Anglia Ruskin University

Faculty of Medical Science

"Evaluation of the role of cerebral collaterals in acute ischaemic stroke due to large vessel occlusion".

Khawar Hussain

The thesis is submitted in fulfillment of the requirements for Doctor of Medicine by Research (MD Res)

Submitted: 20th of November 2018

Word Count: 15750

1.1 Acknowledgements

My special thanks go to my supervisor Professor Iris Grunwald. Her support, guidance and supervision has been incredible. She has undoubtedly helped to make my work a success. I would also like to thank her for the countless meetings and assistance in the image evaluations. She is a wonderful human-being with an amazing work-ethic and I am truly grateful for the opportunity to have worked with her.

Thank you to Dr Stephen Garry, Centre for Statistics, Oxford University, for the statistical support during my MD research.

My parents, who have always been supportive and given me everything in life, I will forever be indebted. Finally, my wife who has been understanding, caring and loving throughout.

1.2 Abstract

Objective: Stroke is a devastating neurological condition affecting over 150,000 people in the United Kingdom every year with an individual suffering a stroke approximately every three and a half minutes. The collateral circulation plays an important role in maintaining blood flow to the tissue that is at risk of developing ischaemia. The aim of my study was to assess the role of collaterals in the development of ischaemic tissue and in clinical outcome.

Methods: Data was derived from a large international study (The SOS Trial: A Study of Survival and Outcome after Stroke ClinicalTrials.gov Identifier: NCT01193569). For all enrolled patients, functional outcome was defined by the modified Rankin Scale (mRS) determined at 90 days after the index event. Collaterals on CT-Angiography (CTA) were scored using the Tan score. This was correlated to development of ischaemic regions using the ASPECTS score as well as the clinical outcome score NIHSS.

Results: My results show that an increasing TAN score appears to be associated with a lower mRS score (p=0.048; 95% CI). There was a positive correlation between ASPECTS score and Tan score (p=0.049). M2 and M4 regions were associated with an increase in NIHSS (p=
0.027; 0.009); M2 and M5 regions were associated with an increase in mRS
(p= 0.019; 0.023). An increase in ASPECTS score (less damage) implied a reduction in the NIHSS and mRS score (better outcome).

Conclusion: Our results have potentially a huge impact on patient selection, as they demonstrate that patients with good collaterals should be transferred for treatment to tertiary care centres for thrombectomy or patient selection according to the salvageability of specific functions. This will hopefully allow patients to have better outcomes after suffering a stroke and reduce morbidity and disability in the long term. More work is required to elucidate further prognostic markers for collateral formation and outcome.

Table of Contents

List of Tables

List of Figures

2 Introduction

Stroke is a devastating neurological condition affecting over 150,000 people in the United Kingdom every year with an individual suffering a stroke approximately every three and a half minutes (Stroke Association., 2016). The collateral circulation plays an important role in maintaining blood flow (Bang et al., 2008) to the tissue that is at risk of developing ischaemia. The aim of my study was to measure collateral flow using CT-angiographic data and to see if collaterals can help identify areas of the brain that are at risk of infarction but may still be salvageable. My research thus focused on patients with known major vessel occlusion (MVO) from a large international study (The SOS Trial: A Study of Survival and Outcome after Stroke ClinicalTrials.gov Identifier: NCT01193569). Patients included in the study presented with acute ischaemic stroke from large vessel thromboembolism in the brain.

The target population was a stroke cohort with a known infarct volume who presented within 8 hours from symptom onset with a NIH stroke scale (NIHSS) score of ≥10. Functional outcome as defined by the Modified Rankin Scale (mRS) was determined at 90 days after the index event for all enrolled patients. CTA imaging was correlated using the TAN score to elucidate collateral formation.

To the best of my knowledge, my MD project is the first study to evaluate a cohort of patients with persistent MVO for their collateral status and its impact on outcome.

There are two types of stroke, ischaemic and haemorrhagic. My thesis will focus on ischaemic stroke which makes up approximately nine out of ten stroke cases. Ischaemic stroke is the result of vessel occlusion from in situ thrombosis, embolism or haemodynamic failure. Embolism may be from artery to artery (30-40%) or from the heart such as an intramural thrombus or an irregular heart rhythm (30-40%) (Ntaios et al., 2017). In 25% of cases, disease of the tunic intima of small penetrating intracranial blood vessels is responsible for lacunar infarction (Howard., 2016).

2.1 Management of acute stroke

The first few hours after an ischaemic stroke are crucial and there are certain factors that need to be addressed to improve outcomes. Firstly, restoring blood flow by using thrombolysis to dissolve or break down an existing clot, thus reperfusing the area of the brain at risk. The most commonly used drug for thrombolytic therapy is tissue plasminogen activator (tPA). Another treatment of choice is endovascular mechanical thrombectomy which includes a wide range of endovascular tools approved for removing thrombi from the neurovasculature in acute ischaemic stroke patients. Evidence suggests that mechanical thrombectomy is appropriate for patients with large proximal intracranial artery occlusions due to emboli of cardiac or arterial origin.

Recent studies confirmed that mechanical thrombectomy in combination with intravenous thrombolysis is an effective treatment for eligible patients (Mistry et al., 2017).

Secondly, looking at collateral vessels and how they have an effect on preserving the ischaemic penumbra (the area surrounding the infarcted area) and the concept of neuroprotection (Newhaus et al., 2017). Thirdly, preventing recurrence with anti-platelet therapy after the event. A haemorrhagic stroke will usually require surgery depending on the co-morbidities and the functional status of the patient.

The initial management of acute stroke focuses on gaining a secure airway, assessing breathing and circulation, followed by an evaluation of the neurological deficits and comorbidities to identify patients who may be eligible for thrombolysis. It also involves identifying those at particular risk for complications of acute stroke. Ideally, patients should have imaging of their brain performed as soon as possible as well as thorough examination by the on-call stroke physicians.

2.2 Imaging in Stroke

Stroke is a major cause of mortality and long-term disability. More than 80% of strokes are from ischaemic damage to the brain due to acute reduction of blood supply. It was calculated that 1.8 million neurons are lost every minute that appropriate treatment is not given (‘time is brain’) (Saver., 2006). It is for this very reason that imaging in stroke is so vitally important and efficient.

Approximately 25–35% of stroke patients present with large vessel occlusion (Malhotra et al., 2017). These patients often present with severe neurological deficits and prognosis is often poor if early treatment is not possible. This group of patients is the target for any endovascular intervention, thus appropriate patient selection based on clinical findings and neuroimaging are of utmost significance.

Alongside bedside investigations (including an electrocardiogram to check for an irregular heart rhythm), observations and routine blood tests, it is crucial to perform a computed tomography (CT) or magnetic resonance imaging (MRI) scan, depending on what is available in hospitals, as soon as possible. Early CT scan changes are seen within 6 hours of stroke onset (Von Kummer et al., 1996); they include: cortical sulcal effacement, loss of the insular ribbon, blurring of the grey-white interface, obscuration of lentiform nucleus and the hyperdense artery sign (intravascular thrombus) as demonstrated in (Fig.1) below. This will also suggest what type of intervention (thrombolysis vs thrombectomy) would be most beneficial.

A cerebral and/or neck CT angiogram/magnetic resonance (MR) angiogram should be performed to exclude arterial dissection and carotid or vertebral occlusive disease. Brain haemodynamic measurements with CT or MRI perfusion allow the identification of viable tissue at risk of infarction (penumbra). Diffusion-weighted imaging (DWI) is the most reliable technique for detecting acute ischaemic stroke as early as 30 minutes from symptom onset (Ledezma et al., 2009).

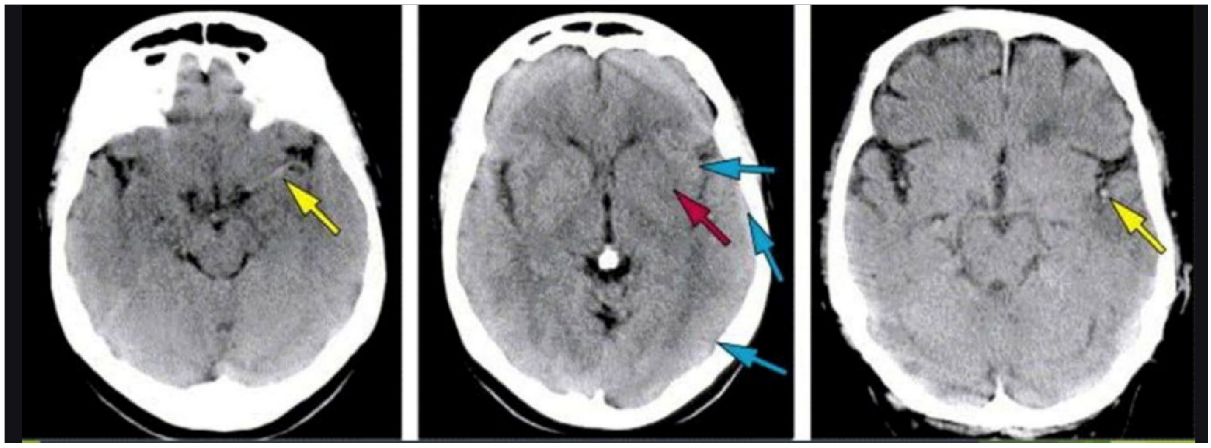

Fig.1 Early changes in an acute stroke demonstrated by hyperdense left MCA sign (yellow arrow) in the left image, hypoattenuated left basal ganglia (red arrow) and cortical swelling (blue arrows) in the centre image.
The right image shows a dot sign in the left sylvian fissure. (*Figure adapted from Mankungiya, 2017*).

CT is the mainstay of imaging available in most hospitals on a round-the-clock basis. Use of CT imaging can readily exclude the presence of an acute cerebral haemorrhage, thus making a significant change in treatment management if required. Prior to performing a scan, the radiologist needs to collect certain clinical data, including the time of symptom onset, clinical findings including results of the National Institutes of Health Stroke Scale (NIHSS) and relevant patient history. The main goals of imaging are firstly to rule out intracranial haemorrhage (as this will determine treatment management), secondly to define the extent of ischaemic damage, to differentiate between the infarct core and the salvageable ischaemic penumbra (Gonzalez, 2012) and to visualise large blood vessel significance.

In computed tomography angiography (CTA), iodinated contrast medium is administered intravenously. The scanning usually starts from the aortic arch up to a level above the circle of Willis when the contrast medium is in the arterial phase. Stenoses and occlusions can be detected with high diagnostic precision in both pre-cranial and intracranial arteries thus revealing the origin of the acute ischaemic stroke. There is, however, a risk of an allergic reaction to the contrast medium and contraindications for patients with impaired renal function.

Quantifying existing irreversible stroke damage and tissue at risk are crucial to identify patients who can benefit from endovascular treatment, especially as there is now level 1A evidence for mechanical clot removal with improved patient outcome in large vessel occlusion (Powers et al., 2015). However, prediction of outcome is difficult, especially in patients with an unknown time window or large infarct volume.

3 Aim

The aim of this study was to evaluate the impact of collaterals on outcome in patients presenting with symptoms of acute ischaemic stroke within 8 hours from symptom onset with an imagingdefined large cerebral vessel occlusion and a known infarct volume. We postulate that collaterals, as seen on CT-Angiography in combination with eloquent areas are predictors of outcome after acute ischaemic stroke due to large vessel occlusion.

3.1 Hypothesis

We hypothesise that:

1. There is a correlation between the collaterals (TAN score) and functional outcome (mRS; NIHSS)
2. There is a correlation between the TAN score and the ASPECTS score
3. Certain ASPECTS areas are correlated to functional outcome (mRS; NIHSS)
4. A higher ASPECTS score correlates to a lower NIHSS and mRS score

4 Background

4.1 Definition of Stroke

The traditional definition of stroke is clinical and based upon the sudden onset of loss of neurological function due to infarction caused by ischaemia or haemorrhage (the two types of stroke) in an area of the brain, spinal cord or retina (Sacco et al., 2013). Stroke has the same origin as transient ischaemic attack (TIA) and the same symptoms; however, stroke symptoms persist for more than 24 hours or may lead to an early death whereas blockage due to TIA will only last for a short time. As the definition is constantly being updated an addition to the above is adding in a requisite about imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) and autopsy revealing ischaemia or haemorrhage causing stroke-like symptoms (Sacco et al., 2013).

More than 80% of strokes stem from ischaemic damage to the brain due to the acute reduction of the blood supply (El-Koussy et al., 2014). It was calculated that 1.8 million neurons are lost every minute that appropriate treatment is not given (Saver et al., 2006), hence the importance of the phrase '*time is brain*'.

Stroke is subdivided according to the so-called TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment) (Adams, 1993): the division is into cardio-embolic ischaemic infarcts, macroangiopathic arterio-arterial ischaemic infarcts, microangiopathic-ischaemic brain infarcts, infarcts with other specific causes, e.g. haematological diseases, vasculopathies and undetermined causes.

4.2 Management of acute stroke

The first few hours after an ischaemic stroke are crucial and there are certain factors that need to be addressed to improve outcomes.

Firstly, restoring blood flow, either by using thrombolysis or thrombectomy to break down, or remove an existing clot thus reperfusing the area of the brain at risk.

Secondly, looking at collateral vessels and how they have an effect on preserving the ischaemic penumbra (the area surrounding the ischaemic infarct) and the concept of neuroprotection.

Thirdly, preventing recurrence with antiplatelet therapy after the event. A haemorrhagic stroke will usually require surgery depending on the co-morbidities and functional status of the patient.

