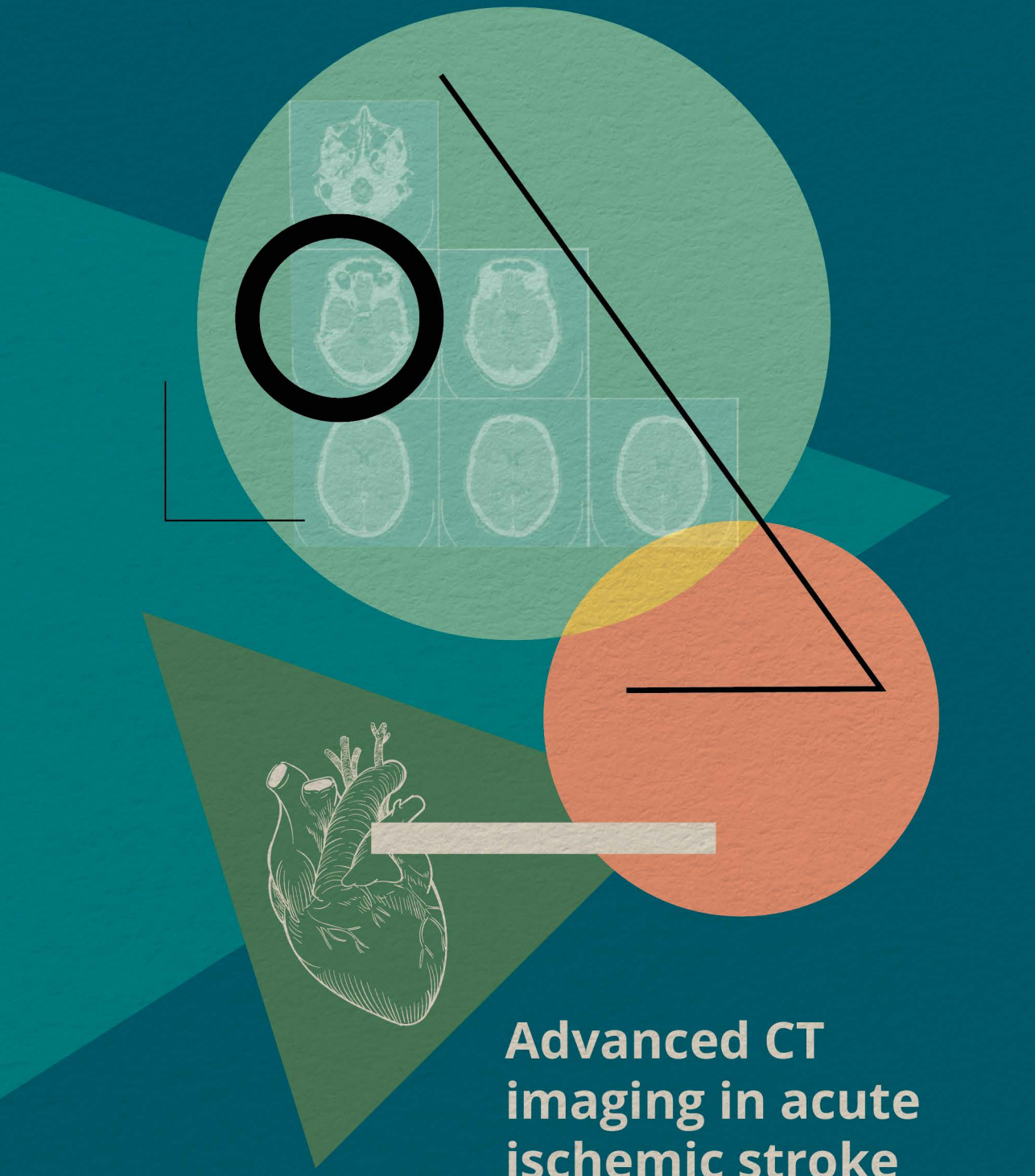

Advanced CT imaging in acute ischemic stroke

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Advanced CT imaging in acute ischemic stroke

Geavanceerde CT beeldvorming bij het acute herseninfarct

(met een samenvatting in het Nederlands)

Proefschrift

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Universiteit Utrecht
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Frans Kauw

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Promotoren:

Prof. dr. B.K. Velthuis
Prof. dr. L.J. Kappelle
Prof. dr. H.W.A.M. de Jong

Copromotor:

Dr. J.W. Dankbaar

Beoordelingscommissie:

Prof. dr. R.M. van den Berg-Vos
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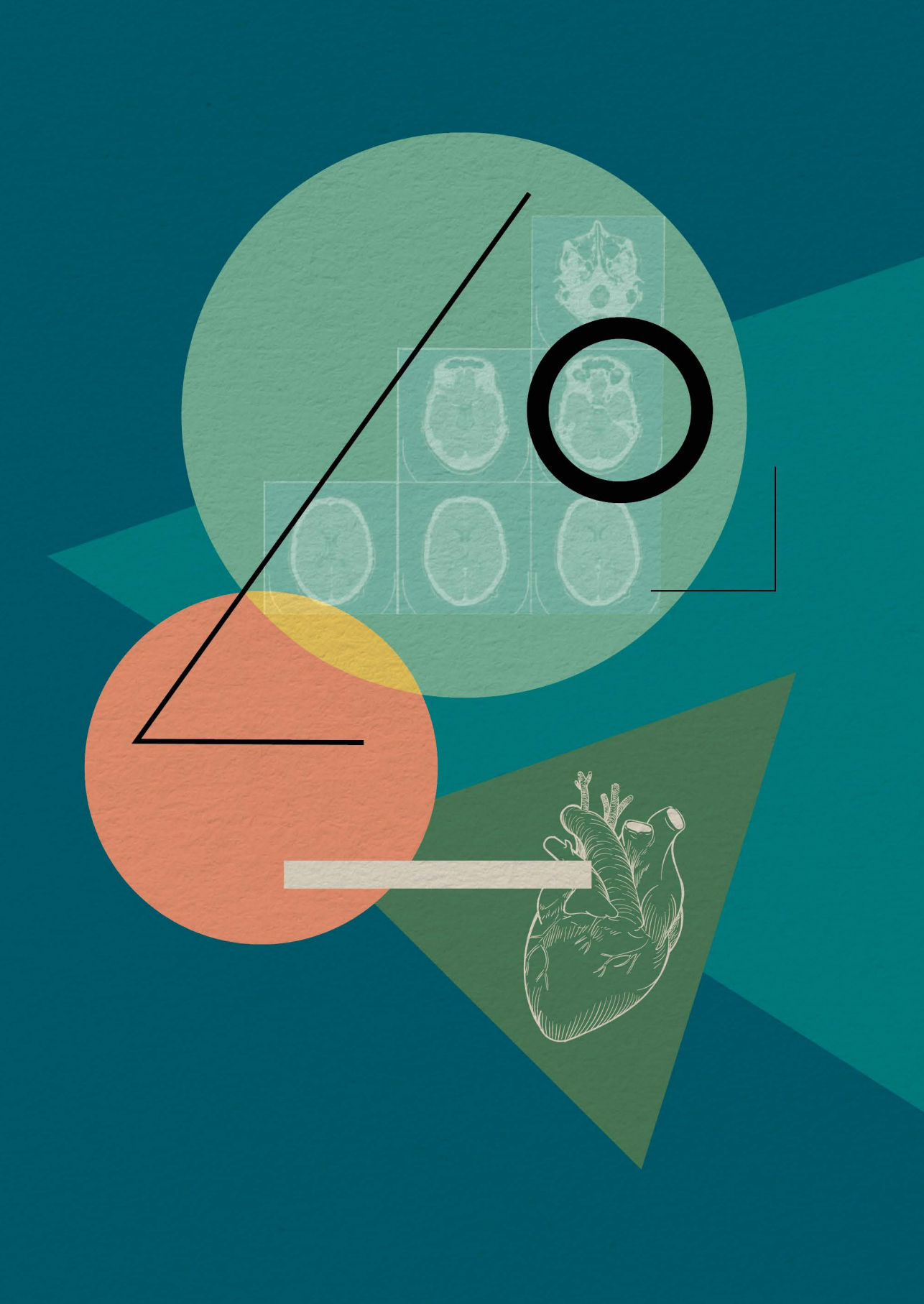

1

GENERAL INTRODUCTION

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Background

Globally, stroke is one of the most prevalent causes of death and the leading cause of long-term disability. Stroke can be ischemic or hemorrhagic. Ischemic stroke occurs when blood flow to a part of the brain is compromised, usually by a blood clot, also known as thrombus. Hemorrhagic stroke occurs when a blood vessel in the brain ruptures and comprises approximately 20% of the strokes. Ischemic stroke is the subject of this thesis.

In ischemic stroke, the obstruction of a brain artery leads to death of brain tissue in the corresponding vascular territory. Depending on which part of the brain is affected, the patient may develop acute neurological deficits such as slurred speech, aphasia, hemianopia, sensory or motor deficits. Quick history taking, focused neurological examination and imaging of the brain should be performed at the emergency department before initiating the proper therapy.

CT imaging in acute ischemic stroke

In most centers, patients with suspected stroke undergo computed tomography (CT) of the brain.[1] The acute stroke imaging protocol may include non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) (Figure 1). Although CT imaging requires a low dose of ionizing radiation, it has certain advantages over MRI in evaluating patients with suspected stroke, such as 24/7 availability, speed and fewer contraindications.[2]

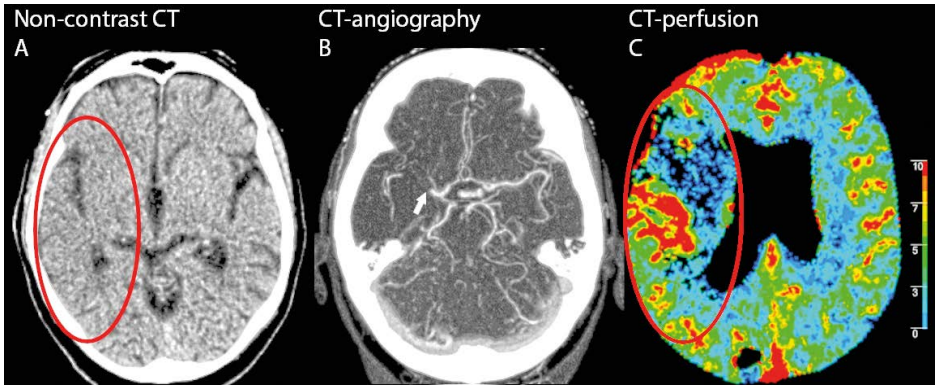

Figure 1. CT images of a patient with acute ischemic stroke. Non-contrast CT (A) shows early ischemic changes in the right hemisphere. An occlusion (arrow) of the M1 segment of the right middle cerebral artery was demonstrated with CT angiography (B) with a corresponding perfusion deficit on CT perfusion (C).

Non-contrast CT

In acute stroke care the NCCT is used to exclude hemorrhage and to determine the presence of ischemia. In case of an uncertain diagnosis after CT, additional magnetic resonance imaging (MRI) may be performed, because the sensitivity for detecting ischemia with diffusion weighted imaging (DWI) MRI is higher (reported 88-100%) than with CT.[3,4] To compete with the better tissue contrast of MRI dual-energy CT, also known as spectral CT, has been developed. CT gray values in CT images are based on both the density of the material in the voxel as well as the average atom number. The dual energy or spectral CT technique is based on the use of two different energy spectra instead of one, allowing differentiation between materials that have different attenuation properties at different energies. While it is also possible to differentiate between materials with conventional CT, certain combinations of density and material type may result in overlapping CT values. Dual-energy CT makes it possible to differentiate more reliably between blood and calcified brain tissue, whereas these materials are less distinguishable with conventional CT. Conventional mono-energy CT is acquired with one X-ray tube and one single layered detector. Acquisition of dual-energy data can be done in multiple manners, which depend on the type of machine. Technical approaches for acquiring dual-energy CT include the use of two X-ray tubes with different energy levels and two single layered detectors, rapid switching between two energy levels by one X-ray tube projecting on one detector, and the use of a dual-layer spectral detector, which can separate the X-ray beam from one X-ray tube in two different energy levels.[5]

In stroke care, some applications of dual-energy CT have been studied. For instance, it is possible to subtract iodine from CTA images to create virtual NCCT images. Studies have shown that these images are more or less comparable with conventional NCCT images with regards to detection of hemorrhage and hyperdense thrombus (hyperdense artery sign).[6–9] In clinical practice, dual-energy virtual NCCT images are used to differentiate between iodine and hemorrhage after endovascular treatment of ischemic stroke.[10–12]

It is unknown whether dual-energy virtual NCCT is similar to conventional NCCT with respect to detection of early ischemic changes. In this thesis, we evaluated whether dual-energy virtual NCCT is non-inferior compared to conventional NCCT regarding detection of early ischemic changes in patients with suspected stroke (**Chapter 2**).

CT perfusion

In addition to NCCT, CTP is routinely performed as part of the stroke protocol in most Dutch hospitals. CTP can visualize areas of reduced perfusion within the brain, making it more sensitive to stroke detection as compared to NCCT. Perfusion maps are acquired by visualizing the in- and outflow of iodine contrast in the brain. The perfusion maps are used to identify salvageable brain tissue at risk for infarction (penumbra) and dead brain tissue (infarct core). Volumes of the penumbra and infarct core can help to decide which treatment is the best choice for patients with acute ischemic stroke. It is therefore essential that the CTP maps are reliable. The CTP maps are generated by automated post-processing of raw CTP data, but failure of this process can occur. In this thesis, we evaluated the incidence and impact of CTP post-processing failures in patients with acute ischemic stroke (**Chapter 3**). When the acquisition is adequate, CTP has high sensitivity (80%) and very high specificity (95%) for infarct detection and has added value to NCCT and CTA, particularly for the detection of infarcts in the posterior fossa.[13,14] However, not all clinical CT scanners have full brain CTP coverage, which may result in false negative findings.[13] In addition, high noise levels and reconstructions with low spatial resolution limit the ability of CTP to identify small volume infarcts.[15,16] In case no stroke is visualized with CT, an MRI is sometimes indicated to ascertain the diagnosis. By improving the detection of small volume stroke by CTP, additional MRI may become unnecessary in the diagnostic pathway, and early detection of these small ischemic strokes may influence acute treatment decisions. One of the aims of this thesis is to improve the detection of small volume infarcts by optimizing the CTP protocol (**Chapter 5**).

CT angiography

CTA is always required in the work-up of acute stroke patients. It is used to demonstrate the arterial occlusion or other vascular abnormalities that may have caused the stroke. The collateral flow to the brain tissue behind an occlusion can be visualized with CTA. The collateral circulation of the brain is a network of blood vessels that preserves blood flow when the normal route is blocked by a thrombus. Collateral vessels can be assessed with various imaging modalities. The grade of collateral filling at baseline has been associated with functional outcome in patients with acute ischemic stroke. [17] It is hypothesized that the ischemic process can be slowed down if collateral vessels can sufficiently take over the perfusion of the brain tissue at risk (the penumbra).[18] In patients who undergo endovascular treatment (EVT), good collateral filling is associated with smaller infarct volumes and with better clinical outcomes compared with poor or absent collateral filling.[18–20]

In the past decade, collateral evaluation has gained much interest and multiple grading systems for different imaging modalities have been developed.[21,22] The visualization of collaterals is dependent on acquisition timing and therefore a single time-frame snapshot of the collaterals may not suffice for accurate assessment.[18] Therefore, it is recommended to assess collateral vessels with a dynamic imaging method such as digital subtraction angiography (DSA), which is not available in the acute stage and only routinely acquired during EVT.[23] Collaterals can also be evaluated over time on the CTP source images. In this thesis, we compared the assessment of collateral filling on single-phase CTA, CTP derived three-phase CTA, multiphase CTA and temporal maximum intensity projection images, and DSA, and evaluated the associations with functional outcome (**Chapter 4**).

The cause of the stroke can also be visualized with CTA. While the majority of strokes originate from thrombi formed in the large arteries due to atherosclerosis, up to one third of the cases with acute ischemic stroke are caused by a cardioembolism which requires a different strategy for secondary prevention (to prevent recurrent stroke).[24] However, the identification of a cardiac source of embolism may be difficult with current cardiologic assessments, particularly in the early stage. Routine cardiac work-up includes electrocardiogram, 72-hour telemetry or Holter, and transthoracic or transesophageal echocardiography.[25] The sensitivity of transthoracic echocardiography for detecting cardiac thrombus is limited and echocardiography is usually performed one to several days after stroke onset, which may influence the chance of detecting cardiac thrombus, especially in patients who have received intravenous thrombolysis.[26] Transesophageal echocardiography has a higher sensitivity than transthoracic echocardiography, but is time-consuming and uncomfortable for the patient, especially in the semi-acute phase of the stroke.[27]

Patients with acute ischemic stroke routinely undergo CTA from head to the aortic arch to evaluate the presence of a large vessel occlusion and a possible stenosis of the carotid artery. In current clinical practice, the heart and thoracic aorta are not routinely covered with CTA.[28] Integrating cardiac CTA into the admission stroke imaging protocol may be an alternative to echocardiography to evaluate the presence of cardiac abnormalities such as thrombus in an early stage (Figure 2). Studies on this topic showed promising results, but they were small, heterogeneous and retrospective in nature.[29] Large prospective studies are needed to confirm the additional value of cardiac CTA in patients with acute ischemic stroke. In this thesis, we investigated the yield of admission non-gated cardiac (spectral) CTA for the identification of cardioembolic sources of stroke in a cohort of patients with transient ischemic attack or acute ischemic stroke (**Chapter 5**, **Chapter 6** and **Chapter 7**).

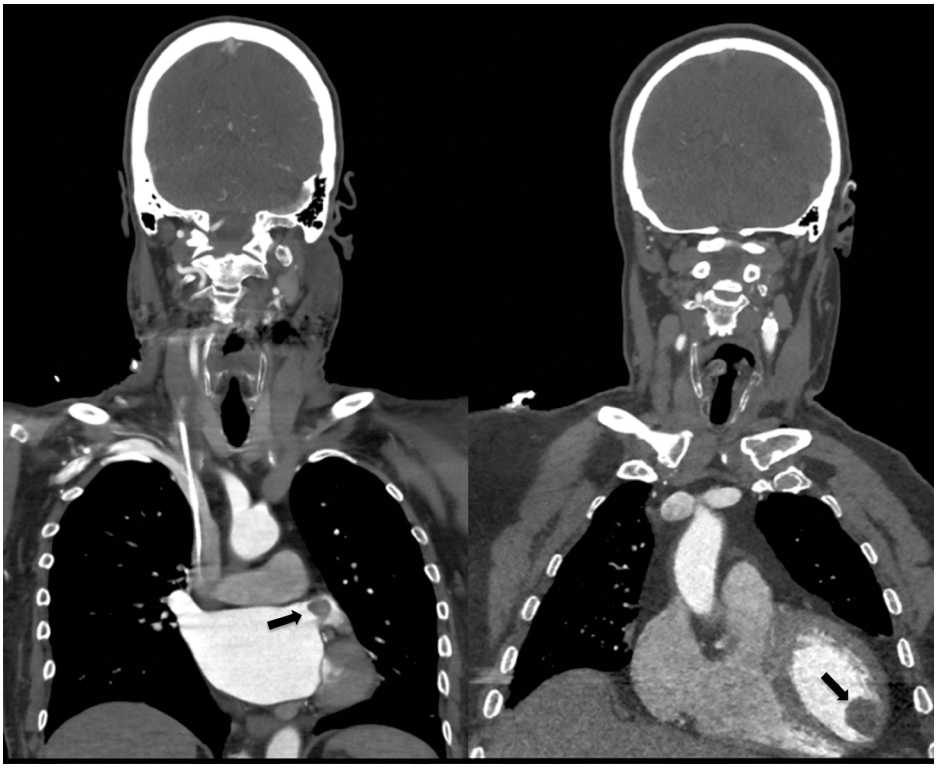

Figure 2. CT angiography images of patients with acute ischemic stroke showing thrombus in the left atrial appendage (left image) and thrombus in the left ventricular apex (right image).

CT imaging predictors of treatment effect, malignant infarction and recurrent stroke

Salvageable brain tissue can be saved with acute stroke therapies such as intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). IVT is a fibrinolytic therapy with the aim to dissolve the occluding blood clot and restore the arterial blood flow. IVT is effective in patients who present in an early time window after symptom onset (<4.5 hours) or after a longer time interval if patients have a sufficiently large penumbra compared to infarct core on CTP.[30]

In anterior circulation stroke, a large vessel occlusion can be treated with EVT.[31–36] A catheter is inserted in the radial or femoral artery and advanced to the occluded artery in the brain to mechanically remove the thrombus. EVT is beneficial in an early time window (within 6 hours), but also up to 24 hours after symptom onset in patients with a favorable mismatch between penumbra and infarct core.[37,38] Nowadays, EVT is also performed in severe cases of a basilar artery occlusion.[39] Several effect modifiers of successful acute stroke therapies have been identified

including collateral filling and type of intracranial internal carotid artery calcification (ICAC).

Treatment effect

ICAC has been associated with ischemic stroke and can be evaluated with CT.[40,41] A medial ICAC pattern, which entails predominant calcification of the tunica media or internal elastic lamina, can be distinguished from an intimal ICAC pattern, which comprises predominant calcification of lipid flakes in the tunica intima. Among these entities, pathophysiology, prognosis and treatment response may differ.[41,42] The pattern of ICAC has been identified as an effect modifier of endovascular treatment in patients with a proximal intracranial occlusion.[43] The association between endovascular treatment and good outcomes such as successful recanalization or favorable functional outcome, but not follow-up infarct volume, was significant in the group with a medial calcification pattern, whereas the association was not significant in the groups without calcification or with an intimal calcification pattern.[43] Hypothetically, calcification of the medial layers of the artery leads to arterial stiffening increasing the pulse pressure more distally.[44,45] As a result, the distal brain perfusion may be impaired and the formation of collateral vessels is triggered. Good collateral filling is, in turn, related to favorable outcome after intravenous thrombolysis or endovascular treatment.[19,20,46] In addition, the culprit thrombus may have different characteristics across the different ICAC patterns influencing treatment effects.[47] If these hypotheses are (partly) correct, the effects of intravenous thrombolysis should also be modified by ICAC pattern. In this thesis, we investigated the effects of IVT across the different ICAC categories (**Chapter 8**).

Malignant infarction

After the event of an acute ischemic stroke, several complications can occur that may hamper recovery and may affect functional outcome.[48] Potential complications include infection, deep vein thrombosis, falls, seizures, malignant edema (ME) formation and hemorrhagic transformation. Of these complications only ME will be discussed further in this thesis.

Development of ME is a life-threatening complication in patients with ischemic stroke and typically occurs in younger patients with a large middle cerebral artery infarction.[49] Such a malignant middle cerebral artery infarction occurs in up to 10% of the patients with large supratentorial stroke.[50] No official definition exists for ME, but stroke researchers often use the combination of clinical deterioration and signs of brain herniation on CT imaging such as midline shift (Figure 3). Usually, the edema develops between the second and fifth day after the stroke, although

onset of symptoms before 24 hours after the stroke may occur. Before surgical intervention was introduced, reported mortality rates associated with malignant MCA infarction ranged between 70 and 80%.[49,51] In a pooled analysis of three randomized trials, early decompressive surgery has been shown to be effective in patients with malignant MCA infarction in terms of improving clinical outcome and reducing mortality rate.[52] Anticipating on development of ME is important, so that the patient can be treated in time. Therefore, prediction of ME in the acute stage is helpful and several predictors and prediction models have been studied.[53] The ratio of the intracranial cerebrospinal fluid (CSF) volume to the intracranial volume (ICV) on admission may be a predictor of ME.[54] Theoretically, the brain has more space to swell, without herniating, when more CSF volume is present. In this thesis, the predictive value of the CSF volume is evaluated in multivariable prediction models (**Chapter 9**, **Chapter 10** and **Chapter 11**).

Recurrent stroke

Recurrent stroke accounts for approximately a quarter of all strokes that occur and has important implications for the long-term outcome of patients.[55] The one-year incidence of recurrent ischemic stroke has been estimated to range from 8 to 14%.[56,57] Several clinical factors have been reported to be associated with recurrent ischemic stroke, but less is known about imaging predictors.[58,59] In this thesis, we systematically reviewed the predictors in the literature and evaluated additional imaging predictors (**Chapter 12** and **Chapter 13**).

To address some of the aforementioned knowledge gaps the 'Early detection of thromboembolic sources and small volume stroke with computed tomography' (ENCLOSE) study was launched. ENCLOSE is a prospective multicenter observational cohort study, which is conducted in adult patients with acute ischemic stroke. The aim of the ENCLOSE study is to improve: 1) early detection of small volume infarcts with thin-slice CTP images and thromboembolic sources with (spectral) cardiac CTA techniques in acute stroke and 2) prediction of recurrent ischemic stroke with CT derived predictors.

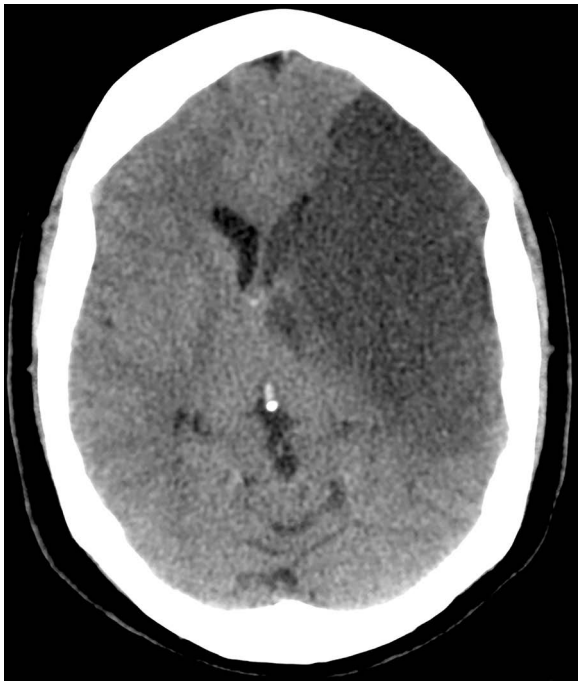

Figure 3. Follow-up non-contrast CT image of a 52-year old female patient with a large middle cerebral artery infarction showing malignant edema leading to a midline shift of more than 5 millimeter

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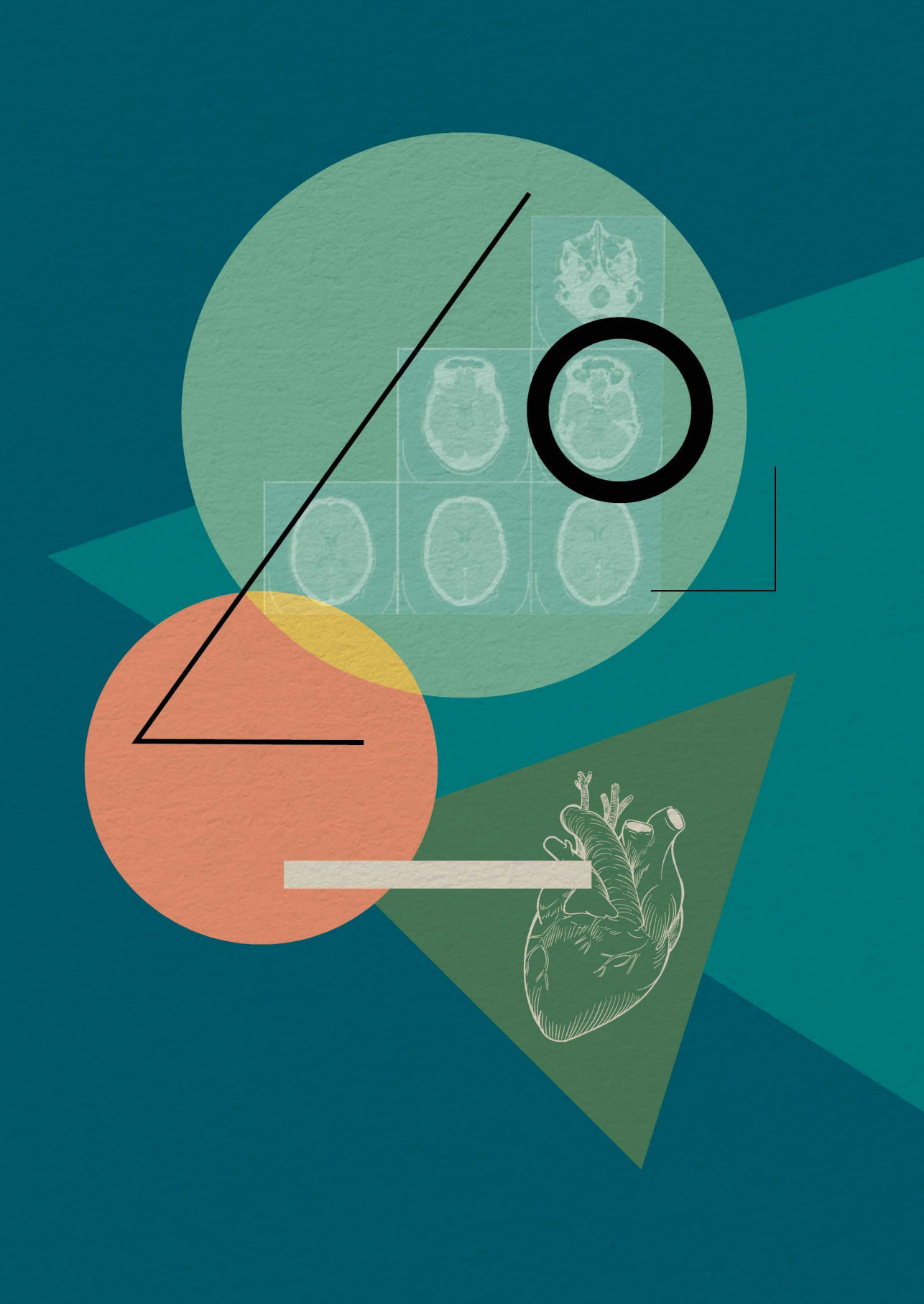

2

DETECTION OF EARLY ISCHEMIC CHANGES WITH VIRTUAL NON-CONTRAST DUAL-ENERGY CT IN ACUTE ISCHEMIC STROKE: A NON-INFERIORITY ANALYSIS

Based on:

Kauw F, Ding VY, Dankbaar JW, van Ommen F, Zhu G, Boothroyd DB, Wolman DN, Molvin L, de Jong HWAM, Kappelle LJ, Velthuis BK, Heit JJ, Wintermark M. Detection of Early Ischemic Changes with Virtual Noncontrast Dual-Energy CT in Acute Ischemic Stroke: A Noninferiority Analysis. AJNR Am J Neuroradiol. 2022 Sep;43(9):1259-1264.

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ABSTRACT

Background and Purpose

Dual-energy virtual non-contrast CT (NCCT) has the potential to replace conventional NCCT to detect early ischemic changes in acute ischemic stroke. In this study, we evaluated whether virtual NCCT is non-inferior compared to standard linearly blended NCCT, a surrogate of conventional NCCT, regarding detection of early ischemic changes with the Alberta Stroke Program Early CT Score (ASPECTS).

Materials and Methods

Adult patients who presented with suspected acute ischemic stroke, and who underwent dual-energy NCCT and CT angiography, and brain MRI within 48 hours, were included. Standard linearly blended images were reconstructed to match a conventional NCCT. Virtual NCCT images were reconstructed from CT angiography. ASPECTS was evaluated on conventional NCCT, virtual NCCT and diffusion weighted imaging MRI, which served as the reference standard. Agreement between CT assessments and the reference standard was evaluated with the Lin's concordance correlation coefficient. Non-inferiority was assessed with bootstrapped estimates of the differences in ASPECTS between conventional and virtual NCCT with 95% confidence intervals (CI).

Results

Of the 193 included patients, 100 patients (52%) had ischemia on diffusion weighted imaging MRI. Compared to the reference standard, the ASPECTS concordance correlation coefficient for conventional and virtual NCCT was 0.23 (0.15-0.32) and 0.44 (95% CI 0.33-0.53), respectively. The difference in concordance correlation coefficient between virtual and conventional NCCT was 0.20 (95% CI 0.01-0.39) and did not cross the pre-specified non-inferiority margin of -0.10.

Conclusion

Dual-energy virtual NCCT is non-inferior compared to conventional NCCT for detection of early ischemic changes with ASPECTS.

BACKGROUND

Computed tomography (CT) of the head is the most commonly utilized modality in the evaluation of stroke.[1] Initial non-contrast CT (NCCT) is the first line study in the evaluation of suspected stroke to exclude intracranial hemorrhage or an alternative explanation for the patient's symptoms. While early ischemic changes can be detected with NCCT, sensitivity is limited relative to diffusion-weighted magnetic resonance imaging (MRI), which remains the reference standard for the detection of cerebral ischemia. However, MRI has limited availability.[2] Early ischemic changes can be evaluated with the Alberta Stroke Program Early CT Score (ASPECTS) on NCCT and are predictive of functional outcome after intravenous thrombolysis and endovascular thrombectomy.[3–5] ASPECTS is used for thrombectomy decision making as the large thrombectomy trials excluded patients with a low ASPECTS score.[6,7]

Dual-energy CT enables acquisition of CT images at two different tube voltages instead of one, and has several applications in neurointervention and neuroradiology.[8] For instance, iodine contrast can be separated from blood components in patients with large vessel occlusion who underwent endovascular thrombectomy.[9,10] Similarly, it is also possible to subtract iodine maps from the CT angiography (CTA) images resulting in virtual NCCT images.

It is unknown whether virtual NCCT is non-inferior to conventional NCCT for detection of early ischemic changes. If virtual NCCT is non-inferior compared to conventional NCCT, then the latter may be omitted from the stroke imaging protocol, which would reduce the radiation exposure to the patient. We performed a non-inferiority analysis comparing virtual NCCT to standard linearly blended NCCT, a surrogate of conventional NCCT, for the detection of early ischemic changes with ASPECTS in patients with acute ischemic stroke.

METHODS

Patient selection

Adult (≥18 years) patients who presented with a suspicion of acute ischemic stroke and who underwent dual-energy CT (Somatom Force, Siemens Healthineers, Germany) between February 2018 and February 2019 were selected for this study. The inclusion criteria were availability of dual-energy NCCT and CTA, and brain MRI within 48 hours after CT. Imaging was routinely performed as part of our standard-of-care stroke protocol. This study was approved by our institutional review board

and complied with the Health Insurance Portability and Accountability Act. The need for informed consent was waived.

Image acquisition and preparation

NCCT and CTA were acquired helically using tube voltages of 80 and 140 kVp with a tin filter, and tube currents of 640 and 320 mAs, respectively. The images were acquired in dual-energy mode. The conventional NCCT was a standard linearly blended reconstruction to match a conventional 120 kVp NCCT. The virtual NCCT was reconstructed from the CTA. The dual-energy datasets were routinely post-processed using available dedicated software (Syngo) that was provided by the vendor to reconstruct virtual NCCT images. Slice thickness of conventional and virtual NCCT was 3 mm.

Diffusion-weighted imaging (DWI) MRI parameters were: TR 6000 ms, TE 78.2 ms, b-values 0 and 1000, flip angle 90°, and slice thickness was 5 mm.

Interobserver study

CT data were saved and presented in a random order to two experienced neuroradiologists (MW and JWD) in the form of videos with fixed window settings (window width 50 HU and window level 40 HU). The reviewers evaluated the presence of early ischemic changes (yes or no) and rated ASPECTS. ASPECTS is a prognostic score and allows quantification of the extensiveness of anterior circulation ischemic stroke.[3] ASPECTS ranges from 0-10, with 0 indicating involvement of all the ASPECTS areas and 10 indicating involvement of none of the ASPECTS areas. One point is subtracted for every involved area. The areas include caudate, internal capsule, lentiform nucleus, insular ribbon, anterior middle cerebral artery (MCA) cortex (M1), MCA cortex lateral to the insular ribbon (M2), posterior MCA cortex (M3), anterior cortex immediately rostral to M1 (M4), lateral cortex immediately rostral to M3 (M5) and posterior cortex immediately rostral to M3 (M6). Two separate scoring rounds were organized per reviewer and the presentations contained a mix of virtual and conventional NCCT images. In case of disagreement, a third reviewer (GZ) was consulted to reach adjudicated assessments.

The DWI images were anonymized and presented to one neurointerventional radiologist with 7 years of experience (JJH) who was blinded to the clinical and other imaging data. The reviewer was able to adjust window settings and evaluated presence of ischemia with ASPECTS, which can also be rated on DWI MRI.[11] We assessed interobserver agreement of early ischemic changes and ASPECTS, as well as the agreement between adjudicated CT assessments and the MRI assessments.

Statistical analysis

We reported frequencies and percentages for categorical characteristics and medians with first (Q1) and third (Q3) quartiles for continuous characteristics. These included symptom laterality (left/right/both/unknown), image assessability (yes/no), as well as MRI-assessed early ischemic changes (presence/absence), overall and for each of the ten brain regions (M1-M6, caudate, lentiform nucleus, internal capsule, and insular cortex). Proportions of the involved brain regions were visualized as bar plots.

The agreement between the two reviewers was quantified by calculating Cohen's kappa, with disagreements weighted according to their squared distance from perfect agreement.[12] The level of agreement was interpreted based on the following intervals for kappa: poor: <0.20; fair: 0.21-0.40; moderate: 0.41-0.60; good: 0.61-0.80; very good: 0.81-1.00. Confidence intervals for kappa statistics were based on 5,000 bootstrap resamples.

Measures of sensitivity and specificity were calculated for virtual and conventional NCCT. We used a global test to compare the sensitivity and specificity.[13]

For reasons of feasibility, we concluded that the maximum study size was 200 patients. Our a priori power calculation determined that this would provide 77% power to show non-inferiority given a non-inferiority margin of -0.10. Concordance between adjudicated CT assessments and the MRI gold standard was quantified using Lin's concordance correlation coefficient (CCC)[14,15], which is also a measure of accuracy against the gold standard. Bootstrapped estimates were obtained of the differences between virtual and conventional CT with two-sided 95% confidence intervals (CI). Noninferiority of virtual NCCT to conventional NCCT was prespecified as the lower boundary greater than -0.10 for the 95% CI of their difference in the CCC. In case the 95% CI of the difference in the CCC was greater than 0, superiority could be inferred.

All analyses were performed in the R statistical computing framework, version 4.0, and the CCC was estimated using the 'epiR' R package.

RESULTS

Imaging assessment was not possible in three of the 196 included patients. As a result, 193 patients remained for the final analysis (Table 1). In 100 patients (52%), ischemia was detected with MRI in different ASPECTS regions.

Table 1. Baseline characteristics

Characteristic	**n (%)**
n	193
Age, mean±SD	67±16
Male sex	103 (53)
Side of symptoms	
Bilateral	11 (6)
Left	59 (31)
Right	53 (28)
Unknown	70 (36)
Presence of early ischemic changes, as determined by DWI MRI	
Overall	100 (52)
M1	8 (4)
M2	13 (7)
M3	18 (9)
M4	26 (14)
M5	33 (17)
M6	29 (15)
Caudate	16 (8)
Lentiform nucleus	21 (11)
Internal capsule	12 (6)
Insular cortex	20 (10)

SD indicates standard deviation; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging.

