79$ ,  $\text{ICC}_{\text{CBV}}=0.73$  and  $\text{ICC}_{\text{NCCT}24\text{h}}=0.93$ . Median interobserver agreement indices for areas and volumes were  $\text{AREA}_{\text{MTT}}$ : 68%,  $\text{AREA}_{\text{CBV}}$ : 90% and  $\text{VOLUME}_{\text{INFARCT}}$ : 80%.

## *Statistics*

The data was analyzed with SPSS version 18 (SPSS Inc., Chicago, Ill). Patients with mRS $\leq$ 2 at 90 days were considered to have experienced good clinical outcome. Group comparisons were performed by using the Student t-test, the Mann-Whitney U test, the Chi-squared test and the Fisher exact test depending on the variable analyzed. The Bonferroni correction was applied to adjust for multiple comparisons.

## **Results**

### *Baseline characteristics*

The median age of the patients was 71 years (interquartile range 58-80 years, 45% female). The 64-row scanner was used to perform the perfusion study with 67 patients (48%). A perfusion defect could be detected in the ASPECTS levels in 70 cases (50%). An additional 9 perfusion defects were found outside the ASPECTS levels. In total, a perfusion defect could be demonstrated in 56% of the PCT studies. Based on the clinical features and the imaging studies, in 16 of the 140 patients evaluated (11%) the ischemic episode involved the posterior circulation.

The median NIHSS score at the admission was 7 (interquartile range 4-12, 54% had NIHSS $<$ 8, 13% had NIHSS $>$ 15) and 24h later the median score was 2. The median mRS was 1 preictally and 2 three months later. Seventy-seven percent of the patients experienced favorable clinical outcome at 90 days (mRS $\leq$ 2). At 24h a local hemorrhagic complication (HI1, HI2, PH1 or PH2) was detected in 5 cases (3.6%) and 4 patients (2.9%) had parenchymal hemorrhage distant to the site of the infarct (PHr1 or PHr2).

The differences in age, admission NIHSS, prestroke mRS, total infarct volume at 24h, number of hemorrhagic complications or onset-to-treatment times were not statistically significant between the patients imaged with the 64-row and the ones examined with the 16-row scanner (Table 1). Further, the clinical outcome (mRS at 90 days) was not significantly different in these groups. There were significantly fewer females in the 16-row group ( $p=0.02$ ).

#### *Comparison of the technical quality of the perfusion studies*

The 16-row studies suffered in quality because of limited anatomic coverage (20mm vs. 80mm) and higher sampling frequency (1/s vs. 0.27/s) that combined with smaller slice thickness (5mm vs. 10mm) rendered the image acquisition more susceptible to motion artifacts. Six studies out of 140 (4%) were deemed not reliably interpretable because of severe motion artifacts and/or because AIF and/or VOF did not peak during the scan due to hemodynamic or technical reasons (Table 2). While all of these studies were performed with the 16-row scanner ( $p=0.03$ ), there were no statistically significant differences between the scanners in AIF or VOF not peaking. However, the AIF and the VOF curves were significantly noisier in the 16-row studies ( $p<0.001$ ). This is in part related to the larger number of motion artifacts in the 16-row group ( $p=0.04$ ). The analysis software was able to completely correct significantly fewer of these artifacts in the 16-row group ( $p=0.001$ ). A typical artifact resulting from minute movement (eg. tremor) that was incompletely corrected by the software but that did not render the study uninterpretable is demonstrated in Figure 1. Both ASPECTS levels were optimally covered in only 29% of the 16-row studies whereas in the 64-row studies both levels were optimally included in the imaging volume in every case ( $p<0.001$ ). In 46 of the 16-row studies (63%) only the lower level was optimally covered. ASPECTS

could not be reliably assigned for the upper level because of this in 26 cases (34%). There were 2 cases (3%) where the lower level could not be scored. Suboptimal slice orientation due to anteroposterior or lateral tilt was found in 9 studies (6%) with no significant differences between the scanners. The 64-row scanner was able to fully or partially visualize also the subtentorial compartment significantly more often because of the larger craniocaudal coverage ( $p<0.001$ ).