The initial management of acute stroke focuses on gaining a secure airway, assessing breathing and circulation, followed by an evaluation of the neurological deficits and co-morbidities to identify patients who may be eligible for thrombolysis or thrombectomy. Obtaining a history of events, possibly from the patient or a relative, is crucial as it provides the clinician with a timeline. It also enables identifying those at particular risk for complications of acute stroke.

4.3 Socio-economic importance

Stroke is a disease of increasing socio-economic importance in aging societies. By 2020, stroke and coronary heart disease are expected to be the leading causes of loss of a healthy life. (Feigin et al., 2003). Two thirds of all stroke survivors suffer from persistent disability. Among them, motor restriction is the most common (Feigin et al., 2003).

Depending on the location and size of the infarction, there will be typical neurological deficits and / or psychopathological symptoms. Thus, clinical neurological deficits after a cerebral infarction may include sensorimotor hemiparesis, disturbance of consciousness, aphasia or dysarthria. These may be transient as in transient ischaemic attack (TIA) with symptoms usually lasting less than 24 hours or persistent as a definitive ischaemic stroke. In the vast majority of cases, patients survive the acute stage but long-term recovery is varying strongly. Sudden hypoperfusion of the supratentorial brain causes a supply deficit with oxygen and glucose with often permanent damage (Rink et al., 2011).

Two thirds of all patients who survive a stroke suffer from persistent disability. Among them, motor restriction is the most common form of disability. Despite intensive physiotherapeutic, occupational therapy and sports medicine rehabilitation efforts, 60-70% of all stroke patients still suffer from limited motor hand function six months after a cerebrovascular stroke event (Feigin V et al., 2003). Especially long-standing strokes, showing persistent hand dysfunction, show little signs of recovery so far.

4.4 Clinical Assessment

Clinical assessment of strokes is dependent of stroke location in the brain, i.e. which vessel(s) are affected. The majority of strokes are supratentorial; as such the acronym FAST, for facial droop, arm drop, speech disturbance and time can be used for clinical assessment. The most important historical feature of stroke is the suddenness of its onset. Almost half of strokes affect the large vessel, the middle cerebral artery (Ng et al., 2007).

An occlusion of the middle cerebral artery (MCA) leads to contralateral brachiofacial sensorimotor hemiparesis, often with central facial palsy. If the dominant hemisphere is affected, patients may show aphasia. In anterior cerebral artery occlusion (ACA), patients suffer from contralateral limb sensorimotor hemiparesis and sometimes bladder dysfunction, as the lower extremity is represented by the homunculus schema at the mantle edge of the motor cortex. In infarcts of the posterior cerebral artery supply area, contralateral hyperaesthesia and homonymous hemianopia are contralateral. Basilar artery occlusion leads to damage to the brainstem and involves a high morbidity and mortality rate of 80-90% without active intervention (Yeung et al., 2014). The cerebrum and occipital lobe are affected, which can lead to hemianopia or blindness. Thus, all brain stem symptoms and also cerebellar symptoms can be present. The symptoms range from blurred vision, speech disorders, dysphagia, peripheral paralysis, centralised respiratory disorder to decreased consciousness and coma. The most severe form of brain stem injury, caused by extensive occlusion of the basilar artery, results in high tetraplegia if the patient survives (Pantke et al., 2014) which is where the so-called locked-in syndrome is derived from and in which no motor function except the eyelid motor can be exercised with fully preserved consciousness.

4.5 Modified Rankin Scale

The Modified Rankin Scale (mRS) is a clinician-reported measure of global disability. It is widely applied for evaluating stroke patient outcomes (Rankin, 1957 and Van Swieten, 1988) and used as an endpoint in randomised clinical trials.

The scale runs from 0-6, ranging from perfect health without symptoms to death. This is illustrated in (Table 1) below;

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

Table 1: Modified Rankin Scale for measuring the degree of disability or dependence in the daily activities of people who experience a stroke.

The mRS has been used often as an endpoint in randomised controlled trials of acute ischaemic stroke treatments based on its straightforward application, acceptable

inter-rater reliability, and ability to discriminate levels of stroke disability (Weimar et al., 2002 and Kwon et al., 2004). Optimising mRS endpoints for acute stroke treatment RCTs involves definition and appropriate statistical analyses. When properly administered, the mRS exhibits a strong relationship with clinical measurements of stroke severity in addition to other disability and outcome endpoints. Construct validity of the mRS has been affirmed by multiple studies in which it has been consistently observed that the location, type and extent of stroke injury are closely related to short and longer-term disability (Banks et al., 2007). However, clinicians should be aware that the mRS grading may be affected by a variety of factors, including patient co-morbidities and socio-economic status. Use of the mRS in RCTs may benefit from a carefully defined endpoint as well as from a form of statistical analysis that is most likely to accurately reflect the effect of treatment.

4.6 MRC Grading

Muscle strength post-stroke is assessed according to the British Medical Research Council.

(The MRC Muscle Scale is licensed under the Open Government License).

The muscle scale grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle. This is outlined below.

Grade 0: no muscle activity

Grade I: visible or palpable muscle contraction without any movement effect

Grade II: movement effect with elimination of gravity

Grade III: movements against gravity possible

Grade IV: movements against moderate resistance

Grade V: normal muscle power

4.7 NIHSS

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. At present, the scale is also widely used as a clinical assessment tool to evaluate the acuity of stroke patients, determine appropriate treatment, and predict patient outcome.

The NIHSS can be used as a clinical stroke assessment tool to evaluate and record the neurological status in acute stroke patients (NIHSS, 2017). The stroke scale is valid for predicting the lesion size and can serve as a measure of stroke severity. The NIHSS has been shown to be a predictor of both short and long-term outcome of stroke patients. Additionally, the stroke scale serves as a data collection tool for planning patient care and provides clarity and simplicity among healthcare staff.

The NIHSS is a 15-item neurological examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness: language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The assessment of a patient usually requires about 10 minutes to complete, dependent on user experience.

The scale is designed to be a simple, effective, and reliable tool that can be administered at the bedside by physicians, nurses or therapists but the evaluation of stroke severity depends upon the ability of the observer to accurately and consistently assess the patient. This is why clinical acumen and knowledge is crucial in difficult and not so straightforward cases.

4.8 Imaging in Stroke

Stroke is a major cause of mortality and long-term disability. More than 80% of strokes are from ischaemic damage to the brain due to the acute reduction of blood supply (Stroke Association, 2016). It was calculated that 1.8 million neurons are lost every minute that appropriate treatment is not given (‘time is brain’) (Saver, 2006). It is for this very reason that imaging in stroke is so vitally important and efficient.

Approximately 25–35% of strokes show large vessel occlusions and patients in this category often present with severe neurological deficits and prognosis is often poor if early treatment is not possible (Smith et al., 2009). It is this group of patients who is the target for any endovascular intervention, thus appropriate patient selection based on clinical findings and neuroimaging are of utmost significance.

Alongside bedside investigations (including an electrocardiogram to check for an irregular heart rhythm), observations and routine blood tests, it is crucial to perform a computed tomography (CT) or magnetic resonance imaging (MRI) scan, depending on what is available in hospitals as soon as possible. Early CT scan changes are seen in 60% (Fig.2) within 6 hours of stroke onset and they include: cortical sulcal effacement, loss of the insular ribbon, blurring of the grey-white interface (red arrow), obscuration of lentiform nucleus and the hyperdense artery sign (intravascular thrombus). This will also allow an idea of what type of intervention (thrombolysis vs thrombectomy) would be most beneficial.

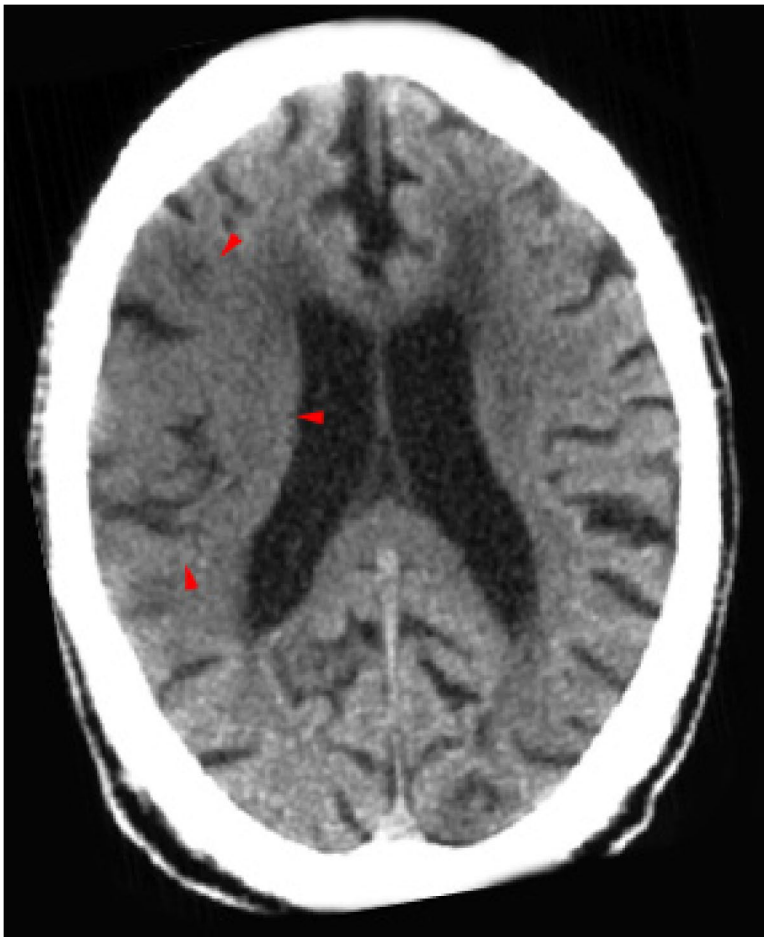

Fig.2 CT Head scan showing a right sided ischaemic stroke (red arrow).

A cerebral and/or neck CT angiogram/magnetic resonance (MR) angiogram should be performed to exclude arterial dissection and carotid or vertebral occlusive disease. Brain haemodynamic measurements with CT or MRI perfusion allow the identification of viable tissue at risk of infarction (penumbra). Diffusion-weighted imaging (DWI) is the most reliable technique for detecting acute ischaemic stroke as early as 30 minutes from symptom onset (Ledezma et al., 2009).

CT is the mainstay of imaging available in most hospitals on a round-the-clock basis. Use of CT imaging can readily exclude the presence of an acute cerebral haemorrhage, thus making a significant change in treatment management if needed. Prior to performing a scan, the radiologist needs to collect certain clinical data including the time of symptom onset, clinical findings including results of the National Institute of Health Stroke Scale (NIHSS) and relevant patient history. The main goals of imaging are firstly to rule out intracranial haemorrhage (as this will determine treatment

management), secondly to define the extent of ischaemic damage, to differentiate between the infarct core and the salvageable ischaemic penumbra (Gonzalez., 2012) and to visualise large blood vessel significance.

In computed tomography angiography (CTA), iodinated contrast medium is administered intravenously. The scanning usually starts from the aortic arch up to a level above the circle of Willis when the contrast medium is in the arterial phase. Stenoses and occlusions can be detected with high diagnostic precision in both pre-cranial and intracranial arteries thus revealing the origin of the acute ischaemic stroke. There is, however, a risk of an allergic reaction to the contrast medium and contraindications for patients with impaired renal function.

4.9 ASPECTS

The extent of ischaemic damage as detected on CT or MRI can be measured by visualising, semi-quantitatively with the Alberta stroke program early CT score (ASPECTS) (Pexman et al., 2001). ASPECTS is a 10-point quantitative topographic CT scan score used in patients with middle cerebral artery (MCA) stroke. Segmental assessment of the MCA vascular territory is performed and 1 point is deducted from the initial score of 10 for every region involved.

ASPECTS is determined from evaluation of two standardised regions of the MCA territory: The basal ganglia level, where the thalamus, basal ganglia, and caudate are visible, and the supra-ganglionic level, which includes the corona radiata and centrum semi-ovale (see Fig.3 below).