Some differences were observed between the observations of reviewer 1 and reviewer 2 (Figure 1). Interobserver agreement regarding presence of early ischemic changes was moderate for conventional (weighted kappa 0.42, 95% CI 0.27-0.56) and virtual NCCT (weighted kappa 0.48, 95% CI 0.36-0.6) (Figure 2). Interobserver agreement regarding ASPECTS was fair for conventional (weighted kappa 0.38, 95% CI 0.23-0.54) and virtual NCCT (weighted kappa 0.27, 95% CI 0.14-0.4).

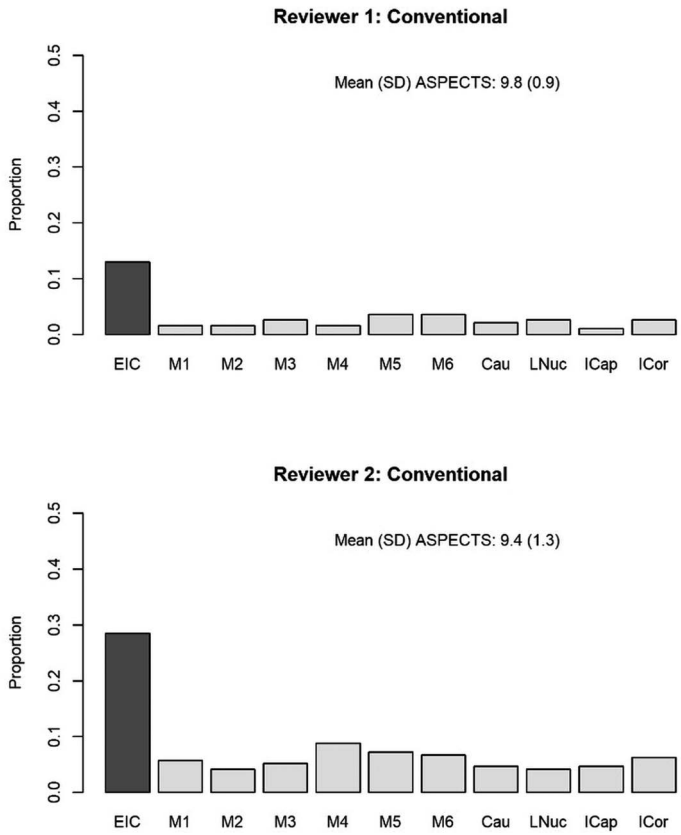

Figure 1a. Proportion of CT scans exhibiting early ischemic changes, by reviewer and modality.

Legend: VNC indicates virtual non-contrast; SD, standard deviation; ASPECTS, Alberta Stroke Program Early CT Score; EIC, early ischemic changes; Cau, caudate nucleus; LNuc, lentiform nucleus; ICap, internal capsule; ICor, insular cortex.

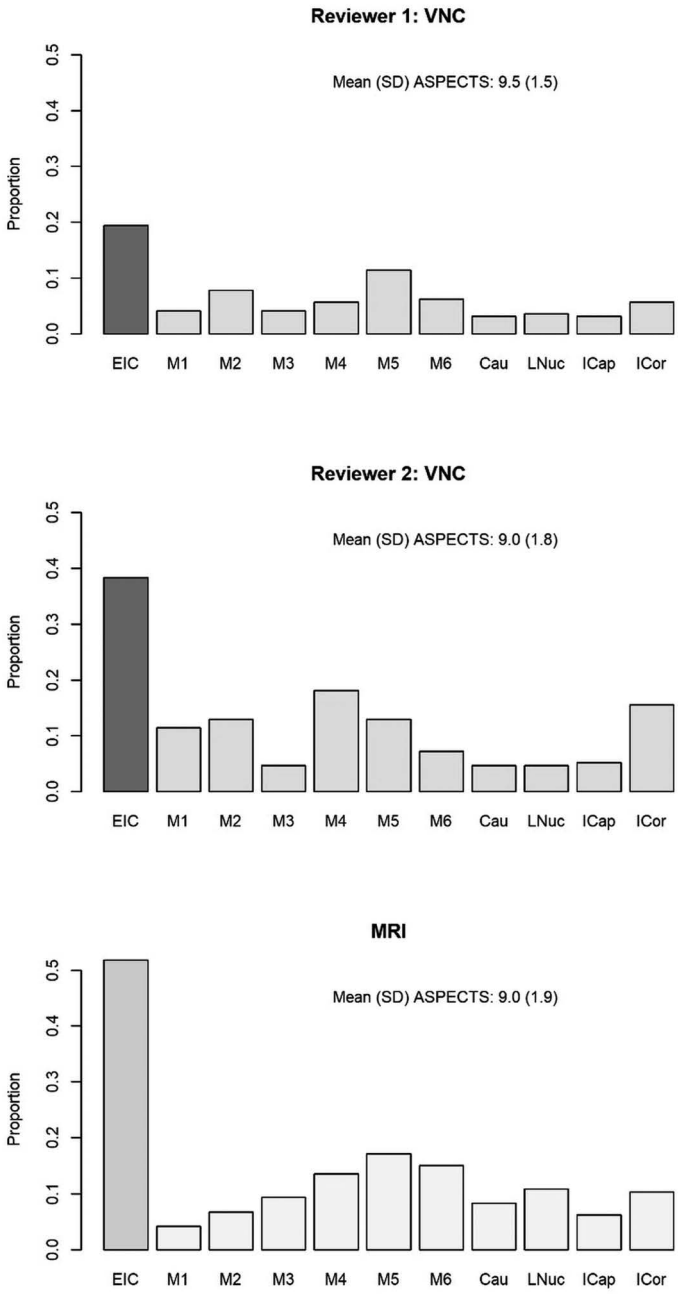

Figure 1b. Proportion of CT scans exhibiting early ischemic changes, by reviewer and modality.

Legend: VNC indicates virtual non-contrast; SD, standard deviation; ASPECTS, Alberta Stroke Program Early CT Score; EIC, early ischemic changes; Cau, caudate nucleus; LNuc, lentiform nucleus; ICap, internal capsule; ICor, insular cortex.

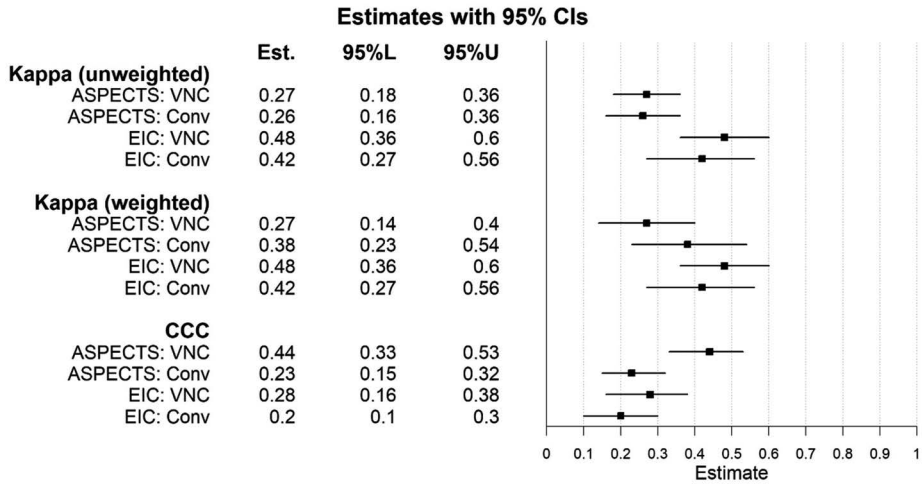

Figure 2. Estimates of interobserver agreement, agreement between CT and reference standard, and accuracy with 95% confidence intervals.

Legend: ASPECTS indicates Alberta Stroke Program Early CT Score; VNC, virtual non-contrast; EIC, early ischemic changes; CCC, concordance correlation coefficient.

Table 2. Adjudicated versus gold standard assessments

VNC	**DWI MRI**	
Adjudicated	No EIC	Has EIC
No EIC	83	63
Has EIC	8	37
Conventional		
Adjudicated		
No EIC	87	73
Has EIC	6	27

VNC indicates virtual non-contrast; EIC, early ischemic changes; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging.

Sensitivity of virtual and conventional NCCT for detection of early ischemic changes was 0.37 (95% CI 0.28-0.47) and 0.27 (95% CI 0.19-0.37), respectively (P=0.078). Specificity was 0.91 (95% CI 0.83-0.96) and 0.94 (95% CI 0.86-0.98), respectively (Table 2). The global test was not significant (P=0.111).

The forest plots (Figure 2) for CCC show overlapping intervals for early ischemic changes and non-overlapping CIs for ASPECTS. The difference in CCC between virtual and conventional NCCT was 0.201 (95% CI 0.014-0.389) regarding ASPECTS and 0.077 (95% CI -0.041-0.191) regarding early ischemic changes. Neither 95% CI for the difference in CCC crossed the prespecified non-inferiority margin of -0.10, thereby establishing non-inferiority of virtual NCCT compared to conventional NCCT with respect to both ASPECTS and early ischemic changes. Furthermore, virtual NCCT was demonstrated to be superior to conventional NCCT with respect to ASPECTS. Example acquisitions of conventional NCCT, virtual NCCT and DWI MRI are shown in Figure 3.

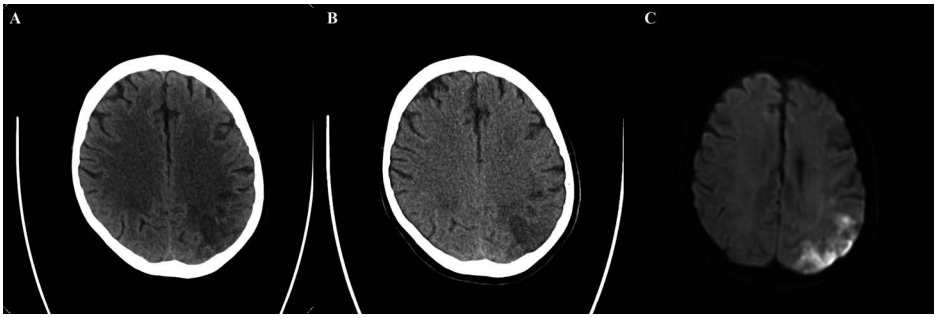

Figure 3. Example case of a 66-year-old male patient who presented with right-sided weakness and numbness (NIHSS 7). Medical history included diabetes mellitus, hypertension, hyperlipidemia, prior smoking and prior ischemic stroke, wherefore the patient used dual anti-platelet therapy. Time between last seen well and CT was fourteen hours. Time between CT and DWI MRI was twelve hours. Conventional non-contrast CT (A) and virtual non-contrast CT (B) showed early ischemic changes in the left parietal lobe (ASPECTS region M6). In the same region, DWI MRI (C) showed hyperintensity indicating diffusion restriction compatible with ischemia.

DISCUSSION

This study shows that detection of early ischemic changes with dual-energy virtual NCCT in patients with suspected stroke is non-inferior compared to standard linearly blended NCCT. Furthermore, virtual NCCT was demonstrated to be superior to conventional NCCT with respect to ASPECTS.

To the best of our knowledge, no studies have evaluated early ischemic changes on CTA based virtual NCCT images. Studies in other fields than neuroradiology have shown contradictory results and the reliability of the virtual NCCT maps seems to be influenced by the clinical indication.[16,17] Excluding intracranial hemorrhage is an important application of NCCT in the acute stroke setting and can also be done with dual-energy virtual NCCT images.[18–20] Dual-energy CT can also be used to distinguish between intracranial hemorrhage and extravasation of iodine contrast after endovascular treatment of stroke.[21–23] In addition, one study showed high sensitivity and specificity for detecting hyperdense artery sign on dual-energy virtual NCCT.[24] Previous studies showed that the detection of the ischemic core with dual-energy virtual NCCT images derived from NCCT (without using a contrast agent) was superior compared to conventional NCCT.[22,25,26] It is difficult to compare that study with our study as the reconstructions were acquired from different CT images (NCCT versus CTA). However, both studies indicate that dual-energy virtual NCCT has the potential to replace conventional NCCT with respect to the detection of early ischemic changes.

The observed interobserver variability with regards to the detection of early ischemic changes and ASPECTS was moderate and fair, respectively, and similar between virtual NCCT and conventional NCCT in this study. ASPECTS is known to suffer from relatively poor intraobserver and interobserver agreement, as was the case in this study.[27] Recently, this was supported by a study that demonstrated a relatively poor interobserver agreement in a large group of 100 readers.[28] The agreement, based on the CCC, between the dual-energy virtual NCCT assessments and MRI assessments regarding presence of early ischemic changes was slightly better than the agreement between conventional NCCT assessments and MRI assessments. With regards to ASPECTS, the CCC showed fair agreement between both CT modalities and MRI, which is in line with a previous study.[29]

The applications of dual-energy CT are becoming increasingly apparent. If dual-energy virtual NCCT of the brain can replace the conventional NCCT this would result in less radiation exposure for the patient. Whether dual-energy virtual NCCT saves

time in the acute stroke work-up needs to be seen as dual-energy reconstructions also take time. Automated dual-energy reconstructions do not add significant time to the imaging protocol, unless manual processing is required. Disadvantages of replacing conventional NCCT with virtual NCCT include the necessity of acquiring a CTA, turning on dual-energy mode and the requirements of added storage and bandwidth. Besides replacing conventional NCCT, future applications of virtual NCCT may include improvement of the conventional NCCT in case of severe movement artefacts and reduction of the radiation dose in a non-acute setting.

Most dual energy CT scanners, using a dual source with dual detector or a mono-source with rapid kVp switching, require that the dual-energy setting is switched on beforehand to acquire dual-energy data.[30] Other detector-based spectral CT scanners have a single source and a single dual-layered detector that is always switched on. In the acute stroke imaging work-up, NCCT needs to be acquired first to exclude intracranial hemorrhage. As the dual-energy virtual NCCT images need to be reconstructed from the CTA, which is often only performed if a NCCT has ruled out an intracranial hemorrhage, it is difficult to omit the conventional NCCT in clinical practice. On the other hand, even in patients who suffer from intracranial hemorrhage, a CTA is often performed to look for cerebral aneurysms, cerebral arteriovenous malformations, or other vascular malformations as the cause of the bleed. Taken together, the role of dual-energy virtual NCCT seems dependent on the indication and on whether a CTA is performed regardless of the findings on NCCT.

Several strengths can be noted in this study. To prevent observation bias, the observers who assessed the CT were blinded to clinical information and MRI images, and, vice versa, the observer who assessed the MRI images was blinded to the CT images. Another strength was the power calculation which helped to achieve a reliable non-inferiority analysis.

A limitation of this study was the potential risk of selection bias as patients were selected who underwent dual-energy CT and DWI MRI. However, besides the imaging criteria, we used wide inclusion criteria (adult patients with a suspicion of acute ischemic stroke). Still, the results of this study need to be validated, preferably in a large prospective study. Due to missing data, extensive patient characteristics were not reported in this study. Although we did not use conventional single source NCCT in this study, standard linearly blended images closely reflect conventional NCCT.[31] Another limitation is the time interval between the acquired CT scan and the DWI MRI. Although the time window was within 48 hours, this theoretically could have resulted in larger or additional infarcts on the MRI compared to the CT. This

may also partially explain the fair agreement between CT and MRI in this study. In addition, MRI is more sensitive for detecting ischemia and therefore ASPECTS may differ between CT and MRI assessments which are acquired simultaneously as small infarcts may be visible on MRI but not on CT. In this study, the dual-energy CT scanner and the software of one vendor was used, which limits the ability to generalize these findings. To increase generalizability, future studies should include a broader range of CT vendors and software.

In conclusion, dual-energy virtual NCCT is non-inferior compared to NCCT for detection of early ischemic changes with ASPECTS.

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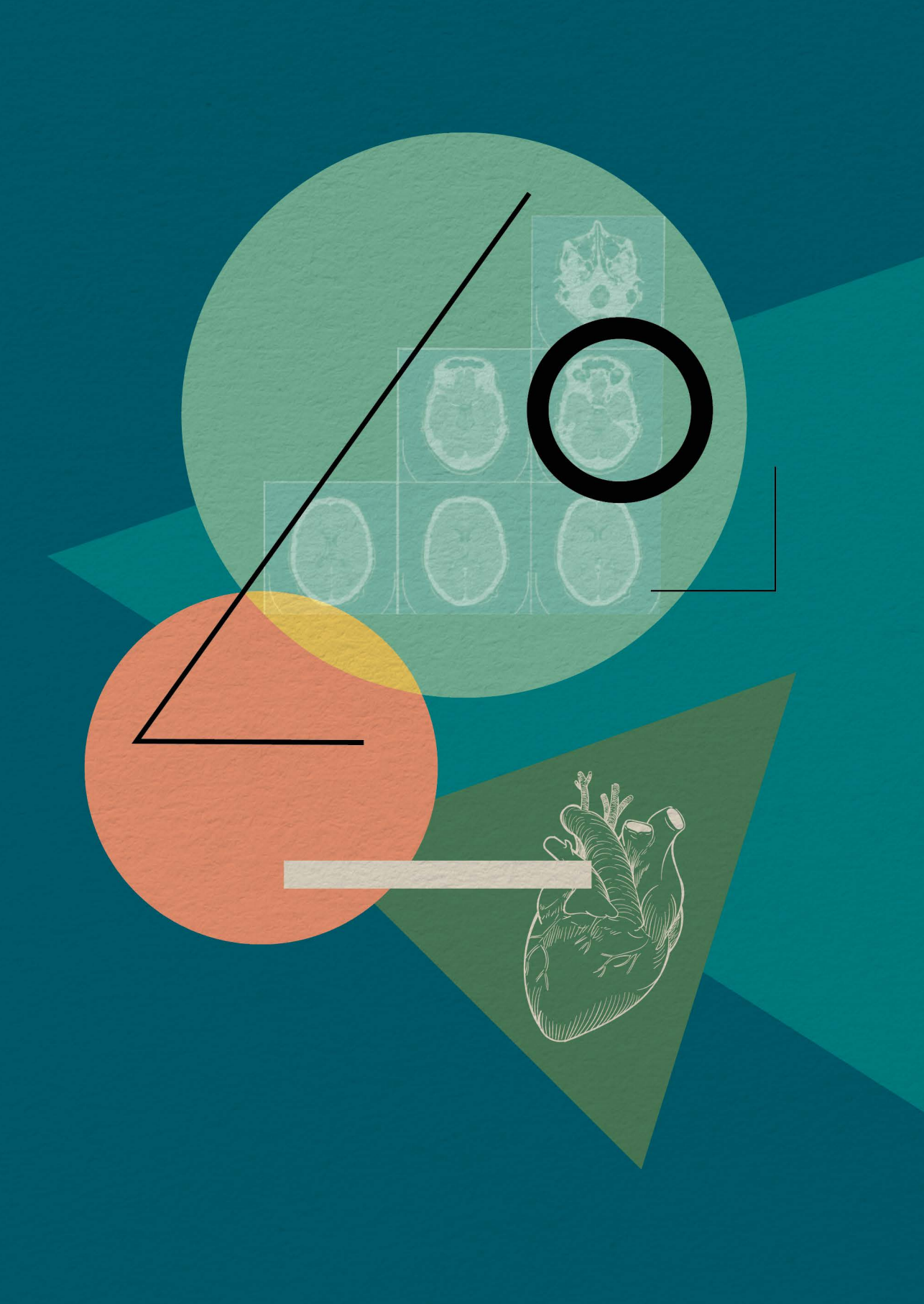

3

COMPUTED TOMOGRAPHY PERFUSION DATA FOR ACUTE ISCHEMIC STROKE EVALUATION USING RAPID SOFTWARE: PITFALLS OF AUTOMATED POSTPROCESSING

Based on:

Kauw F, Heit JJ, Martin BW, van Ommen F, Kappelle LJ, Velthuis BK, de Jong HWAM, Dankbaar JW, Wintermark M. Computed Tomography Perfusion Data for Acute Ischemic Stroke Evaluation Using Rapid Software: Pitfalls of Automated Postprocessing. J Comput Assist Tomogr. 2020 Jan/Feb;44(1):75-77.

DOI: 10.1097/RCT.0000000000000946

ABSTRACT

Computed tomography perfusion (CTP) is increasingly used to determine treatment eligibility for acute ischemic stroke (AIS) patients. Automated post-processing of raw CTP data is routinely used, but it can fail. In reviewing 176 consecutive AIS patients, failures occurred in 20 (11%) patients during automated post-processing by the RAPID software. Failures were caused by motion (n=11;73%), streak artifacts (n=2;13%) and poor contrast bolus arrival (n=2;13%). Stroke physicians should review CTP results with care before they are being integrated in their decision-making process.

INTRODUCTION

Acute ischemic stroke (AIS) patients can be treated with intravenous thrombolysis and endovascular treatment (EVT) in late time windows.[1,2] Treatment eligibility depends on brain perfusion parameter cutoffs, which can be evaluated either by computed tomography (CT) or magnetic resonance imaging (MRI).[2–6]

After the raw CT perfusion (CTP) data have been collected, the data need processing before perfusion parameters can be calculated. Key elements of post-processing include the determination of the symmetry axis and selection of the arterial input function (AIF) and venous output function (VOF). Automated processing is routinely used in stroke imaging protocols, but this method is not perfect, and failures can occur.

A few studies previously discussed failures of automated perfusion post-processing. For instance, in one large EVT trial automated post-processing was successful in only 58% of the cases initially and in 98% of the cases in a second round of post-processing.[7] Previously described failures were mostly caused either by severe motion or by poor arrival of the contrast bolus.[3] Post-processing failures may lead to incorrect volumes of infarct core and penumbra. As treatment eligibility criteria are partly based on these volumes, treatment strategies and patient outcomes may be affected by failures in post-processing CTP data.[5,6]

The goal of this study was to investigate: 1) how often failures occur during automated processing of CTP data, 2) which patient factors are associated with such failures and 3) whether such failures affected patient management.

MATERIALS AND METHODS

Selection of patients

We included consecutive AIS patients undergoing CTP for EVT triage between 2012 and 2018. We excluded patients where no CTP was performed as part of the acute stroke work-up or if the results of automated post-processing were missing from our electronic imaging archive.

Patient characteristics

We collected baseline data including age, sex, admission National Institutes of Health Stroke Scale (NIHSS), time from symptom onset to CTP imaging, administration of intravenous tissue-type plasminogen activator and EVT. Imaging data included side of occlusion and occlusion site as determined on CT angiography (CTA).

Image acquisition

CTP and CTA were performed as part of our routine acute stroke workup, respectively. CTP was performed with cine mode on 80kV and 100mAs with 37 phases at 1 second time interval followed by 33 phases at 3 second time interval on 128-slice scanners. Either one run or two runs with 5mm slices were performed covering at least Alberta Stroke Program Early CT Score levels 1 and 2 of the brain. CTA was performed on 120kV and 225mAs and covered the aortic arch up to the apex of the brain. Slice thickness for CTA was set to 0.625mm. The iodinated contrast dose was 40cc for the CTP runs and 70 cc for the CTA, injected at 4-5cc per second.

Image analysis

Automated post-processing of the CTP images was done by using a commercially available software package (RAPID, iSchemaView, Menlo Park, CA, USA) that uses a proprietary delay-insensitive algorithm.[8,9] Midline axis determination and selection of the AIF and VOF were automatically performed. Processed maps were generated for cerebral blood flow (CBF), cerebral blood volume (CBV) and time-to-maximum (Tmax), as well as for ischemic core (CBF threshold <30% compared to the contralateral normal hemisphere) and penumbra (Tmax threshold >6 seconds). Potential causes of failures were evaluated by two observers (FK and MW) and included incorrect selection of midline axis, incorrect selection of the AIF and VOF, motion, streak artifact, issues of time-attenuation curves related to contrast bolus, either as a result of motion or contrast bolus failure. The observers were blinded to all clinical data, but they had access to all imaging data available at the time of patient evaluation. In case of disagreement between the observers, consensus

was reached by discussion. We reprocessed failures manually by using IntelliSpace software (Philips, Best, the Netherlands).

Outcome assessment

Primary outcome was automated post-processing failure, which was defined as the presence of perfusion abnormalities that were caused by artifacts as verified on follow-up imaging (either CT or MRI), accounting for interval reperfusion. Secondary outcome was inaccurate ischemic core or penumbra volumes as determined with follow-up imaging (either CT or MRI) that might have affected EVT eligibility, defined using the inclusion criteria of the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE-3) trial.[6] Tertiary outcome was poor functional outcome (modified Rankin Scale of 3 or higher) measured approximately 3 months after the stroke.

Statistical analysis

Associations between potential predictors and post-processing failures were tested using binary logistic regression. We reported odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were performed in R (version 3.4.2).

RESULTS

176 AIS patients were included for analysis (Table 1). Automated post-processing failures occurred in 20 (11%) cases. Causes for failures were severe motion (n=14, 70%), streak artifact (n=3, 15%) and poor arrival of contrast bolus (n=3, 15%). No failures were induced by erroneous determination of the midline axis, selection of the AIF or the VOF. One failure caused by motion could be salvaged manually by excluding frames containing motion artifacts at the end of the acquisition. Patients in the failure group were more often male (n=14, 70% vs. n=72, 46%, P=0.045, respectively) and had higher admission NIHSS (mean±SD 18±6 vs. 15±7, P=0.047, respectively) compared to the patients in the non-failure group. In a multivariable model, only higher admission NIHSS was significantly associated with failures (OR 2.2, 95% CI 1.1-5.0, P=0.046) (Table 2).

Table 1. Patient characteristics stratified by automated post-processing failures

Characteristic	**Total** n=176	**Failures** n=20 (11%)	**No failures** n=156 (89%)
Age, mean±SD	72±15	72±14	72±15
Male sex, n (%)	86 (49)	14 (70)	72 (46)
Admission NIHSS, mean±SD	15±7	18±6	15±7
Time from symptom onset to CTP, median (Q1-Q3)	171 (65-377)	293 (113-566)	159 (65-354)
Intravenous tPA, n (%)	88 (50)	9 (45)	79 (51)
EVT, n (%)	126 (72)	12 (60)	114 (73)
- Reperfusion (TICI IIB-III), n (%)	101 (58)	11 (58)	90 (58)
Findings on CTA			
Occlusion side			
- Right	70 (41)	6 (33)	64 (42)
- Left	92 (54)	10 (56)	82 (54)
- Basilar	5 (3)	2 (11)	3 (2)
- Both	3 (2)	0 (0)	3 (2)
Occlusion site			
- ICA or M1 occlusion	57 (32)	7 (35)	50 (32)
- Other occlusion	111 (63)	11 (55)	100 (64)
Causes of failures			
Significant motion	14 (8)	14 (70)	0 (0)
Streak artifacts	7 (4)	3 (15)	4 (3)
Poor contrast bolus arrival	3 (2)	3 (15)	0 (0)
Follow-up			
Poor clinical outcome at 90 days*, n (%)	71 (40)	8 (40)	63 (40)

* Poor clinical outcome was defined as modified Rankin Scale equal or greater than 3.
SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; CTP, computed tomography perfusion; tPA, tissue-type plasminogen activator; EVT, endovascular treatment; TICI, Thrombolysis in Cerebral Infarction; ICA, internal carotid artery.

Table 2. Results of binary logistic regression with respect to automated post-processing failures

Characteristic	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age, per 10 years increase	1.0 (0.8-1.4)	-
Male sex	2.7 (1.0-8.0)	-
Admission NIHSS, per 10 points increase	2.0 (1.0-4.2)	2.2 (1.1-5.0)
Time from symptom onset to CTP, per 60 minutes	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Findings on CTA		
Occlusion side		
- Right	Reference	
- Left	1.3 (0.5-4.0)	1.2 (0.4-3.8)
- Basilar	7.1 (0.8-52.2)	6.0 (0.7-4.7)
Occlusion site		
- ICA or M1 occlusion	0.8 (0.3-2.2)	1.0 (0.4-3.0)
- Other occlusion site	Reference	Reference

* Estimates were adjusted for age and sex.
OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CTP, computed tomography perfusion; ICA, internal carotid artery.

Out of 176 patients, 88 (50%) patients received intravenous tissue-type plasminogen activator and 126 (72%) received EVT based on clinical information and on the interpretation of CTP imaging, which included correction for failures. If CTP results had been used for decision making without correction for processing failures, 130 (73%) patients would have been eligible for EVT. In 5 patients, the automated post-processing failure resulted in artifacts, which made the ischemic core volume larger than what it actually was, and these patients might have been excluded from treatment if the CTP results had been interpreted without correction (Figure 1). In 1 patient, according to follow-up imaging, the automated post-processing failure made the ischemic penumbra volume smaller than what it actually was, and this patient might have been excluded from treatment if the CTP results had been interpreted literally (Figure 2). Thus, in 6 patients (3%), the automated post-processing failures might have resulted in different treatment decisions if the CTP results had been interpreted literally.

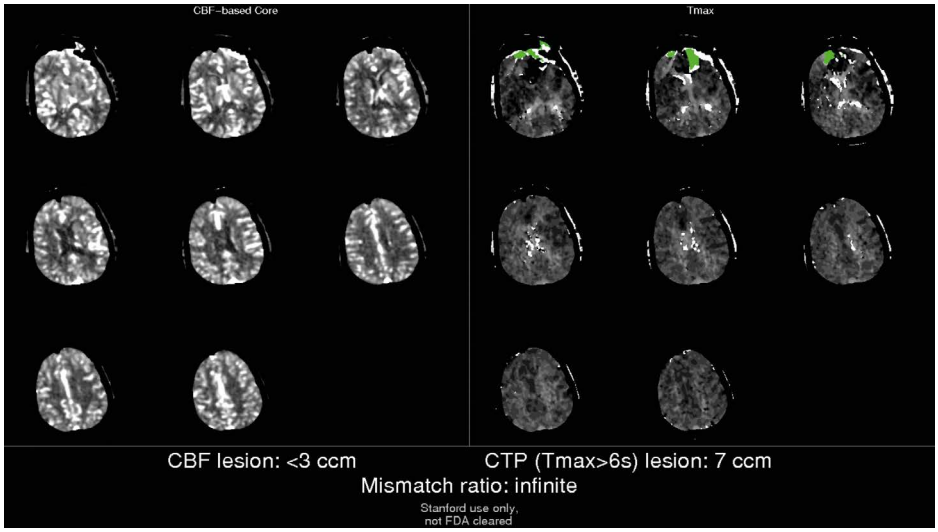

Figure 1. Example of a failure during automated post-processing of CTP data. Green indicates penumbra (Tmax>6s). If the CTP results would have been interpreted literally, this patient would not have been treated because of the artifactual presence of a constituted infarct without any penumbra.

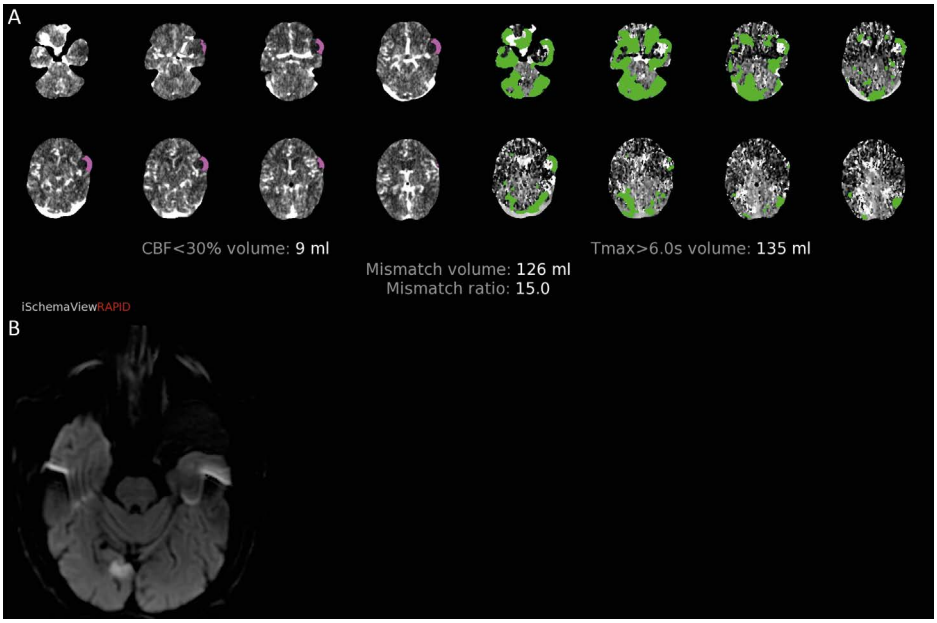

Figure 2. Another example of a post-processing failure (A). Purple indicates infarct core (cerebral blood flow <30%) and green indicates penumbra (Tmax>6.0s). This patient would have been treated if the CTP results would have been interpreted literally because of the artifactual presence of a small ischemic core with a large mismatch. However, on subsequent MRI, a small infarct was seen in a different region of the brain than that identified by CTP, which matched better the patient's presenting symptoms and, together with the lack of a large artery occlusion, explained why the patient did not receive endovascular treatment (B).

Prevalence of poor functional outcome at 90 days after the stroke was similar for the failure group and the non-failure group (40% versus 40%, respectively), but many values were missing for this outcome (n=57;37% and n=11;55%, respectively).

DISCUSSION

In this study, we evaluated prevalence of automated CTP post-processing failures and associated patient factors. Failures occurred in 11% of the patients and were mostly caused by motion and, to a lesser extent, by streak artifacts and poor arrival of contrast bolus. The patient factor significantly associated with failures was higher stroke severity (NIHSS), because such patients are more likely to be agitated and to move during the CTP scanning. Half of the failures led to erroneous ischemic core volumes such that EVT eligibility might have been affected if the CTP results had been interpreted literally.

Our results indicate that the results from automated post-processing perfusion software should be interpreted with caution. Even though the software was successful in 89% of the cases, 11% showed artifacts leading to erroneous ischemic core volume estimations that might have affected patient management in 3% of the cases. Fortunately, CTP failures were recognized and subsequent imaging was done to determine correct infarct volumes, which led to appropriate management for all patients.

Strength of this study was the large sample size of consecutive AIS patients, which minimizes the risk of selection bias.

A limitation of this study was its retrospective nature, which we tried to counterbalance by using consecutive patients in our practice. In addition, the loss to follow-up rate was quite high, and therefore these findings need validation in studies with a prospective design. We only tested one specific software package and the generalization of our conclusions to other software packages will need to be verified. Still, the software program evaluated in our study is widely used, and, therefore, our results are pertinent to current clinical practice.

In conclusion, stroke experts should be aware of the pitfalls of post-processing CTP data especially in patients with more severe strokes.

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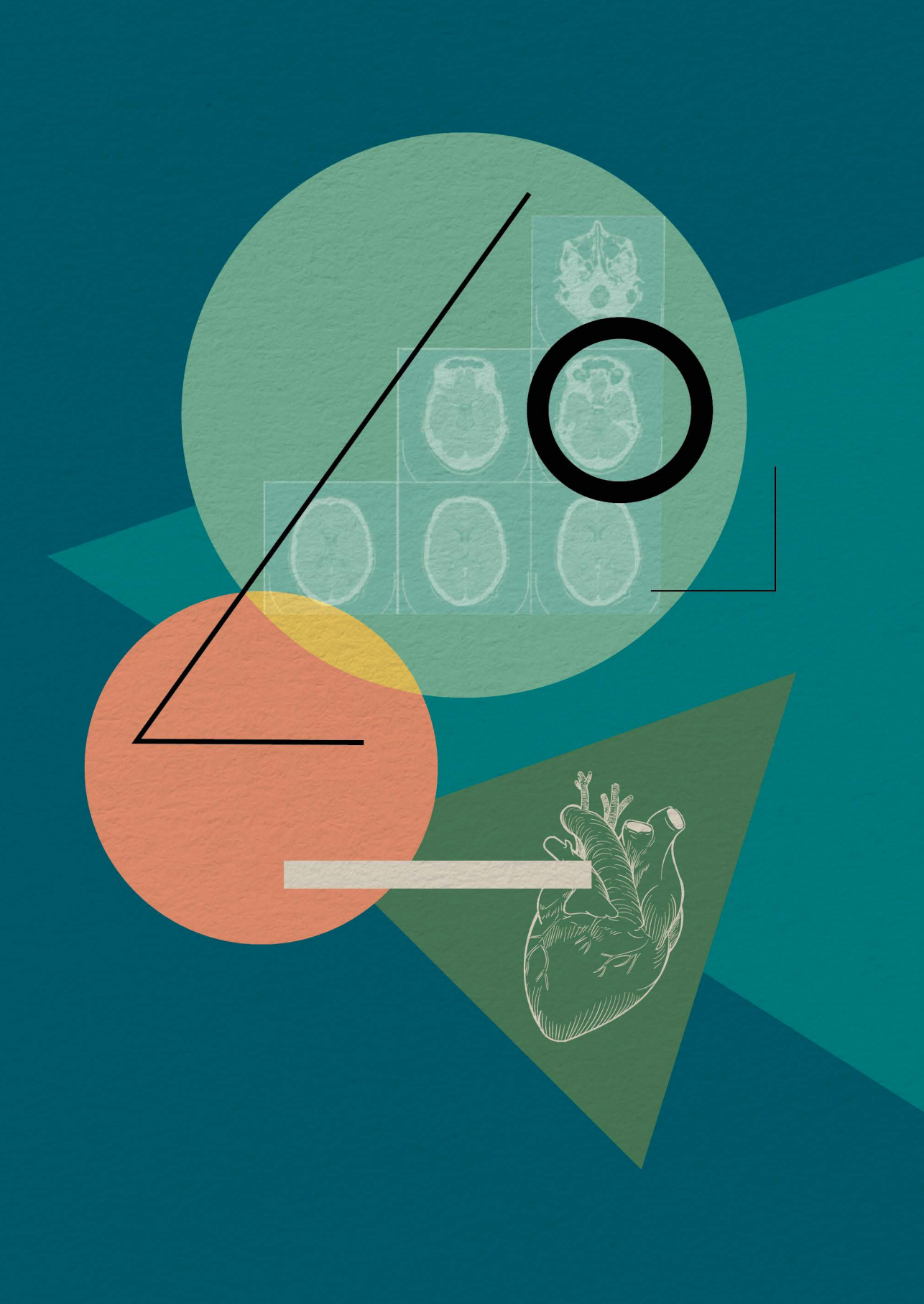

4

COLLATERAL STATUS IN ISCHEMIC STROKE: A COMPARISON OF CT ANGIOGRAPHY, CT PERFUSION AND DIGITAL SUBTRACTION ANGIOGRAPHY

Based on:

Kauw F, Dankbaar JW, Martin BW, Ding VY, Boothroyd DB, van Ommen F, de Jong HWAM, Kappelle LJ, Velthuis BK, Heit JJ, Wintermark M. Collateral Status in Ischemic Stroke: A Comparison of Computed Tomography Angiography, Computed Tomography Perfusion, and Digital Subtraction Angiography. J Comput Assist Tomogr. 2020 Nov/Dec;44(6):984-992.

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ABSTRACT

Objective

To compare assessment of collaterals by single-phase CT angiography (CTA) and CT perfusion derived three-phase CTA, multiphase CTA and temporal maximum intensity projection (tMIP) images to digital subtraction angiography (DSA), and relate collateral assessments to clinical outcome in patients with acute ischemic stroke (AIS).