#### *Comparison of the perfusion defect detection properties*

There were no statistically significant differences between the scanners in the ASPECTS scores for MTT and CBV maps or the ASPECTS mismatch scores (Table 3). Nor were there significant differences when the upper and the lower ASPECTS levels were analyzed individually. When the ASPECTS regions that were missed by the 16-row scanner because of limited anatomic coverage were scored normal and included in the analysis, the average number of regions affected in the upper level diminished reflecting decreased sensitivity in the detection. In the case of MTT the difference became statistically significant when compared to the 64-row scanner ( $p=0.02$ ).

However, there were no significant differences between the scanners in the total MTT and CBV scores or the mean and number of ASPECTS mismatches in this setting either.

There were in total 9 patients (6%) who had perfusion defects that were located entirely outside the regions covered by the ASPECTS levels and the volume between the levels (Table 3). Eight of them were detected by the 64-row scanner ( $p=0.03$ ).

## **Discussion**

We compared the technical quality of perfusion studies performed with a 16-row and a 64-row scanner and analyzed the differences between the scanners in their ability to detect perfusion defects in a clinically managed intravenous thrombolytic therapy cohort.

The 64-row scanner covered 80mm of the z-axis while the 16-row scanner covered 20mm. The coverage of the 64-row scanner was increased by alternating the table between two positions. This procedure can be utilized also with 16-row scanners resulting in 40-mm-coverage. Another method to double the imaging volume is to use two contrast injections and image adjoining 20mm ranges separately. While these techniques improve the detection rate of perfusion defects, the results are still inferior compared to z-axis ranges larger than 40mm [16, 17].

The selection of the scanner the patient was imaged with was based on availability or the preferences of the imaging nurses performing the scanning procedure when both scanners were available. Although the patients were not explicitly randomized to be imaged with either scanner, effectively randomization took place as the presence of a selection bias is very unlikely. This is reflected by close to equal number of PCT studies performed with the scanners during the 2 years and the similarity of other baseline characteristics between the study groups (Table 1).

The 16-row studies suffered in quality because of limited anatomic coverage that often resulted in inadequate visualization of the cranial MCA region evident in the finding that ASPECTS could not be assigned to the upper level in one-third (34%) of the studies (Table 2). This led to significantly decreased sensitivity in the detection of perfusion defects in the upper level (Table 3). However, this has only a mild impact in the overall ASPECTS score as the lower level is weighted considerably heavier (7 vs. 3 regions). Further, there were no significant differences in the number and extent of perfusion mismatches found (Table 3). The 64-row scanner was able to discover a significantly

larger number of perfusion defects entirely outside the volume limited by the ASPECTS levels (Table 3).

Some studies have previously addressed the impact of different z-axis ranges in the detection of perfusion defects. Using a 320-row scanner *Page et al.* found that 160-mm-coverage better defined the extent of the infarct core and the penumbra compared to 40-mm-coverage [17]. *Morhard et al.* observed that 20-mm-coverage missed 24.1% of pathological findings when compared to 96-mm-coverage [18]. *Furtado et al.* found that z-axis coverage of 75mm is required to reliably detect a perfusion mismatch ratio of 0.5 while 50mm was sufficient when a ratio of 0.2 is used [16]. Fifty-five mm need to be covered to estimate if more than one-third of the MCA region is involved. However, if this coverage is not achieved, rules based on ASPECTS provide potential alternatives for excluding patients from thrombolytic therapy [11, 14-15]. *Youn et al.* reported that 80-mm-coverage had significantly higher lesion detection rate compared to 20-mm-coverage [19]. Our results are in congruence with these previous findings. While all these studies had somewhat heterogeneous populations and simulated narrower coverage by selecting ranges of larger volumes imaged with one scanner, we studied patients that all received intravenous revascularization therapy and compared two scanners with different detection widths.