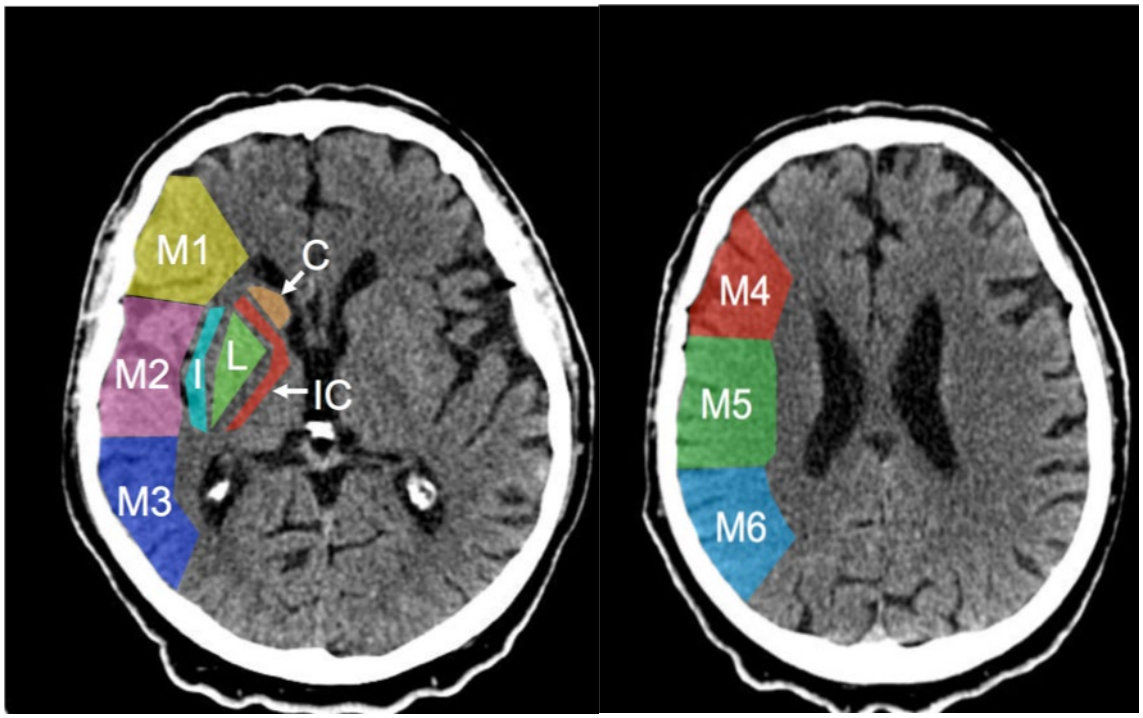

Fig. 3 ***C****- Head of caudate nucleus,* ***I-*** *Insula,* ***IC****- Internal capsule,* ***L****- Lentiform nucleus, Cortical regions (M1M6). CT representation of ASPECTS regions and 10 MCA regions. Figure from https://radiopaedia.org/articles/albertastroke-program-early-ct-score-aspects-1*

All imaging cuts with basal ganglionic or supra-ganglionic structures visible are required to determine if an area is involved. The abnormality should be visible on at least two consecutive cuts to ensure that it is truly abnormal rather than a volume averaging effect. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischaemic change for each of the defined regions. A normal CT scan receives an ASPECT score of 10 points. A score of 0 indicates diffuse involvement throughout the MCA territory.

So how do we use ASPECTS in the clinical environment? Within the first three hours of an MCA stroke onset, baseline ASPECTS values correlate inversely with the severity of NIHSS and with functional outcome which is an important factor in prognosis (Pfaff et al., 2007).

If the area of hypodense acute ischaemic change is larger than one-third of the MCA territory, reperfusion therapy is contraindicated. This is where ASPECTS can also be helpful in identifying patients not suitable for revascularisation (Jauch et al., 2013). Overall, patients with an ASPECTS below 7 are less likely to benefit from

thrombolysis. ASPECTS is however limited by specifically only looking at the middle cerebral artery, so anterior and posterior cerebral artery strokes cannot be directly correlated.

4.10 CT-Angiography

In many UK centres, angiography is performed directly after a non-contrast CT scan is obtained. The role of a non-contrast CT scan is to reveal any contraindications to thrombolysis or thrombectomy. Digital subtraction angiography (DSA) is the gold standard for assessing collaterals but is not always available and computed angiography (CTA) is a non-invasive alternative. CTA obtains a snapshot of the cerebral vessels and provides an approximation of the maximal extent of collaterals. As recruitment of collaterals is dynamic, multiphasic CTA has been proposed to capture the temporal information. CTA source images can also capture the dynamic aspect of collateral circulation (Tong., 2015). Allergy to the contrast dye and renal impairment are the two most common reasons for contraindications to having a CTA.

4.11 Collaterals

In acute ischaemic stroke, collateral circulation plays an important role in maintaining blood flow to the tissue that is at risk of progressing into ischaemia. In acute ischaemic stroke, tissues that remain alive despite low cerebral blood flow but that are at risk for progressing into infarction are considered to be “ischaemic penumbra” (Paciaroni et al., 2009). Both intravenous thrombolysis and endovascular therapies can rescue penumbral tissue by recanalising occluded cerebral arteries. However, even after successful recanalisation, some patients show little neurologic improvement, possibly because the penumbral area had already progressed into the irreversibly damaged ischaemic core or because haemorrhagic transformation occurred after the recanalisation therapy. Collateral circulation has the potential to protect against these ischaemic injuries by maintaining cerebral blood flow, thus saving brain tissue.

Since collateral status is being increasingly recognised as a promising biomarker for patient selection in stroke treatment, there are ongoing efforts to develop a standardised collateral grading system.

The last decade has seen numerous advances in neuroimaging and acute ischaemic stroke therapy (Wintermark et al., 2008 & Kim et al., 2015), especially with the development of endovascular therapy as an approach to blood flow restoration. An essential part is finding the correct conditions for reperfusion that prevent any further damage to cells in the brain without the risk of haemorrhagic transformation. Measuring collateral flow using angiography can help identify areas of the brain that are at risk of infarction and haemorrhage. Collateral vessels can sustain ischaemic regions in the brain when the primary source of arterial blood inflow is shut off. Both factors (site of ischaemia and reperfusion vessels) are important determinants of good outcomes for stroke patients.

An example image is shown below (Fig.4)

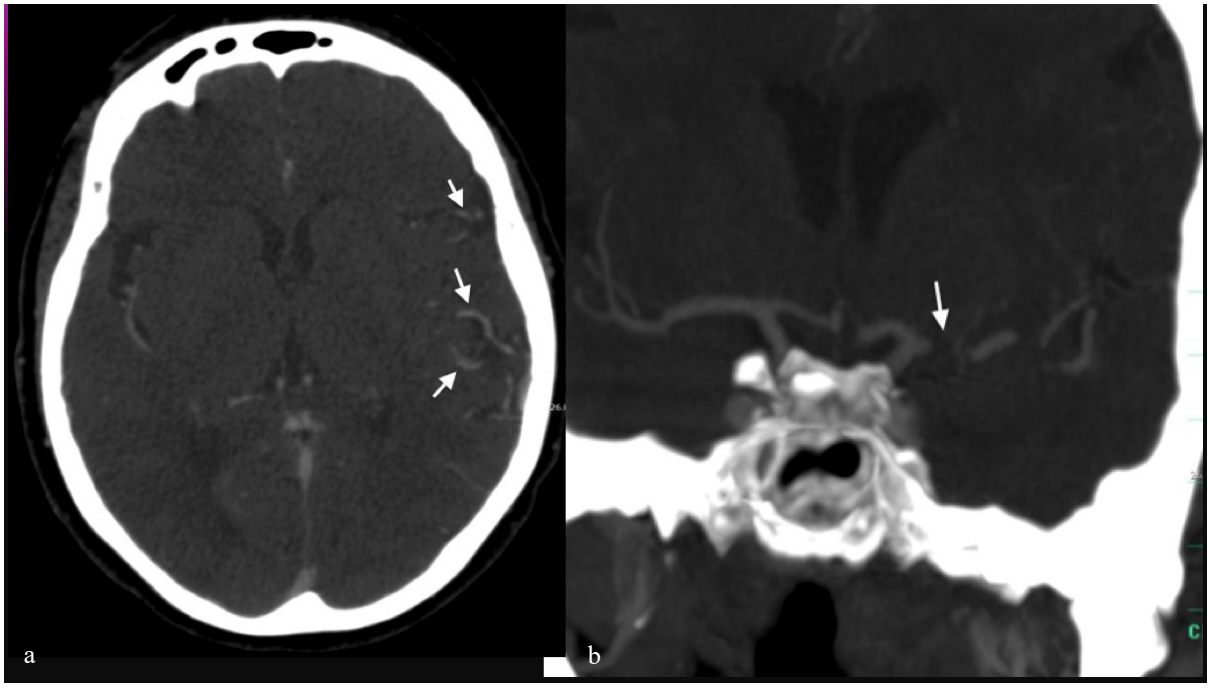

*Fig.4 a. CTA performed showing image on left side, visible **collaterals** noted in M1, M2, M3 regions. b. On right side showing occlusion of the left-MCA.*

In the subsequent digital subtraction angiography (DSA) image (see Fig.5 below), we can see occlusion of the left MCA (white arrow) and good collateral supply (black arrows). One method of assessing collaterals is by using the TAN system (Tan et al., 2007) and this image would represent a TAN score of 3. Further details will be discussed in section (**4.13.3**).

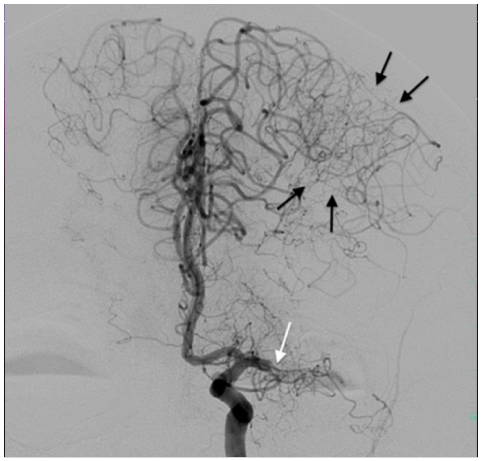

Fig.5 DSA image showing an occluded left MCA (white arrow) and good collateral supply (black arrows).

MRI DWI image of the same patient below (Fig.6) shows a smaller infarct due to collateral formation.

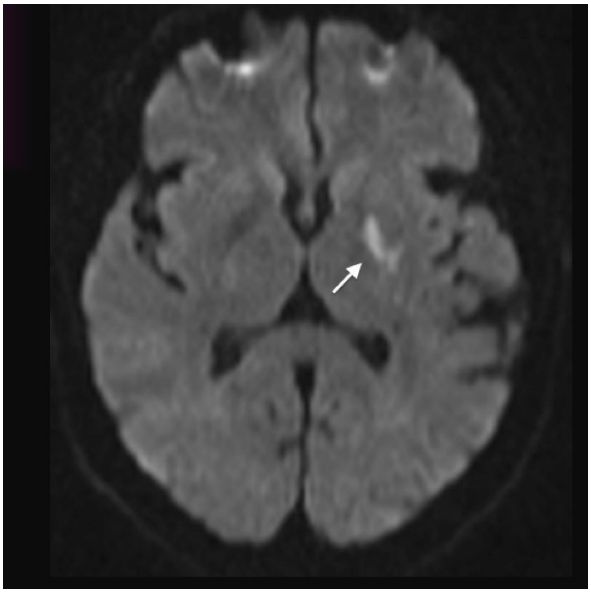

Fig.6 MRI DWI showing a small left sided infarct (white arrow).

This shows the importance of collateral flow in saving brain tissue and overall in reducing infarct size.

Cerebral collateral circulation provides subsidiary blood flow to oligaemic brain tissue when the primary feeding artery is severely stenosed or occluded. The artery anatomy

of collateral circulation includes the Circle of Willis (CW), large-artery communications between the extracranial artery and intracranial artery and leptomeningeal anastomoses that links distal sections of major cerebral arteries. The former is considered as a primary collateral and the latter two as secondary collaterals (Shuaib et al., 2011). The effectiveness of primary collaterals mainly relies on the integrity of the CW. A complete CW, if exists, is usually robust enough to compensate the decreased blood flow caused by a chronic or even abrupt occlusion lying proximally to it. However, absence or hypoplasia of one or more segments of CW is not rare (Kluwer et al., 1998) which may impair its effectiveness of redistributing blood. Capacity of secondary collaterals such as leptomeningeal anastomoses is affected by much more factors than primary collaterals is. Great variation exists in secondary collateral status of healthy adults.

4.12 Angiographic grading systems

Arteriographic demonstration of flow restoration or revascularisation, has two components: recanalisation of the original or primary arterial occlusive lesion and reperfusion past the occlusion and into the distal arterial bed and terminal branches with tissue staining. Complete recanalisation of the primary occlusion may have variable distal patency and perfusion/reperfusion. Complete proximal recanalisation with limited distal perfusion may be associated with a greater central haemorrhage risk into areas supplied by injured penetrating arteries subjected to altered pulse pressures (Tomsick., 2007). With the increasing number of acute ischaemic stroke studies, standards for design and reporting were proposed in 2003 by Higashida et al., including recommendations of the Thrombolysis in Cerebral Infarction (TICI) scale. The TICI grading approach (see Table 2) uses contrast filling and clearance time to further stratify the wide range of partial reperfusion that exists between the TIMI grades 1 (minimal reperfusion) and 3 (complete reperfusion). The Thrombolysis in Myocardial Infarction (TIMI) score (see Table 3) describing distal flow perfusion and revascularisation before and following therapy became a standard for reporting cardiac reperfusion procedure efficacy (TIMI., 2009). It was applied to intracranial thrombolysis, though the TIMI score does not specifically describe both the recanalisation effect and the distal perfusion effect simultaneously.

Grade 0:	**No Perfusion**. No anterograde flow beyond the point of occlusion.
Grade 1:	**Penetration with Minimal Perfusion**. The contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
Grade 2:	**Partial Perfusion**. The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel, e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction.
Grade 2a:	**Partial filling** with <50% of the entire vascular territory is visualized.
Grade 2b:	**Partial filling** with ≥50% of the entire vascular territory is visualized. If complete filling of all of the expected vascular territory is visualised, the filling is slower than normal.
Grade 3:	**Complete Perfusion**. Anterograde flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

Table 2- ***Modified Thrombolysis in Cerebral Infarction (TICI) Perfusion Categories***** *Adapted from Higashida et al, Stroke2003;34:e109-37*

Table 3 – *TIMI Flow Classification**

	Classification of Blood Flow
TIMI 0	No Perfusion
TIMI 1	Penetration without perfusion. Penetration past the initial occlusion, but no distal branch filling
TIMI 2	Partial perfusion of the arterywith incomplete or slow distal branch filling
TIMI 3	Complete perfusion of the artery

*** Adopted from *Chesebro et al. Circulation 1987;76:142-154 and Khatri et al, Stroke 2005;36:2400-2403***

We will now review the current scoring systems that we have extracted from various research papers.