Methods

Consecutive AIS patients, who underwent CT perfusion, CTA, and DSA prior to thrombectomy with occlusion of the internal carotid artery and/or occlusion of the M1 and/or M2 segment of the middle cerebral artery, were included. Two observers assessed all CT images and one separate observer assessed DSA (reference standard) with static and dynamic collateral grading methods. Interobserver agreement and concordance were quantified with Cohen's weighted kappa and concordance correlation coefficient (CCC), respectively. The association between collateral assessments and good clinical outcome (modified Rankin Scale ≤2) was evaluated with odds ratios (OR) and 95% confidence intervals (CI).

Results

Interobserver agreement (n=101) was 0.46 (tMIP), 0.58 (three-phase CTA), 0.67 (multiphase CTA) and 0.69 (single-phase CTA) for static assessments and 0.52 (three-phase CTA) and 0.54 (multiphase CTA) for dynamic assessments. CCC (n=80) was 0.08 (three-phase CTA), 0.09 (single-phase CTA) and 0.23 (multiphase CTA) for static assessments and 0.10 (three-phase CTA) and 0.27 (multiphase CTA) for dynamic assessments. Higher static collateral scores on multiphase CTA (OR 1.7; 95% CI 1.1-2.7) and tMIP images (OR 2.0; 95% CI 1.1-3.4) were associated with good clinical outcome as were higher dynamic collateral scores on three-phase CTA (OR 1.5; 95% CI 1.1-2.2) and multiphase CTA (OR 1.7; 95% CI 1.1-2.6).

Conclusions

Concordance between assessments on CT and DSA was poor. Collateral status evaluated on three-phase CTA and multiphase CTA, but not on DSA, was associated with clinical outcome.

INTRODUCTION

The clinical outcome of acute ischemic stroke (AIS) patients is associated with the grade of collateral filling.[1] It is hypothesized that the ischemic process can be slowed down by collateral vessels perfusing the tissue that is still salvageable, which is termed the penumbra.[2] In patients who undergo endovascular treatment (EVT), good collateral filling is associated with smaller final infarct volumes and better clinical outcomes than when the collateral filling is poor or absent.[2–4]

In the past decade, collateral evaluation has gained much interest and multiple grading systems for different imaging modalities have been developed.[5,6] CT angiography (CTA) is widely used for the evaluation of patients with suspected AIS. It is a fast, relatively inexpensive and non-invasive method for assessing occlusions and potential causes of stroke. A single time-frame snapshot (single-phase CTA) of the collateral status can be assessed and used for treatment guidance and predicting patient outcomes. However, a single time-frame snapshot may make it difficult to grade collateral circulation in case of delayed contrast arrival.[2,7] Multiphase CTA may solve the issues that come with single-phase CTA.[8,9] In addition, multiphase CTA has proven to be superior to grading collaterals on single-phase CTA in terms of interobserver agreement, predicting final infarct core volume and predicting functional outcome.[8,9] Patients with suspected stroke often undergo both CTA and CT perfusion (CTP). CTP is the ultimate multiphase CTA study since it typically includes 40 to 50 time-frames obtained at a one-to-three second temporal resolution and monitors the contrast agent from wash-in to wash-out. Therefore, CTP source images can be used to reconstruct three-phase CTA, multiphase CTA and temporal maximum intensity projection (tMIP) images. Digital subtraction angiography (DSA) is a 2D study with high spatial and temporal resolution and high contrast making it the ultimate dynamic study of the cerebral vessels and the reference standard for assessing collateral circulation in AIS patients.[10] However, DSA is invasive, relatively costly, and time consuming, which is undesirable in the acute stroke setting. DSA is therefore only routinely performed in patients who subsequently undergo EVT.

With regard to collateral assessments, single-phase CTA, CTP derived three-phase CTA, multiphase CTA and tMIP images, and DSA have not been compared before.

Aims

In this study, we aimed to compare assessment of collateral filling on single-phase CTA and CTP derived three-phase CTA, multiphase CTA and tMIP images in terms of interrater reliability and agreement between imaging modalities. In a secondary analysis, we aimed to evaluate the relation between collateral assessments and 90-day clinical outcome.

MATERIALS AND METHODS

Patient selection

Consecutive adult patients with AIS from Stanford Medical Center, who were considered for EVT between 2010 and 2018, were selected for this study. Inclusion criteria were: 1) presence of CTP and CTA images that were acquired as part of the acute stroke protocol and 2) occlusion of the internal carotid artery and/or occlusion of the M1 and/or M2 segment of the middle cerebral artery. Patients were excluded in case of bilateral stroke. DSA cases were excluded if the filming did not extend into the late venous phase, patient motion precluded adequate interpretation, or if only anteroposterior images were available for analysis. The need for informed consent was waived by the local institutional research board for this retrospective analysis of data, which were collected as part of clinical practice. Of the 530 patients who were considered for EVT, 101 were included for the interobserver analysis. 80 patients had interpretable DSA and 74 had clinical outcome assessed at 90 days (Figure 1).

Patient characteristics

Baseline data included demographics and cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, prior cerebrovascular accident, prior coronary artery disease and use of antiplatelet medication or anticoagulants. Furthermore, we collected admission NIHSS and data on treatment including intravenous administration of tissue-type plasminogen activator, EVT and whether reperfusion was achieved, defined as a Thrombolysis in Cerebral Infarction (TICI) score of IIB or III. We also recorded time from symptom onset to treatment.

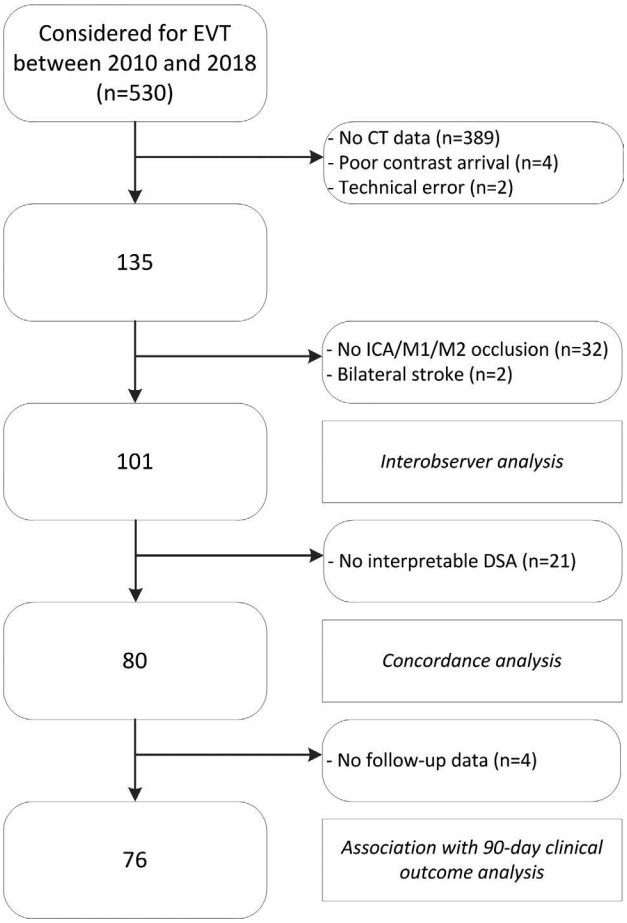

Figure 1. Flowchart of patient selection and analysis steps

Legend: EVT indicates endovascular treatment; CT, computed tomography; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; DSA, digital subtraction angiography.

Image preparation

Single-phase CTA images were created from thin-slice data and saved as 20 mm maximum intensity projection (MIP) images. The images were captured on ASPECTS levels 1 (basal ganglia) and 2 (at the top of the lateral ventricles), respectively.[11]

The CTP source data were used to create three-phase CTA, multiphase CTA and tMIP images. Three-phase CTA images were prepared using the CTP images with the thinnest slice thickness available (ranging from 1.5 mm to 10 mm). The first phase was selected based on the peak of arterial inflow, which was automatically calculated and checked visually. The second phase was timed 8 seconds after the first phase and the third phase was timed 8 seconds after the second phase.[8] Similar to single-phase CTA, 20 mm MIP images were captured on ASPECTS levels 1 and 2, respectively.

Multiphase CTA was created from all the CTP time-phases containing thick slice images (ranging from 5 to 10 mm) on the two ASPECTS levels. In order to assess the collateral score dynamically, the series were saved as video files.

All CTP time-phases were reconstructed into tMIP images, where the highest Hounsfield unit was taken for every voxel with perfusion analysis software (Intellispace Portal, version 6.0, Philips Healthcare, Best, the Netherlands). The MIP thickness was set to 20 mm and the images were captured on ASPECTS levels 1 and 2. The reconstructions were created automatically by the software.

Regarding the reference standard, all the available DSA images, which were acquired after CT, were used for determining the grade of collateral circulation before EVT took place.

Interobserver study

The single-phase CTA, three-phase CTA, multiphase CTA and tMIP images were presented separately to two separate neuroradiologists (JD – 19 years of experience and MW – 21 years of experience). The images were anonymized and placed in a randomized order for the reviews. The observers were blinded to clinical information and other imaging data except for the occlusion site. On single-phase CTA, three-phase CTA, multiphase CTA and tMIP images, the collaterals in the affected territory were graded using a static collateral score: 0) absent collaterals, 1) collaterals filling ≤50% of the occluded territory, 2) collaterals filling >50%, but <100% of the occluded territory and 3) collaterals filling 100% of the occluded territory.[12–14] For three-phase CTA, multiphase CTA and DSA. the modified American Society of Interventional

and Therapeutic Neuroradiology (ASITN) score[15] was used, which enables dynamic grading of collaterals: 0) non-existent or barely visible pial collaterals on the ischemic site during any point of time, 1) partial collateralization of the ischemic site until the late venous phase, 2) partial collateralization of the ischemic site before the venous phase, 3) complete collateralization of the ischemic site by the late venous phase and 4) complete collateralization of the ischemic site before the venous phase.[15,16] Collateral assessment on DSA images was done by a third observer (JH – 6 years of experience) and was used as the reference standard. The decision for choosing one DSA observer was based on previous studies.[17,18] No consensus meetings were arranged.

Clinical outcome

Favorable clinical outcome was defined as a modified Rankin Scale (mRS) ≤2, 90 days after the index event.

Statistical analysis

We reported frequencies and percentages for categorical variables and medians with first (Q1) and third (Q3) quartiles for continuous variables. Since collateral scores are an ordinal variable, the agreement between the two observers was quantified by calculating Cohen's kappa, with disagreements weighted according to their squared distance from perfect agreement.[19] The level of agreement was categorized and based on the kappa values: poor: <0.20; fair: 0.21-0.40; moderate: 0.41-0.60; good: 0.61-0.80; very good: 0.81-1.00. Confidence intervals for kappa statistics were based on 5,000 bootstrap resamples. Concordance between the pooled CT measurements and DSA measurements was quantified using percentages of agreement and concordance correlation coefficients (CCC).[20,21] As clinical decision making is often based on the dichotomized (either poor or good) collateral score, we also evaluated the dichotomized (0-1 versus 2-3) static collateral score and mASITN (0-2 versus 3-4) score with respect to the comparison between CT and DSA.[13,22,23] Lastly, we quantified the relation between the collateral assessments on the original and binary scales and the primary outcome (90-day mRS ≤2) by using binary logistic regression and we adjusted for recanalization status.[24] Association measures were reported as odds ratios (OR) and 95% confidence intervals (CI). The statistical analyses were performed in R (version 3.5.0).

RESULTS

Patients with (n=80) and without (n=21) interpretable DSA acquisitions were compared (Table 1). Median age of the total group (n=101) was 75 (Q1-Q3: 67-82) and 38 (38%) patients were male.

Table 1. Patient characteristics, overall and stratified by availability of DSA

Characteristic	**Total** (n=101)	**DSA** (n=80)	**No DSA** (n=21)
Age, median (Q1-Q3)	75 (67-82)	74 (67-83)	76 (69-81)
Male sex	38 (38)	28 (35)	10 (48)
Admission NIHSS, median (Q1-Q3)	15 (11-20)	14 (11-20)	20 (14-23)
Time from symptom onset to CTP	127 (62-332)	115 (64-324)	195 (58-411)
Intravenous tPA	52 (52)	40 (50)	12 (57)
- Time to tPA (min.), median (Q1-Q3)	87.0 (56-151)	79.0 (55-155)	98 (60-125)
Endovascular treatment	91 (90)	76 (95)	15 (71)
- Reperfusion (TICI IIB-III)	71 (78)	59 (78)	12 (80)
Medical history, n (%)			
Hypertension	81 (80)	64 (80)	17 (81)
Diabetes mellitus	22 (22)	14 (18)	8 (40)
Hyperlipidemia	58 (59)	47 (60)	11 (55)
Smoking status			
- Current	15 (16)	13 (17)	2 (11)
- Former	28 (30)	23 (30)	5 (26)
- Never	52 (55)	40 (53)	12 (63)
Atrial fibrillation	54 (54)	40 (50)	14 (67)
Prior antiplatelet or anticoagulant therapy	56 (56)	47 (59)	9 (45)
Prior CVA	22 (22)	17 (21)	5 (25)
Prior CAD	30 (30)	24 (30)	6 (30)
Imaging findings, n (%)			
Left side occluded on CTA	61 (60)	46 (58)	15 (71)
Occlusion site on CTA			
- ICA	18 (18)	7 (9)	11 (52)

Table 1. Patient characteristics, overall and stratified by availability of DSA (continued)

Characteristic	**Total** (n=101)	**DSA** (n=80)	**No DSA** (n=21)
- M1	54 (54)	50 (63)	4 (19)
- M2	22 (22)	19 (24)	3 (14)
- Multiple sites	7 (7)	4 (5)	3 (14)
Follow-up (n=76), n (%)			
Favorable clinical outcome at 90 days*	47 (62)	38 (59)	9 (75)

* Favorable clinical outcome was defined as modified Rankin Scale equal or smaller than 2. DSA indicates digital subtraction angiography; NIHSS, National Institutes of Health Stroke Scale; CTP, computed tomography perfusion; tPA, tissue-type plasminogen activator; TICI, Thrombolysis in Cerebral Infarction; CVA, cerebrovascular accident; CAD, coronary artery disease; CTA, computed tomography angiography; ICA, internal carotid artery; M1 indicates M1 segment of middle cerebral artery; M2 indicates M2 segment of middle cerebral artery.

Observed static collateral scores (Supplemental table I) were generally high in this population: the number of observations ranged from 0 to 3 (0-3%) for collateral score 0, from 8 to 23 (8-23%) for collateral score 1, from 22 to 44 (22-44%) for collateral score 2 and from 42 to 68 (42-68%) for collateral score 3. Similarly, the number of mASITN scores ranged from 1 to 2 (1-2%) for mASITN 1, from 4 to 19 (4-19%) for mASITN 2, from 17 to 45 (17-45%) for mASITN 3 and from 7 to 47 (7-47%) for mASITN 4.

Disagreements between observers did not differ more than one point on the collateral scales resulting in disagreements between the dichotomized scales in 10 cases.

CTA and DSA images from an example case with good collateral circulation are shown in Figure 2 and Figure 3, respectively. CTA and DSA images from an example case with poor collateral circulation are shown in Figure 4 and Figure 5, respectively.

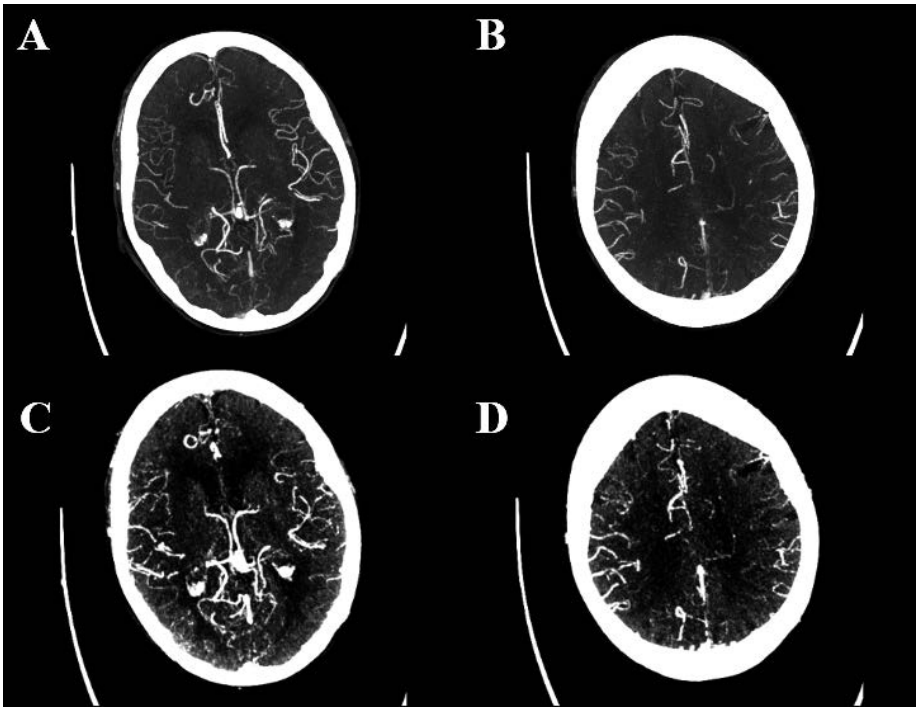

Figure 2. Example case with collateral circulation graded as good by the two observers. Single phase CTA images are shown on ASPECTS levels 1 (A) and 2 (B). Three-phase CTA images were created from PCT source data. The first phase of the three-phase CTA images is shown on ASPECTS levels 1 (C) and 2 (D).

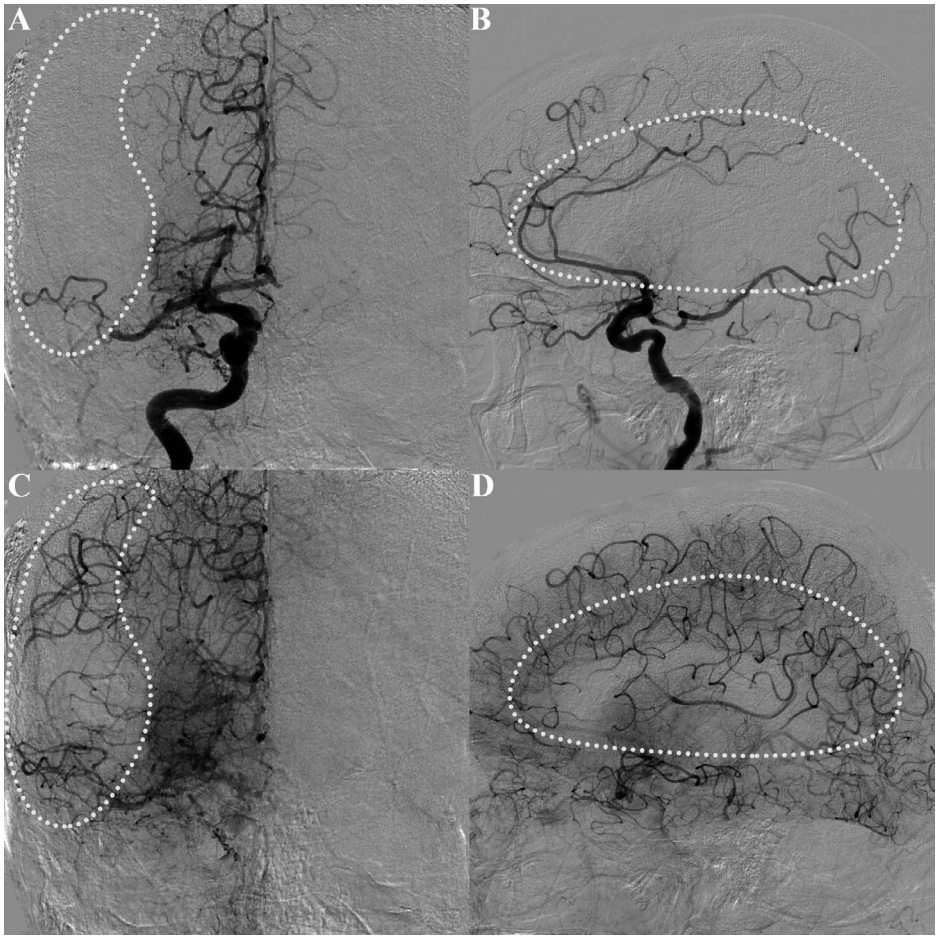

Figure 3. Example case identical to the case in Figure 2. Anteroposterior (A) and lateral (B) digital subtraction angiography views in the early contrast phase are shown. Anteroposterior (C) and lateral (D) views of the late contrast phase show good filling of the collateral circulation in the middle cerebral artery territory (white dotted shapes).

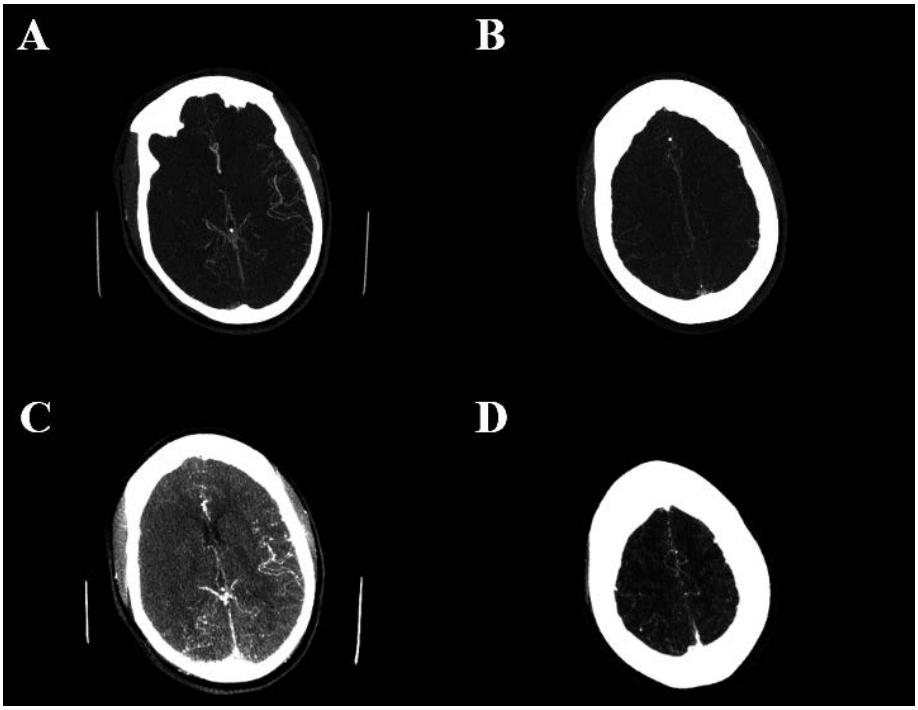

Figure 4. Example case with collateral circulation graded as poor by the two observers. Single phase CTA images are shown on ASPECTS levels 1 (A) and 2 (B). Three-phase CTA images were created from PCT source data. The first phase of the three-phase CTA images is shown on ASPECTS levels 1 (C) and 2 (D).

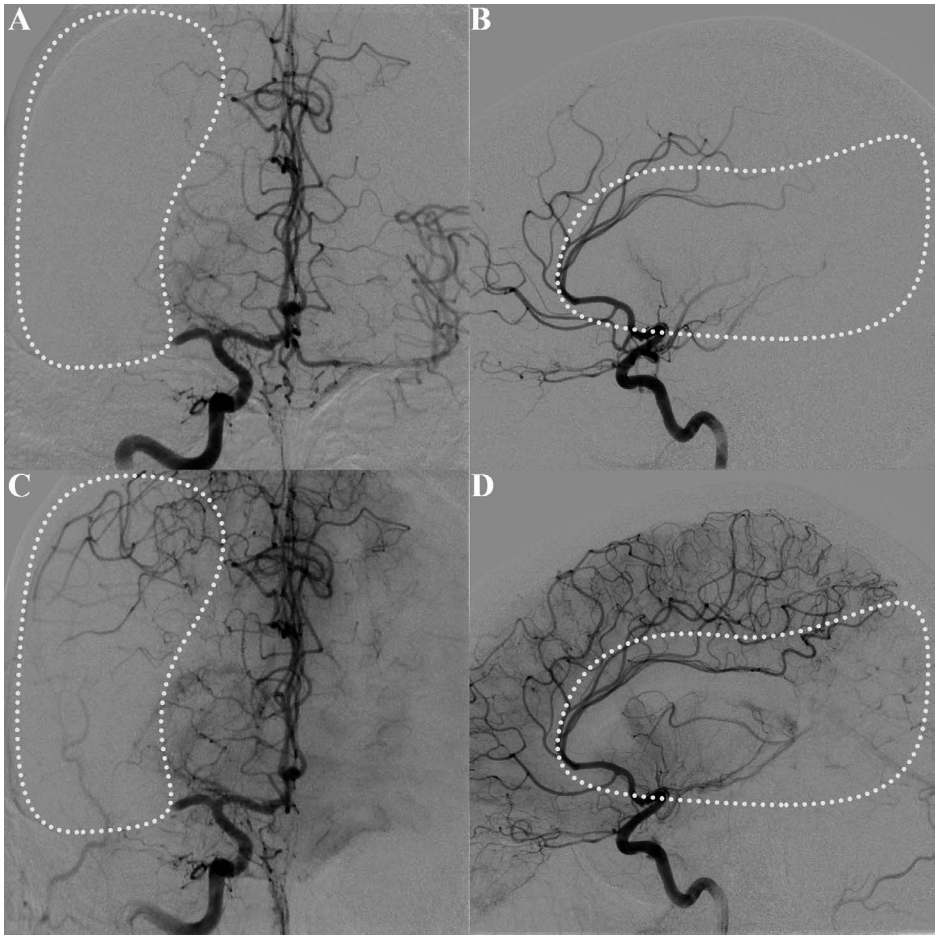

Figure 5. Example case identical to the case in Figure 4. Anteroposterior (A) and lateral (B) digital subtraction angiography views in the early contrast phase are shown. Anteroposterior (C) and lateral (D) views of the late contrast phase show poor filling of the collateral circulation in the middle cerebral artery territory (white dotted shapes).

Interobserver agreement was 0.46 (tMIP), 0.58 (three-phase CTA), 0.67 (multiphase CTA) and 0.69 (single-phase CTA) for static assessments and 0.52 (three-phase CTA) and 0.54 (multiphase CTA) for dynamic assessments (Figure 2).

Concordance between the CT observations and the reference standard (DSA) is summarized in Table 2 and displayed in Figure 6. Agreement (range 29-53%) and concordance (CCC range 0.08-0.27) on the ordinal scale were poor. Agreement improved after dichotomization of the collateral scores (range 54-81%), but concordance remained poor (CCC range: -0.02-0.24).

Table 2. Measures of concordance between collateral scores assessed on CT and DSA

Grading method	**Ordinal score**		**Dichotomized score**	
	Agreement (%)	**CCC (95% CI)**	**Agreement (%)**	**CCC (95% CI)**
CS Single-phase	53	0.09 (-0.06-0.24)	78	0.02 (-0.13-0.17)
CS Three-phase	48	0.08 (-0.06-0.22)	81	-0.11 (-0.26-0.05)
CS Multiphase	41	0.23 (0.08-0.37)	78	0.01 (-0.14-0.15)
CS tMIP	29	0.19 (0.05-0.32)	82	-0.02 (-0.18-0.13)
mASITN Three-phase	29	0.10 (-0.02-0.21)	54	0.12 (-0.01-0.25)
mASITN Multiphase	40	0.27 (0.12-0.40)	60	0.24 (0.09-0.38)

CT indicates computed tomography; DSA, digital subtraction angiography; CCC, concordance correlation coefficient; CI, confidence interval; CS, collateral score; tMIP, temporal maximum intensity projection; mASITN, modified American Society of Interventional and Therapeutic Neuroradiology.

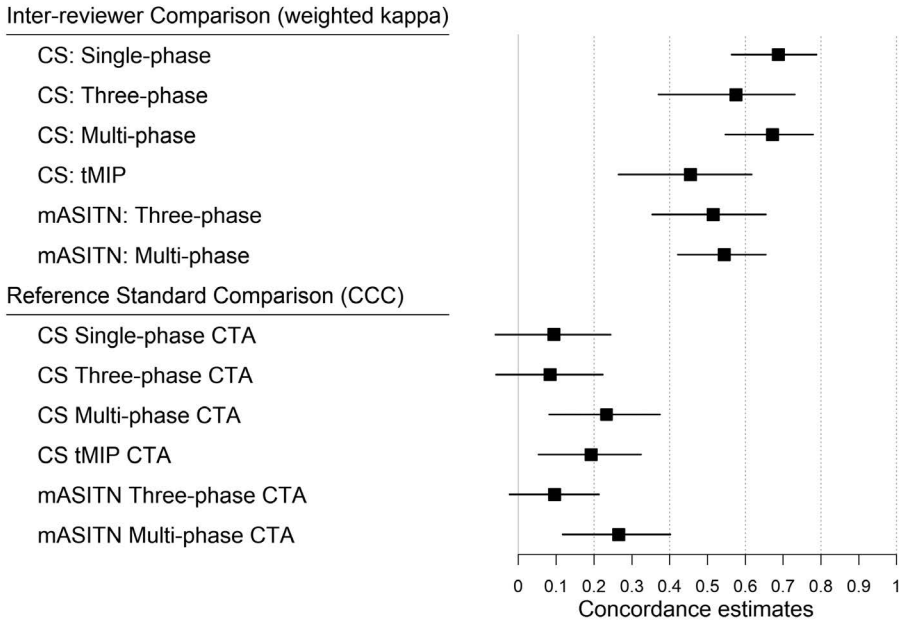

Figure 6. Estimated concordance correlation coefficients (CCC) and weighted kappa statistics with 95% confidence intervals. Confidence intervals for kappa statistics were based on 5,000 bootstrap resamples.

Legend: CS indicates collateral score; tMIP, temporal maximal intensity projection; mASITN, modified American Society of Interventional and Therapeutic Neuroradiology; CCC, concordance correlation coefficient; CTA, computed tomography angiography.

Clinical outcome was successfully collected in 76 (75%) patients. Patient characteristics did not differ significantly between patients who had follow-up and patients who did not have follow-up. Adjusted for recanalization, higher static collateral scores on multiphase CTA (OR 1.7, 95% CI 1.1-2.7) and tMIP (OR 2.0, 95% CI 1.1-3.4) were associated with favorable clinical outcome (Table 3). Similarly, higher mASITN scores on three-phase CTA (OR 1.5, 95% CI 1.1-2.2) and multiphase CTA (OR 1.7, 95% CI 1.1-2.6) were associated with favorable clinical outcome. For single-phase CTA (OR 1.1, 95% CI 0.7-1.8) and three-phase CTA (OR 1.6, 95% CI 1.0-2.6) a positive trend was observed for the association with favorable clinical outcome. No significant associations were found between DSA assessments and clinical outcome.

Table 3. Associations between imaging assessments and favorable 90-day clinical outcome

	Crude OR (95% CI)	Adjusted* OR (95% CI)
Collateral score		
Single-phase	1.1 (0.7-1.7)	1.1 (0.7-1.8)
Three-phase	1.6 (1.0-2.6)	1.6 (1.0-2.6)
Multiphase	1.5 (0.9-2.2)	1.7 (1.1-2.7)†
tMIP	2.0 (1.1-3.5)†	2.0 (1.1-3.4)†
mASITN		
Three-phase	1.5 (1.1-2.1)†	1.5 (1.1-2.2)†
Multiphase	1.5 (1.0-2.1)†	1.7 (1.2-2.6)†
Collateral score DSA		
Original scale	0.7 (0.4-1.4)	0.8 (0.4-1.6)
Binary scale	0.4 (0.1-1.7)	0.4 (0.1-1.9)
mASITN DSA		
Original scale	0.8 (0.5-1.4)	0.9 (0.5-1.6)
Binary scale	1.2 (0.4-3.3)	1.5 (0.5-4.7)

* Estimates were adjusted for recanalization status.
† P<0.05
OR indicates odds ratio; CI, confidence interval; tMIP, temporal maximum intensity projection; mASITN, modified American Society of Interventional and Therapeutic Neuroradiology; DSA, digital subtraction angiography.

DISCUSSION

We compared single-phase CTA and CTP derived three-phase CTA, multiphase CTA and tMIP with DSA with respect to their ability to reliably grade collateral circulation in AIS patients. We evaluated two scoring systems: a static collateral score entailing four categories and a dynamic collateral score (mASITN) entailing five categories. Agreement between the two observers was moderate to good. Collateral assessment achieved similar interobserver agreement for all imaging modalities and concordance with DSA was, in general, poor. Associations with favorable outcome were significant for CTP derived three-phase CTA, multiphase CTA and tMIP assessments, but not for single-phase CTA or DSA assessments.

The observed interobserver agreement in this study was comparable to previously reported measures of agreement. Previous studies found kappa-values for single-

phase CTA of 0.49[13], 0.87[14] and 0.68[17], which is consistent with the results of our study (kappa 0.69). Multiphase CTA has been proposed as a reliable tool for assessing collateral grade in patients with AIS.[8,9] Interobserver agreement was found to be very good (kappa 0.81) in one small study, while we found a kappa of 0.58.[8]

The overall concordance between CT assessments and DSA was poor, despite the reasonable agreement between the observations on CT and DSA. Studies evaluating the concordance between CT and DSA are scarce. One study found poor agreement between single-phase CTA and DSA (kappa 0.24), which is in line with the observations in this study.[17] Another study found a modest correlation between anterior circulation collaterals on CTA and DSA, but different collateral scores were used for each imaging modality.[18] Another study found good agreement (82%) and a correlation (Spearman's correlation coefficient 0.83) between multiphase CTA and DSA.[25] Three-point collateral scales were used, but no concordance measures were given. As a result, the percentage of agreement corresponds with our study, but we were not able to compare concordance measures between multiphase CTA and DSA. An explanation for the observed concordance may be the fact that neurointerventionalists do not usually perform DSA of either the contralateral internal carotid artery or the posterior circulation in anterior circulation stroke. As a result, the DSA assessment of collateral filling is likely to be incomplete relative to information from CTA and CTP. Also, the collateral scales on each modality and technique may be sufficiently different that they do not correlate. CTA lacks the temporal resolution of DSA, and CTA scales cannot capture the time resolved blood flow into the collateral circulation. For instance, if one looks at time point 1 and time point 2, which are separated by 20 seconds on a multiphase CTA, the collateral score might be good on the CTA scale. However, the DSA scale might show that it takes a very long time for the collateral vessels to fill, which might translate to a poor collateral score. Perfusion maps generated from CTP may offer more information than CTA as they allow evaluation of blood flow on a tissue level. However, evaluation of perfusion maps was beyond the scope of this study.

Collateral grading has been established as a predictor of clinical outcome independent of the number of phases acquired with CT.[26–29] In our study, single-phase assessments were not significantly related to favorable clinical outcome, although a positive trend was observed: the more acquired CT phases, the stronger the associations between the collateral grading and clinical outcome. This is in line with a previous study, which reported that the association with clinical outcome was stronger for multiphase assessments than for single-phase assessments.[9] Similarly, one study found that time-invariant CTA was superior to single-phase CTA in terms

of predicting clinical outcome with the collateral score.[7] These results confirm the added value of multiple phase CTA, either created with CTA or with CTP, when it comes to prediction of clinical outcomes.

The association between DSA assessments and clinical outcome has been investigated in one study, but no association was observed.[17] This is in line with our study in which we did not observe an association between DSA assessments and clinical outcome. However, the results from this particular analysis must be interpreted with caution as selection bias cannot be ruled out completely. Still, the selection process in this study reflects routine clinical care and therefore we believe the risk of selection bias is low. Future studies could elucidate whether prediction of clinical outcome is indeed more feasible with CTA than with DSA.

We calculated measures of concordance (CCCs) enabling us to evaluate accuracy and consistency between the CT assessments from two observers and the DSA assessments from one observer. However, CCC and other measures of agreement are sensitive to imbalanced data as was the case in our study. To solve this issue, a case control design may be used, but we did not have enough cases to use such a design. Patients with poor collaterals are unlikely to be selected for EVT, because they likely had larger infarctions that would exclude them from thrombectomy eligibility. As a result, the predominant number of patients with good collateral supply in our study leads to an increased risk of agreement by chance only, resulting in poor CCCs. In our clinic, all patients with suspected AIS either undergo CT or MRI, or both. Selection bias may have been an issue as many patients were excluded from this study because no CT data were available. The majority of these patients was imaged with MRI instead of CT. Evaluation of collateral grading on MRI was beyond the scope of this study. We do not believe that collateral filling is associated with the choice of imaging modality, because it is expected that patients with poor collateral filling preferably undergo CT as their clinical condition is probably worse than patients with good collateral filling. Moreover, poor agreement between assessments on CTA and DSA was also observed in a more balanced population before.[17]

Still, the imbalanced distribution of collateral filling is a limitation of our study, and future studies could therefore reassess measures of correlation between CT and DSA in more balanced populations. Patients, who did not undergo DSA after all, were excluded from the concordance analyses. We do not believe that this elevates the risk of selection bias as the selection process in this study reflects routine clinical care. Another limitation of our study is that we captured and assessed images on the

two ASPECTS levels only. This was done to achieve a standardized assessment. This could have influenced the collateral assessments as the observers were not able to look at the whole vasculature of the brain. Lastly, we did not evaluate commercially available CT grading software for assessing collateral filling in patients with AIS. In our opinion, the method of assessment of collateral filling should also be possible without specialized software since it is not standardly available. However, future studies could compare automated grading tools to collateral grading done by observers.

In conclusion, collateral assessment achieved similar interobserver agreement for all imaging modalities and concordance with DSA was, in general, poor. Collateral status evaluated on multiphase CTA was associated with clinical outcome, which was not the case for DSA.