The limited coverage of a 16-row device makes the positioning of the perfusion imaging volume a crucial factor as small offsets from the optimal placement, minor patient movement after the acquisition of the scout image and disadvantageous slice orientation can mean that either of the ASPECTS levels escapes visualization. Our institution had 18 months experience in routinely performing multimodal stroke evaluations before the study population was imaged so operator inexperience probably plays only a minor role.

Another quality issue was the movement artifacts that were significantly more abundant and severe in the 16-row group (Table 2). This can be mainly attributed to higher sampling frequency (1/s vs. 0.27/s) and smaller slice thickness (5mm vs. 10mm) which seems to make the capture of small scale periodic patient movements like tremor, swallowing, nodding and minor swinging of the head more frequent. This type of movement was poorly corrected by the analysis software. While this does not render the study uninterpretable, it introduces inaccuracies to the measurement of absolute values of the perfusion parameters. On the other hand, lower sampling frequency potentially has this same effect and larger slice thickness may decrease the sensitivity of the detection of small perfusion defects because of averaging. Interestingly, the motion artifacts often coincided with the arrival of the contrast bolus to the central nervous system emphasizing the importance of instructing the patient.

There was no significant difference in the clinical outcome between the study groups (Table 1). This is to be expected as our institutional guidelines on management of stroke did not define any role for PCT findings at the time and so the treatment was essentially the same in both groups.

Our study is limited by retrospective design. There was minor heterogeneity in the details of conventional stroke treatment which is to be expected in a clinically managed population. There were significantly fewer females in the 16-row group. This can be attributed to chance as no selection process that would potentially produce this result could be identified.

In conclusion, PCT studies performed with the 16-row scanner suffered from limited anatomic coverage that decreased the sensitivity to detect perfusion defects in the cranial parts of the MCA region when compared to the 64-row scanner. The 16-row studies also had more motion artifacts resulting from small scale periodic patient movements possibly due to higher sampling frequency.



However, the potential impact of these findings seems to be limited as there were no statistically significant differences in the total ASPECTS scores or the number of perfusion mismatches found. On the other hand, extensive z-axis coverage allows near comprehensive evaluation of both the anterior and the posterior circulation. The possible benefits of the larger z-axis coverage have to be balanced with the radiation exposure.

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### **Disclosures**

We declare that we have no conflict of interest.