4.13 Collateral scoring systems

4.13.1 Miteff system

Firstly, the Miteff system (Miteff et al., 2009) which is a 3-point score that grades middle cerebral artery collateral branches with respect to the Sylvain fissure and which can be performed rapidly. The grades assigned are the following: 3 (if the vessels are

reconstituted distal to the occlusion), 2 (vessels can be seen at the Sylvian fissure), or 1 (when the contrast opacification is merely seen in the distal superficial branches).

4.13.2 Maas system

Secondly, the Maas system (Mass et al., 2008) which is a 5-point score that compares collaterals on the affected hemisphere against those on the unaffected side. It uses the Sylvian fissure vessels or leptomeningeal collaterals as internal controls. The score ranges from 5 (exuberant), 4 (more than those on the contralateral side), 3 (equal to those on the contralateral side), 2 (less than those on the contralateral side), and 1 (no vessel opacification).

We have already discussed ASPECTS as a scoring system for ischaemic stroke, but collaterals can also be scored using the ASPECTS regions described above. Collaterals are scored in regions corresponding to the ASPECTS system. Lenticulostriate arteries in the basal ganglia arising from retrograde-filling MCAs distal to an occlusion are included in the scoring. The system scores the extent of contrast opacification in arteries distal to the occlusion (0, artery not seen; 1, less prominent; 2, equal or more prominent compared with a matching region in the opposite hemisphere) in the 6 ASPECTS cortical regions (M1–6), the caudate, insular ribbon, internal capsule, and lentiform nucleus to form a score from 0 to 10.

4.13.3 Tan Score

Finally, we reviewed a paper by Tan (Tan et al., 2009). This novel collateral grading system was scored on a scale of 0–3. A score of zero indicated absent collateral supply to the occluded MCA territory. A score of 1 indicated collateral supply filling ≤50% but >0% of the occluded MCA territory. A score of 2 was given for collateral supply filling >50% but <100% of the occluded MCA territory. A score of 3 was given for 100% collateral supply of the occluded MCA territory. The authors also validated a novel clot burden system (CBS), which is a scoring system to define the extent of a thrombus found in the proximal anterior circulation by location.
It is scored on a scale of 0–10. A score of 2 is subtracted if a thrombus is found in each of the supraclinoid internal carotid artery (ICA), the proximal half of the MCA trunk, and the distal half of the MCA trunk. A score of 1 is subtracted if a thrombus is found

in the infraclinoid ICA, ACA, and for each affected M2 branch. The thrombus can be partially or completely occlusive. A score of 10 is normal, implying clot absence. A score of 0 implies complete multisegment vessel occlusion.

4.14 Eloquent Cortex

The eloquent cortex is a name used by neurologists for areas of the cortex that if removed will result in loss of sensory processing or linguistic ability and paralysis. The most common areas of the eloquent cortex are in the left temporal and frontal lobes for speech and language, bilateral occipital lobes for vision, bilateral parietal lobes for sensation, and bilateral motor cortex for movement.

Specifically, the localisation of the motor hand area to a hand “knob” area in the precentral gyrus was identified by Yousry et al., 1997. However, the mapping of the eloquent areas of the brain is a complex procedure due to the large variability of functional cortical organisation between individuals (Brett et al., 2002 and Farrell et al., 2007). The morphometry of the hand knob is often changed by the infiltration or extrusion of the tumours that if located in or near the hand knob can alter results. The width, height of hand knob and the distance from tumour to hand knob could serve as anatomic biomarkers related to preoperative neurological motor deficits (Jingshan et al., 2018), specifically in our case looking at the effects of ischaemia in the area post stroke.

The eloquent area itself is shown in the image below (Fig.7). The hand knob area is the cortical representation of motor hand function.

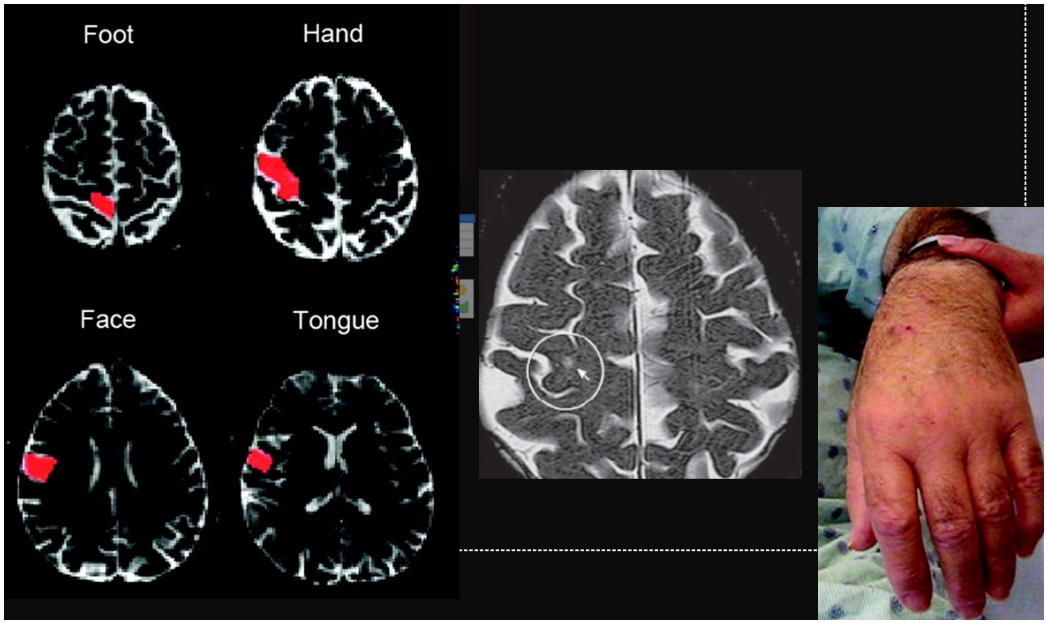

Fig. 7 The eloquent area, represented by the hand knob area (white arrow)- representing motor hand function.

Figure from. "Hand Knob" infarction by *Hall J et al., 2008.*

5 Materials and methods

Data was obtained from the SOS Study: A Study of Survival and Outcome After Stroke (Clinical Trials Identifier NCT01193569), a study to determine the natural history of acute ischaemic stroke from large vessel thromboembolism in the brain. The study was a prospective, observational cohort study that enrolled 146 participants (Study start date: September 2010). The study completion date was December, 2016. In the SOS study, patients did not receive endovascular therapy due to unavailability of the service and were either not eligible or refractory to lytic therapies. All patients had a premorbid mRS of 0. Signed informed consent for this study and usage of the data for subsequent studies was available in all cases and ethical approval was obtained.

Target population

Data for our collaterals evaluation was derived from the SOS study that consisted of a stroke cohort who presented within 8 hours from symptom onset with a National Institute of Health Stroke Scale (NIHSS) of ≧10 and had evidence of persistent occlusion of either the proximal anterior circulation, including the supra-clinoid segment of the ICA through the M1 segment of the MCA.

The inclusion and exclusion criteria in the SOS study were as follows:

5.1 Inclusion Criteria

- Patients had to be from 18 to 85 years of age
- Evidence of proximal anterior circulation large vessel occlusion (TIMI 0-1/TICI 0-1) from CT or MR-Angiography. The target vessel occlusion was allowed to include the supra- clinoid segment of the ICA through the M1 segment of the MCA
- Presented with symptoms consistent with acute ischaemic stroke within 8 hours of symptom onset. Patients who presented within 3 hours had to be ineligible or refractory to IV rt-PA therapy
- At the time of enrolment, the neurological deficit had to result in an NIHSS score of ≧ 10

5.2 Exclusion Criteria

- History of stroke in the past 3 months
- Pre-existing neurological or psychiatric disease that could confound the study results such as a pre-stroke mRS score ≥1
- Known severe allergy to contrast media
- Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg)
- CT evidence of the following conditions before enrolment:
  - Significant mass effect with midline shift
  - Evidence of intracranial haemorrhage
- Treated with endovascular therapy for acute stroke
- Life expectancy less than 90 days

Patients were unable to receive endovascular therapy at the time, due to an inability to provide such service at each centre at the time of trial recruitment.

Additional Inclusion and Exclusion Criteria for purposes of this study

The following criteria were added for our collateral evaluation:

Patients needed to present all of the following:

- Plain, non-contrast enhanced CT at baseline
- Arterial phase CT-Angiography covering the whole vascular territory • Stroke in the Middle Cerebral Artery (MCA) territory
- Patients with a transient ischaemic attack (TIA) were not considered.

5.3 Clinical evaluation

Data for neurological and/or function status was available at:

- Baseline (NIHSS),
- 24-hours (NIHSS),

- 7- days (NIHSS) after hospital presentation (or day of discharge from the hospital, whichever was earlier).

Functional outcome as defined by the modified Rankin Scale (mRS) was available at 90 days after the index event.

Screening

Datasets from 142 SOS patients were screened for availability of baseline CT and source image CT-angiography. CT-angiographies were evaluated to see if the ASPECTS regions were included (high enough coverage) and to make sure the CT-angiography was of sufficient quality (contrast bolus was timed correctly in the arterial and not venous phase). If the bolus was too late and there was no complete arterial filling, the data was excluded.

5.4 Image analysis and Training

For our study baseline and follow-up non-contrast CT scans obtained between 24 to 36 hours after stroke onset were available. In addition, baseline and follow up CT-Angiography was analysed. The ASPECTS score was assessed on baseline and follow-up non-contrast CT scans. All CT-Angiographies were evaluated according to the Tan score.

Image processing

I extracted the baseline CT and conducted multi-planar reconstructions to straighten the anatomy and to show the symmetrical areas as most patients could not be aligned symmetrically in the scanner.

Training

I was trained by my supervisor Professor Grunwald, who has over 25 years of experience as a radiologist, on how to interpret CT imaging and how to correlate this with ASPECTS and the Tan score. My training lasted three months and I then correlated images independently, which were then verified with my supervisor. My scoring was consistent with my supervisors' and I then began to work on our patient sample group. Any difficult cases were discussed with my supervisor.

Image analysis

We scored 1040 (20 x 52 patients) ASPECTS areas. I assessed whether and to what extent early ischaemic signs were present and the extent according to ASPECTS. When available, CT perfusion (multiple time frames) and DSA angiography were read.

I then evaluated the CT-Angiographic images to confirm the vessel occlusion. Here, the CTA source images were evaluated for arterial occlusion and displayed on the Aycan console (Aycan, Würzburg, Germany) as MIP (maximum intensity projection) reconstructions with 10 mm thickness in the coronary and axial planes. The extent of collateralisation in and around the vascular occlusion was mapped and measured by the qualitative Tan score. The modified scale of Tan et al. is the simplest system that classifies the collaterals as "good" if seen in ≥50% of the MCA territory and "poor" when they are seen in <50% of the territory. This system allows a rapid assessment and is less prone to differences in opinion.

This score is shown in Table 4 (below)

Score description
0 no collaterals
1 collateral <50% of the closed area
2 collaterals >50%, but <100% of the closed area
3 collaterals 100% of the closed area

Table 4: Score for the quantification of collaterals in CTA-MIP images in alignment with Tan et al.,

2009)

I then scored the 24-hour control CT scans for established ischaemic stroke in all 1040 regions. (20 regions per patient), looking at the extent of ischaemic damage. I

then scored the overall TAN score for each case. Finally, I correlated the findings to the clinical and functional outcome data (mRS, NIHSS) that was assessed at 3-month follow-up.

5.5 Statistical analysis

For statistical analysis purposes, SPSS version 15.0 (Statistical Package for the Social Sciences) was used. The first step was to test for a normal distribution of the data with an exploratory data analysis and the help of the Kolmogorov-Smirnov test and Shapiro-Wilk Test under descriptive consideration from frequencies, averages, standard deviation as well as the median. All tests were preceded by the formulation of a null hypothesis and an alternative hypothesis. For the consideration of normally distributed mean values of a random sample, the Student t-test was used. Significance levels were presented for both normal and nonnormalised values as follows: $p>0.05$ no significance (ns), $p\leq0.05$ significant (*), $p<0.01$ very significant (**), $p < 0.001$ highly significant (***). Without normal distribution the Utest or Mann-Whitney test was used. The Wilcoxon test was used to study related samples.

6 Results

From 146 patients in the SOS dataset 52 were evaluated. Only patients with a complete dataset including baseline CT, 24h CT, CT-Angiography and CT-Perfusion were included. Patients with posterior circulation stroke were excluded. We also excluded patients that had a combination with an ipsilateral anterior cerebral artery stroke and patients where source data was not available for the CT-Angiography or initial imaging was done using DYNA-CT (A CT-scan acquired on the catheter lab angiography table) or baseline or FU imaging was done using MRI.

6.1 Baseline Patient Characteristics

All 52 patients (26 males and 26 females) had a morphologically proven ischaemic territorial infarction that did not necessarily include the cortex in the cerebral artery area and involvement of the motor system.
The mean age of the patients at the time of the index stroke was 76± 6 years. The most common cerebrovascular risk factor was arterial hypertension (present in 5% of patients), followed by hyperlipidaemia (present in 4% of patients), nicotine abuse (present in 3% of patients) and diabetes mellitus (present in 2% of patients).