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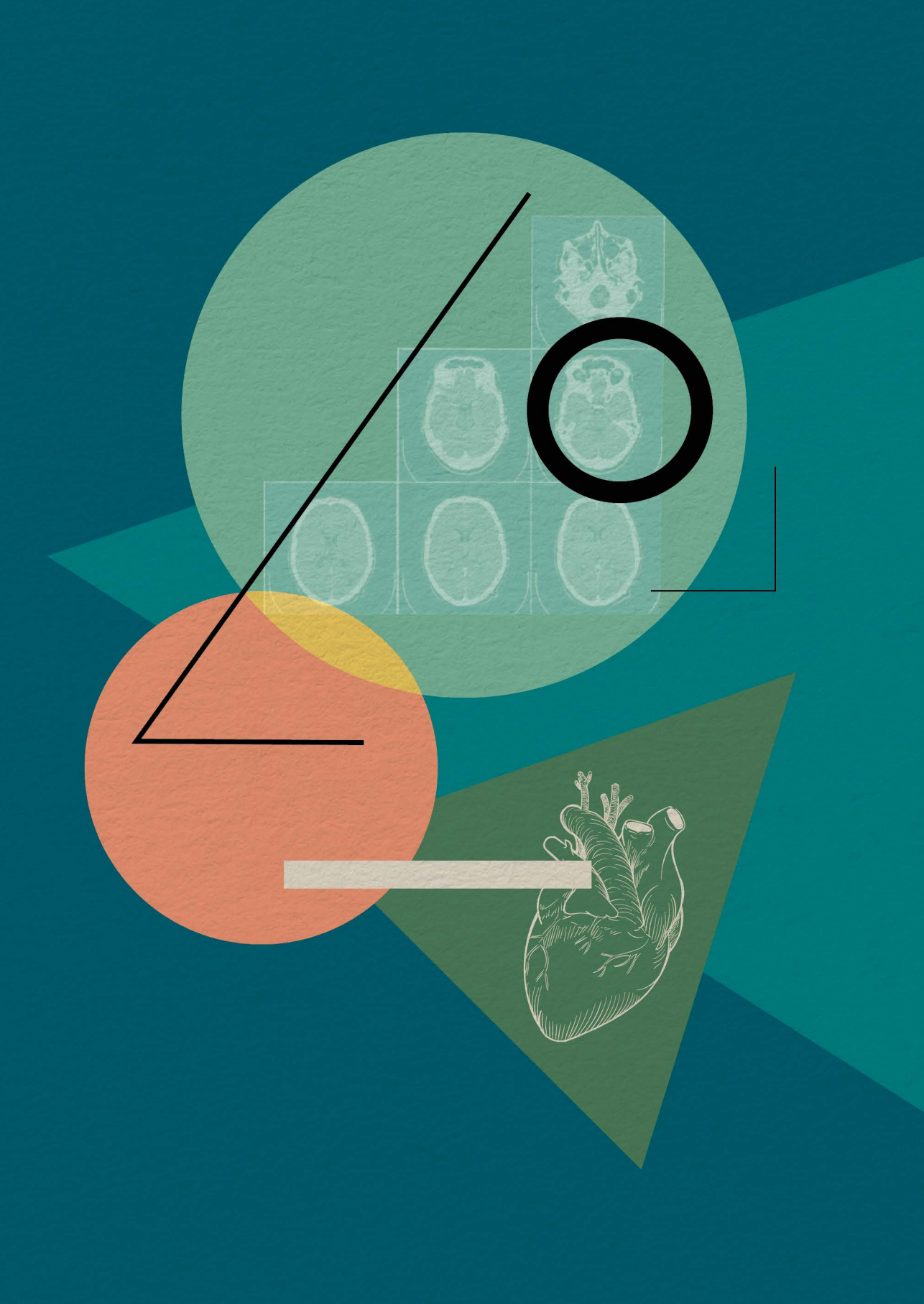
SUPPLEMENTS

Supplemental table I. Agreement between assessments of collateral filling on CT and DSA

	Single-phase CTA		Three-phase CTA		Multiphase CTA		tMIP		DSA
CS	**JWD**	**MW**	**JWD**	**MW**	**JWD**	**MW**	**JWD**	**MW**	**JJH**
0	2	1	1	2	0	1	0	0	3
1	13	16	11	9	23	19	10	8	5
2	44	33	36	22	32	39	30	32	44
3	42	51	53	68	46	42	60	60	28
Not assessable	0	0	0	0	0	0	1	1	21
*Weighted kappa**	*0.69 (0.56-0.79)*		*0.58 (0.37-0.73)*		*0.67 (0.55-0.78)*		*0.46 (0.27-0.62)*		
mASITN									
0	-	-	1	2	1	1	-	-	3
1	-	-	4	9	9	19	-	-	4
2	-	-	43	17	45	39	-	-	45
3	-	-	6	39	23	35	-	-	21
4	-	-	47	34	23	7	-	-	7
Not assessable	-	-	0	0	0	0	-	-	21
*Weighted kappa**	-		*0.52 (0.35-0.65)*		*0.54 (0.42-0.65)*		-		

* 95% confidence intervals were derived from 5,000 bootstrap resamples.

CT indicates computed tomography; DSA, digital subtraction angiography; CTA indicates computed tomography angiography; tMIP, temporal maximum intensity projection; DSA, digital subtraction angiography; CS, collateral score; mASITN, modified American Society of Interventional and Therapeutic Neuroradiology.



5

EARLY DETECTION OF SMALL VOLUME STROKE AND THROMBOEMBOLIC SOURCES WITH COMPUTED TOMOGRAPHY: RATIONALE AND DESIGN OF THE ENCLOSE STUDY

Based on:

Kauw F, van Ommen F, Bennink E, Cramer MJ, Kappelle LJ, Takx RA, Velthuis BK, Viergever MA, Wouter van Es H, Schonewille WJ, Coutinho JM, Majoie CB, Marquering HA, de Jong HW, Dankbaar JW. Early detection of small volume stroke and thromboembolic sources with computed tomography: Rationale and design of the ENCLOSE study. Eur Stroke J. 2020 Dec;5(4):432-440.

DOI: 10.1177/2396987320966420

ABSTRACT

Background

Computed tomography (CT) is the most frequently used imaging modality in acute stroke imaging protocols. Detection of small volume infarcts in the brain and cardioembolic sources of stroke is difficult with current CT protocols. Furthermore, the role of CT findings to predict recurrent ischemic stroke is unclear. With the "Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke" (ENCLOSE) study, we aim to improve: 1) detection of small volume infarcts with thin-slice CTP images and thromboembolic sources with cardiac CT techniques in the acute stage of ischemic stroke and 2) prediction of recurrent ischemic stroke with CT derived predictors.

Methods

ENCLOSE is a prospective multicenter observational cohort study, which will be conducted in 3 Dutch stroke centers (ClinicalTrials.gov Identifier: NCT04019483). Patients (≥18 years) with suspected acute ischemic stroke who undergo CT imaging within 9 hours after symptom onset are eligible for participation. CT imaging includes non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) from base of the heart to the top of the brain. Dual-energy CT data will be acquired when possible and thin-slice CTP reconstructions will be obtained in addition to standard 5 mm CTP data. CTP data will be processed with commercially available software and locally developed model-based methods. The post-processed thin-slice CTP images will be compared to the standard CTP images and to magnetic resonance diffusion weighted imaging (DWI), performed within 48 hours after admission. Detection of cardioembolic sources of stroke will be evaluated on the CTA images. Recurrence will be evaluated 90 days and 2 years after the index event. The added value of imaging findings to prognostic models for recurrent ischemic stroke will be evaluated.

Conclusion

The aim of ENCLOSE is to improve early detection of small volume stroke and thromboembolic sources and to improve prediction of recurrence in patients with acute ischemic stroke.

BACKGROUND

Acute ischemic stroke (AIS) is a medical emergency associated with high rates of mortality and morbidity.[1] Rapid imaging is key in the acute stroke setting as detection of ischemia and cause of the stroke is essential for treatment decisions. Currently, non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) are routinely performed as part of most acute stroke imaging protocols.[2] NCCT is used to exclude hemorrhagic stroke and to identify early signs of ischemia. CTA is required to identify the site and extent of arterial occlusion with the aim to determine eligibility for endovascular treatment (EVT). In addition, evaluation of collateral circulation on CTA helps to guide treatment strategies and predict patient outcomes.[3–5] Important causes of stroke such as large artery atherosclerosis, dissection or cardioembolism can also be identified with CTA. Perfusion maps generated from CTP source data may guide decision making for intravenous thrombolysis (IVT) or EVT in the extended window and in patients with unknown time of onset of stroke (e.g. wake-up stroke) as eligibility strongly depends on infarct core and penumbra volumes.[6–8] In addition, small perfusion defects can pinpoint more distal arterial occlusions that are difficult to detect on CTA. Also, time-invariant CTA, which is derived from the CTP source data, enables accurate assessment of the thrombus extent and the collateral status.[9]

CT imaging has certain advantages over magnetic resonance imaging (MRI) in evaluating patients with suspected AIS, such as 24/7 availability, speed and lower costs. CTP has high sensitivity (80%) and very high specificity (95%) for infarct detection and has added value to NCCT and CTA for posterior infarct detection.[10,11] However, not all clinical CT scanners have full brain CTP coverage, which may result in false negative findings.[10] In addition, high noise levels and reconstructions with low spatial resolution limit the ability of CTP to identify small volume infarcts.[12,13] In this study, small volume stroke was defined as a clinical diagnosis of acute ischemic stroke or transient ischemic attack with one of the following imaging findings: no occlusion visible on the admission CTA scan; an occlusion distal to the A2 segment of the anterior cerebral artery; an occlusion distal to the M1-M2 bifurcation of the middle cerebral artery; an occlusion of the posterior circulation without involvement of the basilar artery.

Stroke etiology has been established as an important predictor of recurrent ischemic stroke.[14] Thromboembolic sources of stroke include large artery atherosclerosis, dissection and cardioembolism. In about a quarter of patients with ischemic stroke, cardioembolism is the cause of the stroke, which requires specific treatment to prevent recurrent events. The cause of the stroke remains

unclear in 20 to 40% of the patients after routine work-up.[15–19] An important cause of this so-called cryptogenic stroke is paroxysmal atrial fibrillation, which often remains undetected in the early stroke phase despite continuous electrocardiogram (ECG) monitoring. Paroxysmal atrial fibrillation may be detected in a later phase, but the treatment-delay causes a prolonged time window of increased recurrence risk.[20] Transthoracic echocardiography is the standard imaging modality to detect cardiac thrombus, but has limited sensitivity for this purpose depending on patient habitus and the available imaging window. Transesophageal echocardiography has a higher accuracy, but is only performed on strict indication, because it is an invasive procedure, uncomfortable for the patient and often requires light sedation. In case of delay in cardiac imaging, the culprit thrombus may have resolved. Cardiac CTA has been proposed as a fast and noninvasive alternative method for depicting cardiac thrombus.[21–23] Non-ECG triggered cardiac CTA can be performed in the acute stroke setting by extending the stroke CTA to include the heart with minor adjustments to the scan parameters, so that the amount of contrast agent, the radiation dose and the acquisition duration do not increase. Alternatively, ECG-triggered cardiac CTA can be performed separately in the same stroke imaging session or soon after treatment. Cardiac CTA is performed as part of routine care in the participating centers of the "Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke" (ENCLOSE) study in patients with suspected AIS. One center will use dual-energy CT, which allows for increased iodine contrast and differentiating between iodine, calcifications, slow flow and motion artefacts. This may facilitate identification of cardiac thrombus and characterization of large artery atherosclerosis. The first goal of ENCLOSE is to improve detection of small volume infarcts and thromboembolic sources with state-of-the-art CT techniques.

The two-year recurrence rate has been estimated to be 12% in patients with AIS.[24] Clinical prediction models have been developed for predicting recurrence, but heterogeneity is high.[25] CT derived predictors have been identified as prognostic for clinical outcome after AIS, but not yet for recurrences.[14] The second goal of ENCLOSE is to prospectively evaluate the added value of CT derived predictors for predicting recurrent ischemic stroke. If applicable, MRI-derived predictors will be evaluated additionally.

METHODS

Study design

ENCLOSE (ClinicalTrials.gov Identifier: NCT04019483) is a prospective multicenter observational cohort study, which will be conducted in three Dutch stroke centers: the University Medical Center (UMC) Utrecht, the Amsterdam UMC - location Academic Medical Center (AMC) and the St. Antonius Hospital - location Nieuwegein. We will include 720 patients with suspected AIS. At presentation, patients undergo clinical evaluation, laboratory testing and CT imaging according to local stroke protocols. The local imaging protocol for stroke includes NCCT, CTP and CTA. Two centers will perform non-ECG triggered CTA from the base of the heart up to the top of the head; one center will perform a non-ECG triggered CTA from the aortic arch to the head and a separate ECG-triggered cardiac CTA. Patients with a suspected small volume infarct will be asked to undergo an additional brain MRI within 48 hours after hospital admission. The included patients will be followed for 2 years to identify recurrent ischemic strokes and to evaluate 90-day clinical outcome.

Inclusion and exclusion criteria

Patients will be included if the following criteria are met: age of 18 years or older, time from symptom onset or last seen well until admission CT is less than 9 hours[26], clinical diagnosis of acute ischemic stroke or transient ischemic attack (TIA), and informed consent from patient or legal representative. Patients, who awake with stroke symptoms, can only be included if they went to sleep without any stroke symptoms and the time from going to sleep until imaging is less than 9 hours. To participate in the MRI part of this study, the patient also has to meet the following criteria: no occlusion visible on the admission CTA scan or an occlusion distal to the A2 segment of the anterior cerebral artery, distal to the M1-M2 bifurcation of the middle cerebral artery or an occlusion of the posterior circulation without involvement of the basilar artery, and no contraindications for undergoing MRI. Patients with another diagnosis such as intracerebral hemorrhage, subarachnoid hemorrhage or tumor, or patients with known contrast allergy or renal failure will be excluded from the study.

Baseline data

The following baseline characteristics will be collected: age, sex, time of symptom onset or last seen well in case of a wake-up stroke, or other strokes with unknown time of onset, National Institutes of Health Stroke Scale (NIHSS) and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The following cardiovascular risk factors will be recorded: history of stroke, coronary heart

disease, atrial fibrillation, congestive heart failure, valvular disease, peripheral artery disease, active cancer, hypertension, dyslipidemia, diabetes mellitus, smoking and medication use. Biometry data include length and weight. Furthermore, therapeutic interventions such as intravenous administration of tissue-type plasminogen activator, endovascular stroke treatment and carotid endarterectomy will be recorded. Laboratory data include levels of hemoglobin, thrombocytes, glucose, HbA1c, creatinine, C-reactive protein, lipids and international normalized ratio. Medication use on hospital discharge will be collected as well.

CT imaging

Acquisition

Patients with suspected ischemic stroke will undergo NCCT, CTP and CTA. One institution will use a dual-energy CT scanner as part of standard care. The local stroke imaging protocols from the three participating hospitals will be used. Contrast and flow parameters for CTP and CTA are shown in Table 1. The acquisition and reconstruction parameters for the different CT scanners are shown in Table 2 and Table 3.

Table 1. Contrast parameters for CT perfusion and CT angiography acquisitions

Center	Scanner	Contrast	CTP				CTA			
			Bolus (ml)	Flow (ml/s)	Saline (ml)	Flow (ml/s)	Bolus (ml)	Flow (ml/s)	Saline (ml)	Flow (ml/s)
UMC Utrecht	Philips Brilliance iCT-256	Ultravist-300 mg/ml	40	6	40	6	65	6	40	6
	Philips IQon spectral CT	Ultravist-300 mg/ml	50	6	40	6	65	6	40	6
Amsterdam UMC	Siemens Force	Iomeron 300 mg/ml	35	6	40	6	50	6	40	6
	Siemens AS+	Iomeron 300 mg/ml	35	6	40	6	50	6	40	6
St. Antonius Hospital	64-Brilliance	Xenetix 300 mg/ml	40	5	50	4	55	4	40	4
	256-Brilliance iCT Philips	Xenetix 300 mg/ml	40	5	50	4	55	4	40	4

CTP indicates computed tomography perfusion; CTA, computed tomography angiography; ml, milliliter; s, second; UMC, university medical center; mg, milligram.

Table 2. Acquisition and reconstruction parameters of the CT perfusion stroke protocols in the participating centers

Center	Scanner	Scan type	Peak Voltage (kVp)	Exposure (mAs)	Beam collimation (mm)	Slice thickness/ increment (mm)	Reconstruction (level), kernel	Matrix
UMC Utrecht	Philips Brilliance iCT-256	Axial	80	150	128x0.625	5.0/5.0 of 1.0/0.8	iDose(5),UB	512x512
	Philips IQon spectral CT	Jog Mode	120	35	64x0.625	5.0/5.0 of 0.9/0.7	iDose(5), UB	512x512
Amsterdam UMC	Siemens Force	Axial	80	84	192x0.6	1.0/0.7	Admire(1), Bv36	512x512
	Siemens AS+	Axial	80	200	32x0.6	5.0/5.9	Saffire(1), H20f	512x512
St. Antonius Hospital	64-Brilliance	Axial	80	125	64x0.625	5.0/5.288	iDose(3) , B	512x512
	256-Brilliance iCT Philips	Axial	80	125	128x0.625	5.0/5.0	iDose(5), B	512x512

kVp indicates kilovoltage peak; mAs, milliampere-seconds; mm, millimeter; UMC, university medical center.

Table 3. Acquisition and reconstruction parameters of the CT angiography stroke protocols in the participatingcenters

Center	Scanner	Scan type	Peak Voltage (kVp)	Exposure (mAs)	Pitch	Beam collimation (mm)	Slice thickness/ increment (mm)	Reconstruction (level), kernel	Matrix
UMC Utrecht	Philips Brilliance iCT-256	Helical	100	AEC	0.914	128x0.625	3.0/3.0 or 0.9/0.45	iDose(3), B	512x512
	Philips IQon spectral CT	Helical	120	AEC	0.609	64x0.625	5.0/5.0 or 0.9/0.7	iDose(5), B	512x512
Amsterdam UMC	Siemens Force	Helical	100	200	0.55	192x0.6	1.0/0.7	Admire(1), Bv36	512x512
	Siemens AS+	Helical	100	200	0.55	128x0.6	1.0/1.0	Saffire(1), I46f	512x512
St. Antonius Hospital	64-Brilliance	Helical	100	230	1.033	64x0.625	2.0/1.5	iDose(3), B	512x512
	256-Brilliance iCT Philips	Helical	100	230	0.763	128x0.625	2.0/1.5	iDose(3), B	512x 512

kVp indicates kilovoltage peak; mAs, milliampere-seconds; mm, millimeter; UMC, university medical center; AEC, automatic exposure control.

Analysis
The acquired admission CT data are stored on an online secured server in the University Medical Center Utrecht. Standard post-processing of the data with 5 mm CTP reconstructions will be performed with Intellispace software (Philips Healthcare, Best, the Netherlands). In addition, the thin-slice CTP source data will also be reconstructed with iterative reconstruction and processed with in-house developed CTP software to enable detection of small volume strokes on admission CTP.[27] If the subject is scanned on the Philips IQon Spectral CT, the dual-energy CTP dataset will be used to reconstruct images including virtual monoenergetic images, virtual non-contrast images and iodine maps. The obtained perfusion maps will be evaluated for the presence and location of a focal perfusion deficit matching a part of a cerebral artery flow-territory. Fat and calcium volume of internal carotid artery atherosclerotic plaque will be determined on dual-energy CTA. The admission non-gated cardiac CTA will be evaluated for presence of thrombus, patent foramen ovale or other septal defects, signs of previous myocardial ischemia, aneurysm, atrial morphology, signs of endocarditis and signs of cardiomyopathy. Imaging assessments will be done by experienced observers, who will be blinded to clinical data.

Follow-up data

Cardiac imaging
In case follow-up imaging of the heart (e.g. transthoracic or transesophageal echocardiography, CT or MRI) is performed, the same variables will be evaluated as for baseline cardiac CTA. Other remarkable findings will be noted. Findings from continuous ECG monitoring or Holter ECG will also be recorded.

MR imaging
Patients who fulfill the selection criteria for the MRI part of this study will undergo MRI of the brain and neck within 48 hours after presentation. MRI findings will serve as the gold standard for the detection of cerebral ischemia. The MRI protocol will include diffusion weighted imaging (DWI) and 3D fluid attenuated inversion recovery (FLAIR) sequences of the brain, and, if feasible, MR angiography (MRA) of the neck, vessel wall imaging of the intracranial arteries, and simultaneous non-contrast angiography and intraplaque hemorrhage (SNAP) sequences of the extracranial carotid arteries.[28] Participants will be scanned on 3T MRI scanners from different vendors. If 3T MRI is not available for logistic reasons, FLAIR and DWI sequences can be acquired on 1.5T MRI scanners instead. In case an MRI is performed as part of

routine clinical care within 48 hours after CT imaging, the acquired FLAIR and DWI images will be used instead of performing an additional study MRI.

Recurrence and clinical outcome

As part of routine care, patients will be contacted for follow-up evaluation at 90 days in the outpatient clinic or by telephone by stroke nurses, who are trained and certified to evaluate the modified Rankin Scale (mRS). The 90-day clinical outcome of the patient will be evaluated with the mRS. A Dutch structured questionnaire, which was based on previous studies, was used to assess the mRS by telephone.[29,30] In addition, patients will be asked for a second follow-up evaluation by telephone after 2 years. At 2 years, the patients will be asked whether a recurrent stroke has occurred and, if applicable, when and where the patient was treated for the recurrence (Figure 1). A discharge summary on the recurrent event will be requested from the hospital or general practitioner.

Data entry and monitoring

Clinical data and imaging findings are registered with electronic case report forms in an online secured database (OpenClinica, LLC, Waltham, USA). Patient names and identification numbers will be replaced by a study code. To assess the quality and validity of the research data, independent and qualified monitors will be appointed to monitor the study in the participating centers.

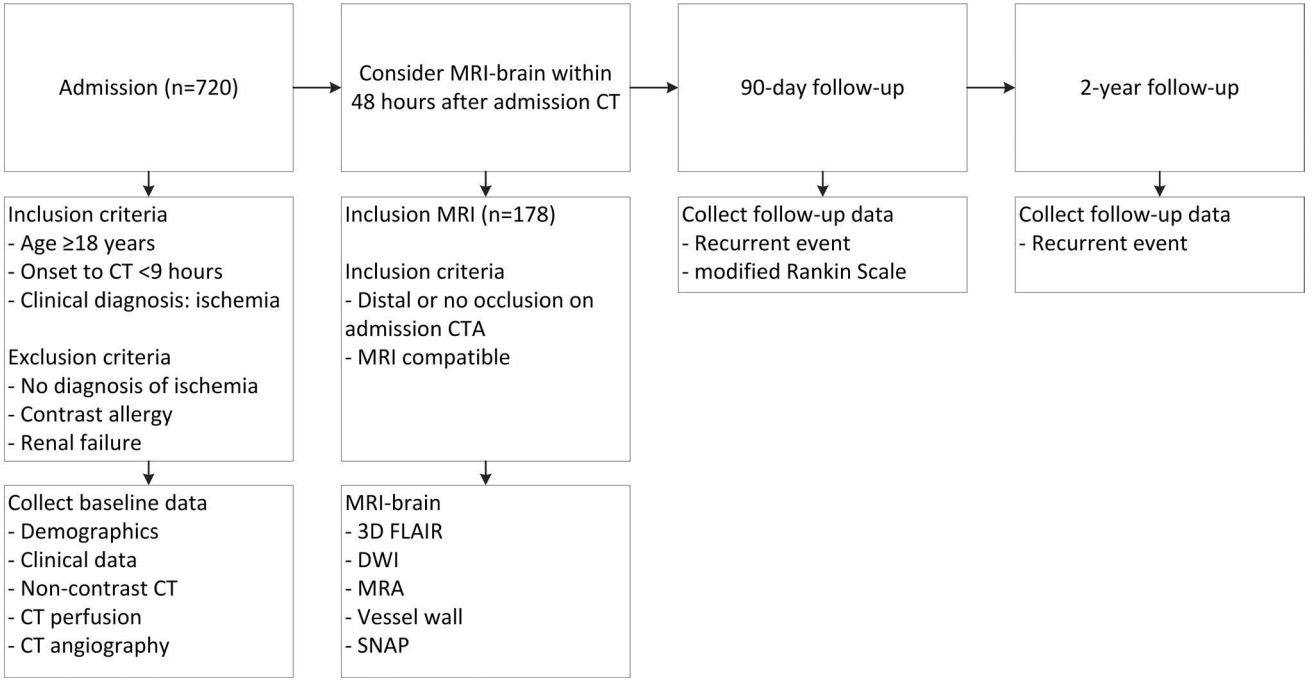


Figure 1. Flowchart of patient selection, study procedures and outcome evaluations

Legend: Distal occlusion on admission CTA is defined as an occlusion distal to the A2 segment of the anterior cerebral artery, distal to the M1-M2 bifurcation of the middle cerebral artery or an occlusion of the posterior circulation excluding basilar and vertebral artery occlusions.CT indicates computed tomography; MRI, magnetic resonance imaging; A2, A2 segment of anterior cerebral artery; M1-M2, junction between M1 and M2 segments of the middle cerebral artery; CTA, computed tomography angiography; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion weighted imaging; MRA, magnetic resonance angiography; SNAP, simultaneous non-contrast angiography and intraplaque hemorrhage.

Statistical analysis

Ischemia detection

Sample size

Over 30,000 people suffer from an ischemic stroke in the Netherlands each year.[31] About 30% of them will have an intracranial large artery occlusion and 70% will have a minor stroke or TIA. As a result, 500 of the 720 subjects are possible candidates for small volume infarct detection. Assuming that at least half of the 500 patients will give informed consent for the extra follow-up MRI and do not have contraindications for undergoing MRI, we should have 250 potential patients for the part of the study that concerns small volume stroke detection. Based on the historical cohort (Dutch Acute Stroke Study: 2009-2013, METC number 08-373), we expect to improve the sensitivity of CTP for small volume stroke detection from 0.45 to at least 0.75, which approaches the sensitivity of MRI (0.88-1.00).[32] With a minimal acceptable lower 95% confidence level of 0.6 for the increased sensitivity we will need about 107 MRI subjects.[33] We expect that about 60% of patients with suspected stroke and no large artery occlusion on admission will have an infarct on follow-up imaging.[34] This means that we need to include at least 178 patients for the MRI part of this study.

Diagnostic value

The diagnostic properties to detect cerebral ischemia of both the standard CTP and the high-resolution CTP images will be compared to the reference standard (DWI). The DWI images will be evaluated by an experienced neuroradiologist. Sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals will be calculated. We hypothesize that the high-resolution CTP will have superior sensitivity compared to the standard CTP for detection of ischemia. The diagnostic values will be compared between the CTP protocols with the McNemar test and with receiver operating characteristic curves. A p-value lower than 0.05 will be considered significant.

Recurrent stroke prediction

Sample size

For this study, a prediction model containing a maximum of six predictors will be developed for recurrent stroke. Therefore, at least 60 patients with a recurrent stroke are needed according to statistical guidelines.[35] Ischemic stroke is estimated to recur in approximately 10% of the included patients.[36] When accounting for a loss to follow-up rate of 10%, the required sample size will be approximately 650. Based on a historical stroke cohort (Dutch Acute Stroke Study: 2009-2013, METC number

08-373), we expect a participation rate of 90%.[37] Thus, a minimum of 720 patients need to be asked for study participation. In a period of 36 months, at least 720 patients with suspected ischemic stroke will visit the UMC Utrecht, the Amsterdam UMC - location AMC and the St. Antonius hospital - location Nieuwegein.

Candidate predictors

In this study, clinical and imaging predictors of recurrent stroke will be analyzed. Previously identified clinical predictors include cardiovascular risk factors such as higher age, prior stroke, prior myocardial infarction, atrial fibrillation, hypertension, diabetes mellitus and hyperlipidemia.[25] Predictors that can be determined on imaging modalities include old infarcts on NCCT, ASPECTS on CTP and CTA findings such as occlusion or stenosis, collateral filling in the occluded area, carotid plaque characteristics and presence of a cardioembolic source. Stroke subtype (TOAST classification) is based on both clinical and imaging data.

Model derivation

Complete case analysis will be performed as we expect only few missing values. A multivariable model containing all candidate predictors will be developed. The best predictive variables will be selected with backward selection. Akaike's information criterion will be used to determine the best model fit. Hazard ratios and 95% confidence intervals will be calculated with Cox proportional hazards models. The proportionality hazards assumption will be checked by visual inspection of the Schoenfeld residual plots. The performance of the final model will be evaluated with measures of discrimination and calibration. Discrimination will be assessed with receiver operating characteristic (ROC) curves and c-statistics. Calibration will be assessed with calibration plots.

Ethical considerations

Written informed consent will be acquired from patient or legal representative. The ability of the patient to give informed consent will be evaluated in order to determine whether the patient or the legal representative should be asked for written informed consent. Patients, who are incapable of giving informed consent, will not be asked to undergo MRI. In case the patient dies before informed consent can be acquired, the patient will be included without obtaining informed consent from his/her legal representative as it is undesirable to burden the legal representative with this request. The ENCLOSE study has been approved by the medical ethics committee of the UMC Utrecht.

DISCUSSION

CTP has good sensitivity (80%) and specificity (95%) for brain infarct detection.[10,11] However, accurate detection of small volume infarcts is still difficult with CTP, because of noise and limited spatial resolution.[38] In addition, evaluation of the posterior fossa is often hampered by streak artefacts.[39] In case no stroke is visualized with CT, an MRI is sometimes indicated to ascertain the diagnosis. By improving the detection of small volume stroke by CTP, additional MRI may become unnecessary in the diagnostic pathway and early detection of these small ischemic stroke may influence acute treatment decisions.

Cardiac CTA may be a fast and noninvasive method for depicting cardiac thrombus in the acute stroke phase. It has some advantages over (delayed) echocardiographic imaging and may facilitate in starting anticoagulant treatment in time. Adding cardiac CTA to the standard stroke imaging protocol will cost less than 2 seconds, and the additional radiation exposure will be marginal.

Prediction of recurrences has been subject of multiple studies.[25] However, developed clinical models for long-term prediction have limited discriminative ability with c-statistics not greater than 0.7.[25] Adding imaging predictors to clinical models may improve their predictive value.

For this study, we will not exclude particular subgroups of patients with acute ischemic stroke for reasons of clinical applicability and generalizability. We select on acquisition timing as CT findings such as ischemia may differ between patients who present in an early time window when compared with patients who present in a late time window. Different kinds of CT scanners will be used as multiple centers are involved in this study. Although this can lead to heterogeneity of imaging acquisitions, it enables generalization of the results to other stroke centers.

In conclusion, the ENCLOSE study aims to increase the diagnostic accuracy of CTP for detection of small volume infarcts and the diagnostic yield of CTA for cardioembolic sources of stroke. The study also aims to improve prognostic models for predicting recurrent ischemic stroke. CT derived predictors, including predictors derived from early cardiac CTA, will be used to improve prognostication of recurrent ischemic stroke.

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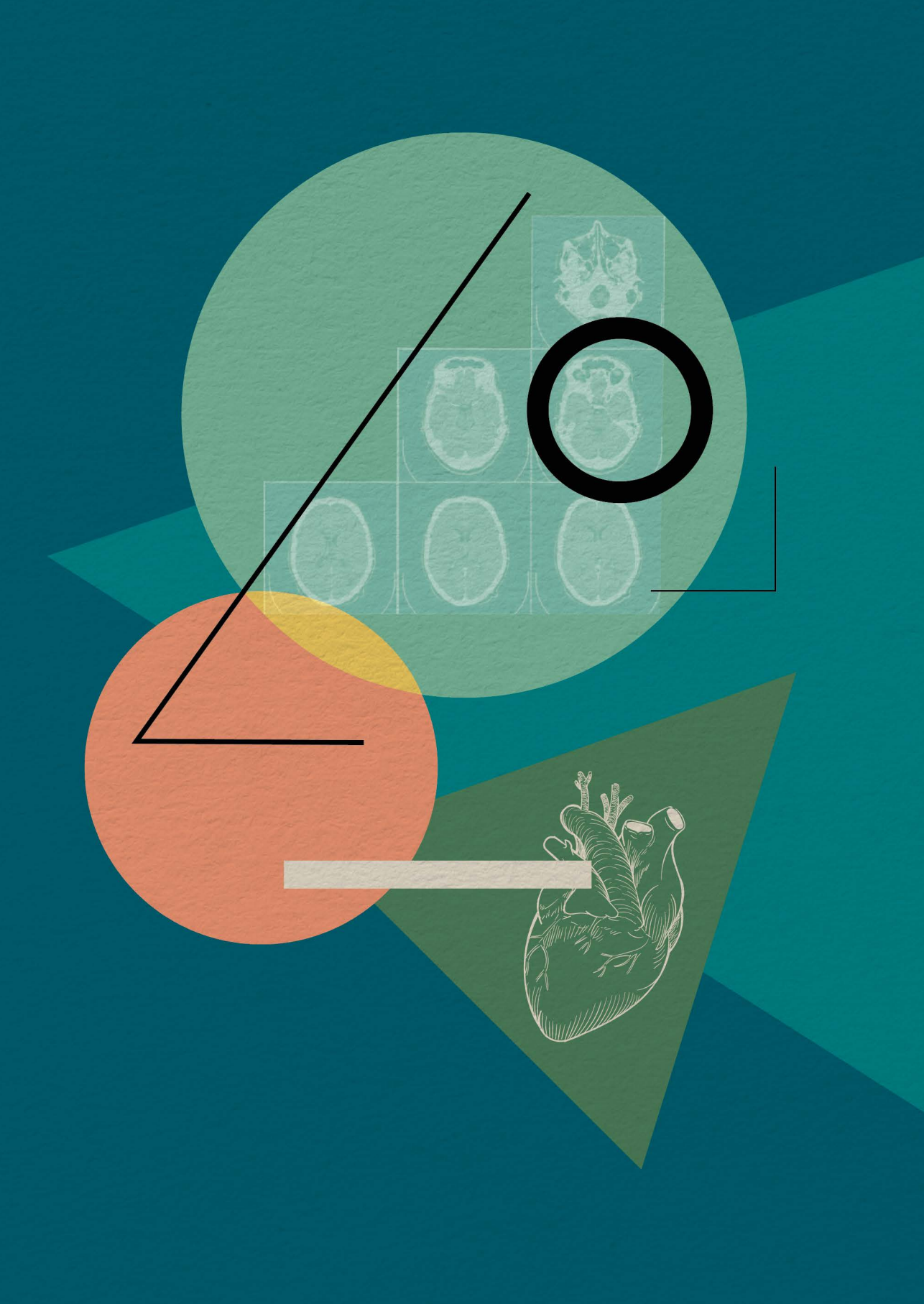

6

A CHANGE OF HEART: YIELD OF CARDIAC IMAGING IN ACUTE STROKE WORKUP

Based on:
Kauw F, Dankbaar JW, Habets J, Cramer MJM, de Jong HWAM, Velthuis BK, Kappelle LJ. A Change of Heart: Yield of Cardiac Imaging in Acute Stroke Workup. Case Rep Neurol. 2018 May 30;10(2):118-123.

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ABSTRACT

This case report describes a patient who experienced a recurrent ischemic stroke within 24 hours. Dual-energy CT (DECT) angiography on admission showed two intracardiac thrombi, one in the left ventricle and one in the left atrial appendage. Following the second ischemic event, repeated CT angiography (CTA) showed that the ventricular thrombus had considerably diminished, which suggests that the recurrent brain infarction was caused by cardioembolism. This case emphasizes: 1) the potential benefit of cardiac evaluation through CTA in the acute stroke setting and 2) the use of DECT angiography for detection of thrombus and differentiating between thrombus, myocardial wall and slow flow of contrast.

BACKGROUND

Patients with a recent ischemic stroke are at risk for a recurrence.[1] In 20-30%, an ischemic stroke is caused by a cardioembolism.[2] Dysfunction of the atria or ventricles of the heart may cause stasis of blood, which may lead to the formation of thrombus. To prevent subsequent cardioembolic arterial occlusion in the brain, treatment with anticoagulants should be promptly considered in patients with an impaired mechanical function of the heart or atrial fibrillation (AF).[3,4]

In current clinical practice, stroke patients are monitored by electrocardiogram (ECG) for presence of AF. Transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) may be necessary in individual patients to check for the presence of intracardiac thrombus. Excluding thrombus in the left atrial appendage (LAA), with complex anatomy, is particularly difficult on TTE.[5] Detection of intracardiac thrombus may be improved by visualizing the heart at the first presentation of stroke patients. It has been suggested to perform cardiac CT angiography (CTA) instead of echocardiography in addition to stroke imaging protocols.[6,7] Dual energy CT (DECT) can detect intracardiac thrombus and is considered better than conventional CT because of its superior tissue contrast. This improves the differentiation between thrombus, myocardial wall and areas with little contrast material such as the LAA.[8]

In the University Medical Center Utrecht, the Netherlands, non-ECG-gated DECT angiography that covers the base of the heart up to the crown of the head, is routinely performed in patients with an acute stroke. To show the potential importance of this new technique in the acute stroke setting, we describe a patient with two intracardiac thrombi who had a recurrent ischemic stroke within one day after admission.

CASE DESCRIPTION

A 76-year-old male was transferred to the emergency department after he was found sitting in the garden with impaired speech and weakness of his left extremities. The patient was last seen well almost four hours before his friends found him. Relevant past medical history included ischemic cardiomyopathy (left ventricular ejection fraction 30%), AF, pacemaker implantation, and chronic obstructive pulmonary disease (COPD). Medication included acenocoumarol, digoxin, antihypertensive medication, and a statin. Neurological examination showed dysarthria, left sided hemianopia, left sided facial palsy and paralysis of the left extremities. ECG showed AF with a ventricular paced rhythm. The international normalized ratio was 1.4. A

non-contrast head CT (IQon Spectral CT, Philips Healthcare, Best, the Netherlands) showed a hyperdense vessel sign of the right middle cerebral artery (MCA) and early signs of ischemic stroke (Figure 1A). CTA, from head to heart, and CT perfusion showed an occlusion of the proximal right MCA with a large perfusion deficit in the MCA flow territory (Figure 1B-C).

Two intracardiac thrombi were visible on CTA, one in the left ventricle and one in the left atrial appendage (Figure 2A-C). The visibility of the left ventricular thrombus was improved by using the iodine setting and low keV mono-energetic DECT reconstructions of the CTA. Atherosclerotic plaques were found in both internal carotid arteries, but there was no significant stenosis. The patient received intravenous thrombolysis followed by endovascular treatment. Successful recanalization of the MCA was achieved at first pass using a penumbra suction system one hour after presentation to the emergency room.

A few hours after endovascular treatment, consciousness of the patient deteriorated and he developed respiratory failure. A repeated non-contrast head CT excluded cerebral hemorrhage and thoracic CT excluded pneumonia or pneumothorax. Transthoracic echocardiography was inconclusive due to limited acoustic windows caused by COPD.

One day later, the patient woke up with a quadriplegia. A repeated stroke protocol CT showed a new hypodensity and perfusion deficit in the left hemisphere (Figure 1D-F). On CTA and DECT reconstructions, the thrombus in the left ventricle of the heart was clearly reduced in size. The thrombus in the left atrial appendage was unaltered in size compared to admission imaging (Figure 2C-D). No arterial occlusion could be found on the CTA. No therapeutic options remained and the patient died the same day. Autopsy was not permitted.