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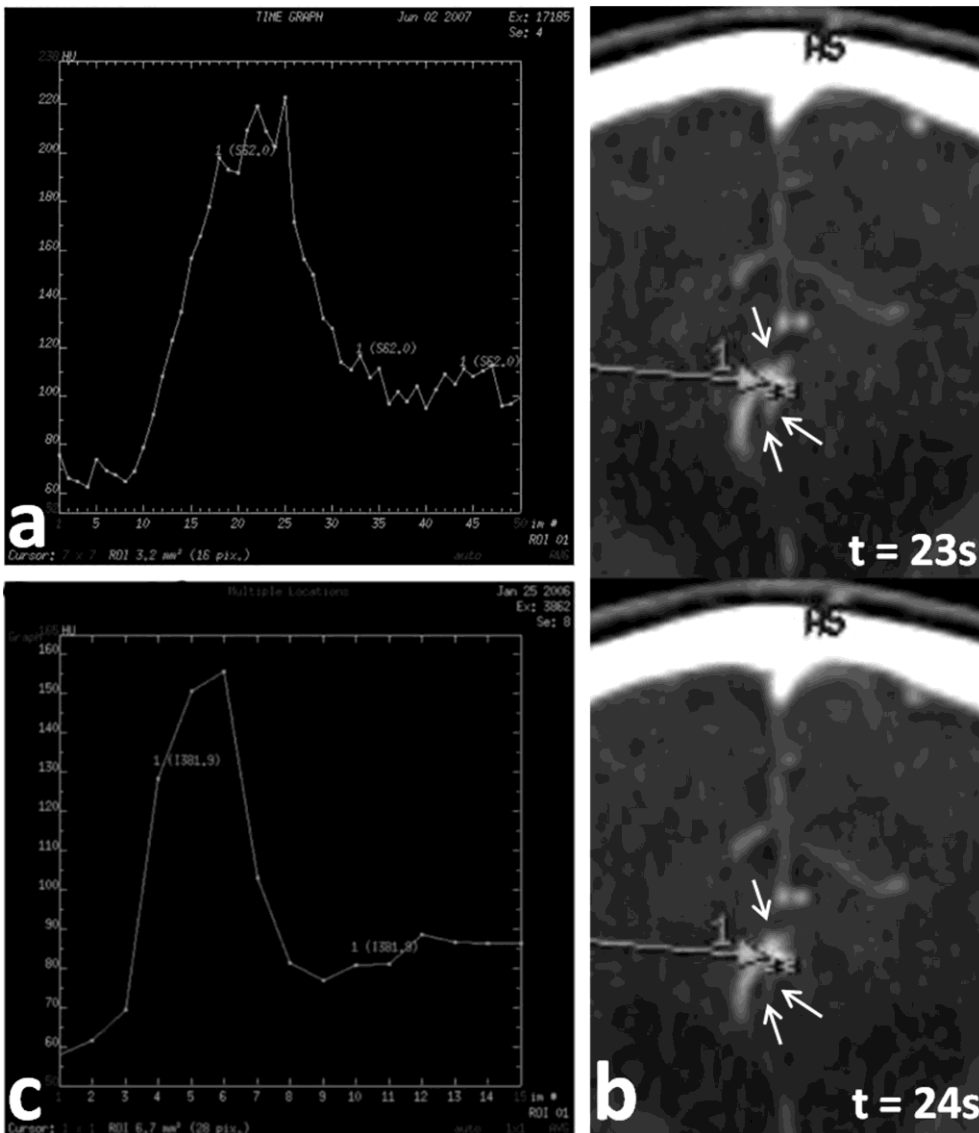
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**Figure 1: A typical artifact in a 16-row study resulting from minute movement that was incompletely corrected by the software.** The serrated appearance of the contour of the time-density curve is a result of small scale movement of the head (Panel **a**). Especially the segments where the rate of change of the density is slow are affected. Panel **b** demonstrates this movement between consecutive acquisitions of the same 5mm slice 1s apart in the surroundings of the region-of-interest of the AIF positioned in the left anterior cerebral artery. There is minor rotation of the head in the axial plane. A typical smooth time-density curve obtained with the 64-row scanner is shown in Panel **c**.



**Table 1. Baseline characteristics in the 64-row and the 16-row groups.** All values mean  $\pm$  SD or number of patients (percentage).

	<b>64-row (n = 67)</b>	<b>16-row (n = 73)</b>	<b>p</b>
<b>Age</b>	67.1 $\pm$ 14.4	70.0 $\pm$ 13.7	0.22
<b>Female gender</b>	37 (55%)	26 (36%)	0.02
<b>Admission NIHSS</b>	8.4 $\pm$ 6.1	8.5 $\pm$ 6.0	0.92
<b>mRS, prestroke</b>	0.6 $\pm$ 0.8	0.9 $\pm$ 0.8	0.10
<b>mRS <math>\leq</math>2 at 90 days</b>	51 (76%)	57 (78%)	0.78
<b>Total infarct volume at 24h (ccm)</b>	23.0 $\pm$ 54.2	20.7 $\pm$ 42.4	0.77
<b>Hemorrhagic complication</b>	4 (6%)	4 (5%)	0.90
<b>Onset-to-treatment time (min)</b>	133 $\pm$ 27	131 $\pm$ 28	0.74

**Table 2. Comparison of the technical quality of the perfusion studies.** AIF = Arterial Input Function, ASPECTS = Alberta Stroke Program Early CT Score, VOF = Venous Output Function.