- 92.3% (48/52) of the patients were right-handed, 5.8% (3/52) left-handed and 1.9% (1/52) ambidextrous.

- 54% (28/52) of patients suffered a stroke on the right side of the brain and 46% (24/52) suffered a stroke on the left side of the brain (*Fig.8*).

- 40.4% (21/52) of stroke lesions were reported within the dominant hemisphere of the patient, whereas 59.6% (31/52) of ischaemic changes appeared in the non-dominant hemisphere.

- 100% (28/28) of stroke lesions on the right side occurred in the non-dominant hemisphere. 87.5% (21/24) of stroke lesions on the left side occurred in dominant hemisphere and 12.5% (3/24) within non-dominant hemisphere.

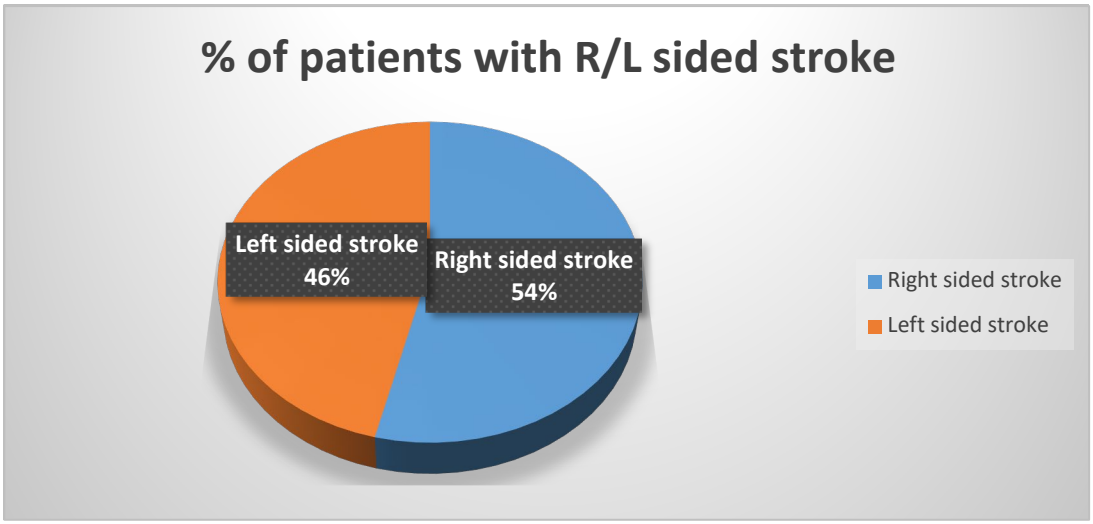

Fig.8 Pie-chart illustrating the % of patients suffering a right/left sided stroke

6.2 Baseline Imaging Results

Collaterals

Collaterals were scored according to the Tan Score. The distribution was as follows:

TAN score (See Table 5 and Fig. 9 below)

- TAN score = 0 in 8 %
- TAN score = 1 in 27 %
- TAN score = 2 in 44 %
- TAN score = 3 in 21 %

TAN	TAN_Score (NIHSS Correlation)	
	Number	Percentage (%)
0	4	7.69
1	14	26.92
2	23	44.23
3	11	21.15
Missing	0	0

Table 5: Distribution of Tan scores.

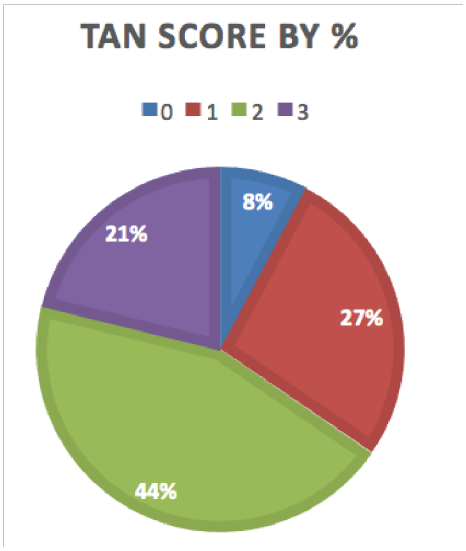

Fig. 9 Pie Chart of individual TAN Scores represented in a pie-chart in percentage. TAN score of 0: no collateral, TAN score of 3: full collaterals.

None of the images had evidence of ICH at baseline.

mRS score was recorded at 90 days as a marker of patient outcome. The distribution of the scores from 0-6 were as follows

- 0- 0%
- 1- 1.2%
- 2- 5.1%
- 3- 15.4%
- 4- 37.6%
- 5- 15.4%
- 6- 25.3%

ASPECTS regions were affected as follows (See Fig.10 below):

- M1 48%
- M2 76%
- M3 50%
- M4 35%
- M5 67%
- M6 39%

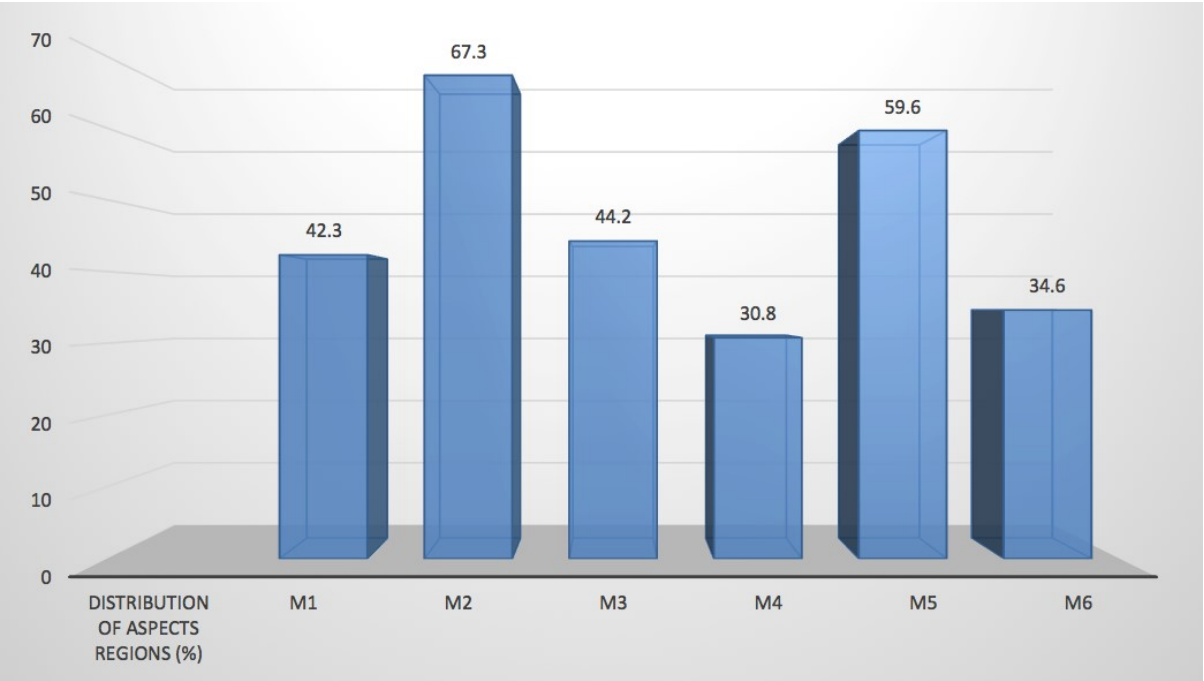

Fig.10 Distribution of ASPECTS regions by %. M2 and M5 were more affected than the other areas.

67.5% of patients had a drop in ASPECT's score from baseline to 24hrs, with an average decrease of two points.

6.3 Statistical Results

1) Correlation between TAN score (collaterals) and outcome (mRS; NIHSS)

An increasing TAN score appears to be associated with a lower mRS score (p=0.048; 95% CI) meaning that patients with better collaterals had a better outcome (Table 6 below).

This however did not reach significance on the NIHSS score.

Table 6

Region	NIHSS coefficient	NIHSS p-value	mRS coefficient	mRS p-value
TAN score	-1.12 (-4.01, 1.76)	0.436	-0.60 (-1.20, -0.005)	0.048

2.) Correlation between TAN score and ASPECTS score

Class	FU_ASPECTS (Tan)		
	Number	Percentage (%)	Cumulative percentage (%)
0	6	11.53	11.53
1	6	11.53	23.07
2	4	7.69	30.76
3	10	19.23	50.00
4	7	13.46	63.46
5	6	11.53	75.00
6	3	5.76	80.76
7	2	3.84	84.61
8	4	7.69	92.30
9	1	1.92	94.23
10	1	1.92	96.15
Braki	2	3.84	100.00

*Table 7: There was a positive correlation between the Tan score and the ASPECTS score (*p*=0.049; p<0.05).*

3.) correlation between individual ASPECTS areas and functional outcome (mRS; NIHSS)

We used linear regression models for NIHSS, and ordinal logistic regressions for mRS. In both cases a coefficient equal to zero implies no effect of damage in the region, greater than zero implies an increase in NIHSS or mRS score, and less than zero implies a reduction in score.

Table 8 (below) shows that M2 and M4 are associated with an increase in NIHSS. M2 and M5 are associated with an increase in mRS.

Region	NIHSS coefficient	NIHSS p-value	mRS coefficient	mRS p-value
M1	2.91 (-1.81, 7.62)	0.220	1.10 (-0.01, 2.21)	0.051
M2	6.01 (0.71, 11.30)	0.027	1.50 (0.24, 2.75)	0.019
M3	2.81 (-1.91, 7.52)	0.236	0.46 (-0.59, 1.52)	0.390
M4	6.50 (1.74, 11.25)	0.009	0.94 (-0.18, 2.06)	0.100
M5	2.64 (-2.38, 7.66)	0.294	1.35 (0.19, 2.51)	0.023
M6	3.88 (-0.91, 8.66)	0.109	1.16 (0.026, 3.15)	0.045

Table 8: M2 and M4 are associated with an increase in NIHSS. M2 and M5 are associated with an increase in mRS.

4.) Does a higher ASPECTS score (more affected areas) correlate with a better functional outcome? (lower mRS and lower NIHSS)

Here a coefficient less than zero implies that an increase in ASPECTS score (less damage) implies a reduction in NIHSS and mRS scores.

Both outcomes are significant (Table 9).

This is also illustrated by Fig. 11 and Fig.12 (below) respectively.

Region	NIHSS coefficient	NIHSS p-value	mRS coefficient	mRS p-value
ASPECTS score	-0.99 (-1.92, -0.05)	0.039	-0.32 (-0.52, -0.12)	0.002

Table 9: an increase in ASPECTS score (less damage) implies a reduction in NIHSS and mRS scores (better outcome) (p= 0.039; 0.002).

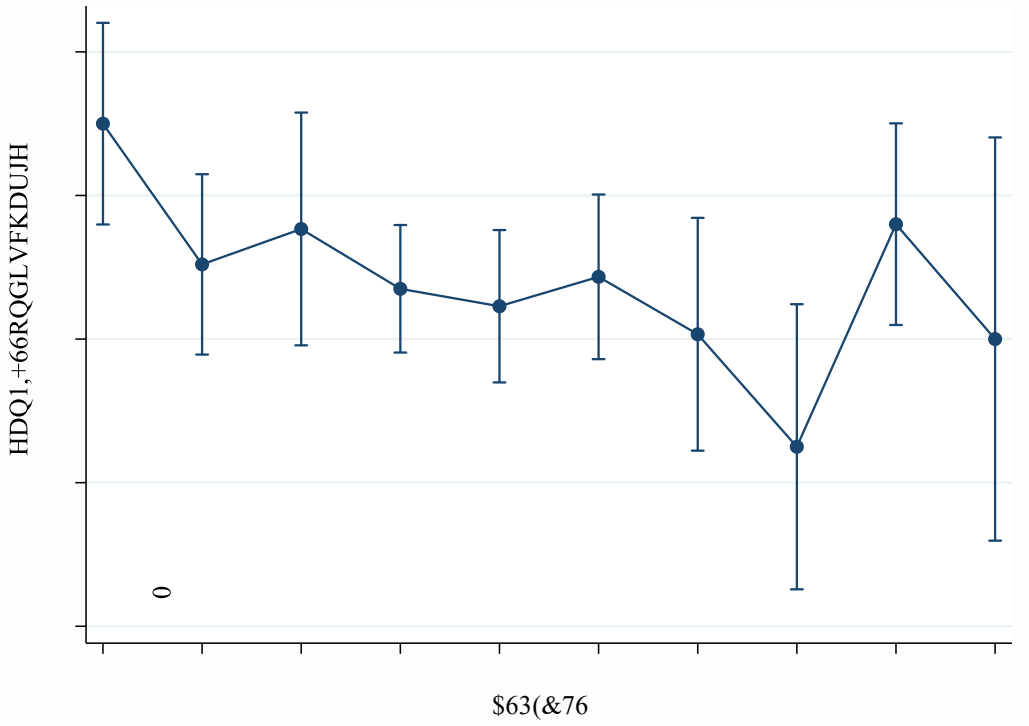

Fig. 11 Graph showing mean NIHSS at discharge with ASPECTS score, showing a statistically significant result