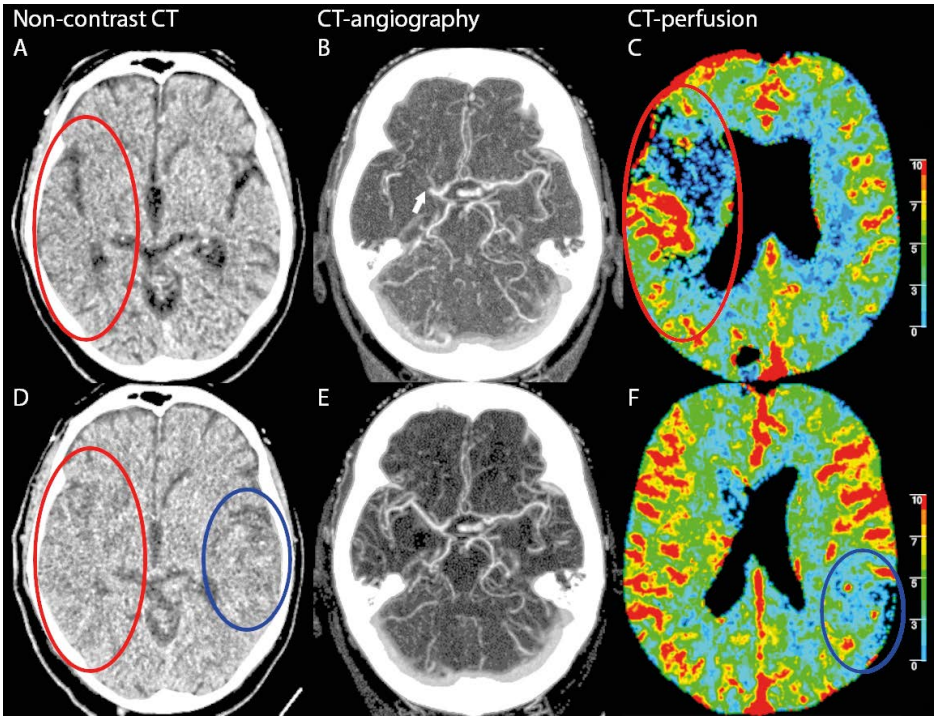

Figure 1. Head CT images of the patient

Legend: Top row with admission imaging of A: non-contrast CT with early signs of ischemic stroke (red oval), B: CT angiography (CTA) with occlusion (white arrow) of the proximal middle cerebral artery, C: CT perfusion (CTP) showing perfusion deficit in the territory of the right middle cerebral artery (red oval). Bottom row with follow-up imaging D: non-contrast CT with ischemic alterations in both hemispheres (red and blue ovals), E: follow-up CTA without a visible occlusion, F: CTP showing a new perfusion deficit in the left parietal region (blue oval).

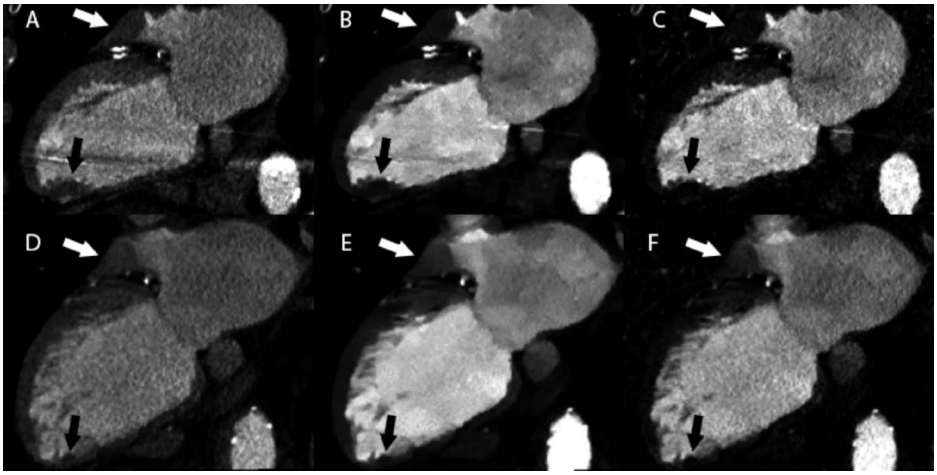

Figure 2. Cardiac dual-energy CT angiography images of the patient

Legend: CTA with two chamber view of the left ventricle. Admission CTA with A: conventional (120kV), B: 40keV and C: iodine setting showing two thrombi, one in the left atrial appendage (white arrow) and one in the left ventricle (black arrow). Follow-up CTA with D: conventional (120kV), E: 40keV and F: iodine setting showing diminution of the ventricular thrombus (black arrow) and the unaltered left atrial appendage thrombus (white arrow).

DISCUSSION

This case report describes an acute ischemic stroke patient with an MCA occlusion and two intracardiac thrombi as possible culprits on CTA, one in the left ventricle and one in the LAA. Repeated imaging after early recurrence of ischemic stroke demonstrated a diminished left ventricular thrombus. The culprit was thereby identified.

Evidence on presence of intracardiac thrombus and risk of recurrent ischemic stroke is scarce. Only one study investigated the relation between presence of intracardiac thrombus and stroke recurrence prospectively, but no association was found.[9] However, the number of outcome events was low, the study was performed in a selected population, and follow-up duration was limited.

In our case, a bilateral hemispheric stroke without significant carotid artery disease or dissection makes a cardioembolic source of the occlusion likely. The left ventricular thrombus was probably caused by myocardial wall motion abnormalities after previous myocardial infarction resulting in local stasis of blood. The left atrial appendage thrombus was probably caused by stasis of blood during the presence

of AF. To detect intracardiac thrombus, ECG-triggered cardiac CTA has been shown to be of comparable diagnostic value when compared to TEE.[7,10] However, specificity of ECG-triggered cardiac CTA for detecting thrombus in the left atrial appendage is limited, because hypo-attenuation in the left atrial appendage may reflect slow blood flow in that area, which mimics presence of thrombus. Slow-flow artifacts in areas such as the left atrial appendage can be avoided by giving a pre-bolus of contrast. In our stroke work-up, the first bolus of contrast for the CTP provides this pre-contrast. The accuracy of differentiating intracardiac thrombus from stasis of blood can further be raised by using DECT reconstructions, with split energy layers, instead of conventional CTA.[11] In our case, the thrombi were best visible on the 40 keV images compared to the 120 kV images, and showed no iodine uptake on the iodine map, demonstrating the value of DECT with dual layer detector.

DECT is a technique that gathers additional information through analysis of both high and low energy levels. This specific CT application has gained interest in the last decade as it may improve detection and differentiation of tissue types throughout the body.[12,13] There are several methods of acquiring dual-energy data, as well as depicting the iodine content in maps. Currently, three different CT types with dual-energy data can be used in the clinic: 1) dual source DECT that has two x-ray tubes at different kV settings projecting on the corresponding two detectors, 2) single source DECT that has one x-ray tube that can rapidly switch between 2 kV settings projecting on one detector and 3) dual-layer detector CT that has one source and a single double-layered detector, which enables differentiation between high and low energy levels. The advantage of DECT with dual layer detector, that was used in our institution, is that the dual-energy information is always available and not only in predefined specific protocols, as is the case in the other methods.

With the high speed of current CT scanners, cardiac CTA can be implemented into the acute stroke imaging protocol without delaying the acute stroke work-up.[6] However, there may be exposure to an additional low dose of radiation when a separate ECG-triggered cardiac CTA is added to the stroke imaging protocol. DECT using the dual-layer detector method can keep the radiation dose stable as the low kV data can be used to improve the contrast image quality and enable cardiac thrombus detection without ECG-triggering. We think that the diagnostic yield of cardiac CTA and the clinical relevance outweighs the possible additional low dose of radiation for the patient.

CONCLUSION

This case emphasizes the potential benefit of: 1) cardiac evaluation through CTA in the acute stroke setting and 2) use of DECT for detection of thrombus and differentiating between thrombus, myocardial wall and slow flow of contrast. Larger studies should demonstrate whether implementation of cardiac DECT angiography into acute stroke imaging protocols is beneficial.

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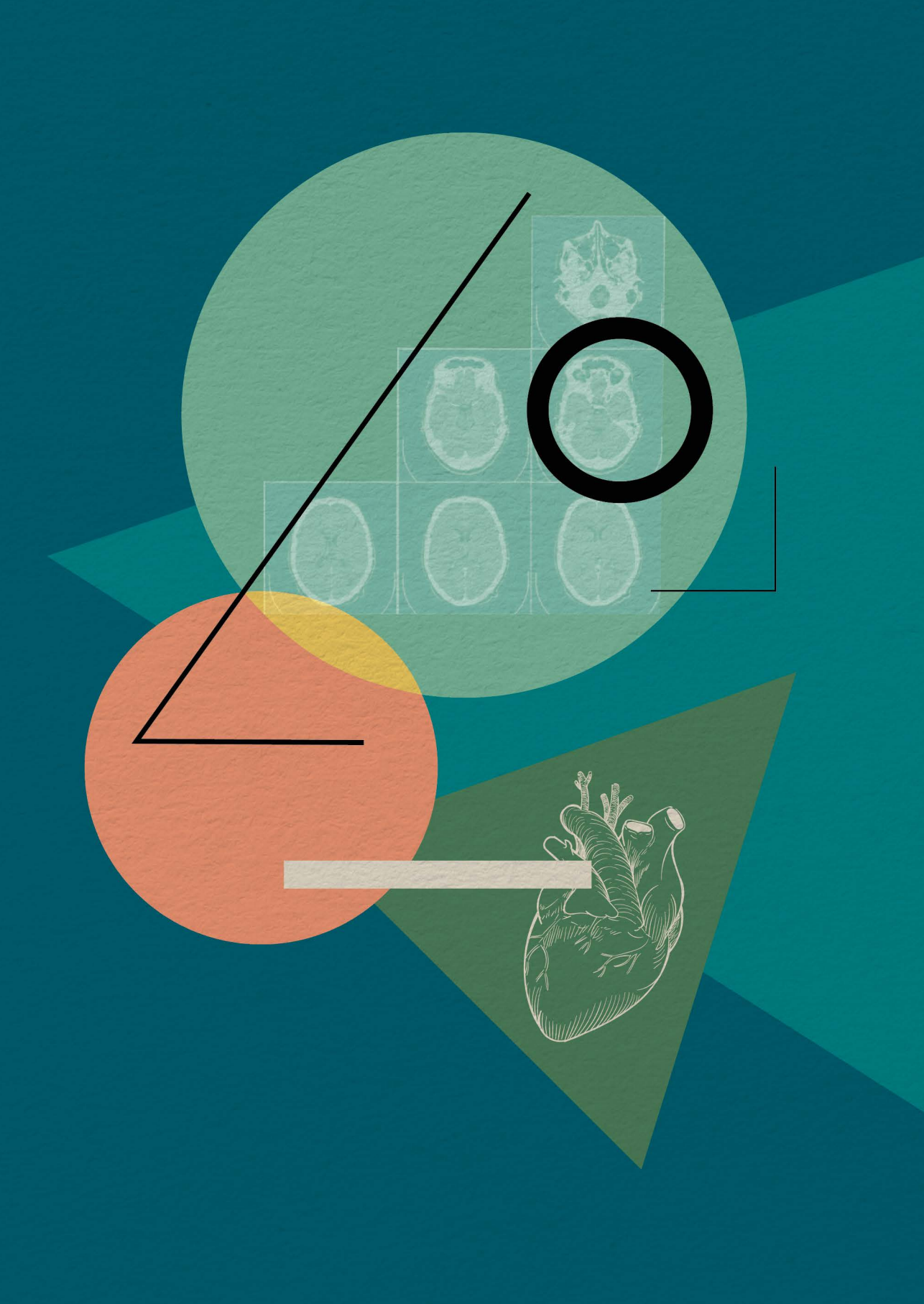

7

DETECTION OF CARDIOEMBOLIC SOURCES WITH NON-GATED CARDIAC CT ANGIOGRAPHY IN ACUTE STROKE: RESULTS FROM THE ENCLOSE STUDY

Based on:
Kauw F, Velthuis BK, Takx RA, Guglielmo M, Cramer MJ, van Ommen F, Bos A, Bennink E, Marquering HA, Kappelle LJ, de Jong HW, Dankbaar JW. Detection of Cardioembolic Sources With Nongated Cardiac Computed Tomography Angiography in Acute Stroke: Results From the ENCLOSE Study. Stroke. 2023 Mar;54(3):821-830.

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ABSTRACT

Background

Identifying cardioembolic sources in patients with acute ischemic stroke is important for the choice of secondary prevention strategies. We prospectively investigated the yield of admission (spectral) non-gated cardiac CT angiography (CTA) to detect cardioembolic sources in stroke.

Methods

Participants of the "Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke" (ENCLOSE) study with transient ischemic attack or acute ischemic stroke with assessable non-gated head-to-heart CTA at the University Medical Center Utrecht were included between June 2017 and March 2022. Presence of cardiac thrombus on cardiac CTA was based on a Likert scale and dichotomized into certainly or probably absent versus possibly, probably or certainly present. The diagnostic certainty of cardiac thrombus was evaluated again on spectral CT reconstructions. The likelihood of a cardioembolic source was determined post hoc by an expert panel in patients with cardiac thrombus on CTA. Parametric and nonparametric tests were used to compare the outcome groups.

Results

Forty-four (12%) of 370 included patients had a cardiac thrombus on admission CTA: 35 (9%) in the left atrial appendage (LAA) and 14 (4%) in the left ventricle. Patients with cardiac thrombus had more severe strokes (median NIHSS 10 versus 4, P=0.006), higher clot burden (median clot burden score 9 versus 10, P=0.004) and underwent endovascular treatment more often (43% versus 20%, P<0.001) than patients without cardiac thrombus. LAA thrombus was present in 28% and 6% of the patients with and without atrial fibrillation, respectively (P<0.001). The diagnostic certainty for LAA thrombus was higher for spectral iodine maps compared with the conventional CTA (P<0.001). The presence of cardiac thrombus on CTA increased the likelihood of a cardioembolic source according to the expert panel (P<0.001).

Conclusions

Extending the stroke CTA to cover the heart increases the chance of detecting cardiac thrombi and helps to identify cardioembolic sources in the acute stage of ischemic stroke with more certainty. Spectral iodine maps provide additional value for detecting LAA thrombus.

BACKGROUND

The recurrence risk in patients with transient ischemic attack (TIA) or acute ischemic stroke (AIS) depends on the etiology.[1] Around one third of AIS cases are caused by cardioembolism, requiring a different strategy for secondary prevention than an atherosclerotic cause of stroke.[2] In a quarter of the cases the etiology of the stroke remains unknown (i.e. cryptogenic stroke). Occult atrial fibrillation (AF) might explain some cryptogenic strokes and these patients may need anticoagulant therapy instead of oral antiplatelet therapy.[3] Identifying these patients remains difficult with current cardiologic investigations including electrocardiogram (ECG), telemetry, Holter, loop recorder and transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE).[4,5] Echocardiography is often performed days later, which may influence the chance of detecting cardiac thrombus after intravenous thrombolysis. TEE has a higher sensitivity than TTE for left atrial appendage (LAA) thrombus, but a lower sensitivity for left ventricle (LV) thrombus and is semi-invasive, time-consuming and patient unfriendly.[6] CT angiography (CTA) may be a non-invasive alternative with superior visualization of the LAA and LV.

Patients with acute ischemic stroke routinely undergo CTA from head to the aortic arch to visualize the intracranial and extracranial arteries. The heart and aorta are not routinely covered with CTA although both are potential causes of stroke.[7] Studies have demonstrated that integrating cardiac CTA into the admission stroke imaging protocol is a promising alternative to echocardiography, but these studies were small, heterogeneous and retrospective.[8] In addition, a previous study showed that dual-energy CT has additional value compared to conventional single source CT.[9] With spectral or dual-energy CT high and low energy data are acquired with different approaches, enabling reconstruction of spectral images, including virtual monoenergetic images, iodine maps and effective atomic number (Z-effective) maps.[10,11] In a previous study, iodine maps helped to distinguish between cardiac thrombus and slow flow in the LAA.[9] Large prospective studies are needed to confirm the additional value of implementing spectral cardiac CTA into the admission stroke imaging protocol. With the "Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke" (ENCLOSE) study, we investigated the yield of admission spectral non-gated cardiac CTA for identifying cardioembolic sources of stroke in a consecutive series of patients with acute ischemic stroke.

METHODS

Data availability

Source data will not be made available, since no patient approval was obtained for sharing anonymized data. However, detailed analytic methods and study materials will be available to other researchers upon reasonable request.

Study design

Patients were selected from the ENCLOSE study (ClinicalTrials.gov Identifier: NCT04019483), a prospective observational cohort study in the University Medical Center (UMC) Utrecht and Amsterdam UMC, the Netherlands. The rationale and design of ENCLOSE have been described before.[12] In short, consecutive patients with TIA or AIS who underwent non-contrast CT (NCCT), CT perfusion (CTP) and CTA were included between June 2017 and March 2022. This study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.[13]

Patient selection

All patients with suspected TIA or AIS undergo non-gated head-to-heart CTA as part of standard care at the UMC Utrecht. Inclusion criteria for ENCLOSE were age ≥18 years; clinical diagnosis of TIA or AIS and admission CT within nine hours from symptom onset or last seen well. Patients without an assessable cardiac CTA were excluded.

Ethics Approval and Data Availability

The ENCLOSE study was approved by the medical ethics committee of the UMC Utrecht. Written informed consent was obtained from the patient or the legal representative.

Data collection

Demographics, medical history, stroke characteristics and use of antiplatelet, direct oral anticoagulant (DOAC) or vitamin K antagonist (VKA dichotomized into <2 and ≥2 international normalized ratio (INR)) were registered. Stroke etiology was determined by the treating neurologist with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[14] Evaluation of cardioembolic sources such as echocardiography was performed in case of cryptogenic stroke or suspected cardioembolic source.

Imaging acquisition

In the acute stage all patients underwent NCCT, CTP and non-gated head-to-heart CTA (Brilliance iCT-256, IQon Spectral CT or Spectral CT 7500, Philips Healthcare, Best, the Netherlands) without increasing the iodine contrast agent dose used for standard stroke head-to-arch CTA. The CT parameters have been described before.[12] For Spectral CT, extra 1 mm spectral CTA maps (monoenergetic 40 keV maps, iodine maps and Z-effective) were reconstructed.

Imaging analysis

The quality of the cardiac CTA was graded with a 5-point Likert scale: very poor (non-diagnostic) – poor – moderate – good – excellent; based on the level of noise, motion artifacts and cardiac blood pool attenuation.[15] Possible findings related to cardioembolic sources of stroke were evaluated on the non-gated cardiac CTA including left atrial abnormalities (thrombus, patent foramen ovale, atrial septal defect, atrial septal aneurysm, LAA morphology), ventricle abnormalities (thrombus, ventricular septal defect, myocardial ischemia, cardiomyopathy, left ventricular aneurysm, cardiac tumor), aortic or mitral valve abnormalities (non-calcified thickening, calcifications, prosthetic valve, endocarditis), coronary artery calcifications and abnormalities of the ascending aorta and aortic arch (dissection and plaque characteristics). Thrombus was distinguished from slow flow and was defined as a homogeneous, hypodense filling defect with a clear border and low CT value (<100 HU) on standard CTA.[16] The presence of cardiac thrombus was based on a 5-point Likert scale and dichotomized into certainly absent or probably absent versus possibly, probably or certainly present. LAA morphologies were categorized as chicken wing, windsock, cauliflower or cactus.[17] Myocardial ischemia was assessed on cardiac CTA with the 5-point Likert scale and was defined as subendocardial curvilinear low attenuation. Coronary calcifications were graded on a 4-point scale: absent, mild (minimal calcification), moderate (moderate calcification, up to two vessels) and severe (severe calcification in one vessel or moderate in all three vessels). Ascending aorta and aortic arch plaques were characterized by evaluating low attenuation plaque (<30 HU) as an indicator of a lipid rich core, irregular surface and ulceration (>2mm).

Early ischemic changes on brain NCCT and perfusion defects on CTP were graded with the Alberta Stroke Program Early CT Score (ASPECTS).[18] Early ischemic changes in the posterior circulation were graded with the posterior circulation ASPECTS (pc-ASPECTS).[19] ASPECTS and pc-ASPECTS range from 0 to 10 and one or two points were subtracted for every ASPECTS or pc-ASPECTS area involved. Presence of old infarcts was also assessed on NCCT. Anterior circulation occlusions were graded with the

clot burden score and posterior circulation occlusions with the Basilar Artery on Computed Tomography Angiography (BATMAN) score.[20,21] Both scores range from 0 to 10 and one or two points were subtracted for every occluded vessel segment.

The three spectral CT reconstructions (mono-energetic 40 keV map, iodine map and Z-effective map) were assessed after the standard CTA image assessment for change in diagnostic certainty for presence of LAA or LV thrombus.

Cardiac imaging assessments were done by a senior radiology resident with 10 years of cardiac imaging experience (RT) and a radiologist specialized in cardiovascular and neurovascular imaging with 20 years of experience (BV). The first 24 patients were assessed by both observers to align evaluation methods. The brain imaging assessments were done by a radiologist specialized in stroke imaging with 15 years of experience (JD). The observers were blinded for clinical data.

Outcome measures

The primary outcome was presence of cardiac thrombus on admission non-gated cardiac CTA.

The secondary outcome was the diagnostic certainty of cardiac thrombus evaluated on the spectral CT reconstructions.

The tertiary outcome was the likelihood of a cardioembolic source of the stroke determined by a panel of experts. A reference standard for the detection of a cardioembolic source of the stroke does not exist, in which case a panel diagnosis can serve as the reference standard.[22] The advantage of a panel diagnosis is that it closely reflects decision-making in clinical practice. A panel of experts, including two radiologists (JD and BV) and two cardiologists (MC and MG) with respectively 20 and 8 years of experience, were consulted. After patient discharge all available clinical and imaging data from patients with a cardiac thrombus were presented by a neutral member (FK) with the aim to reach a consensus diagnosis by discussion. The panel rated the likelihood of a cardioembolic source of the stroke with four categories: certainly absent, possibly present, probably present and certainly present. The panel also decided whether referral to the cardiologist was indicated. Staged unblinding, exposing the clinical and imaging data in two phases to the panel, was used to avoid incorporation bias. In each phase the panel needed to reach consensus on the diagnosis and referral. In phase 1, the clinical characteristics, the admission ECG and the admission NCCT, CTP and CTA without the cardio-aortic part were presented to the panel. In phase 2, directly following the decision in phase 1,

the additional admission non-gated cardiac CTA was presented. The difference in the determined likelihood of a cardioembolic source of the stroke between phase 1 and 2 served as the outcome.

Another outcome was AF, which was a history of AF (previously known paroxysmal, persistent or permanent AF) or newly detected AF with ECG, telemetry or Holter during admission or 90-day follow-up.

Other outcomes included echocardiography findings within 90 days after the index event, changes in oral anticoagulant medication, 90-day recurrence and functional outcome, which was determined with the modified Rankin Scale (mRS) 90 days after the stroke by a trained research nurse (Supplemental results).

Statistical analysis

Frequencies and means or medians were reported for baseline characteristics and findings on admission non-gated cardiac CTA (descriptive analysis). Complete case analysis was performed, because few missing values were expected.

Parametric and nonparametric tests were used to compare the groups with and without the primary outcome. The secondary and tertiary outcomes were analyzed with the Chi-squared test. A p-value lower than 0.05 was considered statistically significant. The analyses were performed with R: A language and environment for statistical Computing version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Descriptive analysis

Of the 389 patients who participated in ENCLOSE, 370 (68 with TIA; 302 with AIS) were included with an assessable cardiac CTA (Figure 1). The LV was not fully displayed in 17 patients. Mean age was 67±14 years and 61% were male (Table 1).

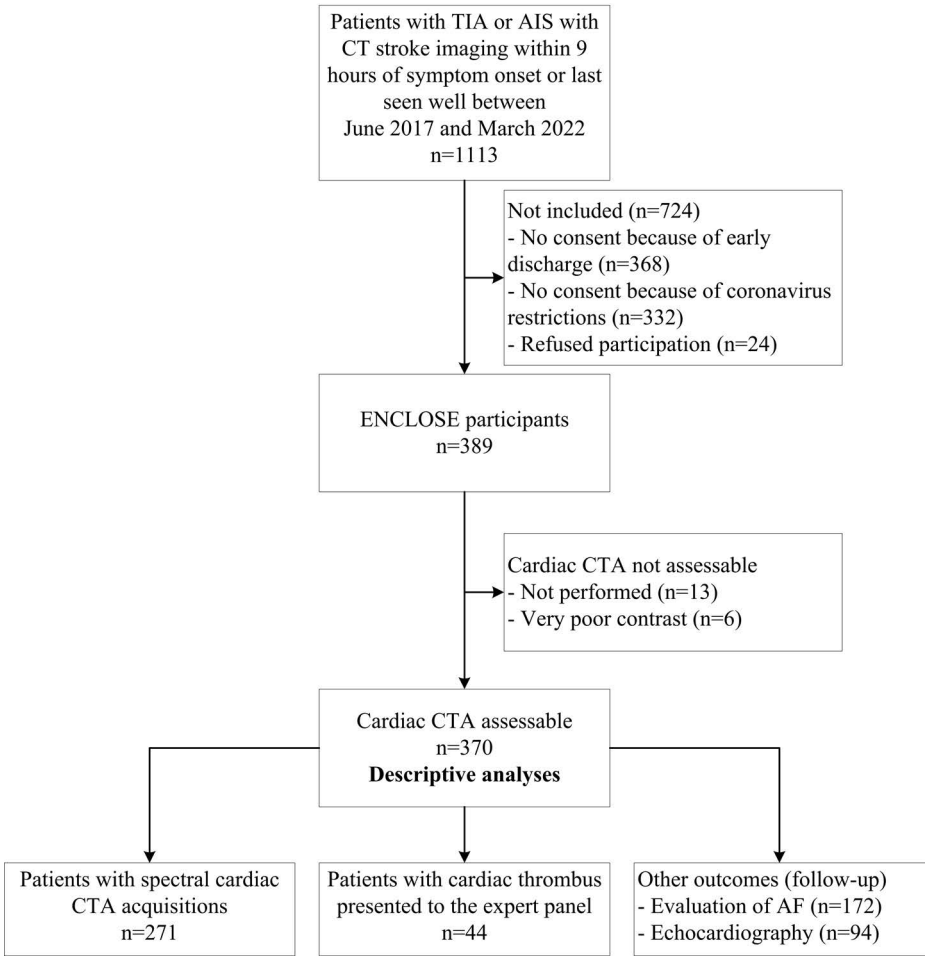

Figure 1: Flowchart of patient selection

Legend: TIA indicates transient ischemic attack; AIS, acute ischemic stroke; CTA, computed tomography angiography; AF, atrial fibrillation.

Table 1. Patient characteristics stratified by cardiac thrombus on admission non-gated cardiac CTA

Characteristic, n (%)	**Total** n=353	**Thrombus*** n=44 (12)	**No thrombus** n=309 (88)	**P value**
Age, mean±SD	67±14	71±14	67±14	0.046
Male sex	214 (61)	28 (64)	186 (60)	0.662
Admission NIHSS, median (Q1-Q3)	4 (1-12)	10 (3-17)	4 (1-10)	0.006
Intravenous thrombolysis	127 (36)	16 (36)	111 (36)	0.954
Endovascular treatment	80 (23)	19 (43)	61 (20)	<0.001
TOAST classification				<0.001
- Large vessel disease	73 (21)	6 (14)	67 (22)	
- Cardioembolism	84 (24)	27 (61)	57 (18)	
- Small vessel disease	54 (15)	3 (7)	51 (17)	
- Other	47 (13)	2 (5)	45 (15)	
- Undetermined	95 (27)	6 (14)	89 (29)	
Medical history				
Ischemic stroke	46 (13)	9 (20)	37 (12)	0.118
Transient ischemic attack	51 (14)	3 (7)	48 (16)	0.124
Myocardial infarction	44 (12)	11 (25)	33 (11)	0.007
Angina pectoris	10 (3)	1 (2)	9 (3)	0.811
Atrial fibrillation	58 (16)	19 (43)	39 (13)	<0.001
Coronary intervention	17 (5)	2 (5)	15 (5)	0.929
Coronary surgery	22 (6)	3 (7)	19 (6)	0.864
Peripheral artery disease	12 (3)	2 (5)	10 (3)	0.654
Malignancy	69 (20)	6 (14)	63 (20)	0.291
Hypertension	181 (51)	22 (50)	159 (51)	0.857
Hyperlipidemia	112 (32)	15 (34)	97 (31)	0.719
Diabetes mellitus type 2	52 (15)	6 (14)	46 (15)	0.827
Smoking				0.294
- Current smoking	75 (24)	9 (24)	66 (24)	
- Previous smoking	106 (34)	9 (24)	97 (35)	
- Never smoked	132 (42)	20 (53)	112 (41)	

Table 1. Patient characteristics stratified by cardiac thrombus on admission non-gated cardiac CTA (continued)

Characteristic, n (%)	**Total** n=353	**Thrombus*** n=44 (12)	**No thrombus** n=309 (88)	**P value**
Drug use				
Antiplatelet	108 (31)	14 (32)	94 (30)	0.851
VKA	29 (8)	12 (27)	17 (6)	<0.001
- International normalized ratio ≥2	18 (64)	7 (58)	11 (69)	0.569
DOAC	36 (10)	4 (9)	32 (10)	0.795
Antihypertensive medication	181 (51)	26 (59)	155 (50)	0.268
Lipid lowering medication	126 (36)	18 (41)	108 (35)	0.440
Antidiabetic medication	48 (14)	5 (11)	43 (14)	0.644
Brain CT findings				
NCCT ASPECTS, median (Q1-Q3)	10 (10-10)	10 (9-10)	10 (10-10)	0.136
NCCT pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.799
NCCT old infarcts	143 (41)	18 (41)	125 (40)	0.954
CTP ASPECTS	10 (6-10)	7 (4-10)	10 (6-10)	0.004
CTP pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.682
Clot burden score	10 (9-10)	9 (7-10)	10 (9-10)	0.004
Batman score	10 (10-10)	10 (10-10)	10 (10-10)	0.541

* Presence of thrombus was defined by possible to certain presence as rated by the observer. CTA indicates computed tomography angiography; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; TOAST, Trial of Org 10172 in Acute Stroke Treatment; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; CT, computed tomography; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; pc, posterior circulation; CTP, CT perfusion.

The quality of the admission non-gated cardiac CTA was poor in 34 (9%), moderate in 74 (20%), good in 161 (44%) and excellent in 101 (27%) patients (Supplemental table I). Poor and moderate quality of the CTA was mainly due to limited cardiac blood pool attenuation. In 44 (12%) patients, a possible, probable or certain cardiac thrombus was detected: 35 (9%) had a thrombus in the LAA (none in the LA) and 14 (4%) in the LV, of which 5 (1%) in both. One additional patient had a thrombus in a LV assist device (not counted as a primary outcome). Cardiac thrombus was found in 7 (10%) of the 68 TIA patients; this proportion did not differ from the AIS group (13%, P=0.647). Possible, probable or certain myocardial ischemia was present in 97 (27%) patients. Other relevant findings (Supplemental table I) included moderate

to severe coronary calcification (n=189, 51%), aortic dissection (n=7, 2%), ascending aorta plaque (n=61, 17%) and aortic arch plaque (n=157, 43%). In respectively the ascending aorta and aortic arch plaques, 5% versus 6% had a low attenuation plaque, 10% versus 41% an irregular surface and 2% versus 9% an ulceration.

Cardiac thrombus

Patients with a cardiac thrombus on CTA were older (mean 71 versus 64, P=0.046), had higher NIHSS (median 10 versus 4, P=0.006), lower CTP ASPECTS (median 7 versus 10, P=0.004), lower clot burden score (median 9 versus 10, P=0.004) and underwent endovascular treatment more often (43% versus 20%, P<0.001) compared to patients without a cardiac thrombus (Table 1). Patients with cardiac thrombus more often had a medical history of myocardial infarction (25% versus 11%, P=0.007), AF (43% versus 13%, P<0.001) and VKA use (27% versus 6%, P<0.001) compared to patients without a cardiac thrombus. The results were comparable for the 35 patients with LAA thrombus (Supplemental table II). Seventeen (49%) of these 35 patients had a history of AF and 13 (37%) used oral anticoagulation: 9 a VKA and 4 a DOAC (Supplemental table III). Six (17%) of the 35 patients with LAA thrombus had a TIA at baseline, 3 with a history of AF (2 with VKA and 1 with DOAC use) and 1 with AF during follow-up. Of the 309 patients without a history of AF, 18 (6%) had LAA thrombus (Supplemental table III). In addition, of the 301 patients who did not use oral anticoagulation 22 (7%) had LAA thrombus, whereas 13 (19%) of the 69 patients with anticoagulation use had LAA thrombus. LAA morphology differed between patients with and without AF (Supplemental table IV). Patients with LV thrombus more often had a LV aneurysm (29% versus 2%, P<0.001), previous myocardial ischemia (77% versus 26%, P<0.001) and dilated cardiomyopathy (43% versus 5%, P<0.001) compared to patients without a LV thrombus (Supplemental table V).

Spectral CT

Spectral cardiac CTA acquisitions were acquired in 271 (73%) patients (Supplemental table VI). The observers mostly found no difference in usefulness of the three spectral reconstructions, but they found iodine maps more useful in patients with cardiac thrombus than in patients without cardiac thrombus (50% versus 17% respectively, P<0.001). In addition, the diagnostic certainty for LAA thrombus was higher for iodine maps (Supplemental table VII) compared to the conventional CTA (P<0.001). Example cases are shown in Figure 2 and Figure 3.

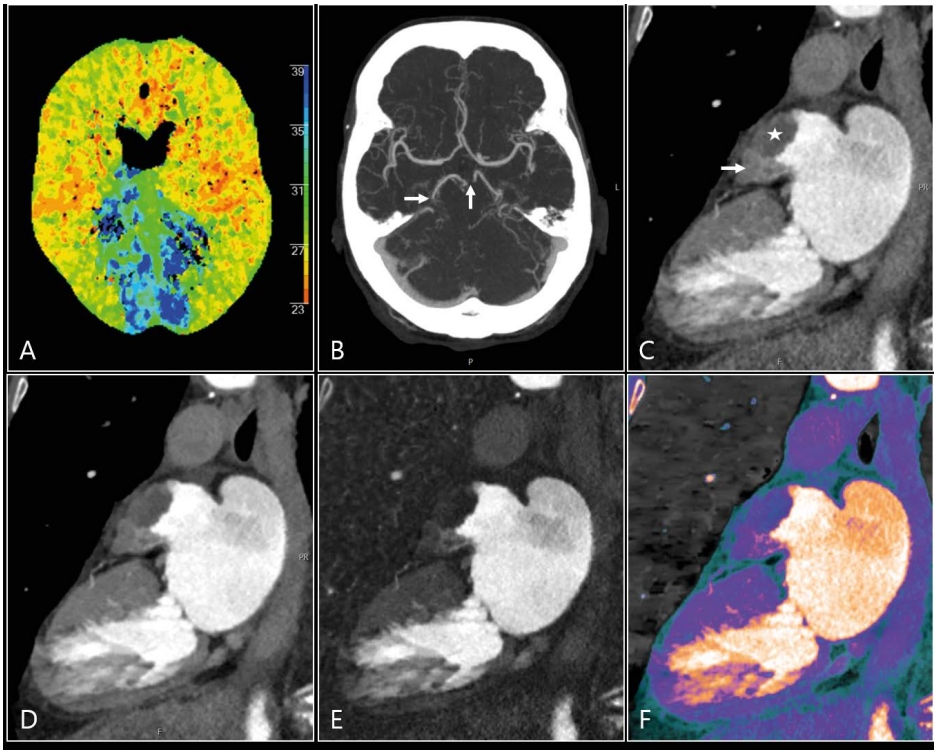

Figure 2. A 71-year-old male patient with loss of consciousness (E1M2V1; NIHSS 36), previous myocardial infarction without anticoagulant or antiplatelet medication and atrial fibrillation de novo. CTP showed bioccipital and right thalamic perfusion defects (A). CTA showed left P1 and right P2 segment occlusions of the posterior cerebral arteries (arrows in B) and thrombus (star) combined with slow flow phenomenon (arrow) in the LAA on sagittal reconstruction (C). The thrombus is homogeneous (attenuation 51±14 HU) versus inhomogeneous slow flow (attenuation 131±23 HU). Spectral CT reconstructions include mono-energetic 40 keV (D), iodine map (E) and Z-effective (F). The iodine concentration (E) is 0.25±0.6 mg/ml in the thrombus versus 2.56±1 mg/ml in the slow flow.

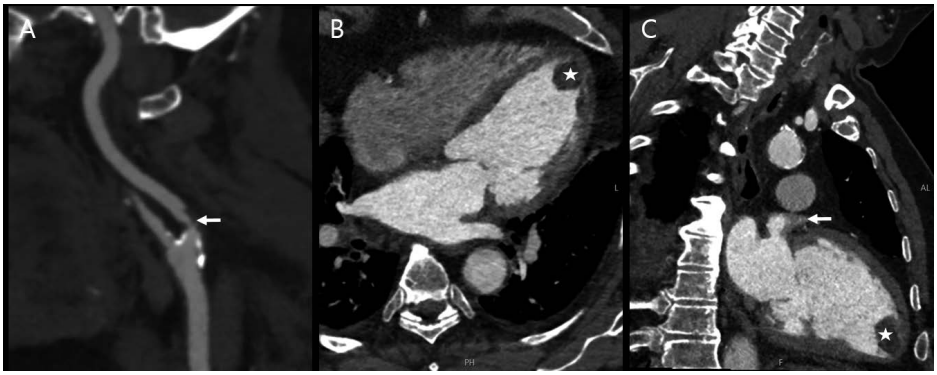

Figure 3. A 87-year-old male patient with sudden onset of aphasia and right-sided hemiparesis (NIHSS 13), a medical history of acetylsalicylic acid for cardiovascular risk management and previous myocardial ischemia on his electrocardiogram. The CTA excluded arterial occlusions and showed a >70% stenosis of the left internal carotid artery (arrow in A) and thrombus in the left ventricular apex (star on four chamber (B) and two chamber view (C)). There was slow flow visible in the left atrial appendage (arrow in C) with an inhomogeneous aspect, an attenuation of 174 ± 56 HU and an iodine concentration of 6.58 ± 1.4 mg/ml; that was not suspect for thrombus. No atrial fibrillation was detected in the week between the stroke and his death.

Panel diagnosis

All patients (n=44) with possible to certain presence of cardiac thrombus on CTA were presented to the expert panel. The likelihood of a cardioembolic source of the stroke significantly increased after the cardiac CTA was presented to the panel (Table 2, P<0.001).

Table 2. Results from the expert panel meetings concerning patients with possible to certain presence of cardiac thrombus on non-gated cardiac CT angiography

Panel diagnosis, n (%)	**Phase 1** n=44	**Phase 2** n=44	**P value**
Likelihood of cardio embolic cause			<0.001
- Certainly not	0 (0)	0 (0)	
- Possibly yes	20 (45)	6 (14)	
- Probably yes	24 (55)	8 (18)	
- Certainly yes	0 (0)	30 (68)	
Referral to cardiology	44 (100)	44 (100)	-

CT indicates computed tomography.

DISCUSSION

Main findings of this prospective study included detection of cardiac thrombi with admission non-gated head-to-heart CTA in 12% of the patients with TIA or AIS. A medical history of myocardial infarction, AF or VKA use were associated with presence of cardiac thrombus on CTA. Spectral iodine maps improved the diagnostic certainty of LAA thrombus. Presence of any cardiac thrombus was associated with higher stroke severity and a higher clot burden resulting in a higher rate of endovascular treatment and a higher 90-day mRS. According to an expert panel, the additional information provided by the admission non-gated cardiac CTA helped significantly to diagnose cardioembolic stroke.

Clinical perspective

Early detection of a cardioembolic source of stroke can help to initiate proper prophylactic treatment. In our study, 6% of the patients without AF and 7% of the patients without oral anticoagulation had LAA thrombus and most patients either started or continued with a DOAC or a VKA after a thrombus was detected. About one third of the patients with LAA thrombus and a history of AF did not use oral anticoagulation. Almost one fifth of the patients with oral anticoagulation use had LAA thrombus. The use of VKA was associated with presence of LAA thrombus, which could not be fully explained by low INR values (<2). Conversely, DOAC use was not associated with LAA thrombus, which is compatible with previous studies that showed that DOAC use is more effective for preventing stroke or systemic embolism than VKA use in patients with AF.[23] Taken together, our results may impact both patients with and without known AF or oral anticoagulation use, but prevention strategies and prediction of recurrence need further evaluation.