	<b>64-row (n = 67)</b>	<b>16-row (n = 73)</b>	<b>p</b>
<b>Both ASPECTS levels optimally covered</b>	67 (100%)	21 (29%)	< 0.001
<b>Motion artifacts</b>	36 (54%)	52 (71%)	0.04
<b>Incompletely corrected motion artifacts</b>	8 (12%)	33 (42%)	0.001
<b>Noisy AIF and/or VOF</b>	1 (1%)	28 (38%)	< 0.001
<b>Arterial phase not finished</b>	2 (3%)	4 (5%)	0.68
<b>Venous phase not finished</b>	5 (7%)	7 (10%)	0.77
<b>Multiple boluses</b>	0 (0%)	1 (1%)	1.00
<b>Suboptimal slice orientation</b>	2 (3%)	7 (10%)	0.17
<b>Subtentorial parenchyma not visualized</b>	1 (1%)	31 (42%)	< 0.001
<b>ASPECTS score not interpretable</b>	0 (0%)	31 (42%)	< 0.001
<b>Study not reliably interpretable</b>	0 (0%)	6 (8%)	0.03

**Table 3. Comparison of the perfusion defect detection properties.** The ‘16-row (n=67)’ column heading refers to the inclusion of patients with ASPECTS regions that were missed by the 16-row scanner because of limited anatomic coverage. These regions were scored normal. In the n = 42 population these patients were excluded.  $p_1$ : 64-row (n=67) vs. 16-row (n=42),  $p_2$ : 64-row (n=67) vs. 16-row (n=67). ASPECTS = Alberta Stroke Program Early CT Score, CBV = Cerebral Blood Volume, MTT = Mean Transit Time, NCCT = Non-contrast Computed Tomography.

	<b>64-row (n = 67)</b>	<b>16-row (n = 42)</b>	<b><math>p_1</math></b>	<b>16-row (n = 67)</b>	<b><math>p_2</math></b>
<b>ASPECTS regions affected</b>					
MTT lower ASPECTS level (mean $\pm$ SD)	1.4 $\pm$ 2.0	1.1 $\pm$ 1.6	0.74	1.5 $\pm$ 2.0	0.74
MTT upper ASPECTS level (mean $\pm$ SD)	0.9 $\pm$ 1.1	0.7 $\pm$ 1.1	0.54	0.5 $\pm$ 1.0	0.02
CBV lower ASPECTS level (mean $\pm$ SD)	0.7 $\pm$ 1.4	0.5 $\pm$ 1.2	0.35	0.6 $\pm$ 1.2	0.77
CBV upper ASPECTS level (mean $\pm$ SD)	0.3 $\pm$ 0.7	0.3 $\pm$ 0.7	0.87	0.2 $\pm$ 0.6	0.25
<b>ASPECTS score</b>					
MTT (mean $\pm$ SD)	7.8 $\pm$ 3.0	8.2 $\pm$ 2.6	0.70	7.9 $\pm$ 2.8	0.97
CBV (mean $\pm$ SD)	9.0 $\pm$ 1.9	9.2 $\pm$ 1.7	0.50	9.0 $\pm$ 2.0	0.85
NCCT 24h (mean $\pm$ SD)	8.3 $\pm$ 2.6	8.7 $\pm$ 1.9	1.00	8.6 $\pm$ 2.1	0.99
ASPECTS mismatch (mean $\pm$ SD)	1.2 $\pm$ 2.0	1.0 $\pm$ 1.3	0.98	1.2 $\pm$ 2.0	0.92
<b>Number of patients</b>					
ASPECTS mismatch present (%)	28 (42%)	19 (45%)	0.72	30 (45%)	0.73
Perfusion defect not in ASPECTS regions (%)	8 (12%)	1 (2%)	0.15	1 (1%)	0.03
Perfusion mismatches in total (%)	36 (54%)	20 (48%)	0.53	31 (46%)	0.39