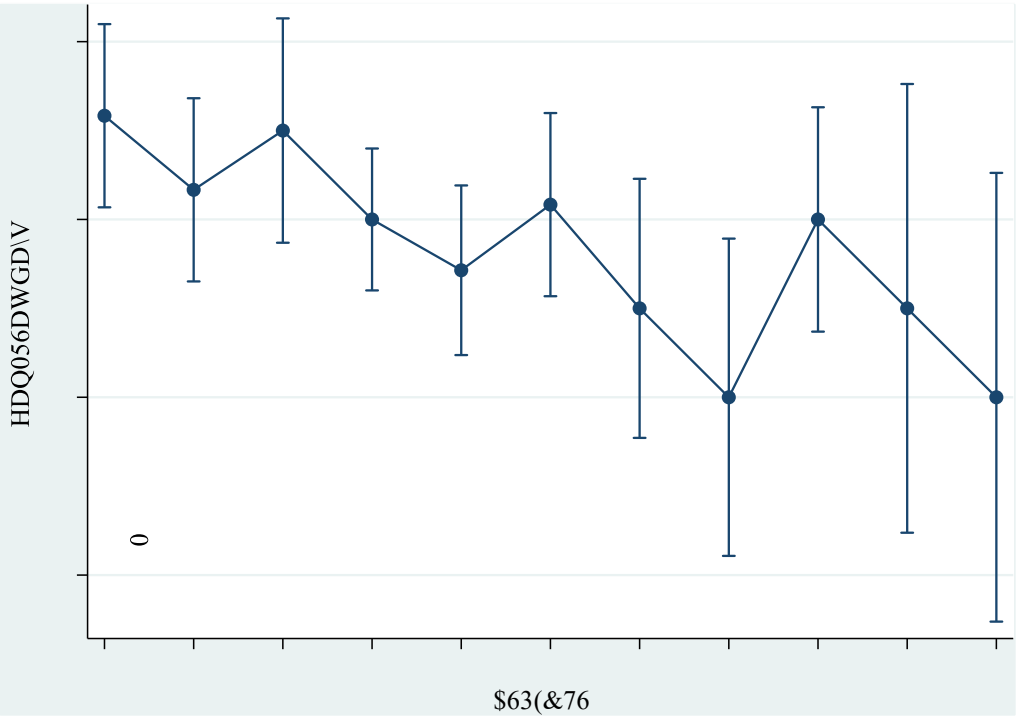

Fig. 12 Graph showing mean mRS at 90 days against ASPECTS score, again the statistical analysis revealed a significant result.

5.) Does having a stroke in the dominant side predict a lower mRS or NIHSS?

If the coefficient is greater than zero, having the dominant side affected implies an increase in NIHSS or mRS scores. There appeared to be no effect.

Region	NIHSS coefficient	NIHSS p-value	mRS coefficient	mRS p-value
Dominant side?	2.91 (-1.78, 7.60)	0.218	0.25 (-0.76, 1.25)	0.630

Table 10: Having a stroke on the patient's dominant side did not predict a lower outcome measure (mRS/NIHSS)

7 Discussion

A lot has happened in the acute treatment of ischaemic stroke. In the past, only intravenous lysis therapy was available, which had to be applied within three hours after exclusion of bleeding by CT or MRI. Today different rules apply. Not only has the timeframe of thrombolysis been extended to 4.5 hours (Hacke et al., 2008) but mechanical thrombectomy has expanded the treatment spectrum in ischaemic stroke (Smith et al., 2008). In early 2015, five independent randomised trials were published: ESCAPE (Goyal et al., 2015) EXTENDIA (Campbell et al., 2015), MR CLEAN (Berkhemer et al., 2015), REVASCAT (Jovin et al., 2015) and SWIFT-PRIME (Saver et al., 2005). These studies demonstrated the real superiority of endovascular stroke treatment. Interventional techniques are now available in all major stroke centres but questions now revolve around patient selection, whether to transport a stroke patient to a specialist thrombectomy centre and which patients may benefit beyond the 6-hour window from recanalisation, whether by intravenous lysis or by endovascular intervention.

Studies such as the one by Nogueira et al. (2018) (DAWN) and Albers et al. (2018) (DEFUSE-3) have begun to shift the paradigm away from the traditional time windows for interventional endovascular therapy. The DAWN Study (Nogueira et al.,2018) triaged patients with wake-up and late presenting strokes for neurointervention with the Trevo device according to DWI or CTP Assessment. The trial showed that the time window for endovascular treatment may be extended to 24 hours after the patient was last known to be well if patients are carefully selected on the basis of a disproportionately severe clinical deficit in comparison with the size of the stroke on imaging. In the DAWN study, infarct volume was seen as a predictor of outcome (smaller infarct volume patient's being chosen for the study).

The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial (Albers et al., 2018) showed that patients with anterior circulation stroke and remaining, intact ischemic brain tissue who received thrombectomy 6-16 hours after last known well, had better functional outcomes than patients treated with standard medical therapy. Patients needed to have an initial infarct size of less than

70 ml and a ratio of the volume of ischaemic tissue on perfusion imaging to infarct volume of 1.8 or more.

Patient selection in these studies was crucial as patients were chosen based on their infarct volume, identified by perfusion scanning or DWI-MRI.

My study adds a different but critical angle to the literature, to what is already known and has ramifications for patient selection suitable for stroke therapies.

The patient group in my study had suffered a stroke with persistent large vessel occlusion but, importantly, they were **not** recanalised. In fact, occlusion of the vessel was confirmed 2-4 days post event. Thus, clinical results will not be confounded by early reperfusion caused by reopening of the vessel. My study results have shown that those patients with poor collaterals will have less salvageable brain tissue and hence poorer outcomes. Our results also suggest that those with good collaterals may potentially have areas of the brain which remain salvageable, whether that be temporary or permanent and it is in this cohort of patient's where treatment could still be beneficial, regardless of a time-window. This also has implications for secondary referrals to thrombectomy capable centres. I will now go on to explain these results in more detail.

In our study we evaluated a unique group of patients that presented with persistent large vessel occlusion. My results showed an increasing TAN score appears to be associated with a lower mRS score ($p=0.048$; 95% CI). There was a positive correlation between the ASPECTS score and the Tan score ($p=0.049$; $p<0.05$). The M2 and M4 regions were associated with an increase in NIHSS ($p= 0.027$; 0.009); the M2 and M5 regions were associated with an increase in mRS ($p= 0.019$; 0.023). An increase in ASPECTS score (less damage) implied a reduction in the NIHSS and mRS score (better outcome).

We found a positive correlation between the ASPECTS score and the Tan score. This is in accordance with studies on patients with recanalisation therapies (Bang et al.,

2011). A low ASPECTS score was positively correlated with the Tan score (0.049, $p<0.005$).

Collaterals have already been reported to affect the rate of infarct growth, perfusion providing indirect information about this downstream collateral supply to the ischaemic tissue. Vagal et al. investigated associations between computed tomography angiography (CTA) of collaterals and parameters of perfusion in the IMS III trial. The authors showed an association between the status of collaterals in the CTA and the CTP parameters as part of a randomised study design. The limitations of their study lie in the post-hoc analysis, along with a small sample size. In addition, the IMS III study was a multicentre study with significant heterogeneity in the technique of CTA and varying recanalisation rates.

In our study we concentrated only on patients with persistent LVO. All patients had repeat CTA to demonstrate persistent occlusion, having the advantage that changes in NIHSS cannot be attributed to vessel recanalisation but instead to the extent of collateral supply and eloquent area. The extent of this collateral supply is shown in the analysis of 3,681 patients with carotid stenosis treated since 1995 at the Western University in Ontario (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995 and Johnson et al., 1995). In 316 patients, the carotid artery was already occluded when the patients presented in the clinic. Of those patients, only one (0.6%) had a stroke previously. Three more patients (0.9 %) suffered a stroke during follow up. The analysis showed that neither the extent of the stenosis nor any occlusion of the other carotid type made the stroke predictable.

The selection of patients for thrombolytic therapy is conventionally based on a strict time windows (4.5 hours for intravenous thrombolysis, and 6-8 hours for mechanical thrombectomy) as well as the extent of infarction in the initial CT imaging. ASPECTS scores of 5 or 6 and above have been applied in previous thrombectomy studies. However, these criteria are insufficient to predict the individual outcome of a patient. It is all about balancing the benefit of reperfusion versus the risk of haemorrhage.

An individual selection based on individual physiological criteria (Jovin et al., 2002) would be a better example e.g. the neurological outcome after stroke depends, among

others, on the residual blood flow during vascular occlusion (Muir et al., 2006). This can be determined by means of the perfusion CT parameters (Schaefer et al., 2007). A cerebral blood volume (CBV) below 2 ml / 100 g of brain tissue in CT perfusion is considered to be already infarcted with a statistical probability of 93% (Wintermark et al., 2006). Lansberg et al. published the CRISP study (CT Perfusion to Predict Response to Recanalisation in Ischaemic Stroke Project), which addressed prediction of CT perfusion in terms of outcome. The aim of the study was to find out if patients with infarct core mismatch in CT perfusion benefitted from thrombectomy as compared to patients without mismatch in CT perfusion. They found that patients with a mismatch in CT perfusion had a 6.6-fold higher chance of a good outcome after mechanical thrombectomy. A good outcome was rated as a reduction of the NIHSS by at least 8 points or as a NIHSS $\leq$ 1 point 30 days after intervention (Lansberg et al., 2017). However, the study cannot be compared directly with ours, as our patients were not recanalised. There are currently various semi quantitative (visual penumbra estimation, ASPECTS evaluation studies (Aviv et al., 2008 and Lee et al., 2008) and quantitative evaluation algorithms (Klotz et al., 1999).

Occlusion localisation could be considered as another important parameter for deciding on thrombectomy. However, there are currently no studies in which thrombectomy was performed in a highly selected patient population (occlusions of the major cerebral arteries) based on collateral status. Outcome after thrombectomy depends, among other things, on the residual blood flow maintained by the collateral system. These are inter- individually very diverse and differently developed (Fisher et al., 2006). Despite the great potential for characterising the collaterals by means of invasive methods such as digital subtraction angiography or noninvasive methods such as CT or MR- angiography or even transcranial Doppler sonography, until recently, no great importance was attributed to this methodology. Thus, so far, collaterals play no established role in acute stroke imaging. As early as 2004, Schramm et al. showed that the extent of collaterals in CT angiography is a surrogate parameter for residual blood flow. Later, Christoforidis et al. were able to demonstrate the connection between collateral systems and clinical outcome or bleeding events in two studies. Finally, Tan et al. demonstrated that CTA-MIP reconstruction is better at assessing collateral circuits than CTA source images. Furthermore, his working group developed a semi quantitative score based on the visual assessment of the extent of collaterals in

the ischaemic stream area. In a heterogeneous patient population, they were able to show in a retrospective analysis that this score correlated with the final infarct volume with a good scorer agreement (Tan et al., 2007).

Modern imaging techniques including the collateral status could help physicians find their way to the best therapy. However, there is still a lack of data. The role of collaterals and their consequences for stroke care and especially patient selection are still under discussion. Some academics see collateral blood flow as an indicator of a better therapeutic outcome, as the damage caused by arterial occlusion is partially offset by these alternative routes of delivery. Collateral recruitment depends on a range of collateral features including the size of the vessel, the direction of flow, the patency of the pathways and the speed of filling (Liebeskind et al., 2003; Malhotra & Liebeskind et al., 2020). The lack of collateral circulation, on the other hand, was shown to be a risk factor for secondary haemorrhage and space-occupying infarcts.
Whether the existence of good collaterals will guide decisions about treatment options is still a topic of discussion, as is the most appropriate modality for assessing the collateral status. In addition to collateralisation, there are a few other parameters that could help gauge the sense or nonsense of recanalisation. An approach is to use not only standard perfusion measurements in assessing ischaemic damage, but also more complex parameters such as cerebral blood volume (CBV), or the mean transit time of the blood (MTT). Recently it was shown that perfusion could be used to reliably identify brain areas with the help of CT perfusion imaging, which would still benefit from thrombectomy up to 12 hours (Wannamaker et al., 2018). In doing so, CBV perfusion of a brain area affected by the stroke was correlated to the MTT. If the MTT area was significantly larger than the CBV disturbed area, it was assumed that the socalled penumbra tissue could still be saved by recanalisation.

We found that ASPECTS on follow up correlated with the improvement of the NIHSS between admission and discharge, i.e. the short-term outcome. This is consistent with previously published studies (Aviv et al., 2007 and Popiela et al., 2008). Perfusion CT in acute stroke: prediction of vessel recanalisation and clinical outcome in intravenous thrombolytic therapy (Kloska et al., 2007), in which ASPECTS-CBV was identified as the best predictor of outcome in patients treated with or without thrombolysis.

However, these studies invariably used the mRS after three months to identify the outcome.

A high initial NIHSS has been described as a predictor of a worse outcome (Wechsler et al, 2003). Interestingly, in the present study there was no correlation between initial NIHSS and outcome which seems to contradict the widely accepted finding that patients with high NIHSS are generally poor outcome candidates after thrombolysis (Gasparotti et al., 2007). However, contrary to other studies, none of our patients had a recanalisation of the vessel and the initial NIHSS was already high with minimal inclusion criteria of NIHSS.