Admission non-gated cardiac CTA also helps detect other cardiac abnormalities such as LV aneurysm, myocardial ischemia and cardiomyopathy which are also associated with LV thrombus formation. Plaque in the ascending aorta or aortic arch may be the cause of the stroke in patients with cryptogenic stroke.[24] A previous study demonstrated that the detection rate of aortic plaque is higher for CTA compared to TEE.[25] We found more plaque, with more low attenuation plaque (lipid-rich core), irregular surface or ulceration, in the aortic arch than in the ascending aorta. These plaque characteristics are associated with an increased risk of stroke.[26] These results show that admission non-gated cardiac CTA can also help to identify aortic embolic sources of AIS. Extending the CTA coverage may reveal abnormalities in the lung, such as aspiration/lobar pneumonia or pulmonary nodules, but this was beyond the scope of this study.[27]

Technical perspective

Current guidelines recommend TTE or TEE for the detection of cardiac thrombi, although the sensitivity is limited, TEE is semi-invasive, and both do not outperform CTA.[4,8] We investigated non-gated cardiac CTA, whereby the standard head-aortic arch stroke CTA was extended to cover the whole heart in <5 seconds extra scan time, without extra iodine contrast material and with an acceptable increase of the radiation dose of 2 millisievert. The yield of cardiac CTA was higher than echocardiography in our study and in a recent ECG-gated CTA study.[28] To minimize motion artifacts cardiac CTA is usually acquired with ECG-gating, but requires a separate scan costing extra iodine contrast agent, radiation dose and time in a situation where "time is brain" in AIS compared to non-gated CTA.[29] A disadvantage of non-gated CTA could be that metric measurements such as left atrial enlargement, which has been associated with stroke, are unreliable as compared to measurements on ECG-gated CTA.[30] We could not evaluate left atrial enlargement as the cardiac phase differed between scans. Whether the diagnostic value of non-gated cardiac CTA is equivalent to ECG-gated CTA in AIS is unknown. Technical improvements of CT scanners allow faster acquisition times, which should improve image quality and reduce motion artifacts without increasing the radiation dose in non-gated cardiac CTA.[29] Different scanner types including conventional scanners were used and therefore our results seem largely generalizable to other centers.

Detecting LAA thrombi, and differentiation from slow flow effects, has often been researched. The combination of a dual-phase early and late CT, dual-enhancement single-phase CT and spectral CT have shown that CT can accurately detect LAA thrombi without significantly increasing the radiation dose.[9,31,32] Our stroke CT protocol with a contrast bolus for CTP prior to CTA combines the dual-enhancement single-phase CTA concept that is routinely used to rule out LAA thrombus prior to pulmonary vein ablation in patients with AF, with additional information from the spectral energy reformats.[16] Our study showed that the iodine mapping was most useful for detecting LAA thrombi, which is in line with previous spectral CT studies where iodine concentration measurement helped to differentiate between thrombus and stasis of blood (slow flow).[9,33]

Limitations

The time window of 9 hours was chosen before the extended treatment window trials were published. Many patients could not be included because of logistic reasons such as coronavirus restrictions and early discharge home or to their referring hospital. Since logistic reasons were the main cause why patients could not be included, the risk of selection bias seems low.

The absence of a reference standard, knowing that TEE and TTE do not outperform CTA, implied that we could not analyze sensitivity or specificity. Only patients with a possible to certain cardiac thrombus were presented to the expert panel which could have influenced the decision making but also represents the expected clinical pathway for future stroke patients. The inclusion of patients without cardiac thrombus will probably not affect the results as the diagnostic certainty of a cardioembolic source of the stroke is not expected to change in case of a negative cardiac CTA. In addition, staged unblinding helped to avoid incorporation bias.

Conclusion

In conclusion, extending the stroke CTA to cover the heart enables detection of cardiac thrombi and helps to identify cardioembolic sources in acute stroke with more certainty. Spectral iodine maps provide additional diagnostic value for detecting LAA thrombus. Future studies should investigate the impact of admission cardiac CTA on prevention strategies and etiology of stroke recurrence.

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SUPPLEMENTS

Supplemental results

Follow-up
Echocardiography was performed in 94 (25%) patients within 90 days after the index event. With echocardiography, one LAA and three LV thrombi were found, which were also found with admission cardiac CTA. With cardiac CTA, respectively 11 and 6 additional LAA thrombi and LV thrombi were identified.

Of the 44 patients with cardiac thrombus, 4 (9%) used a DOAC, 12 (27%) used VKA, and 14 (32%) oral antiplatelet therapy on admission. Ten patients died during admission. Of the remaining 34 patients, 12 (35%) used a DOAC at discharge: 5 started, 3 switched from a VKA and 2 continued taking a DOAC. Ten patients (29%) used a VKA at discharge: 2 started and 8 continued; and 10 patients (29%) started with oral antiplatelet therapy at discharge. After discharge, 2 patients switched from oral antiplatelet therapy to a DOAC after atrial fibrillation was detected with Holter during outpatient follow-up; 1 patient switched from oral antiplatelet therapy to a VKA, because of a decreased ejection fraction and persistent left ventricular apex thrombus on MRI; 1 patient temporarily used oral antiplatelet therapy at discharge before switching to a VKA, because of comorbidities; and 1 patient switched from oral antiplatelet therapy to a DOAC after he had a recurrent ischemic stroke and suspicion of atrial fibrillation.

During 90 days of follow-up, 30 (12%) of the 256 patients with available follow-up data had a recurrent stroke and the median mRS was 2 (Q1-Q3 1-6). Patients with cardiac thrombus had a significantly higher mRS than patients without cardiac thrombus (median 2 versus 2; mRS>2: 47% versus 37%, respectively, P=0.035). The recurrence rate was not significantly different between patients with and without cardiac thrombus (13% versus 11%, P=0.747).

Supplemental table I. Other findings on admission non-gated cardiac CTA

Finding, n (%)	n=370
Quality of cardiac CTA, Likert scale	
Poor	34 (9)
Moderate	74 (20)
Good	161 (44)
Excellent	101 (27)
Valves	
Aortic valve	
- Non-calcified thickening > 2 mm	8 (2)
- Annular or valve leaflets calcifications*	64 (17)
- Prosthesis	13 (3)
Mitral valve	
- Non-calcified thickening > 2 mm	20 (5)
- Annular or valve leaflets calcifications*	31 (8)
- Prosthesis	4 (1)
Endocarditis	0 (0)
Ascending aorta and aortic arch	
Aortic dissection	7 (2)
Plaque ascending aorta	61 (17)
Calcification ascending aorta*	31 (8)
Plaque ascending aorta	61 (17)
- Low attenuation plaque	3 (5)
- Irregular surface	6 (10)
- Ulceration	1 (2)
Plaque aortic arch	157 (43)
Calcification aortic arch*	129 (35)
Plaque aortic arch	157 (43)
- Low attenuation plaque	10 (6)
- Irregular surface	63 (41)
- Ulceration	14 (9)

* Presence of calcifications was defined as moderate to severe calcifications as rated by the observer.
CTA indicates computed tomography angiography; mm, millimeter.

Supplemental table II. Patient characteristics stratified by left atrial appendage thrombus on admission non-gated cardiac CTA

Characteristic, n (%)	**Total** n=370	**LAA thrombus*** n=35 (9)	**No LAA thrombus** n=335 (91)	**P value**
Age, mean±SD	67±14	72±15	67±14	0.067
Male sex	224 (61)	21 (60)	203 (61)	0.945
Admission NIHSS, median (Q1-Q3)	4 (1-12)	12 (2-18)	4 (1-11)	0.022
Intravenous thrombolysis	133 (36)	12 (34)	121 (36)	0.830
Endovascular treatment	86 (23)	15 (43)	71 (21)	0.004
TOAST classification				<0.001
- Large vessel disease	75 (20)	5 (14)	70 (21)	
- Cardioembolism	91 (25)	21 (60)	70 (21)	
- Small vessel disease	56 (15)	2 (6)	54 (16)	
- Dissection	27 (7)	0 (0)	27 (8)	
- Other	22 (6)	2 (6)	20 (6)	
- Undetermined	99 (27)	5 (14)	94 (28)	
Medical history				
Ischemic stroke	48 (13)	8 (23)	40 (12)	0.067
Transient ischemic attack	53 (14)	3 (9)	50 (15)	0.307
Myocardial infarction	45 (12)	8 (23)	37 (11)	0.042
Angina pectoris	10 (3)	1 (3)	9 (3)	0.953
Atrial fibrillation	61 (17)	17 (49)	44 (13)	<0.001
Coronary intervention	18 (5)	2 (6)	16 (5)	0.806
Coronary surgery	24 (7)	3 (9)	21 (6)	0.599
Peripheral artery disease	12 (3)	2 (6)	10 (3)	0.386
Malignancy	71 (19)	6 (17)	65 (19)	0.747
Hypertension	190 (51)	17 (49)	173 (53)	0.729
Hyperlipidemia	117 (32)	10 (29)	107 (32)	0.683
Diabetes mellitus type 2	54 (15)	5 (14)	49 (15)	0.957
Smoking				0.156
- Current smoking	77 (23)	7 (21)	70 (24)	
- Previous smoking	111 (34)	7 (21)	104 (35)	
- Never smoked	140 (43)	19 (58)	121 (41)	

Supplemental table II. Patient characteristics stratified by left atrial appendage thrombus on admission non-gated cardiac CTA (continued)

Characteristic, n (%)	Total n=370	LAA thrombus* n=35 (9)	No LAA thrombus n=335 (91)	P value
Drug use				
Antiplatelet	114 (31)	8 (23)	106 (32)	0.284
VKA	29 (8)	9 (26)	21 (6)	<0.001
- International normalized ratio ≥2	19 (66)	5 (56)	14 (70)	0.449
DOAC	39 (11)	4 (11)	35 (10)	0.857
Antihypertensive medication	191 (52)	19 (54)	172 (51)	0.740
Lipid lowering medication	131 (35)	13 (37)	118 (35)	0.821
Antidiabetic medication	49 (13)	5 (14)	44 (13)	0.848
Brain CT findings				
NCCT ASPECTS, median (Q1-Q3)	10 (10-10)	10 (9-10)	10 (10-10)	0.163
NCCT pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.513
NCCT old infarcts	148 (40)	13 (37)	135 (40)	0.717
CTP ASPECTS	10 (6-10)	7 (3-10)	10 (6-10)	0.005
CTP pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.390
Clot burden score	10 (9-10)	9 (7-10)	10 (9-10)	0.003
Batman score	10 (10-10)	10 (10-10)	10 (10-10)	0.325
Atrial findings on cardiac CTA				
ASD or PFO*	64 (17)	8 (23)	56 (17)	0.365
Atrial septal aneurysm	3 (1)	0 (0)	3 (1)	0.573
Left atrial appendage morphology				0.301
- Chicken wing	117 (32)	16 (46)	101 (30)	
- Windsock	199 (54)	15 (43)	184 (55)	
- Cauliflower	36 (10)	3 (9)	33 (10)	
- Cactus	18 (5)	1 (3)	17 (5)	
Ventricular findings on cardiac CTA				
Left ventricular thrombus	15 (4)	5 (15)	10 (30)	<0.001
Myocardial ischemia*	97 (27)	13 (38)	84 (26)	0.136
Coronary calcification#	189 (52)	19 (56)	170 (52)	0.652

Supplemental table II. Patient characteristics stratified by left atrial appendage thrombus on admission non-gated cardiac CTA (continued)

Characteristic, n (%)	Total n=370	LAA thrombus* n=35 (9)	No LAA thrombus n=335 (91)	P value
Follow-up 90 days				
Recurrence	30 (12)	2 (8)	28 (12)	0.588
mRS, median (Q1-Q3)	2 (1-6)	3 (1-6)	2 (1-5)	0.105

* Presence of thrombus, ASD or PFO, or myocardial ischemia was defined as possible to certain presence as rated by the observer.
CTA indicates computed tomography angiography; LAA, left atrial appendage; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; TOAST, Trial of Org 10172 in Acute Stroke Treatment; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; CT, computed tomography; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; pc, posterior circulation; CTP, CT perfusion; ASD, atrial septal defect; PFO, patent foramen ovale; mRS, modified Rankin Scale.

Supplemental table III. Frequency of left atrial appendage thrombus by presence of atrial fibrillation and oral anticoagulant therapy

Characteristic, n (%)	Total n=370	LAA thrombus* n=35	No LAA thrombus n=335	P value
AF				<0.001
- No history, no follow-up	198 (54)	6 (17)	192 (57)	
- No history, undetected (with follow-up)	82 (22)	5 (14)	77 (23)	
- History	61 (16)	17 (49)	44 (13)	
- Newly detected (with follow-up)	29 (8)	7 (20)	22 (7)	
Baseline oral anticoagulant therapy				
All				<0.001
- None	301 (81)	22 (63)	279 (83)	
- DOAC	39 (11)	4 (11)	35 (10)	
- VKA	30 (8)	9 (26)	21 (6)	
Without history of AF and no follow-up				0.322
- Total	198	6	192	
- None	182 (92)	5 (83)	177 (92)	
- DOAC	9 (5)	1 (17)	8 (4)	

Supplemental table III. Frequency of left atrial appendage thrombus by presence of atrial fibrillation and oral anticoagulant therapy (continued)

Characteristic, n (%)	**Total** n=370	**LAA thrombus*** n=35	**No LAA thrombus** n=335	**P value**
- VKA	7 (4)	0 (0)	7 (4)	
Without history and undetected AF				0.506
- Total	82	5	77	
- None	74 (90)	4 (80)	70 (91)	
- DOAC	2 (2)	0 (0)	2 (3)	
- VKA	6 (7)	1 (20)	5 (7)	
With history of AF				0.060
- Total	61	17	44	
- None	21 (34)	6 (35)	15 (34)	
- DOAC	23 (38)	3 (18)	20 (46)	
- VKA	17 (28)	8 (47)	9 (21)	
With newly detected AF				0.167
- Total	29	7	22	
- None	24 (83)	7 (100)	17 (77)	
- DOAC	5 (17)	0 (0)	5 (23)	
- VKA	0 (0)	0 (0)	0 (0)	

* Presence of thrombus was defined as possible to certain presence as rated by the observer.
AF indicates atrial fibrillation; LAA, left atrial appendage; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Supplemental table IV. Atrial findings on non-gated cardiac CTA stratified by history of atrial fibrillation or newly detected atrial fibrillation

Atrial finding, n (%)	**Total** n=172	**AF** n=90	**No AF** n=82	**P value**
LAA thrombus*	29 (17)	24 (27)	5 (6)	<0.001
ASD or PFO*	39 (23)	15 (17)	24 (29)	0.053
Atrial septal aneurysm	1 (1)	0 (0)	1 (1)	0.293
Left atrial appendage morphology				0.007
- Chicken wing	58 (34)	40 (44)	18 (22)	
- Windsock	93 (55)	39 (43)	56 (68)	
- Cauliflower	15 (9)	8 (9)	7 (9)	
- Cactus	4 (2)	3 (3)	1 (1)	

* Presence of thrombus, ASD or PFO was defined as possible to certain presence as rated by the observer.
CTA indicates computed tomography angiography; AF, atrial fibrillation; LAA, left atrial appendage; ASD, atrial septal defect; PFO, patent foramen ovale.

Supplemental table V. Patient characteristics stratified by left ventricular thrombus on admission non-gated cardiac CTA

Characteristic, n (%)	**Total** n=351	**LV thrombus*** n=14 (4)	**No LV thrombus** n=337 (43)	**P value**
Age, mean±SD	67±14	65±13	67±14	0.527
Male sex	213 (61)	10 (71)	203 (60)	0.401
Admission NIHSS, median (Q1-Q3)	4 (1-12)	13 (6-15)	4 (1-11)	0.025
Intravenous thrombolysis	127 (36)	6 (43)	121 (36)	0.596
Endovascular treatment	79 (23)	7 (50)	72 (21)	0.012
TOAST classification				0.057
- Large vessel disease	73 (21)	3 (21)	70 (21)	
- Cardioembolism	83 (24)	8 (57)	75 (22)	
- Small vessel disease	54 (15)	1 (7)	53 (16)	
- Dissection	25 (7)	0 (0)	25 (7)	
- Other	22 (6)	1 (7)	21 (6)	
- Undetermined	94 (27)	1 (7)	93 (28)	

Supplemental table V. Patient characteristics stratified by left ventricular thrombus on admission non-gated cardiac CTA (continued)

Characteristic, n (%)	Total n=351	LV thrombus* n=14 (4)	No LV thrombus n=337 (43)	P value
Medical history				
Ischemic stroke	46 (13)	1 (7)	45 (13)	0.500
Transient ischemic attack	51 (15)	1 (7)	50 (15)	0.423
Myocardial infarction	44 (13)	4 (29)	40 (12)	0.064
Angina pectoris	10 (3)	1 (7)	9 (3)	0.324
Atrial fibrillation	56 (16)	2 (14)	54 (16)	0.862
Coronary intervention	17 (5)	1 (7)	16 (5)	0.683
Coronary surgery	22 (6)	0 (0)	22 (7)	0.323
Peripheral artery disease	12 (3)	1 (7)	11 (3)	0.434
Malignancy	69 (20)	1 (7)	68 (20)	0.229
Hypertension	181 (52)	6 (43)	175 (52)	0.506
Hyperlipidemia	111 (32)	6 (43)	105 (31)	0.356
Diabetes mellitus type 2	52 (15)	1 (7)	51 (15)	0.410
Smoking				0.331
- Current smoking	74 (24)	4 (44)	70 (23)	
- Previous smoking	106 (34)	2 (22)	104 (34)	
- Never smoked	131 (42)	3 (33)	128 (42)	
Drug use				
Antiplatelet	108 (31)	8 (57)	100 (30)	0.029
VKA	28 (8)	3 (21)	26 (8)	0.068
- International normalized ratio ≥2	18 (64)	2 (67)	16 (64)	0.927
DOAC	35 (10)	0 (0)	35 (10)	0.204
Antihypertensive medication	181 (52)	9 (64)	172 (51)	0.331
Lipid lowering medication	125 (36)	6 (43)	119 (35)	0.563
Antidiabetic medication	48 (14)	1 (7)	47 (14)	0.468
Brain CT findings				
NCCT ASPECTS, median (Q1-Q3)	10 (10-10)	10 (8-10)	10 (10-10)	0.024
NCCT pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.747

Supplemental table V. Patient characteristics stratified by left ventricular thrombus on admission non-gated cardiac CTA (continued)

Characteristic, n (%)	**Total** n=351	**LV thrombus*** n=14 (4)	**No LV thrombus** n=337 (43)	**P value**
NCCT old infarcts	142 (40)	7 (50)	135 (40)	0.458
CTP ASPECTS	10 (6-10)	7 (5-10)	10 (6-10)	0.058
CTP pc-ASPECTS	10 (10-10)	10 (10-10)	10 (10-10)	0.879
Clot burden score	10 (9-10)	9 (6-10)	10 (9-10)	0.075
Batman score	10 (10-10)	10 (10-10)	10 (10-10)	0.029
Ventricular findings on cardiac CTA				
Ventricular septal defect	2 (1)	0 (0)	2 (1)	0.772
Left ventricular aneurysm	10 (3)	4 (29)	6 (2)	<0.001
Cardiac tumor	0 (0)	0 (0)	0 (0)	-
Myocardial ischemia*	95 (27)	10 (77)	85 (26)	<0.001
Cardiomyopathy				<0.001
- Dilated	23 (7)	6 (43)	17 (5)	
- Non-compaction	7 (2)	1 (7)	6 (2)	
- Hypertrophy	12 (3)	1 (7)	11 (3)	
Coronary calcification†	181 (52)	9 (64)	172 (51)	0.348
Follow-up 90 days				
Recurrence	28 (12)	2 (22)	26 (11)	0.309
mRS, median (Q1-Q3)	2 (1-6)	2 (2-5)	2 (1-6)	0.184

* Presence of thrombus or myocardial ischemia was defined as possible to certain presence as rated by the observer.
† Presence of coronary calcification was defined as moderate to severe calcification as rated by the observer.
CTA indicates computed tomography angiography; LV, left ventricular; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; TOAST, Trial of Org 10172 in Acute Stroke Treatment; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; CT, computed tomography; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; pc, posterior circulation; CTP, CT perfusion; mRS, modified Rankin Scale.

Supplemental table VI. Most useful spectral CT reconstructions of non-gated cardiac CTA for thrombus detection

Finding, n (%)	**Total** n=258	**Thrombus*** n=34	**No thrombus** n=224	**P value**
Most useful spectral CT reconstruction				<0.001
No difference	184 (71)	16 (47)	168 (75)	
40 keV	18 (7)	1 (3)	17 (8)	
Iodine maps	55 (21)	17 (50)	38 (17)	
Z-effective	1 (0)	0 (0)	1 (0)	

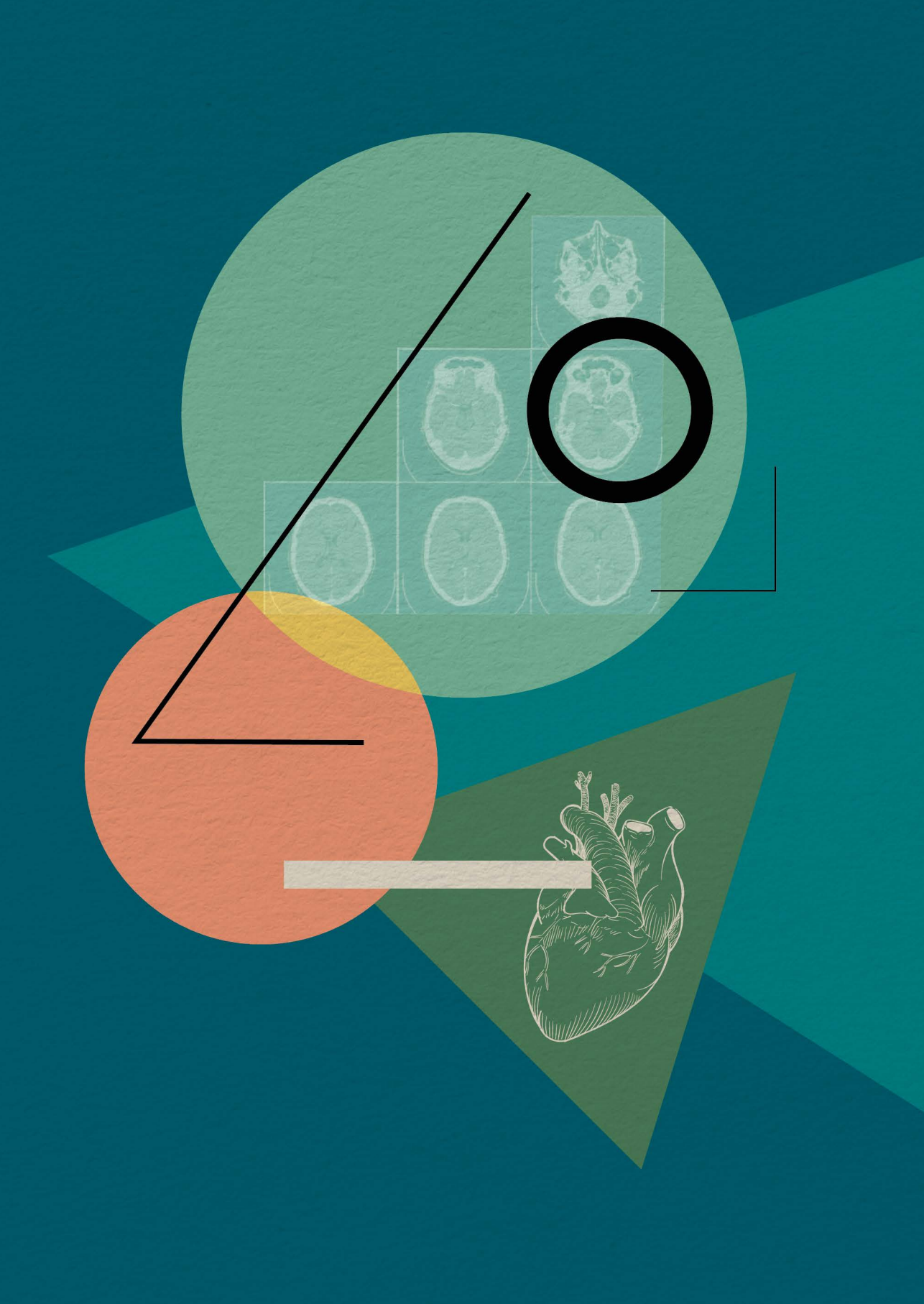
* Presence of thrombus was defined as possible to certain presence as rated by the observer. CT indicates computed tomography; CTA, computed tomography angiography; keV, kiloelectron volt.

Supplemental table VII. Diagnostic certainty for left atrial appendage thrombus of conventional CTA and iodine maps

	Conventional CTA					
Certainty, n (%)	Certainly not	Probably not	Possibly yes	Probably yes	Certainly yes	Total*
Iodine maps						
Certainly not	151	63	2	0	0	216
Probably not	5	23	3	0	0	31
Possibly yes	0	0	4	0	0	4
Probably yes	0	0	7	3	0	10
Certainly yes	0	0	3	3	4	10
Total*	156	86	19	6	4	271

* P<0.001

CTA indicates computed tomography angiography.



8

EFFECT OF INTRAVENOUS THROMBOLYSIS IN STROKE DEPENDS ON PATTERN OF INTRACRANIAL INTERNAL CAROTID ARTERY CALCIFICATION

Based on:
Kauw F, de Jong PA, Takx RAP, de Jong HWAM, Kappelle LJ, Velthuis BK, Dankbaar JW; Dutch Acute Stroke Study (DUST) investigators. Effect of intravenous thrombolysis in stroke depends on pattern of intracranial internal carotid artery calcification. Atherosclerosis. 2021 Jan;316:8-14.

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ABSTRACT

Background and aims

The pattern of intracranial internal carotid artery calcification (ICAC) has been identified as an effect modifier of endovascular treatment in patients with acute ischemic stroke, but it is unclear whether it modifies the effect of intravenous thrombolysis. The purpose of this study was to evaluate the association between intravenous thrombolysis and 90-day clinical outcome, follow-up infarct volume, intracranial hemorrhage and recanalization across different patterns of ICAC.

Methods

Patients with acute ischemic stroke were selected from the Dutch Acute Stroke Study, a prospective multicenter observational cohort study. ICAC pattern was determined on admission thin-slice non-contrast CT and categorized as absent, intimal, medial or indistinguishable. The primary outcome was the ordinal 90-day modified Rankin Scale. Other outcomes included follow-up infarct volume, intracranial hemorrhage, recanalization and collateral status. Associations were quantified with regression analyses and stratified by ICAC pattern.

Results

Of 982 patients, 609 (62%) received intravenous thrombolysis and 381 (39%) had a 90-day modified Rankin Scale of 3-6. Intravenous thrombolysis was associated with a lower 90-day modified Rankin Scale in the group without ICAC (adjusted OR 0.3; 95% CI 0.1-0.9) and in the group with a medial ICAC pattern (adjusted OR 0.5; 95% CI 0.3-0.8), but not in the groups with intimal (adjusted OR 0.9; 95% CI 0.5-1.5) or indistinguishable patterns (adjusted OR 0.6; 95% CI 0.2-1.8). The associations between intravenous thrombolysis and follow-up infarct volume and intracranial hemorrhage were not significant for any of the ICAC pattern groups. Intravenous thrombolysis was only associated with recanalization in the group with a medial ICAC pattern (adjusted OR 3.5; 95% CI 1.2-11.0). Compared to an intimal ICAC pattern, a medial ICAC pattern was associated with good collateral status (adjusted OR 2.6; 95% CI 1.1-6.0).

Conclusions

Intravenous thrombolysis was significantly associated with favorable clinical outcome and successful recanalization in the group with a medial ICAC pattern, but not in the group with an intimal ICAC pattern.

INTRODUCTION

Intracranial internal carotid artery calcification (ICAC) has been associated with ischemic stroke and can be evaluated with computed tomography (CT).[1,2] A medial ICAC pattern, which entails predominant calcification of the tunica media or internal elastic lamina, can be distinguished from an intimal ICAC pattern, which entails predominant calcification of lipid flakes in the tunica intima. Among these entities, pathophysiology, prognosis and treatment response may differ.[2,3] Recently, the pattern of ICAC has been identified as an effect modifier of endovascular treatment in patients with a proximal intracranial occlusion.[4] The association between endovascular treatment and good outcomes such as successful recanalization or favorable functional outcome, but not follow-up infarct volume, was significant in the group with a medial calcification pattern, whereas the association was not significant in the groups without calcification or with an intimal calcification pattern.[4] Hypothetically, calcification of the medial layers of the artery leads to arterial stiffening increasing the pulse pressure more distally.[5,6] As a result, the distal brain perfusion may be impaired and the formation of collateral vessels is triggered. Good collateral filling is, in turn, related to favorable outcome after intravenous thrombolysis or endovascular treatment.[7–9] In addition, the culprit thrombus may have different characteristics across the different ICAC patterns influencing treatment effects.[10] If these hypotheses are correct, the effects of intravenous thrombolysis should also be modified by ICAC pattern, but no large studies investigating this modification exist.

To gain more insight in the proposed pathophysiological pathways, we performed five separate analyses. First, we evaluated the association between intravenous thrombolysis and 90-day clinical outcome in a large cohort of consecutive patients with ischemic stroke stratified by ICAC pattern. Second, we evaluated the association between intravenous thrombolysis and follow-up infarct volume. Third, we evaluated the association between intravenous thrombolysis and intracranial hemorrhage as a complication of treatment. Fourth, we evaluated the association between intravenous thrombolysis and recanalization in a subgroup of patients with an intracranial occlusion of the anterior circulation stratified by ICAC pattern. Fifth, we investigated the association between ICAC pattern and collateral status in a subgroup of patients with an occlusion of the M1 segment of the middle cerebral artery.

MATERIALS AND METHODS

Descriptive data that support the findings of this study are available from the corresponding author upon reasonable request. This research was reported following the STROBE guidelines.[11]

Patient selection

All patients participated in the Dutch Acute Stroke Study (DUST), a prospective multicenter observational cohort study in the Netherlands (ClinicalTrials.gov; Identifier: NCT00880113). Adult patients with suspected ischemic stroke were included. A detailed description of the design has been published previously.[12] This study was approved by the medical ethics committees of the participating hospitals. Signed informed consent was taken from all participants or their families. In case the patient died, the need for informed consent was waived by the medical ethics committee.

From the original 1476 patients enrolled in the DUST, imaging data were incomplete for 83 patients, 155 had no definite diagnosis of ischemic stroke, 241 had no admission thin-slice non-contrast CT, which was required for ICAC pattern evaluation, and 15 had no follow-up data, leaving 982 patients in whom we could investigate the association between intravenous thrombolysis and 90-day clinical outcome stratified by ICAC pattern (analysis 1). Data on follow-up infarct volume were available in 581 patients (analysis 2). Data on intracranial hemorrhage were available in 855 patients (analysis 3). The association between intravenous thrombolysis and recanalization status stratified by ICAC pattern was analyzed in 220 patients with an intracranial anterior circulation occlusion, a focal perfusion deficit and follow-up non-contrast CT, CT perfusion and CT angiography 3 days (±2 days) after admission (analysis 4).

The association between ICAC pattern and collateral status was analyzed in patients with an occlusion of the M1 segment of the middle cerebral artery (analysis 5).[13] Of the 169 patients with an M1 occlusion, 21 were excluded: 14 patients with poor image quality and 7 with a scanning level that was too low (at the level of the posterior circulation) to evaluate collateral filling in the territory of the middle cerebral artery. Thus, 148 patients were included for analysis 5.

Baseline data

Data were extracted from the prospectively collected DUST database and included demographics (age and sex), pre-stroke modified Rankin Scale (mRS), admission National Institutes of Health Stroke Scale (NIHSS), intravenous thrombolysis defined as intravenous administration of tissue-type plasminogen activator, endovascular treatment and cardiovascular risk factors including hypertension, diabetes mellitus, atrial fibrillation, myocardial infarction, dyslipidemia and smoking.

Imaging protocol

The DUST imaging protocol has been described previously.[12] In brief, non-contrast CT, CT perfusion and CT angiography were performed on admission and planned three days after the stroke. Scanners from different vendors were used. Non-contrast CT was acquired on 120 kVp and 300-375 mAs per rotation and slice reconstruction thickness was set to 1 mm.

CT perfusion was acquired on 80 kVp and 150 mAs, and slice thickness was 5 mm. Successive image frames were acquired every 2 seconds for the duration of 50 seconds in dynamic mode. In the meantime, nonionic contrast material and saline were administered. CT angiography was performed of the aortic arch up to the vertex of the skull. CT perfusion was used to determine the scan delay after intravenous injection of contrast material and to calculate the time to peak arterial enhancement. Otherwise, the scan delay was calculated by trigger-based Hounsfield unit threshold measurement of aortic arch contrast enhancement.

Imaging analysis

One of three observers, who all have >5 years of stroke imaging experience, evaluated the CT acquisitions. The observers were blinded for clinical information except for side of symptoms.

Time between symptom onset and CT was recorded. Occlusion location and collateral status were determined on admission CTA. Collateral filling of the affected middle cerebral artery territory was evaluated and categorized as either poor (≤50% of the occluded territory) or good (>50% of the occluded territory).[14] The ICAC pattern evaluation was based on a previously developed CT score.[2] The pattern of ICAC was assessed on admission thin-slice non-contrast CT and categorized into four categories: no calcification, predominant intimal calcification pattern, predominant medial calcification pattern and indistinguishable pattern (too little calcification to determine the pattern).

Outcome measures

The primary outcome was the ordinal 90-day mRS (analysis 1). The secondary outcome was infarct volume, which was determined on non-contrast CT performed 3±2 days after the admission CT (analysis 2). Hypodense infarcted areas were manually delineated on every single axial slice. The surface of these areas was subsequently multiplied by the slice thickness to obtain the infarct volume, which was expressed in milliliters. Observers were blinded for admission CT angiography and CT perfusion when they delineated the infarcts. The tertiary outcome was intracranial hemorrhage, which was defined as a visible hemorrhage on follow-up non-contrast CT 3±2 days after the admission CT (analysis 3). The quaternary outcome was recanalization of the middle cerebral artery or the anterior cerebral artery, which was evaluated on follow-up CTA (analysis 4).[15,16] Four grades of recanalization were used: 0 = no flow/patency; 1 =minimal flow/patency; 2 =partial flow <50% of expected territory; 3 = partial flow >50% of expected territory; 4 = complete flow/patency. In this study, a dichotomized measure for recanalization was used: grades 3-4 versus grades 0-2. The quinary outcome was poor collateral filling compared to good collateral filling on admission CTA (analysis 5).[14]

Statistical analysis

The distributions of continuous variables were assessed by inspecting histograms. Normally distributed variables were reported as means with standard deviations and non-normally distributed variables were reported as medians with first and third quartiles (Q1-Q3). Characteristics were compared between groups with either parametric or nonparametric tests depending on the variable distribution.

In analysis 1, the association between intravenous thrombolysis and shift towards higher 90-day mRS was quantified with ordinal logistic regression. The interaction term containing intravenous thrombolysis and ICAC pattern was evaluated in a model with age, sex and internal carotid artery or M1 occlusion. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted for other parameters and stratified by ICAC pattern.[4] In model 1, the effect of intravenous thrombolysis was adjusted for age, sex and internal carotid artery or M1 occlusion. Model 2 was adjusted for the same covariates as model 1 and cardiovascular risk factors including smoking, diabetes mellitus, atrial fibrillation, myocardial infarction and hypertension. Model 3 was adjusted for the same covariates as model 2 and pre-stroke mRS, admission NIHSS, collateral score and time from symptom onset to CT. The proportional odds assumption was not violated as the plotted distance between coefficients across the ordinal categories were relatively equal. The collinearity assumption was violated for several covariates, but not for intravenous thrombolysis.

In analysis 2, the association between intravenous thrombolysis and follow-up infarct volume was evaluated with multiple linear regression. The natural log of follow-up infarct volume was used, so that the assumptions of normal residual distribution and homoscedasticity were respected. As such, we reported the back transformed regression coefficients (exp(β)). Effect estimates were adjusted in the same way as was done for the 90-day mRS.

In analysis 3, the association between intravenous thrombolysis and intracranial hemorrhage was evaluated with binary logistic regression.

In analysis 4, the association between intravenous thrombolysis and recanalization status was adjusted for age and sex, and stratified by ICAC pattern.

In analysis 5, the association between ICAC pattern and collateral status was adjusted for age and sex.

A P value lower than 0.05 was considered significant. Analyses were performed in R version 3.5.0 with packages car, gmodels, base, stats and MASS.

RESULTS

Of the 982 patients with mean age 67±14 years, 570 (58%) were male, 609 (62%) received intravenous thrombolysis and 381 (39%) had 90-day mRS 3-6. Baseline characteristics were stratified by the dichotomized 90-day mRS (Table 1), intravenous thrombolysis (Supplemental table I) and ICAC pattern (Supplemental table II). An example of a patient with a medial ICAC pattern and an example of a patient with an intimal ICAC pattern are shown in Figure 1.

Compared to the intimal ICAC pattern group, the patients with a medial ICAC pattern were older (P<0.001), were more often female (P<0.001), had higher NIHSS (P<0.001) and smoked more often (P<0.001). Frequencies of stroke subtype differed significantly (P<0.001) between the ICAC pattern groups (Supplemental table III).

Distributions of the 90-day mRS among the treatment groups are shown for every single ICAC pattern in Figure 2. The effect of intravenous thrombolysis on the 90-day mRS was significantly modified by ICAC pattern in the interaction analysis (P=0.026), but ICAC pattern was not significantly associated with 90-day mRS (P=0.058).

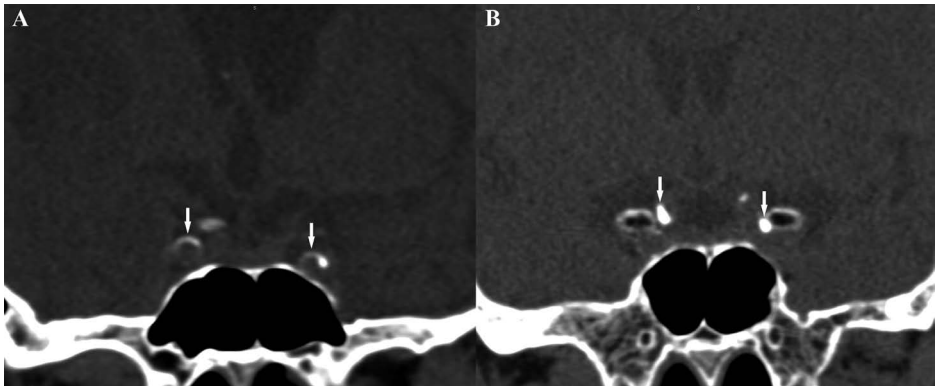

Figure 1. Examples of patients with predominantly medial (A) and intimal (B) intracranial internal carotid artery calcifications.