Handedness: An explanation for the negative predictive value of previous studies could be related to the assignment of brain areas to functions. In the primary areas of the cerebral cortex with sensorimotor function, the assignment of anatomy to function is very reliable and varies little between individuals. However, this applies to a limited extent only to secondary areas of the cerebral cortex such as the language. The language areas vary in individual humans not only with respect to the speech-dominant hemisphere, but also anatomically within certain limits, so that the exact anatomical assignment on an individual basis is limited. Thus, it may be that in some patients a speech disorder was present, which was already in an infarcted area, which we had mistakenly not assigned to the language function. Also, we did not pay attention to the handedness of the patients, so that we could not draw any indirect conclusions about the language dominant hemisphere. In the case of stroke in the right hemisphere, problems with orientation, attention, and creativity, among others, may occur; however, this is not reflected in our conventional functional tests (mRS and NIHSS). If the left hemisphere is damaged, the language is often disturbed which strongly reflects in both scores.

We conclude that strokes affect the patients left hemispheres more often (Hedna et al., 2013) but left sided strokes are not more severe, yet are causing more deficits in conventional outcome tests. The speech region is in right-handed patients on the left side of the brain (and in a percentage of left-handers). If loss of the language or loss of the ability to speak and count occurs, the deficit will be dramatic. In addition, in left sided infarction, the right hand is affected, which is also a serious drawback for those

who are right-handed. Although patients with a left sided infarct had a better outcome on their NIHSS, it is wrong to believe that right sided infarcts are harmless. They also lead to hemiplegia with orientation disorders and visual field defects. The patient often does not notice partial visual field defects which can lead to tragic accidents when in traffic. Neglect of the paralysed body side and attention deficits are other stroke symptoms in the right hemisphere. It has also been reported that patients with right sided strokes are more prone to depression (MacHale et al., 1998). Deficits of the left side, such as the speech disorders, are more obvious, whilst right hemispheric stroke symptoms can sometimes go unnoticed.

Our results showed that M2 and M4 areas were associated with an increase in NIHSS ($p= 0.027$; 0.009) meaning more disability and M2 and M5 areas were associated with an increase in mRS ($p= 0.019$; 0.023) and greater morbidity. These areas in the brain do not have one specific function but have a complex overlay of roles, which are still to be fully elucidated. What we can say from our results is patients with good collaterals in the M2 and M4 region, where no stroke developed, were more likely to have a lower NIHSS score.

But what of those patients who present outside of the time window. One in five strokes are classified occur during sleep (wake-up stroke). People with wake-up stroke have traditionally been considered ineligible for recanalisation therapies because the time of stroke onset is unknown. The DAWN and DEFUSE-3 trials have shown the efficacy of thrombectomy in selected patients with occlusion of proximal vessels in the anterior circulation up to 24 h after suspected onset of symptoms. A recent Cochrane review (Roaldsen et al., 2018) has also shown there is insufficient evidence from randomised controlled trials for recommendations concerning recanalisation therapies for wake-up stroke. Our study has shown that patients who present outside the time window for traditional recanalisation therapies may potentially have salvageable brain tissue depending on their collateral status. Whether or not these patients would benefit from systemic recanalisation therapies or endovascular therapies is yet to be determined, but the importance of collaterals cannot be forgotten and may offer a lifeline for a specific subsection of patients.

How do our results compare with what is already known?

The majority of research on collaterals has focused on stroke patients receiving intravenous thrombolysis within 4.5 hours from last known well or undergoing ET within 6 hours from last known well. The effect of leptomeningeal collaterals for acute ischaemic stroke patients with large vessel occlusion in the late window (>6 hours from last known normal) remains unknown. Areas of the brain that typically lack or have poor leptomeningeal collateral support, such as the basal ganglia, are likely to be infarcted more rapidly in proximal ICA/MCA occlusions (Shapiro et al., 2020).

DEFUSE 3 provided evidence that ischaemic stroke patients with occlusion of the cervical or intracranial internal carotid artery or the proximal middle cerebral artery and salvageable brain tissue on perfusion imaging, benefit from ET as opposed to medical therapy alone, 6 to 16 hours after last known well (Albers et al., 2018). Although multiphase CTA has been shown to very accurately measure collateral status (Menon et al., 2015) the DEFUSE 3 cohort had a single phase CTA, which has also been validated as a reliable modality for collateral measurement and is widely used clinically. Some studies have demonstrated that good collateral status is associated with reduced ischaemic core growth (de Havenon et al. 2019). De Havenon et al., 2019 looked to determine if collateral status on baseline CT angiography (CTA) impacted neurologic outcome, ischaemic core growth and moderated the effect of endovascular thrombectomy (ET) in the late window. They found that good collaterals were associated with significantly smaller ischaemic core volume and less ischaemic core growth, a reliable biomarker of neurologic outcome. They did not however find that good collaterals affected neurological outcomes. There could be several explanations for this, firstly the collateral circulation ultimately fails in the majority of stroke patients with large vessel occlusion who are not recanalised (Lansberg et al., 2001). The ischaemic core of the DEFUSE 3 patients with good collaterals, particularly those who were not recanalised, may have continued to grow after the 24-hour follow-up imaging and ultimately be comparable to patients with poor collaterals. Limitations of their study included selection bias (CTA as baseline imaging only),

Further assessment of collaterals in our cohort and others' at various intervals (up to five days) after acute stroke insult may help to answer these questions such as also provide valuable information on collateral evolution over time. As previously discussed, this is dependent on dynamic factors, such as intravascular volume, adrenergic tone, blood pressure, brain oedema, temperature and medications being administered (Rocha et al., 2017).

Without a better understanding of collateral evolution, we will not fully appreciate their effect on neurologic outcome or comprehend how to therapeutically modify that effect. There is also a lack of consensus on the optimal collateral grading system based on non-invasive imaging modalities in acute ischaemic stroke (Ravindran et al., 2020)

Crucially, our study results show that those patients with good collaterals potentially have brain tissue which is still salvageable - and the selection of these patients for transfer to a tertiary centre, for endovascular treatments, is key. We speculate that, in the future, stroke physicians will treat patients not just on infarct volumes (as in the DAWN study), but will also include the collateral status. Collaterals also have an important role to play in the survival and sustenance of hypoperfused tissue following an acute ischaemic stroke, especially in assisting patient selection for endovascular therapy, in an extended time window and identifying those who are more likely to benefit, so that the benefits of acute neurointervention are compounded and therefore translated into a significant favourable clinical advantage (Amaro et al., 2019; Beretta et al., 2017; Nishijima et al., 2015).

The first attempts have already been made. Artificial Intelligence companies such as Brainomix Inc. (Brainomix Inc. Oxford, UK) have added assessment and scoring of collaterals to their e-stroke portfolio. Their software now automatically calculates infarct volume by recognising subtle differences in brain densities, identifies occluded vessels and analyses the collateral status. The game changer in our study is that it negates the need for CT-perfusion scans, which add to the complexity of stroke imaging. This saves time and also protects the patient from additional radiation and contrast agent. Also, perfusion imaging and interpretation is currently only available in a few selected centres in the UK whereas CTA, which is required to identify large

vessel occlusion strokes, is available in most centres in the United Kingdom. Assessment of collateral status would remove the need for any additional imaging (except baseline CT) and could help decide which patients are suitable candidates for transfer to tertiary stroke centres for intervention. For patients with poor collaterals that cannot be recanalised in time, we would expect the areas affected to develop ischaemic tissue early. This has immediate effect on the clinical management as patients with poor collatereals will develop malignant brain swelling early. They thus require diligent, clinical monitoring with decompressive surgery being discussed/planned at an early stage, where as those with good collaterals are likely to have more reserve and will potentially develop a smaller infarct with more brain tissue staying alive.

Limitations:

A limitation of our study was the small sample size, and this was predominantly down to patient's not matching our inclusion criteria, alongside missing source image data-sets. Our data only evaluated anterior circulation strokes and a complete dataset was required to assess late opening of the vessel and infarct volume at 24 hours.

Another limitation is that the thrombus length was not evaluated. Riedel et al. postulated that very long thrombi are more difficult to resolve with intravenous lysis than short thrombi and this may play a role in recanalisation. However, we could show that none of our patients recanalized, thus diminishing this confounder.

Neurological outcome is also dependent on the side and localisation of the occlusion. Although we differentiated between dominant and non-dominant hemisphere in our analysis we did not differentiate between different eloquent areas which, except for the hand knob, would have required additional functional imaging.

Although our patients had confirmed large vessel occlusions at days 2-4 post admission, we cannot be sure that the vessel did not spontaneously recanalise at a later date. However, we would expect most ischemic damage to have developed by this time. Unfortunately, funding did not permit an in-person assessment (NIHSS) at 90 days and only the mRS was collected (via telephone interview), thereby limiting a

more detailed analysis of specific neurological function. However, mRS is considered a universal outcome measure in the majority of stroke studies.

Advantages:

Our study is the first study evaluating the role of collaterals in patients with persistent MVO and opens a paradigm for those who are not amenable to thrombolysis or endovascular treatment yet may have a good outcome.

A particular strength of our study is that we also evaluated the dominant hemisphere in patients which is commonly ignored and is known to have a huge impact on outcome.

One advantage of our study was that in most cases collaterals could be visualised by CT angiography as well as by MRI. Furthermore, patients with different occlusion sites were included in our study. Patients in the PROACT study (ClinicalTrials.gov Identifier: NCT03767595) showed only M1 or M2 occlusions. Arnold et al. treated both proximal M1 and M2 segments and distal occlusions (M3 and M4 segments) of the middle cerebral artery.

None of the previous studies have evaluated eloquent regions such

as the ▪ Central Region Hemiparesis for hemi-hyperaesthesia.

- Internal capsule for hemi-hyperaesthesia + hemiparesis
- Parieto-occipital region for hemianopia
- Frontal region for Broca aphasia
- Tempero-parietal region for Wernicke aphasia and hemi-neglect.

8 Conclusion

Pathophysiologic measures of existing collaterals can characterise brain reserve prior to endovascular thrombectomy and will likely facilitate patient selection for this promising but expensive treatment, which is currently subject to arbitrary time parameters that derive from population studies, before modern imaging techniques were available. Overall, my results revealed that collateral formation has a significant impact on patient outcome with statistically significant results in the M4, M5 and M6 areas, especially in the eloquent cortex affecting motor hand movement. My results add weight by moving away from rigid time windows for potential stroke treatments. The assessment of patients from initial imaging and collateral formation will only help to serve this important lifesaving treatment and adds another tool to a stroke physician's arsenal. We hope that in the future patients will be treated according to their own clinical merit. The importance of mechanical thrombectomy and access to interventional clinicians will be key in treating these patients. This is only the start of what is the first study to evaluate the role of collaterals in persistent large vessel occlusion and their impact on outcome.

9 References

Amaro, S., Renú, A., Laredo, C., Castellanos, M., Arenillas, J. F., Llull, L., Chamorro, Á.. Relevance of collaterals for the success of neuroprotective therapies in acute ischaemic stroke: Insights from the randomized URICO-ICTUS trial. (2019) Cerebrovascular Diseases, 47(3-4), 171–177

Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al.; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. (2018) N Engl J Med.

Alexandrov AV, Demchuk AM, Wein TH, Grotta JC. Yield of transcranial Doppler in acute cerebral ischemia. Stroke 1999;30:1604–1609

Aviv RI, Mandelcorn J, Chakraborty S, Gladstone D, Malham S, Tomlinson G, Fox AJ, Symons S. Alberta
Stroke Program Early CT Scoring of CT Perfusion in Early Stroke Visualization and Assessment. AJNR Am J Neuroradiol 2007;28(10):1975–1980.

Bang OY, Saver JL, Buck BH, Alger JR, Starkman S, Ovbiagele B, Kim D, Jahan R, Duckwiler GR, Yoon
SR, Viñuela F, Liebeskind DS. Impact of collateral flow on tissue fate in acute ischaemic stroke. J Neurol Neurosurg Psychiatry. 2008;79:625–629.

Bang OY, Saver JL, Kim SJ. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. Stroke 2011;42:693-699

Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007 Mar;38(3):1091-6.1

Berkhemer OA, Fransen PS, Beumer D, et al.: A randomised trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372: 11–20.

Beretta, S., Versace, A., Carone, D., Riva, M., Dell'Era, V., Cuccione, E., Ferrarese, C.. Cerebral cllateral therapeutics in acute ischemic stroke: A randomized preclinical trial of four modulation strategies. (2017) Journal of Cerebral Blood Flow and Metabolism, 37, 3344–3354

Brett, M., Johnsrude, I. S., and Owen, A. M. The problem of functional localization in the human brain. (2002) Nat. Rev. Neurosci. 3, 243–349.

Campbell BC, Mitchell PJ, Kleinig TJ, et al.: Endovascular therapy for ischemic stroke with perfusionimaging selection. N Engl J Med 2015; 372: 1009–18)

Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 1987; 76:142-154.

Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. AJNR Am J Neuroradiol 2005;26(7):1789–1797.

Christoforidis GA, Karakasis C, Mohammad Y, Caragine LP, Yang M, Slivka AP. Predictors of Hemorrhage Following Intra-Arterial Thrombolysis for Acute Ischemic Stroke: The Role of Pial Collateral Formation. AJNR Am J Neuroradiol 2008;30(1):165–170.)

de Havenon A, Mlynash M, Kim-Tenser MA, et al. Results From DEFUSE 3: Good Collaterals Are Associated With Reduced Ischemic Core Growth but Not Neurologic Outcome. Stroke. 2019;50(3):632638.

Demchuk AM, Burgin WS, Christou I, et al. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. Stroke 2001;32:89–93

Eastwood JD, Lev MH, Azhari T, Lee T, Barboriak DP, Delong DM, Fitzek C, Herzau M, Wintermark M, Meuli R, Brazier D, Provenzale JM. CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke. Radiology 2002;222(1):227–236.