Legend: Coronal views of non-contrast CT images depicting the brain and the anatomical locations of the intracranial internal carotid artery are shown. Calcifications are marked with white arrows. The medial pattern is characterized by the thin continuous circular line of calcification and the intimal pattern by the thick dots of calcification.

Table 1. Baseline characteristics stratified by the dichotomized 90-day modified Rankin Scale

Characteristic	**Total** n=982	**mRS 0-2** n=601	**mRS 3-6** n=381	**P value***
Age, mean±SD	67±14	65±13	71±14	<0.001
Male sex, n (%)	570 (58)	372 (62)	198 (52)	0.003
Pre-stroke mRS ≤2	912 (94)	590 (99)	322 (86)	<0.001
Admission NIHSS, median (Q1-Q3)	6 (3-12)	5 (3-9)	11 (6-17)	<0.001
Intravenous thrombolysis, n (%)	609 (62)	379 (63)	230 (60)	0.435
Endovascular treatment, n (%)	65 (7)	33 (6)	32 (8)	0.099
Hypertension, n (%)	508 (52)	290 (49)	218 (58)	0.010
Diabetes mellitus, n (%)	144 (15)	71 (12)	73 (19)	0.002
Atrial fibrillation, n (%)	133 (14)	68 (12)	65 (17)	0.014
Myocardial infarction, n (%)	120 (12)	61 (10)	59 (16)	0.019
Dyslipidemia, n (%)	318 (33)	184 (32)	134 (36)	0.193
Current smoking, n (%)	263 (29)	168 (29)	95 (28)	0.824
Time between symptom onset and CT, min, median (Q1-Q3)	124 (77-197)	127 (80-194)	120 (72-204)	<0.001
ICA or M1 occlusion, n (%)	258 (27)	91 (15)	167 (44)	<0.001
Poor collateral score, n (%)	130 (13)	40 (7)	90 (24)	<0.001
ICA calcification				<0.001
- Dominantly media	468 (48)	261 (43)	207 (54)	
- Dominantly intima	299 (30)	185 (31)	114 (30)	
- Absent	108 (11)	80 (13)	28 (7)	
- Indistinguishable	107 (11)	75 (13)	32 (8)	

* Either parametric or nonparametric tests were used depending on the variable distribution. mRS indicates modified Rankin Scale; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; CT, computed tomography; ICA, internal carotid artery; M1 indicates M1 segment of the middle cerebral artery.

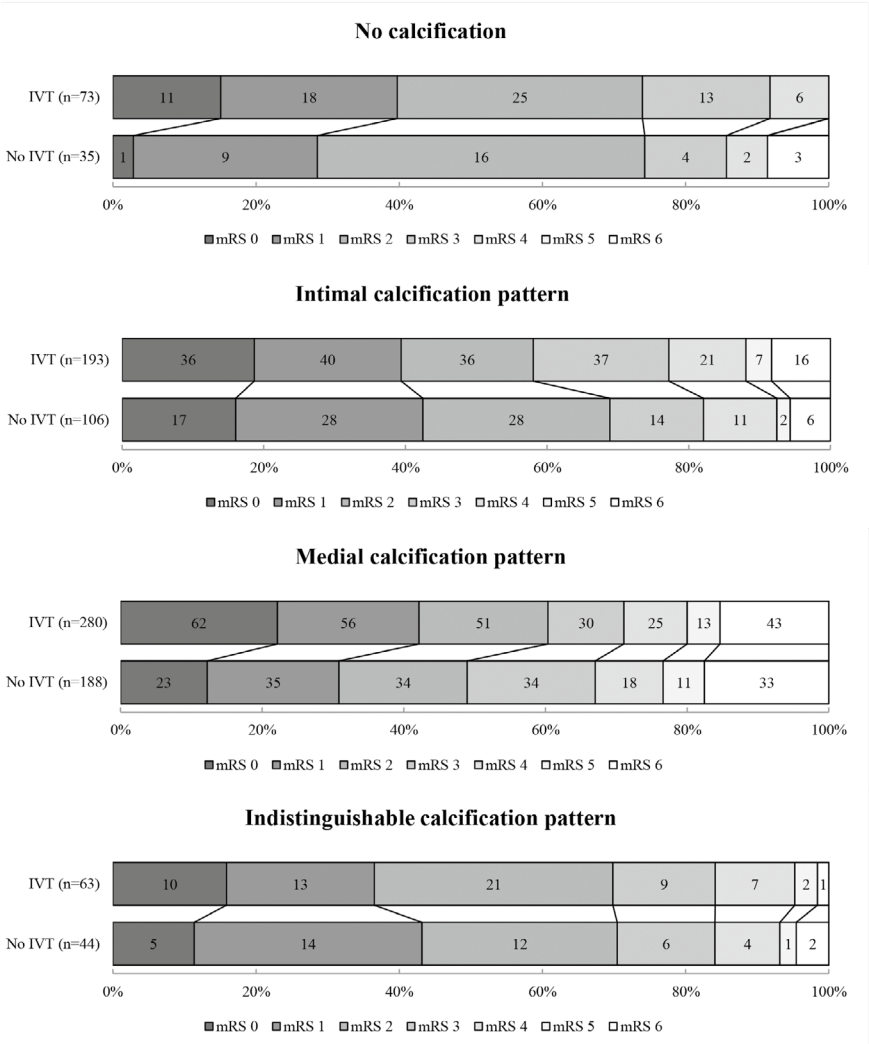

Figure 2. Distributions of 90-day modified Rankin Scale for patients treated with intravenous thrombolysis and untreated patients stratified by intracranial internal carotid artery calcification pattern.

Legend: IVT indicates intravenous thrombolysis; mRS, modified Rankin Scale.

In analysis 1, the adjusted OR for the association between intravenous thrombolysis and higher 90-day mRS was 0.3 (95% CI 0.1-0.9) in the group without ICAC, 0.5 (95% CI 0.3-0.8) in the group with a medial ICAC pattern, 0.9 (95% CI 0.5-1.5) in the group with an intimal ICAC pattern and 0.6 (95% CI 0.2-1.8) in the group with an indistinguishable pattern (Table 2).

In analysis 2 (n=581), no significant associations were observed between intravenous thrombolysis and follow-up infarct volume (Table 3).

In analysis 3 (n=855), 90 (11%) patients had intracranial hemorrhage (Table 4). No significant associations were observed between intravenous thrombolysis and intracranial hemorrhage for any of the ICAC groups.

In analysis 4 (n=220), intravenous thrombolysis was significantly associated with successful recanalization in the group with a medial ICAC pattern (adjusted OR 3.5; 95% CI 1.2-11.0), but not in the groups without ICAC (adjusted OR 0.5, 95% CI 0.0-5.9), with an intimal ICAC pattern (adjusted OR 2.1; 95% CI 0.7-6.2) or with an indistinguishable pattern (adjusted OR 9.9; 95% CI 0.4-754.5) (Table 5).

In analysis 5, 102 (69%) out of 148 patients with an M1 occlusion had a good collateral status. A medial ICAC pattern was significantly associated with good collateral status (adjusted OR 2.6; 95% CI 1.1-6.0) compared to an intimal ICAC pattern (Supplemental table IV).

Table 2. Association between intravenous thrombolysis and shift towards a higher ordinal 90-day modified Rankin Scale stratified by intracranial internal carotid artery calcification pattern

IVT versus no IVT	Model 1* OR (95% CI)	Model 2† OR (95% CI)	Model 3‡ OR (95% CI)
Total sample (n=982)	0.7 (0.6-0.9)§	0.7 (0.6-0.9)§	0.6 (0.4-0.8)§
No calcification (n=108)	0.6 (0.3-1.3)	0.5 (0.2-1.2)	0.3 (0.1-0.9)§
Medial calcification (n=468)	0.6 (0.4-0.9)§	0.6 (0.4-0.8)§	0.5 (0.3-0.8)§
Intimal calcification (n=299)	1.1 (0.7-1.6)	1.0 (0.7-1.6)	0.9 (0.5-1.5)
Indistinguishable (n=107)	0.8 (0.4-1.6)	1.0 (0.5-2.3)	0.6 (0.2-1.8)

* Model contains age and sex and ICA or M1 occlusion.
† Model contains same covariates as model 1 and smoking, diabetes mellitus, atrial fibrillation, myocardial infarction and hypertension.
‡ Model contains same covariates as model 2 and pre-stroke mRS, admission National Institutes of Health Stroke Scale, collateral score and time between symptom onset and CT.
§ P<0.05
IVT indicates intravenous thrombolysis; OR, odds ratio; CI, confidence interval.

Table 3. Association between intravenous thrombolysis and larger follow-up infarct volume stratified by intracranial internal carotid artery calcification pattern

IVT versus no IVT	Model 1* exp(β) (95% CI)	Model 2† exp(β) (95% CI)	Model 3‡ exp(β) (95% CI)
Total sample (n=581)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	1.0 (0.7-1.4)
No calcification (n=74)	0.6 (0.2-1.4)	0.4 (0.2-1.1)	0.5 (0.2-1.3)
Medial calcification (n=249)	1.6 (1.0-2.5)	1.7 (1.0-2.7)§	1.6 (1.0-2.7)
Intimal calcification (n=186)	1.1 (0.6-1.9)	0.9 (0.5-1.6)	0.6 (0.3-1.1)
Indistinguishable (n=72)	2.2 (0.9-5.3)	2.9 (1.0-7.8) §	1.1 (0.3-4.1)

* Model contains age, sex and ICA or M1 occlusion.
† Model contains same covariates as model 1 and smoking, diabetes mellitus, atrial fibrillation, myocardial infarction and hypertension.
‡ Model contains same covariates as model 2 and pre-stroke mRS, admission National Institutes of Health Stroke Scale, collateral score and time between symptom onset and CT.
§ P<0.05
IVT indicates intravenous thrombolysis; OR, odds ratio; CI, confidence interval.

Table 4. Association between intravenous thrombolysis and intracranial hemorrhage stratified by intracranial internal carotid artery calcification pattern

IVT versus no IVT	Model 1* OR (95% CI)	Model 2† OR (95% CI)	Model 3‡ OR (95% CI)
Total sample (n=855)	1.6 (1.0-2.7)§	1.8 (1.1-3.1)§	1.6 (0.8-3.5)
No calcification (n=101)	2.7 (0.6-18.4)	3.7 (0.7-36.6)	5.1 (0.5-96.8)
Medial calcification (n=385)	1.6 (0.8-3.2)	1.7 (0.8-3.9)	1.9 (0.6-7.0)
Intimal calcification (n=278)	2.2 (0.9-6.2)	2.1 (0.8-6.1)	1.6 (0.4-7.0)
Indistinguishable (n=91)	0.8 (0.2-3.4)	0.8 (0.1-6.7)	0.5 (0.0-21.7)

* Model contains age and sex and ICA or M1 occlusion.
† Model contains same covariates as model 1 and smoking, diabetes mellitus, atrial fibrillation, myocardial infarction and hypertension.
‡ Model contains same covariates as model 2 and pre-stroke mRS, admission National Institutes of Health Stroke Scale, collateral score and time between symptom onset and CT.
§ P<0.05
IVT indicates intravenous thrombolysis; OR, odds ratio; CI, confidence interval.

Table 5. Association between intravenous thrombolysis and successful recanalization in patients with intracranial anterior circulation occlusion stratified by intracranial internal carotid artery calcification pattern

IVT versus no IVT	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Total sample (n=220)	2.5 (1.3-4.9)†	2.5 (1.3-4.9)†
No calcification (n=32)	0.7 (0.0-6.4)	0.5 (0.0-5.9)
Medial calcification (n=78)	3.3 (1.1-9.8)†	3.5 (1.2-11.0)†
Intimal calcification (n=83)	2.0 (0.7-5.7)	2.1 (0.7-6.2)
Indistinguishable (n=27)	9.5 (1.1-102.2)†	9.9 (0.4-754.5)

* Model contains age and sex.
† P<0.05
IVT indicates intravenous thrombolysis; OR, odds ratio; CI, confidence interval.

DISCUSSION

In this study, we evaluated ICAC pattern as a potential effect modifier of intravenous thrombolysis in patients with acute ischemic stroke. The beneficial effect of intravenous thrombolysis on the 90-day mRS was significant in the group without ICAC and in the group with a medial ICAC pattern, but not in the groups with intimal or indistinguishable ICAC patterns (analysis 1). In analysis 2 and 3, the effect of intravenous thrombolysis on follow-up infarct volume or intracranial hemorrhage was not significant for any of the ICAC pattern groups.

In analysis 4, the effect of intravenous thrombolysis on recanalization was only significant in the group with a medial ICAC pattern. In analysis 5, the medial ICAC pattern was associated with good collateral status compared to the intimal ICAC pattern. These results indicate that the benefit from intravenous thrombolysis depends on ICAC pattern, and that collateral filling is a contributing factor in the pathophysiological process.

Two studies have evaluated treatment effects across patterns of ICAC using a CT based grading system. In the first study, no significant association was found between intravenous thrombolysis and the dichotomized 90-day mRS in groups with different ICAC patterns.[17] They did observe a trend towards worse clinical outcomes in the group with a medial ICAC pattern. However, the sample size was relatively small, its design was retrospective and dichotomized outcomes were used.[17] In the second study, which was a recent MR CLEAN subgroup analysis, ICAC pattern was identified as an effect modifier of endovascular treatment, which is in line with the results from our study.[4] One similarity is the observed larger benefit from treatment in patients with a medial ICAC pattern compared to an intimal ICAC pattern. Furthermore, effects on 90-day mRS and recanalization were significant, whereas this was not the case for follow-up infarct volume. The selection of study participants differed between the studies. The MR CLEAN subgroup study included patients with a proximal intracranial arterial occlusion, whereas we did not select patients on whether an occlusion was present. Because the presence of proximal intracranial occlusions affects patient outcomes, we adjusted for this variable in our analyses. Another difference between the previous study and our study is the used design. We evaluated a prospective consecutive observational cohort, whereas the previous study analyzed a subgroup of a randomized controlled clinical trial. Both designs required appropriate adjustment of potential confounders. Despite the differences between the studies, the observed effects are quite similar, but validation of our findings in randomized controlled clinical trials is desirable.

Some pathophysiologic mechanisms that underlie the observed effects have been proposed. Risk factors and their relation with ICAC pattern have been investigated previously in this cohort and were verified in another.[4,18] Risk factors for medial ICAC pattern include age, female sex, pulse pressure, diabetes mellitus, previous vascular disease and positive family history, whereas age, pulse pressure, smoking, hypertension and positive family history have been associated with a predominantly intimal ICAC pattern.[18] Calcification of the medial layer leads to arterial stiffening and, consequently, to higher pulse pressures distal to the calcification site. Consequently, the possible impaired distal microcirculation of the brain may trigger the pathway of collateral vessel formation. In this study, we found a relation between medial ICAC pattern and presence of collateral vessels in the brain supporting this hypothesis. Another theory is that the ICAC pattern is related to characteristics of the occluding thrombus influencing treatment effects.[19] We were not able to evaluate this hypothesis as thrombus characteristics were not routinely collected in the DUST. Taken together, our findings indicate that the proposed distinctions in etiology across ICAC patterns also modify the effect of intravenous thrombolysis in patients with acute ischemic stroke.

Besides the intimal and medial ICAC patterns, there are also patients without ICAC or with an indistinguishable ICAC pattern. In this study, patients without ICAC also benefited from intravenous thrombolysis with respect to the 90-day mRS. In this group, ischemic stroke was more often caused by non-atherosclerotic etiologies such as cardioembolic stroke or carotid artery dissection. Compared with other etiologies, cardioembolic stroke has been associated with better outcomes after intravenous thrombolysis, but this is the opposite for cervical artery dissection.[20,21] Thus, the benefit from intravenous thrombolysis in patients without ICAC cannot fully be explained by the etiology of the stroke. The indistinguishable ICAC pattern consists of patients with calcifications that are too limited in severity to classify.[2] In our study, the group with an indistinguishable pattern was rather small, which could have caused the wide confidence intervals for the associations between intravenous thrombolysis and patient outcomes. Larger studies should indicate whether patients with an indistinguishable ICAC pattern should be treated as a distinct patient group or not.

If the results from this study are verified in future studies, some implications can be considered for stroke care and research. For instance, as treatment response may depend on ICAC pattern, the eligibility criteria for intravenous thrombolysis may need reevaluation, with possibly stricter indications for intravenous thrombolysis in those with intima dominance. In addition, ICAC pattern evaluation may contribute

to understanding why certain patients with ischemic stroke benefit from acute treatment and why certain patients do not. The grade of collateral filling may play a role in the causal chain of ICAC pattern influencing the clinical outcome in patients with ischemic stroke treated with intravenous thrombolysis. Good collateral circulation has been associated with favorable clinical outcome after intravenous treatment or endovascular treatment and is therefore often assessed in clinical practice and scientific studies.[7–9] This is not yet the case for ICAC pattern and the exact mechanisms causing the effect modification of intravenous thrombolysis or endovascular treatment need to be elucidated before ICAC pattern can have a place in routine clinical practice or stroke research. Future observational studies and randomized controlled trials involving intravenous thrombolysis or endovascular treatment could stratify by ICAC pattern to evaluate treatment effects across the different patterns. With regard to prevention of stroke, this study helps in understanding the association between ICAC patterns and ischemic stroke. It is likely that the different ICAC patterns require different prevention strategies as different risk factors have been identified. This is a rapidly evolving field with many questions still to be answered.[22]

A strength of this study was the prospective design, which resulted in a minimal number of missing data and loss to follow-up. The results are highly generalizable as this was a multicenter study and no particular stroke subgroups have been excluded from this study.

Admission thin-slice non-contrast CT data were not available in 241 patients. We do not believe this has induced selection bias as we do not expect the availability of thin-slice instead of thicker slice CT reconstructions to be related to either ICAC pattern or stroke outcomes. Furthermore, misclassification could have occurred as determination of ICAC pattern is based on a CT score and histology could not be evaluated. However, in a previous study the interrater agreement turned out to be good and the agreement between the CT score and histology was reasonable.[2] Besides, misclassification is unrelated to ICAC pattern (non-differential).[2] It should be noted that patients with predominantly medial ICAC can also have, to a lesser extent, intimal ICAC and vice versa. Although this could have biased the regression slopes towards zero, this did not lead to insignificant results. In the DUST study, length and weight were not routinely measured and, therefore, we were not able to use body mass index as a covariate. The impact of this limitation seems limited as body mass index does not seem to be associated with outcome in patients who received intravenous thrombolysis.[23] Instead of using time from onset of symptoms to treatment, we chose to include time from onset of symptoms to CT imaging as

a surrogate, because not all patients were treated in this study. Another limitation of this study was the limited power in analyses 3 and 4. As a result, we were not able to add more than two covariates to the regression models. Although we still observed significant associations in these regression models, verification in larger cohorts is desirable.

Various patterns of arteriosclerosis often co-exist. In this study, we used a validated scoring system that aims to diagnose the dominant calcification pattern. The resolution of CT is insufficient to visualize the layers of the arterial wall, but thin-slice non-contrast CT is of sufficient quality to reliably assess this dominant pattern of ICAC. Nowadays thin-slice non-contrast CT is acquired in most stroke centers. We anticipate refinement and automation of the ICAC calcification score and showed in this study the potential relevance of finding the dominant pattern. The results of this study may have direct implications for stroke care, but validation of these results in future studies is warranted.

In conclusion, intravenous thrombolysis was significantly related to favorable clinical outcome and successful recanalization in the group with a medial ICAC pattern, but not in the group with an intimal ICAC pattern. Compared to the intimal ICAC pattern, the medial ICAC pattern was related to good collateral filling on admission CTA.

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SUPPLEMENTS

Supplemental table I. Baseline characteristics stratified by intravenous thrombolysis

Characteristic	**Total** n=982	**No IVT** n=373	**IVT** n=609	**P value***
Age, mean±SD	67±14	69±13	67±14	<0.001
Male sex, n (%)	570 (58)	214 (57)	356 (59)	0.789
Pre-stroke mRS ≤2	912 (94)	336 (92)	576 (95)	0.125
Admission NIHSS, median (Q1-Q3)	6 (3-12)	4 (3-9)	8 (4-14)	<0.001
Endovascular treatment, n (%)	65 (7)	22 (6)	43 (7)	0.570
Hypertension, n (%)	508 (52)	204 (55)	304 (50)	0.172
Diabetes mellitus, n (%)	144 (15)	67 (18)	77 (13)	0.028
Atrial fibrillation, n (%)	133 (14)	68 (18)	65 (11)	0.001
Myocardial infarction, n (%)	120 (12)	48 (13)	72 (12)	0.732
Dyslipidemia, n (%)	318 (33)	147 (41)	171 (29)	<0.001
Current smoking, n (%)	263 (29)	100 (28)	163 (29)	0.772
Time between symptom onset and CT, min, median (Q1-Q3)	124 (77-197)	231 (135-346)	91 (65-135)	<0.001
ICA or M1 occlusion, n (%)	258 (27)	77 (21)	181 (30)	0.002
Poor collateral score, n (%)	130 (13)	38 (10)	92 (15)	0.031
ICA calcification				0.303
- Dominantly media	468 (48)	188 (50)	280 (46)	
- Dominantly intima	299 (30)	106 (28)	193 (32)	
- Absent	108 (11)	35 (9)	73 (12)	
- Indistinguishable	107 (11)	44 (12)	63 (10)	

* Either parametric or nonparametric tests were used depending on the variable distribution. IVT indicates intravenous thrombolysis; SD, standard deviation; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ICA, internal carotid artery; M1 indicates M1 segment of the middle cerebral artery.

Supplemental table II. Baseline characteristics stratified by medial and intimal patterns of intracranial internal carotid artery calcification

Characteristic	**Medial** n=468	**Intimal** n=299	**P value***
Age, mean±SD	74±11	67±11	<0.001
Male sex, n (%)	237 (51)	199 (67)	<0.001
Pre-stroke mRS ≤2	421 (91)	283 (95)	0.081
Admission NIHSS, median (Q1-Q3)	6 (3-12)	6 (3-11)	<0.001
Intravenous thrombolysis, n (%)	280 (60)	193 (65)	0.217
Endovascular treatment, n (%)	29 (6)	10 (3)	0.113
Hypertension, n (%)	268 (58)	176 (59)	0.806
Diabetes mellitus, n (%)	88 (19)	43 (14)	0.130
Atrial fibrillation, n (%)	81 (18)	34 (11)	0.026
Myocardial infarction, n (%)	61 (13)	50 (17)	0.204
Dyslipidemia, n (%)	162 (36)	116 (40)	0.298
Current smoking, n (%)	90 (21)	103 (36)	<0.001
Time between symptom onset and CT, min, median (Q1-Q3)	131 (79-198)	122 (76-201)	<0.001
ICA or M1 occlusion, n (%)	117 (25)	74 (25)	1.000
Poor collateral score, n (%)	52 (11)	45 (15)	0.128

* Either parametric or nonparametric tests were used depending on the variable distribution. SD indicates standard deviation; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ICA, internal carotid artery; M1 indicates M1 segment of the middle cerebral artery.

Supplemental table III. Frequencies of stroke etiology classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification across different patterns of intracranial internal carotid artery calcification

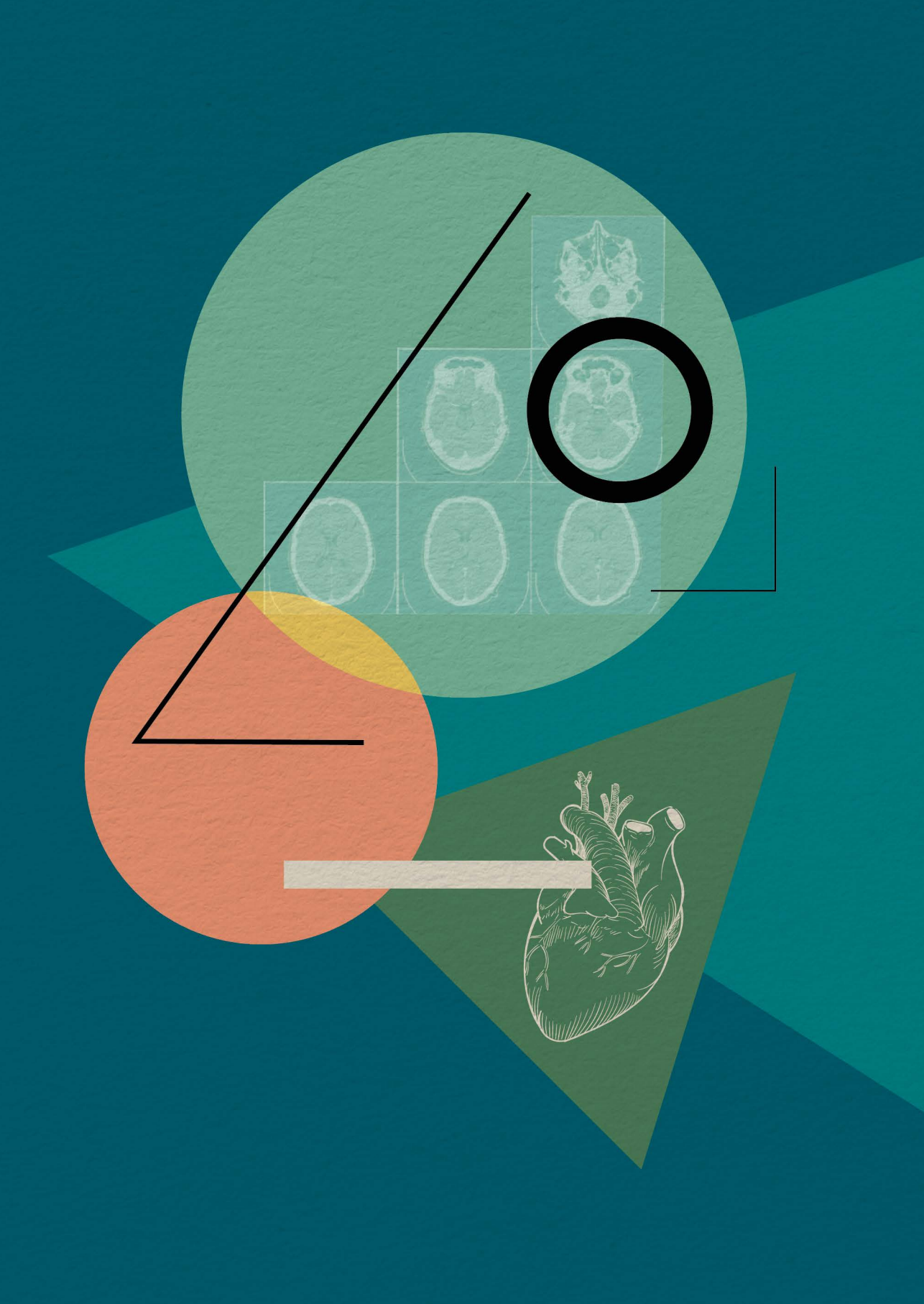
	Pattern of intracranial internal carotid artery calcification*			
TOAST classification*	Absent (n=72)	Intimal (n=219)	Medial (n=337)	Indistinguishable (n=75)
Large artery atherosclerosis, n (%)	26 (36)	106 (48)	160 (48)	30 (40)
Cardioembolism, n (%)	16 (22)	51 (23)	92 (27)	21 (28)
Small vessel disease, n (%)	10 (14)	39 (18)	63 (19)	13 (17)
Dissection, n (%)	18 (25)	7 (3)	7 (2)	9 (12)
Other, n (%)	2 (3)	16 (7)	15 (5)	2 (3)
Unknown, n (%)	36 (33)	80 (27)	131 (28)	32 (30)

***** Frequencies of stroke subtype differed significantly between ICAC pattern groups (P<0.001). Toast indicates Trial of Org 10172 in Acute Stroke Treatment.

Supplemental table IV. Association between intracranial internal carotid artery calcification pattern and good collateral status (versus poor collateral status) in patients with an occlusion of the M1 segment of the middle cerebral artery

Characteristic	**OR (95% CI)**
Age	1.0 (0.9-1.0)
Male sex	0.7 (0.4-1.6)
ICAC pattern	
- Dominantly intimal	Reference
- Absent	1.8 (0.4-7.4)
- Dominantly medial	2.6 (1.1-6.0)
- Indistinguishable	1.2 (0.4-3.7)

OR indicates odds ratio; CI, confidence interval; ICAC, intracranial internal carotid artery calcification.



9

INTRACRANIAL CEREBROSPINAL FLUID VOLUME AS A PREDICTOR OF MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION

Based on:

Kauw F, Bennink HE, de Jong HWAM, Kappelle LJ, Horsch AD, Velthuis BK, Dankbaar JW; DUST (Dutch Acute Stroke Study) investigators. Intracranial Cerebrospinal Fluid Volume as a Predictor of Malignant Middle Cerebral Artery Infarction. Stroke. 2019 May 16;50(6): 1437-1443.

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ABSTRACT

Background and purpose

Predicting malignant middle cerebral artery (MCA) infarction can help to identify patients who may benefit from preventive decompressive surgery. We aimed to investigate the association between the ratio of intracranial cerebrospinal fluid (CSF) volume to intracranial volume (ICV) and malignant MCA infarction.

Methods

Patients with an occlusion proximal to the M3 segment of the MCA were selected from the Dutch Acute Stroke Study (DUST). Admission imaging included non-contrast CT, CT perfusion and CT angiography. Patient characteristics and CT findings were collected. The ratio of intracranial CSF volume to ICV (CSF/ICV) was quantified on admission thin-slice non-contrast CT. Malignant MCA infarction was defined as a midline shift of greater than 5 mm on follow-up non-contrast CT, which was performed three days after the stroke or in case of clinical deterioration. To test the association between CSF/ICV and malignant MCA infarction, odds ratios (OR) and 95% confidence intervals (CI) were calculated for three multivariable models by using binary logistic regression. Model performances were expressed as the area under the receiver operating characteristic curves (AUROC) and compared by using the likelihood ratio test.

Results

Of the 286 included patients, 35 (12%) developed malignant MCA infarction. CSF/ICV was independently associated with malignant MCA infarction in three multivariable models: 1) with age and admission NIHSS (OR 3.3; 95% CI 1.1-11.1), 2) with admission NIHSS and poor collateral score (OR 7.0; 95% CI 2.6-21.3) and 3) with terminal ICA or proximal M1 occlusion and poor collateral score (OR 7.7; 95% CI 2.8-23.9). The performance of model 1 (AUROC 0.795 versus 0.824, P=0.033), model 2 (AUROC 0.813 versus 0.850, P<0.001) and model 3 (AUROC 0.811 versus 0.856, P<0.001) improved significantly after adding CSF/ICV.

Conclusions

The CSF/ICV ratio is associated with malignant MCA infarction and has added value to small clinical and imaging prediction models.

INTRODUCTION

Development of malignant edema (ME) is a life-threatening complication and typically occurs in younger patients with a large middle cerebral artery (MCA) infarction.[1] Such a malignant MCA infarction occurs in up to 10% of the patients with large supratentorial stroke.[2] No official definition exists for ME, but stroke researchers often use the combination of clinical deterioration and midline shift on CT imaging, although some only use the imaging definition.[3,4] Usually, the edema develops between the second and fifth day after the stroke, although onset of symptoms before 24 hours after the stroke is not uncommon. Before surgical intervention was introduced, reported mortality rates associated with malignant MCA infarction ranged between 70 and 80%.[1,5] In a pooled analysis of three randomized trials, early decompressive surgery has been shown to be effective in patients with malignant MCA infarction in terms of improving clinical outcome and reducing mortality rate.[6] Anticipating on development of ME is important, so that the patient can be treated in time. Therefore, prediction of ME is helpful.

Single predictors of malignant MCA infarction have been investigated previously and include both clinical and imaging factors. Clinical features that are present on admission have been related to ME and include age, vomiting, National Institutes of Health Stroke Scale (NIHSS) and coma.[7–11] However, the predictive value of clinical parameters regarding malignant MCA infarction is limited and therefore imaging factors are an important addition to prediction models. Imaging factors, that have been associated with ME independently of age and NIHSS, include early signs of ischemia on non-contrast CT (NCCT), larger volume of deficits on cerebral blood volume (CBV) maps, higher blood-brain permeability estimates on CT perfusion (CTP), more proximal thrombus location, higher clot burden score, and poor collateral scores on CT angiography (CTA).[10–13] Similarly, larger size of the MCA infarction on diffusion weighted imaging (DWI) has been found to be associated with ME.[8,14]

Another potential predictor of ME may be the volume of intracranial cerebrospinal fluid (CSF) on admission. Theoretically, the brain has more space to swell, without herniating, when more CSF volume is present. In order to assess the predictive value of CSF volume in relation to ME, we evaluated a large prospective cohort of patients with MCA infarction.

METHODS

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

Patient selection

Patients were selected from a prospective multicenter observational cohort study, the Dutch Acute Stroke Study (DUST), which was conducted between May 2009 and August 2013.[15] Patients, who participated in DUST, were adult (18 years or older), had suspected ischemic stroke based on clinical signs, presentation within 9 hours after onset of neurologic deficits and NIHSS ≥2, or 1 if an indication for intravenous administration of tissue-type plasminogen activator was present.[15] Exclusion criteria were contraindications for undergoing CT including contrast allergy and renal failure, or the presence of other causes for the neurological deficits on brain CT. Patient characteristics were collected and all patients underwent CT imaging including NCCT, CTP and CTA on hospital admission. This study was approved by the medical ethics committees of the participating hospitals. Signed informed consent was taken from all participants or their families. In case the patient died, the need for informed consent was waived by the medical ethics committee.

For the current study, we selected patients from DUST who had an occlusion proximal to the M3 segment of the MCA. Furthermore, patients were excluded if thin-slice NCCT at baseline was unavailable. Since we were only interested in midline shift caused by ME as outcome, patients were excluded if hemorrhagic transformation causing mass effect was present on follow-up CT.

Baseline data

The following patient characteristics were collected at baseline: age, sex, NIHSS, time from symptom onset to CT scan, intravenous administration of tissue-type plasminogen activator, endovascular treatment, cardiovascular risk factors and previous medical history of cardiovascular disease.

Imaging protocol

The imaging protocols have been described previously.[15] In short, NCCT, CTP and CTA scans were acquired as part of the acute stroke protocol. Follow-up NCCTs were planned on the 3rd day after the stroke or at the moment of clinical deterioration. CT scanners (Philips, Siemens, Toshiba, General Electric Company) with varying collimation widths, ranging from 40 to 320 slices, were used in this study. The tube

settings for the NCCT were 120kVp and 300-375 mAs per rotation. Slices were reconstructed with a thickness of 1 mm.

CTP was performed with 80 kVp and 150 mAs with a slice thickness of 5 mm. In dynamic mode, successive image frames were acquired (every 2 seconds for the duration of 50 seconds), while nonionic contrast material and saline were administered.[15] Both ASPECTS levels were included in the CTP coverage.[16]

CTA covered the head and neck from aortic arch to cranial vertex. The scan delay after intravenous injection of contrast was calculated from time to peak arterial enhancement on CTP or by trigger-based Hounsfield unit threshold measurement of contrast enhancement in the aortic arch.

Imaging analysis

Imaging data were evaluated by one of three observers, who all have more than 5 years of experience in stroke imaging.[17] The observers were only informed about the side of symptoms before evaluation.

Baseline NCCT scans were evaluated for presence of hyperdense vessel sign and early signs of ischemia, which were quantified by using the Alberta Stroke Program Early CT Score (ASPECTS).[16]

Fully automated intracranial CSF volume estimation was based on gray value histograms of the NCCT brain parenchyma. To this end, first the brain was coarsely segmented into three tissue regions (gray matter, white matter, and CSF) by registering the International Consortium for Brain Mapping (ICBM) 152 nonlinear atlas[18,19] to the NCCT scan using penalized elastic deformation.[20] Aided by this segmentation, three Gaussian mixture models were fitted to the histograms of coarsely segmented tissue regions (Figure 1). The use of a mixture model allows for volume measurement in noisy data, without the need for precise segmentation. The area under each Gaussian curve reflects the volume of the particular tissue region.

The intracranial volume (ICV) was defined as the sum of the gray matter, white matter, and CSF atlas regions, i.e. the sum of the areas under the three histograms. The intracranial CSF volume was defined as the sum of the areas under the curve of the CSF distributions of the Gaussian mixtures inside those masks.

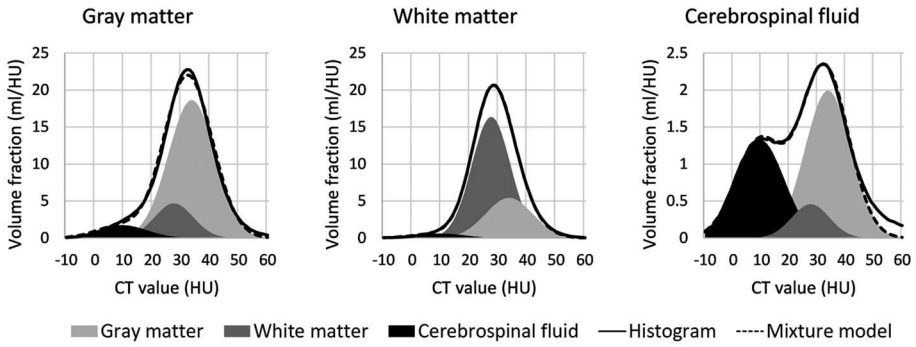

Figure 1. Gaussian mixture models fitted to non-contrast CT histograms

Legend: An example of Gaussian mixture models fitted to three non-contrast CT histograms: coarsely segmented gray matter, white matter and cerebrospinal fluid (CSF). The solid line represents the measured intensity histogram, whereas the dashed line represents the mixture model. The mixture model consists of three Gaussian distributions: gray matter (light gray, mean=33.6 HU), white matter (dark gray, mean=27.0 HU), and CSF (black, mean=9.5 HU). Note that the gray matter histogram is dominated by the gray matter peak, the white matter histogram by the white matter peak, and the CSF histogram by both the CSF and gray matter peaks.

ME was defined as a midline shift of greater than 5 mm. Types of hemorrhagic transformation including hemorrhagic transformation with mass effect (type PH2) were evaluated by using the European Cooperative Acute Stroke Study (ECASS) criteria.[21]

ASPECTS was also evaluated on perfusion maps, which included cerebral blood volume (CBV) and mean transit time (MTT) and were calculated by using commercially available CTP software (Extended Brilliance Workstation 4.5, Philips Healthcare).

On baseline CTA, intracranial artery occlusions and collateral status were evaluated.[22–24] The most proximal occlusion was used if multiple occlusions were present, with the exception of a tandem lesion of the extra-cranial ICA and MCA, in which case the MCA occlusion was used.[25] The collateral score was categorized as either poor or good (cutoff 50%) compared to the contralateral hemisphere by visual inspection of the maximum intensity projection images.[17]

Outcome measures

The primary outcome was the presence of ME on follow-up imaging. The secondary outcome measure was clinical outcome after 90 days. Poor clinical outcome was defined as a score of 3 or greater on the modified Rankin Scale (mRS).