El-Koussy, M. et al., 2014. Imaging of acute ischemic stroke. European Neurology, 72(5-6), p.309-316.

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA. 1995;272:1421-1428

Farrell, D. F., Burbank, N., Lettich, E., and Ojemann, G. A. (2007). Individual variation in human motorsensory (rolandic) cortex. J. Clin. Neurophysiol. 24, 286–293.

Fisher M, Garcia JH. Evolving stroke and the ischemic penumbra. Neurology 1996;47(4):884–888.

Gonzalez RG: Low signal, high noise and large uncertainty make CT perfusion unsuitable for acute ischemic stroke patient selection for endovascular therapy. J Neurointerv Surg 2012; 4: 242–245.

Gasparotti R, Grassi M, Mardighian D, Frigerio M, Pavia M, Liserre R, Magoni M, Mascaro L, Padovani
A, Pezzini A. Perfusion CT in Patients with Acute Ischemic Stroke Treated with Intra-Arterial Thrombolysis: Predictive Value of Infarct Core Size on Clinical Outcome. AJNR Am J Neuroradiol 2009;30(4):722– 72.

Goyal M, Demchuk AM, Menon BK, et al.: Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372: 1019–30).

Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317– 1329.

Hall J, Flint AC “Hand Knob” infarction. Journal of Neurology, Neurosurgery & Psychiatry 2008;79:406.

Hedna VS, Bodhit AN, Ansari S, et al. Hemispheric differences in ischemic stroke: is left-hemisphere stroke more common?. J Clin Neurol. 2013;9(2):97–102. doi:10.3988/jcn.2013.9.2.97

Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke 2003;34:e109–e137

Howard, R.S., 2016. The management of ischaemic stroke. Anaesthesia & Intensive Care Medicine, 17(12), p.591-595.

Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 870–947

Jingshan, L., Shengyu, F., Xing, F., Zheng, W., Chuanbao, Z., Zenghui, Q. Tao, J. (2018). Morphometry of the Hand Knob Region and Motor Function Change in Eloquent Area Glioma Patients. Clinical Neuroradiology.

Johnson BF, Verlato F, Bergelin RO, Primozich JF, Strandness E Jr. Clinical outcome in patients with mild and moderate carotid artery stenosis. J Vasc Surg. 1995;21(1):120-126

Jovin TG, Gebel JM, Wechsler LR. Intra-arterial thrombolysis for acute ischemic stroke. J Stroke Cerebrovasc Dis 2002;11(3-4):148–161

Khatri P, Neff J, Broderick JP, Khoury JC, Carrozzella J, Tomsick T. Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. Stroke 2005;36:2400–2403

Kim D, Liebeskind DS. Neuroimaging advances and the transformation of acute stroke care. Semin Neurol 2005;25:345–361

Kim S, Lee M, Park S, Lee S. Prediction of clinical outcome with baseline and 24-hour perfusion CT in acute middle cerebral artery territory ischemic stroke treated with intravenous recanalization therapy.
Neuroradiology 2008;50(5):391–396.

Kloska SP, Dittrich R, Fischer T, et al. Perfusion CT in acute stroke: prediction of vessel recanalization and clinical outcome in intravenous thrombolytic therapy. Eur Radiol 2007;17:2491–98

Kluwer W Osborn AG . Kluwer W , Diagnostic cerebral angiography. Second edition, 1998

König M, Kraus M, Theek C, Klotz E, Gehlen W, Heuser L. Quantitative Assessment of the Ischemic Brain by Means of Perfusion-Related Parameters Derived From Perfusion CT. Stroke 2001;32(2):431– 437.

Kwon S, Hartzema AG, Duncan PW, Min-Lai S. Disability measures in stroke: relationship among the Barthel Index, the Functional Independence Measure, and the Modified Rankin Scale. Stroke.
2004;35:918–923.

Lansberg MG, O'Brien MW, Tong DC, Moseley ME, Albers GW. Evolution of cerebral infarct volume assessed by diffusion-weighted magnetic resonance imaging. Arch. Neurol 2001;58:613–617.

Lansberg MG, Christensen S, Kemp S, Mlynash M, Mishra N, Federau C, Tsai JP, Zaharchuk G, Marks MP, Albers GW. Computed tomographic perfusion to Predict Response to Recanalization in ischemic stroke. Ann Neurol 2017; 81: 849–856.

Ledezma CJ, Fiebach JB, Wintermark M. Modern imaging of the infarct core and the ischemic penumbra in acute stroke patients: CT versus MRI. Expert Rev Cardiovasc Ther. 2009;7:395–403

Maas M, Lev M, Ay H, Singhal A, Kemmling A and Walter J Koroshetz, et al. Collateral vessels on ct angiography predict outcome in acute ischemic stroke. Stroke, 40(9):3001–3005, 2009 SEP

MacHale SM, O'Rourke SJ, Wardlaw JM, et al. Depression and its relation to lesion location after strokeJournal of Neurology, Neurosurgery & Psychiatry 1998;64:371-374

Malhotra K, Gornbein J, Saver JL. Ischemic strokes due to large-vessel occlusions contribute disproportionately to stroke-related dependence and death: a review. Front Neurol. 2017;8:651.

Malhotra, K., & Liebeskind, D. S. Collaterals in ischemic stroke. (2020) Brain Hemorrhages, 1(1), 6–12.

Mankungiya B. Thrombolysis in acute stroke. https://slideplayer.com/slide/9406596/. Last accessed Nov 2017.

Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology 2015;275:510–520.

Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, et al.. Mechanical thrombectomy outcomes with and without intravenous thrombolysis in stroke patients: a meta-analysis.Stroke. 2017

Miteff F, Levi C, Bateman G, Spratt N, McElduff P, and Parsons M. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. Brain, 132(8):2231–2238, 2009

Muir KW, Buchan AM, Kummer R von, Rother J, Baron J. Imaging of acute stroke. Lancet Neurol 2006;5(9):755–768.

National Institutes of Health Stroke Scale (NIHSS) 2017. http://www.nihstrokescale.org/. Last accessed Nov 2017.

Neuhaus A, Couch Y, Hadley G, Buchan AM, Neuroprotection in stroke: the importance of collaboration and reproducibility, Brain, Volume 140, Issue 8, August 2017, Pages 2079–2092

Nishijima, Y., Akamatsu, Y., Weinstein, P. R., & Liu, J. (2015). Collaterals: Implications in cerebral ischemic diseases and ther-apeutic interventions. Brain Research, 1623, 18–29.

Ng YS, Stein J, Ning M, Black-Schaffer RM. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. Stroke. 2007; 38:2309–2314

Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.

Ntaios G, Hart RG. Embolic Stroke. Circulation. 2017; 136:2403–2405.

Paciaroni M, Caso V, Agnelli G: The Concept of Ischemic Penumbra in Acute Stroke and Therapeutic Opportunities. Eur Neurol 2009;61:321-330

Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al: Use of the Alberta Stroke
Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol 2001; 22: 1534–1542.

Pfaff J, Herweh C, Schieber S, Schönenberger S, Bösel J, Ringleb PA, Möhlenbruch M, Bendszus M and Nagel S. American Journal of Neuroradiology Aug 2017, 38 (8) 1594-1599

Popiela T, Pera J, Chrzan R, Strojny J, Urbanik A, Słowik A. Perfusion computed tomography and clinical status of patients with acute ischaemic stroke. Neurol. Neurochir. Pol. 2008;42(5):396–401.

Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi
AA, Kidwell CS, Meschia JF, Ovbiagele B, Yavagal DR; on behalf of the American Heart Association
Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.Stroke. 2015; 46:3020–3035

Rankin L. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J. 1957;2:200 –215.

Ravindran, AV, Killingsworth, MC, Bhaskar, S. Cerebral collaterals in acute ischaemia: Implications for acute ischaemic stroke patients receiving reperfusion therapy. Eur J Neurosci. 2020; 00: 1– 24

Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke. 2011;42(6):1775-1777.

Rink C, Khanna S. Significance of brain tissue oxygenation and the arachidonic acid cascade in stroke Antioxid. Redox Signal., 14 (10) (2011)

Roaldsen MB, Lindekleiv H, Mathiesen EB, Berge E. Recanalisation therapies for wake-up stroke.
Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD010995.

Rocha M, Jovin TG. Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke:
Clinical and Research Implications. Stroke 2017;48:2621–2627.

Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 2064–89

Saver JL: Time is brain–quantified. Stroke 2006; 37: 263–266.

Saver JL, Goyal M, Bonafe A, et al.: Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015; 372: 2285–95

Schaefer PW, Roccatagliata L, Ledezma C, Hoh B, Schwamm LH, Koroshetz WJ, Gonzalez GR, Lev MH.
First-Pass Quantitative CT Perfusion Identifies Thresholds for Salvageable Penumbra in Acute Stroke
Patients Treated with Intra-arterial Therapy. AJNR Am J Neuroradiol 2006;27(1):20–25)

Schramm P, Schellinger PD, Klotz E, Kallenberg K, Fiebach JB, Kulkens S, Heiland S, Knauth M, Sartor
K. Comparison of Perfusion Computed Tomography and Computed Tomography Angiography Source Images With Perfusion-Weighted Imaging and Diffusion-Weighted Imaging in Patients With Acute Stroke of Less Than 6 Hours' Duration. Stroke 2004;35(7):1652–1658.)

Shapiro, M., Raz, E., Nossek, E., Chancellor, B., Ishida, K., & Nelson, P. K. (2020). Neuroanatomy of the middle cerebral artery: Implications for thrombectomy. Journal of NeuroInterventional Surgery, 12, 768.

Shuaib A , Butcher K , Mohammad AA , et al . Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. Lancet Neurol 2011;10:909–21.

Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, et al.; Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial.Stroke. 2008; 39:1205–1212.

Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. Stroke 2009;40:3834-3840.

Stroke Association. 2016. Stroke Statistics. Available at (https://www.stroke.org.uk/sites/default/files/stroke_statistics_2015.pdf). Last accessed Nov 19th 2018).

Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol 2007;61(6):533–543.

Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct.AJNR Am J Neuroradiol. 2009; 30:525–531

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7

Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I findings—TIMI Study Group. N Engl J Med 1985;312:932–36

Tomsick T. TIMI, TIBI, TICI: I came, I saw, I got confused. AJNR Am J Neuroradiol 2007;28:382-384

Vagal A, Meganathan K, Kleindorfer DO, Adeoye O, Hornunq R, Khatri P. Increasing use of computed tomographic perfusion and computed tomographic angiograms in acute ischemic stroke from 2006 to 2010. Stroke. 2014;45:1029–1034.

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Inter- observer agreement for the assessment of handicap in Ban.

Von Kummer R, Nolte PN, Schnittger H, Thron A, Ringelstein EB. Detectability of cerebral hemisphere ischemic infarcts by CT within 6 hours of stroke. Neuroradiology.1996;38:31-33.

Wannamaker R, Guinand T, Menon BK, Demchuk A, Goyal M, Frei D, et al.. Computed tomographic perfusion predicts poor outcomes in a randomized trial of endovascular therapy. Stroke. 2018; 49:1426– 1433

Wechsler LR, Roberts R, Furlan AJ, Higashida RT, Dillon WP, Roberts HC, Rowley HA, Pettigrew LC, Callahan AS, III, Bruno A, Fayad P, Smith WS, Firszt CM, Schulz GA. Factors Influencing Outcome and Treatment Effect in PROACT II. Stroke 2003;34(5):1224–1229.

Weimar C, Kurth T, Kraywinkel K, Wagner M, Busse O, Haberl RL, Diener HC. Assessment of functioning and disability after ischemic stroke. Stroke. 2002;33:2053–2059.

Wintermark M, Albers GW, Alexandrov AV, et al. Acute stroke imaging research roadmap. AJNR Am J Neuroradiol 2008;29:e23–e30

Yousry, T. A., Schmid, U. D., Alkadhi, H., Schmidt, D., Peraud, A., Buettner, A., et al. Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. (1997) Brain 120, 141–157.

10 Abbreviations:

A: Artery
ACA: Anterior cerebral artery
ICA: Internal Carotid Artery
MCA: Middle Cerebral artery
ASPECTS: Alberta Stroke Program Early CT Score
C: contrast
CBF: Cerebral Blood Flow
CBV: Cerebral Blood Volume
CCT: cranial computed tomography
CRISP: CT Perfusion to Predict Response to Recanalization in Ischemic Stroke
CT: Computed Tomography
CTA: Computed Tomography Angiography
CW: Circle of Willis
DAWN study: DWI or CTP Assessment with Clinical Mismatch in the Triage of
Wake Up and Late Presenting Strokes
DSA: Digital subtraction angiography
DWI: Diffusion Weighted Imaging
EPITHET: Echoplanar Imaging Thrombolytic Evaluation Trial
ESCAPE: Endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times
EXTEND-IA: Extending the time for thrombolysis in emergency neurological deficits with intra-arterial therapy
FDA: Food and Drug Administration
FLAIR Fluid Attenuated Inversion Recovery
MRA: Magnetic resonance angiography
MR Clean Multi-centre randomised clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands.
mRS: Modified Rankin
Score MRI: Magnetic
resonance imaging MTT:
Mean Transit Time:
NIHSS National Institute of Health Stroke
Scale rt-PA: reverse- Tissue plasminogen
activator
SWIFT-PRIME: Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke

TICI: thrombolysis in cerebral infarction

TIMI: Thrombolysis in myocardial infarction