Statistical analysis

Patient characteristics and outcomes were compared between the patients included for this study and the patients who were excluded because of unavailability of thin-slice NCCT images by using variable-dependent statistical tests (Supplemental table I). Similarly, patient characteristics were compared between patients with and without malignant MCA infarction. The intracranial CSF volume was adjusted for ICV by calculating the ratio of CSF volume to ICV (CSF/ICV). Odds ratios (OR) and 95% confidence intervals (CI) were calculated by using binary logistic regression. Potential predictors were identified by screening the literature. Complete case analysis was performed as no missing values were present for the predictors of interest. Because of the limited number of outcomes, we could only select 3 potential predictors per model. Because younger patients have a higher risk of developing ME than older patients, we added age to one of the models. Similarly, we added NIHSS to two of the models. The third model contained two imaging parameters: terminal ICA or M1 occlusion and poor collateral score. Subgroup analyses were done for the patient group aged from 18 to 60 and for the group with NIHSS of 16 or higher. Variance inflation factors were calculated to test the collinearity assumption, which was not violated. Receiver operating characteristic (ROC) curves were plotted from the predicted probabilities. The areas under the ROC curves (AUROC) were calculated and model performances were compared by using the likelihood ratio test, so that the added value of CSF/ICV could be calculated. The described analyses were performed in R (version 3.4.2).

RESULTS

We selected 472 patients with an MCA occlusion proximal to the M3 segment (Supplemental figure I). We excluded 179 cases, because no thin-slice NCCT was available at baseline. At follow-up, seven patients had hemorrhagic transformation with mass effect (PH-2) and were thus excluded. The final analysis included 286 patients, of whom 35 (12%) developed ME. No more than 10 (3%) missing values were present for the patient characteristics except for smoking (n=24; 8%). Twenty-two (33%) of the 69 patients with terminal ICA or proximal M1 occlusion developed ME. Twelve (6%) of the 217 patients with an occlusion distal to the terminal ICA or proximal M1 segment developed ME.

The patients without baseline thin-slice NCCT and without PH-2 during follow-up were compared with the included patients (Supplemental table I). In the group that was excluded because of unavailability of thin-slice NCCT images, 19/175 (11%) patients developed malignant MCA infarction. This number was not significantly different from the included group (P=0.766).

Patient characteristics of the selected study population are summarized in Table 1. Crude ORs are shown in Supplemental table II. Age was significantly lower in the ME group than in the non-ME group (OR 1.5, 95% CI 1.2-2.0). Admission NIHSS was higher in the ME group than in the non-ME group (OR 1.2, 95% CI 1.1-1.3). No large differences were observed between the two groups regarding treatment or cardiovascular risk factors. Specific imaging findings on admission that were more prevalent in the ME group than in the non-ME group included hyperdense vessel sign (OR 3.5, 95% CI 1.7-8.0), lower ASPECTS (OR 1.8, 95% CI 1.5-2.1), terminal ICA or proximal M1 occlusion (OR 7.3, 95% CI 3.5-16.0) and poor collateral score (OR 7.3, 95% CI 3.4-16.7). Decrease in CSF/ICV was significantly associated with malignant MCA infarction (OR 4.5, 95% CI 1.9-11.7). Examples illustrating the association between CSF/ICV and ME are shown in Figure 2. Prevalence of poor clinical outcome 90 days after the stroke was higher in the ME group than in the non-ME group (97% vs. 47%, respectively, P<0.001).

Table 1. Patient characteristics

Characteristic	**Total** n=286	**ME** n=35 (12%)	**No ME** n=251 (88%)	**P value***
Age, mean±SD	67±14	59±16	68±14	0.003
Male sex, n (%)	162 (57)	23 (66)	139 (55)	0.248
Admission NIHSS, median (Q1-Q3)	13 (7-17)	18 (14-20)	12 (7-16)	<0.001
Time from symptom onset to scan, minutes, median (Q1-Q3)	113 (68-160)	135 (81-231)	104 (67-157)	0.187
Intravenous tPA, n (%)	201 (70)	21 (60)	180 (72)	0.155
Endovascular treatment, n (%)	33 (12)	6 (17)	27 (11)	0.268
Medical history				
Hypertension, n (%)	145 (51)	17 (49)	128 (51)	0.753
Diabetes mellitus, n (%)	36 (13)	2 (6)	34 (14)	0.191
Hyperlipidemia, n (%)	80 (28)	8 (23)	72 (29)	0.440
Smoking currently, n (%)	79 (30)	8 (29)	71 (30)	0.847

Table 1. Patient characteristics (continued)

Characteristic	Total n=286	ME n=35 (12%)	No ME n=251 (88%)	P value*
Former smoking, n (%)	83 (32)	8 (29)	75 (32)	0.708
Never smoked, n (%)	100 (38)	12 (43)	88 (38)	0.589
Atrial fibrillation, n (%)	47 (17)	6 (17)	41 (17)	0.936
History of stroke/TIA, n (%)	56 (20)	7 (21)	49 (20)	0.883
History of MI, n (%)	41 (15)	6 (17)	35 (14)	0.641
Imaging findings				
Hyperdense vessel sign, n (%)	126 (44)	24 (71)	102 (41)	<0.001
NCCT ASPECTS, median (Q1-Q3)	10 (8-10)	7 (3-8)	10 (8-10)	<0.001
CSF volume, mL, mean±SD	171±65	137±57	175±65	<0.001
ICV volume, mL, mean±SD	1322±155	1307±161	1324±154	0.556
CSF/ICV percentage, mean±SD	13±5	11±4	13±5	<0.001
CBV ASPECTS, median (Q1-Q3)	7 (5-9)	3 (1-5)	8 (6-10)	<0.001
MTT ASPECTS, median (Q1-Q3)	3 (2-6)	0 (0-2)	4 (2-6)	<0.001
Terminal ICA/proximal M1 occlusion, n (%)	69 (24)	22 (63)	47 (19)	<0.001
Poor collateral score, n (%)	89 (31)	25 (71)	64 (25)	<0.001
Follow-up				
Time between admission and follow-up CT, days, median (Q1-Q3)	3.0 (2.0-4.0)	2.2 (1.4-3.9)	3.0 (2.1-4.0)	0.063
Poor clinical outcome at 90 days†, n (%)	151 (53)	34 (97)	117 (47)	<0.001

* Either parametric or nonparametric tests were performed depending on the variable distribution.

† Poor clinical outcome was defined as modified Rankin Scale equal or greater than 3.

ME indicates malignant edema; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; tPA, tissue-type plasminogen activator; TIA, transient ischemic attack; MI, myocardial infarction; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; CSF, cerebrospinal fluid; ICV, intracranial volume; CBV, cerebral blood volume; MTT, mean transit time; ICA, internal carotid artery; CBS, clot burden score.

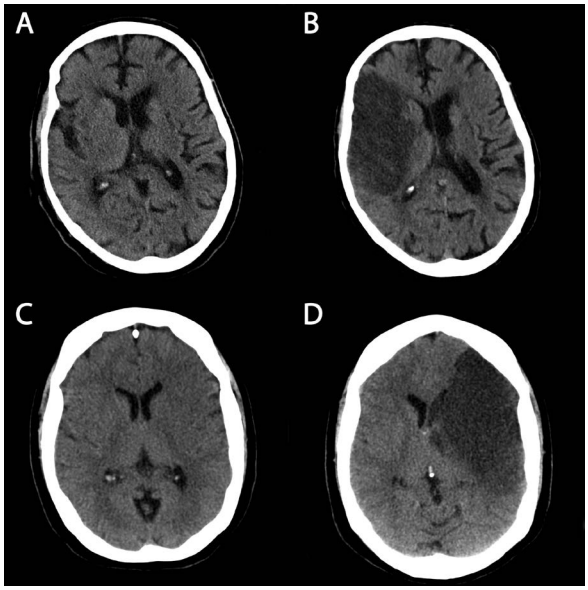

Figure 2. Examples illustrating the association between the ratio of intracranial cerebrospinal fluid volume to intracranial volume and malignant MCA infarction

Legend: First example of a baseline non-contrast CT image of a 81-year old male with a large MCA infarction due to an occlusion of the proximal M1 segment (A). The ratio of intracranial cerebrospinal fluid volume to intracranial volume (CSF/ICV) was 0.19. On follow-up non-contrast CT, demarcation of the infarction is visible, but no midline shift has occurred (B). Second example of a baseline non-contrast CT image of a 52-year old female with a large MCA infarction due to an occlusion of the proximal M1 segment (C). The CSF/ICV was 0.08. On follow-up non-contrast CT, malignant edema has developed leading to a midline shift of more than 5 mm (D).

The results of the multivariable analysis are shown in Table 2 and details of the ROC curves in Table 3 and Figure 3. In model 1, CSF/ICV was associated with ME, independent of age and admission NIHSS (OR 3.3, 95% CI 1.1-11.3). The model with CSF/ICV had a significantly better performance than the model without CSF/ICV when comparing the AUROCs (0.824 versus 0.795, respectively, P=0.033). In model 2, CSF/ICV was associated with ME, independent of admission NIHSS and poor collateral score (OR 7.0, 95% CI 2.6-21.3). A significant difference was observed between the performance of the model with CSF/ICV and the model without CSF/ICV (AUROC 0.850 versus 0.813, respectively, P<0.001). In model 3, CSF/ICV was associated with ME, independent of the presence of a terminal ICA or proximal M1 occlusion and poor collateral score (OR 7.7, 95% CI 2.8-23.9). Furthermore, a significant difference was found between the performance of model 3 with CSF/ICV and without CSF/ICV (AUROC 0.856 versus 0.811, respectively, P<0.001).

Table 2. Multivariable prediction models and the association with malignant middle cerebral artery infarction

Factor	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age, per 10 years decrease	1.4 (1.0-1.9)		
Admission NIHSS, per point increase	1.2 (1.1-1.3)	1.2 (1.1-1.3)	
Terminal ICA/proximal M1 occlusion			7.8 (3.4-19.3)
Poor collateral score		5.5 (2.4-13.6)	8.2 (3.5-21.0)
CSF/ICV, per 10% decrease	3.3 (1.1-11.1)	7.0 (2.6-21.3)	7.7 (2.8-23.9)

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume.

Table 3. Comparison of clinical and imaging models with and without the ratio of intracranial cerebrospinal fluid volume to intracranial volume

Factor	AUROC	95% CI	P value
Age + NIHSS	0.795	0.727-0.863	
Age + NIHSS + CSF/ICV	0.824	0.761-0.887	
Difference	0.029		0.03
NIHSS + Poor collateral score	0.813	0.751-0.849	
NIHSS+ Poor collateral score+ CSF/ICV	0.850	0.795-0.885	
Difference	0.037		<0.001
ICA/proximal M1 occlusion + Poor collateral score	0.811	0.737-0.886	
ICA/proximal M1 occlusion + Poor collateral score + CSF/ICV	0.856	0.772-0.939	
Difference	0.045		<0.001

AUROC indicates area under the receiver operating characteristic curve; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume; CS, collateral score.

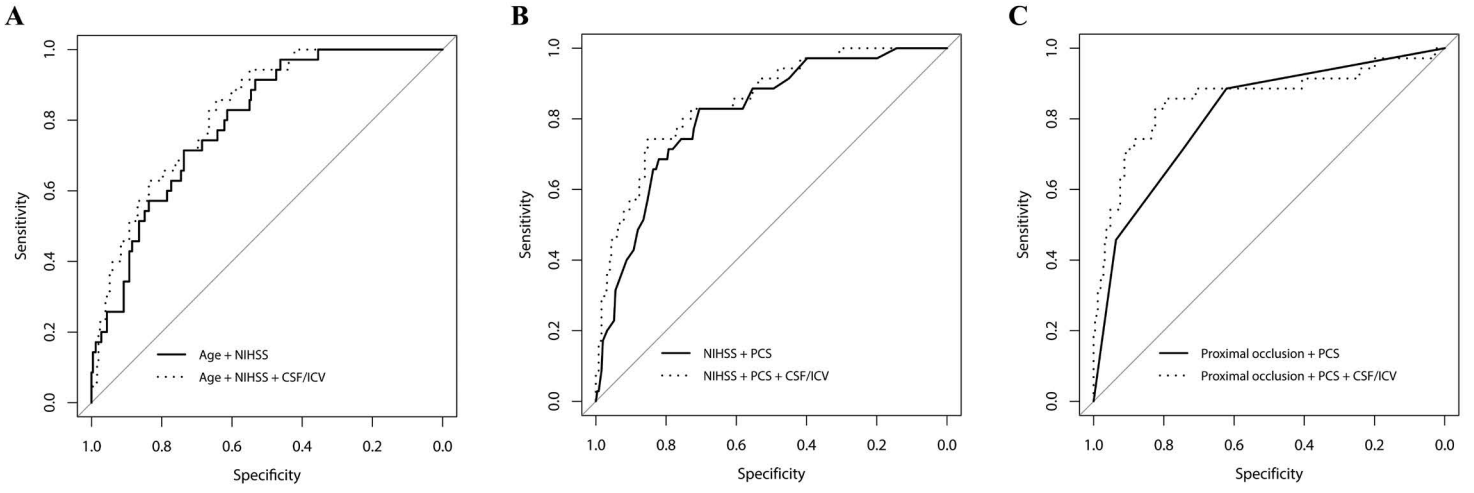

Figure 3. Performance of prediction models with and without the ratio of intracranial cerebrospinal fluid volume to intracranial volume

Legend: Clinical prediction model (A), prediction model with clinical and imaging predictors (B) and imaging prediction model (C) with and without the ratio of intracranial cerebrospinal fluid volume to intracranial volume (CSF/ICV), respectively. NIHSS indicates National Institutes of Health Stroke Scale; PCS, poor collateral score; proximal occlusion, terminal internal carotid artery or proximal M1 occlusion.

Of the 87 patients aged from 18 to 60, 20 (23%) developed ME (Supplemental table III). In this group of patients, no significant associations between CSF/ICV and ME were observed in the three multivariable models (Supplemental table IV). The three models did not improve significantly after CSF/ICV was added (Supplemental table V).

Of the 95 patients with an NIHSS of 16 or higher, 21 (22%) developed ME (Supplemental table VI). In this group of patients, no associations between CSF/ICV and ME were observed in the three multivariable models (Supplemental table VII). Only model 2 improved significantly (P=0.047) after CSF/ICV was added (Supplemental table VIII).

DISCUSSION

In this study, we evaluated the added value of the ratio of intracranial CSF volume to ICV in predicting ME. By building three statistical models we showed that CSF/ICV is a predictor of malignant MCA infarction independent of 1) age and NIHSS, 2) NIHSS and poor collateral score and 3) terminal ICA or proximal M1 occlusion and poor collateral score. When comparing performances of the models with and without CSF/ICV, the three models improved significantly after CSF/ICV was added.

Our results are in accordance with the only previous study that investigated the association between intracranial CSF volume and ME.[26] In the previous study, which had a retrospective design, half of the 52 patients with terminal carotid or proximal M1 occlusion developed ME, while in our study 12% developed ME. This difference can be explained by the different use of selection criteria. In the previous study, patients with an ICA or proximal M1 occlusion were included, while in our study, we also included patients with a distal M1 or M2 occlusion. In our study, 33% (22/69) of the patients with terminal ICA or proximal M1 occlusion developed ME. As expected, the presence of a terminal ICA or proximal M1 occlusion was associated with the development of ME as compared to the presence of a more distal occlusion. Nonetheless, 6% of the patients with an occlusion of the distal M1 segment or M2 segment of the MCA also developed ME. This implies that future studies should not only address the most proximal MCA occlusions, although these patients face the highest risk of developing malignant MCA infarction.

As brain volume shrinks with increasing age, it is not surprising that patients who develop ME are typically younger than patients who do not develop ME as there is less space for the brain to swell without causing herniation.[1] Similar to atrophy,

previous stroke, which is typically a disease of the elderly, may lead to an increase of the ratio of intracranial CSF volume to ICV. In our study, patients with malignant MCA infarction were indeed younger than the patients without malignant MCA infarction. We did not formally test the correlation between age and CSF/ICV, but the assumption of collinearity between predictors was not violated. Moreover, when adjusted for age and admission NIHSS, CSF/ICV was still significantly related to ME and the clinical model improved significantly after CSF/ICV was added. The observed associations did not hold in the subgroup analyses of patients aged from 18 to 60 and patients with an NIHSS of 16 or higher. Although the odds ratios indicated a positive association between CSF/ICV and malignant MCA infarction for these subgroups, the power was too low for the associations to reach significance.

Similar to the clinical model, CSF/ICV was of added value to the imaging prediction model. In fact, the AUROC of the imaging model was even higher than the AUROC of the clinical model. However, we did not formally test the difference between the performances of the clinical and imaging models as this was not our primary research question. Still, these results emphasize the need for the use of imaging findings for the prediction of malignant MCA infarction and, perhaps, other complications of stroke.

One strength of this study was the prospective design. As a consequence, we only had few missing data and a low number of drop outs, which minimizes the risks of information bias and selection bias, respectively. Another strong point of this study was the quantification of the intracranial CSF volume and ICV by applying a brain atlas on the CT scans. Since this is an entirely automated technique for quantifying brain volumes, neither observation bias nor interrater reliability is an issue for this measurement of interest. Furthermore, this method is robust to CT noise, loss of gray-white differentiation or other early ischemic changes on NCCT as the volumes are derived from mixture model histograms and not directly from segmentations.

One of the limitations of this study was the large number of exclusions due to the unavailability of thin-slice NCCT images, which was not a standard procedure for the DUST study. We chose to exclude those patients, because volume measurements would be less precise on thick slice images and for the sake of the uniformity of the measurements. However, we do not think that excluding patients in this manner influences the results, since the collection of thin-slice data is a random feature and neither related to CSF volume nor the development of ME. Furthermore, no large relevant differences were observed between the characteristics of the included and excluded patient groups. In general, thin-slice NCCT data are nowadays routinely

acquired as part of stroke imaging protocols. Another drawback of this study was the limited number of outcomes. As a consequence, we could not add more than three variables to the prediction models and we were not able to include CTP variables or build a large prognostic model. Unfortunately, we did not have a sufficient large sample size either for developing a new clinically usable prediction model or for validating a previously developed model.[10] In the future, larger cohorts with MCA infarction should be evaluated for the purpose of developing a prediction model that can be readily used in clinical practice. We used a dichotomized measure of midline shift as the primary outcome. Although dichotomizing this measure may lead to loss of information, we think that interrater variability is lower than when a continuous measure was used, but we were not able to formally test this assumption.

We did not use clinical information to define malignant MCA infarctions. Although some previous studies used both clinical and imaging information for defining ME, we think that solely using the quantitative measure of midline shift is sufficient to identify malignant MCA infarction as has been done previously.[4] We did not collect data on treatment of malignant MCA infarction. As a result, we were not able to evaluate whether patients, who have been treated, would have been treated sooner, or patients, who have not been treated, would have been treated after taking into account the results of this study. Still, we found that CSF/ICV significantly improves three types of prediction models. As a consequence, patients at risk for malignant MCA infarction can be recognized and treated earlier. In the future, larger prediction models need to be developed and their influence on patient management and clinical outcome should be evaluated.

In conclusion, the CSF/ICV ratio is associated with malignant MCA infarction and has added value to small clinical and imaging prediction models.

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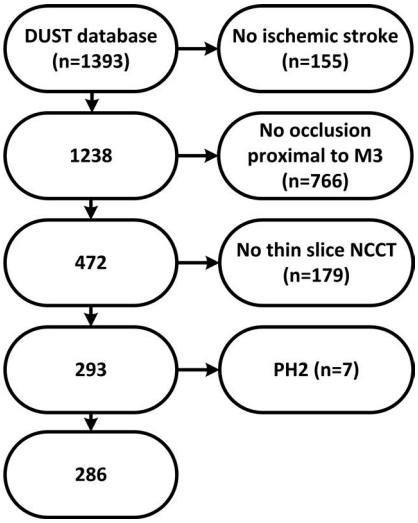
SUPPLEMENTS



Supplemental figure I. Flowchart of patient selection

Legend: DUST indicates Dutch Acute Stroke Study; NCCT, non-contrast CT; PH2, parenchymal hemorrhage type 2 according to European Cooperative Acute Stroke Trials classification.

Supplemental table I. Characteristics of patients with and without thin-slice non-contrast CT images

Characteristic	**Included** n=286	**Excluded** n=175	**P value***
Age, mean±SD	67±14	65±15	0.090
Male sex, n (%)	162 (57)	102 (58)	0.803
Admission NIHSS, median (Q1-Q3)	13 (7-17)	13 (9-19)	0.061
Time from symptom onset to scan, minutes, median (Q1-Q3)	113 (68-160)	85 (62-135)	0.011
Intravenous tPA, n (%)	201 (70)	131 (75)	0.339
Endovascular treatment, n (%)	33 (12)	27 (15)	0.288
Medical history			
Hypertension, n (%)	145 (51)	89 (51)	1.000
Diabetes mellitus, n (%)	36 (13)	25 (15)	0.651
Hyperlipidemia, n (%)	80 (28)	45 (27)	0.800

Supplemental table I. Characteristics of patients with and without thin-slice non-contrast CT images (continued)

Characteristic	**Included** n=286	**Excluded** n=175	**P value***
Smoking			0.792
- Smoking currently, n (%)	79 (30)	45 (30)	
- Former smoking, n (%)	83 (32)	52 (35)	
- Never smoked, n (%)	100 (38)	53 (35)	
Atrial fibrillation, n (%)	47 (17)	24 (14)	0.491
History of stroke/TIA, n (%)	56 (20)	25 (14)	0.180
History of MI, n (%)	41 (15)	15 (9)	0.093
Imaging findings			
Hyperdense vessel sign, n (%)	126 (44)	106 (62)	<0.001
NCCT ASPECTS, median (Q1-Q3)	10 (8-10)	10 (8-10)	0.717
CBV ASPECTS, median (Q1-Q3)	7 (5-9)	7 (5-9)	0.054
MTT ASPECTS, median (Q1-Q3)	3 (2-6)	4 (3-6)	0.021
Terminal ICA/proximal M1 occlusion, n (%)	69 (24)	48 (27)	0.496
Poor collateral score, n (%)	89 (31)	48 (28)	0.534
Follow-up			
Malignant MCA infarction, n (%)	35 (12)	19 (11)	0.766
Poor clinical outcome at 90 days*, n (%)	151 (53)	86 (50)	0.576

* Either parametric or nonparametric tests were performed depending on the variable distribution.
† Poor clinical outcome was defined as modified Rankin Scale equal or greater than 3.
SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; tPA, tissue-type plasminogen activator; TIA, transient ischemic attack; MI, myocardial infarction; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; CSF, cerebrospinal fluid; ICV, intracranial volume; CBV, cerebral blood volume; MTT, mean transit time; ICA, internal carotid artery; CBS, clot burden score; MCA, middle cerebral artery.

Supplemental table II. Association between potential predictors and malignant middle cerebral artery infarction

Characteristic	OR (95% CI)
Age, per 10 years decrease	1.5 (1.2-2.0)
Male sex	1.5 (0.7-3.3)
Admission NIHSS, per point increase	1.2 (1.1-1.3)
Intravenous tPA	0.6 (0.3-1.2)
Endovascular treatment	1.7 (0.6-4.3)
Imaging findings	
Hyperdense vessel on NCCT	3.5 (1.7-8.0)
NCCT (pc-)ASPECTS score, per point decrease	1.8 (1.5-2.1)
CSF volume, per 100 mL decrease	3.1 (1.6-6.5)
CSF/ICV per 10% decrease	4.5 (1.9-11.7)
CBV (pc-)ASPECTS score, per point decrease	1.7 (1.5-2.1)
Terminal ICA/proximal M1 occlusion	7.3 (3.5-16.0)
Poor collateral score	7.3 (3.4-16.7)

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue-type plasminogen activator; NCCT, non-contrast CT; ASPECTS, Alberta Stroke Program Early CT Score; CSF, cerebrospinal fluid; ICV, intracranial volume; CBV, cerebral blood volume; ICA, internal carotid artery.

Supplemental table III. Subgroup characteristics: patients aged from 18 to 60

Characteristic	Total n=87	ME n=20 (23%)	No ME n=67 (77%)	P value*
Age, mean±SD	50±8	48±10	50±7	0.439
Male sex, n (%)	58 (67)	14 (70)	44 (66)	0.719
Admission NIHSS, median (Q1-Q3)	12 (7-17)	16 (13-18)	12 (7-15)	0.001
Imaging findings				
CSF/ICV percentage, mean±SD	9±4	9±4	10±4	0.418
Terminal ICA/proximal M1 occlusion, n (%)	22 (25)	12 (60)	10 (15)	<0.001
Poor collateral score, n (%)	25 (29)	13 (65)	12 (18)	<0.001
Follow-up				
Poor clinical outcome at 90 days†, n (%)	43 (50)	19 (95)	24 (36)	<0.001

* Either parametric or nonparametric tests were performed depending on the variable distribution.
† Poor clinical outcome was defined as modified Rankin Scale equal or greater than 3.
ME indicates malignant edema; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume; ICA, internal carotid artery.

Supplemental table IV. Subgroup analysis: multivariable prediction models and the association with malignant middle cerebral artery infarction in patients aged from 18 to 60

Factor	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age, per 10 years decrease	1.3 (0.7-2.7)		
Admission NIHSS, per point increase	1.2 (1.1-1.3)	1.1 (1.0-1.3)	
Terminal ICA/proximal M1 occlusion			9.6 (2.5-36.7)
Poor collateral score		5.5 (1.6-18.5)	9.6 (2.6-35.6)
CSF/ICV, per 10% decrease	2.4 (0.5-12.5)	1.7 (0.3-10.8)	1.1 (0.2-8.1)

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume.

Supplemental table V. Subgroup analysis: comparison of clinical and imaging models with and without the ratio of intracranial cerebrospinal fluid volume to intracranial volume in patients aged from 18 to 60

Factor	AUROC	95% CI	P value
Age + NIHSS	0.736	0.612-0.860	
Age + NIHSS + CSF/ICV	0.754	0.630-0.877	
Difference	0.018		0.278
NIHSS + Poor collateral score	0.800	0.690-0.910	
NIHSS+ Poor collateral score+ CSF/ICV	0.812	0.704-0.919	
Difference	0.012		0.545
ICA/proximal M1 occlusion + Poor collateral score	0.836	0.706-0.936	
ICA/proximal M1 occlusion + Poor collateral score + CSF/ICV	0.840	0.706-0.966	
Difference	0.004		0.916

AUROC indicates area under the receiver operating characteristic curve; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume.

Supplemental table VI. Subgroup characteristics: patients with NIHSS of 16 or higher

Characteristic	Total n=95	ME n=21 (22%)	No ME n=74 (78%)	P value*
Age, mean±SD	68±15	61±19	69±13	0.084
Male sex, n (%)	46 (48)	12 (57)	34 (46)	0.365
Admission NIHSS, median (Q1-Q3)	18 (17-20)	19 (18-22)	18 (17-20)	0.042
Imaging findings				
CSF/ICV percentage, mean±SD	13±4	12±5	13±4	0.119
Terminal ICA/proximal M1 occlusion, n (%)	33 (35)	12 (57)	21 (28)	0.015
Poor collateral score, n (%)	47 (50)	17 (81)	30 (41)	0.001
Follow-up				
Poor clinical outcome at 90 days†, n (%)	74 (79)	21 (100)	53 (73)	0.007

* Either parametric or nonparametric tests were performed depending on the variable distribution.

† Poor clinical outcome was defined as modified Rankin Scale equal or greater than 3.

ME indicates malignant edema; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume; ICA, internal carotid artery.

Supplemental table VII. Subgroup analysis: multivariable prediction models and the association with malignant middle cerebral artery infarction in patients with NIHSS of 16 or higher

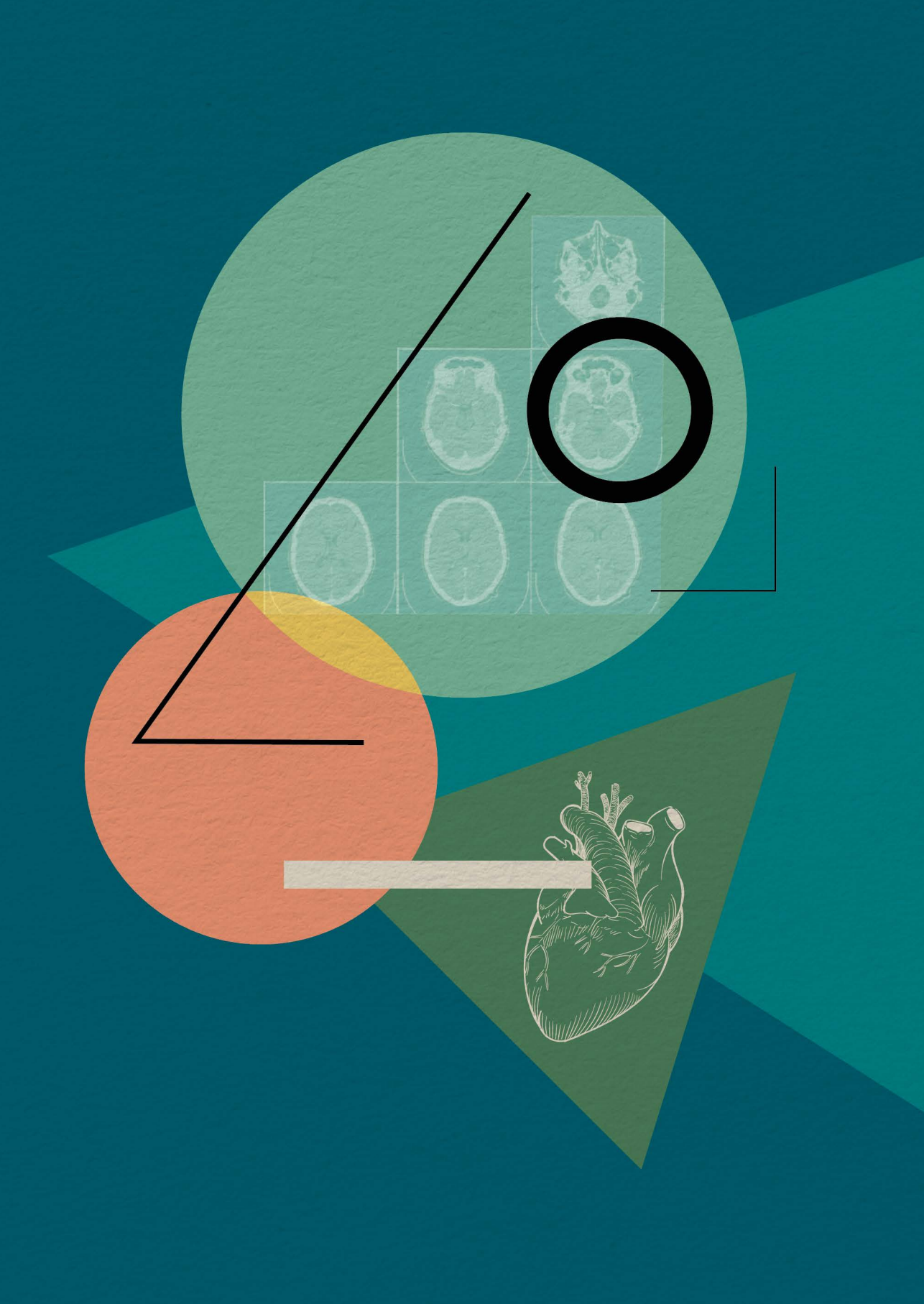
Factor	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Age, per 10 years decrease	1.4 (0.9-2.0)		
Admission NIHSS, per point increase	1.2 (1.0-1.5)	1.2 (1.0-1.4)	
Terminal ICA/proximal M1 occlusion			3.7 (1.2-11.3)
Poor collateral score		5.7 (1.7-19.6)	7.0 (2.0-24.9)
CSF/ICV, per 10% decrease	1.9 (0.5-7.8)	3.5 (0.9-13.0)	3.1 (0.9-11.0)

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume.

Supplemental table VIII. Subgroup analysis: comparison of clinical and imaging models with and without the ratio of intracranial cerebrospinal fluid volume to intracranial volume in patients with NIHSS of 16 or higher

Factor	AUROC	95% CI	P value
Age + NIHSS	0.674	0.537-0.811	
Age + NIHSS + CSF/ICV	0.714	0.586-0.841	
Difference	0.040		0.355
NIHSS + Poor collateral score	0.753	0.645-0.860	
NIHSS+ Poor collateral score+ CSF/ICV	0.777	0.650-0.905	
Difference	0.024		0.047
ICA/proximal M1 occlusion + Poor collateral score	0.767	0.634-0.898	
ICA/proximal M1 occlusion + Poor collateral score + CSF/ICV	0.796	0.648-0.944	
Difference	0.029		0.070

AUROC indicates area under the receiver operating characteristic curve; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; CSF, cerebrospinal fluid; ICV, intracranial volume



10

MALIGNANT INFARCTION AFTER ENDOVASCULAR TREATMENT: INCIDENCE AND PREDICTION

Based on:
Bernsen* MLE, Kauw* F, Martens JM, van der Lugt A, Yo LS, van Walderveen MA, Roos YB, van der Worp HB, Dankbaar JW, Hofmeijer J. Malignant infarction after endovascular treatment: Incidence and prediction. Int J Stroke. 2021 Apr 9:17474930211006290.
*authors contributed equally as co-first authors

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ABSTRACT

Background

Early prediction of malignant infarction may guide treatment decisions. For patients who received endovascular treatment, the risk of malignant infarction is unknown and risk factors are unrevealed.

Aims

The objective of this study is to estimate the incidence of malignant infarction after endovascular treatment in patients with an occlusion of the anterior circulation, to identify independent risk factors, and to establish a model for prediction.

Methods

We analyzed patients who received endovascular treatment for a large vessel occlusion in the anterior circulation within 6.5 hours after symptom onset, included in the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) Registry between March 2014 and June 2016. We compared patients with and without malignant infarction. Candidate predictors were incorporated in a multivariable binary logistic regression model. The final prediction model was established using backward elimination. Discrimination and calibration were evaluated with the area under the receiver operating characteristic curve (AUROC) and the Hosmer-Lemeshow test.

Results

Of 1445 patients, 82 (6%) developed malignant infarction. Independent predictors were lower age, higher NIHSS, lower ASPECTS, internal carotid artery occlusion, lower collateral score, longer times from onset to groin puncture, and unsuccessful reperfusion. The AUROC of a prediction model combining these features was 0.83 (95% CI: 0.79-0.88) and the Hosmer-Lemeshow test indicated appropriate calibration (P=0.937).

Conclusion

The risk of malignant infarction after endovascular treatment started within 6.5 hours of stroke onset is approximately 6%. Successful reperfusion decreases the risk. A prediction model combining easily retrievable measures of age, ASPECTS, collateral status, and reperfusion shows good discrimination between patients who will develop malignant infarction and those who will not.

INTRODUCTION

Malignant infarction, characterized by severe space-occupying edema formation, is a life-threatening complication of ischemic stroke, with case fatality rates of up to 78%.[1] The reported incidence depends on the definition of malignant infarction and the study population, and ranges from two percent in unselected cohorts of patients with ischemic stroke to thirty percent in patients with an occlusion of the middle cerebral artery (MCA).[2–6]

The only treatment option of proven benefit is surgical decompression through a large hemicraniectomy and duraplasty.[7,8] This treatment is beneficial if applied within 48 hours of stroke onset, possibly with greater benefit after earlier treatment.[7,9] Only few factors allow reliable prediction of life-threatening edema formation.[10] Lesion volume of >82cc on diffusion-weighted imaging (DWI) within 6h after symptom onset predicted a 'malignant' evolution with 98% specificity, but with low sensitivity.[11]

As the risk of malignant infarction seems to increase with infarct size, a relatively high incidence is expected in patients with occlusions of the proximal segments of the anterior circulation who present with severe neurological deficits.[10] A large reduction of the need for surgical decompression has been described after endovascular treatment (EVT) with a stent retriever and successful reperfusion has been associated with reduced midline shift in the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), which suggests that malignant infarction can be prevented with early recanalization.[12–14] Still, even patients with successful EVT may develop malignant infarction.[15] Size of the ischemic area, timing and degree of reperfusion, and collateral status may affect this risk.[3]

We aimed to estimate the incidence of malignant infarction in patients with ischemic stroke in the anterior circulation who undergo EVT, identify predictors of malignant infarction after EVT, and develop a prediction model.

METHODS

Design

We analyzed patients who were included in the MR CLEAN Registry[16]. The MR CLEAN Registry is a prospective, observational study in all centers that perform EVT in the Netherlands. In this registry, all patients who underwent EVT (defined as entry into the angiography suite and arterial puncture) between March 16, 2014 and June 15, 2016 were included for the current analysis. The MR CLEAN Registry was approved by the ethics committee of the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2014-235).

Patients

Inclusion criteria for the present study were: age of 18 years or older, intracranial arterial occlusion in the anterior circulation (internal carotid artery (ICA), ICA terminus (ICA-T) or middle (M1/M2) or anterior (A1/A2) cerebral artery), and groin puncture within 6.5 hours of symptom onset.

Identification of patients with malignant infarction

The primary outcome measure was malignant infarction based on clinical and radiological reports. Patients who underwent hemicraniectomy or died because of life-threatening edema formation were classified as having 'malignant infarction'. First, we selected patients who died within one week after stroke onset and patients who underwent hemicraniectomy. Subsequently, from this subgroup, letters of discharge in combination with scan reports (if available) were used to identify the cause of death or reason for hemicraniectomy. Letters of discharge were screened for indications of malignant infarction such as decreased arousal, pupillary changes and a (rapid) decline in neurological status. Scan reports were screened for marks of space occupying edema such as midline shift greater than 5 mm. If midline shift was not measured, we relied on other parameters such as herniation. Patients with symptomatic intracranial hemorrhage or another known cause of death, such as infection, myocardial infarction or pulmonary embolism, were classified as 'no malignant infarction'. Patients with an unknown cause of death were excluded from further analysis.

Treatment

Patients were treated according to national guidelines for the treatment of acute ischemic stroke, including intravenous thrombolysis, if indicated. The necessity of decompressive surgery was left to the judgment of the attending stroke team.

Imaging

ASPECTS was graded from 0 to 10, with 1 point subtracted for any evidence of early ischemic changes in each defined region on NCCT.[17] In our study, proximal occlusion site was defined as an ICA or ICA-T occlusion. Collaterals were graded on a 4-point scale ranging from 0 (absent collaterals) to 3 (excellent collaterals).[18] The eTICI score ranges from 0 (no antegrade reperfusion of the territory of the occluded artery) to 3 (complete antegrade reperfusion). Successful reperfusion was defined as eTICI 2B-3. Intracranial hemorrhage was classified on follow-up imaging according to the Heidelberg criteria and was considered symptomatic if the patient had died or had deteriorated neurologically.[19]

Candidate predictors

Candidate predictors were selected based on the available literature and results of univariable analysis.[11,13,20–23] These included age, history of hypertension, statin use, baseline NIHSS, admission glucose level, ASPECTS, proximal occlusion site, collateral score, time from onset to groin puncture, and reperfusion grade.

Statistical analyses

Baseline characteristics are presented in a descriptive way for patients with and without malignant infarction. Differences between groups were tested with Pearson's chi-square test in case of ordinal/nominal variables and Mann-Whitney-U or unpaired t-test in case of continuous variables.

We performed a multivariable binary logistic regression analysis. All candidate predictors were included and backward elimination was applied to identify the most efficient final model. We used a p-value of 0.05 as the cutoff value. The collinearity assumption was not violated according to the variance inflation factors. The discriminative ability and calibration of the model were evaluated with the area under the receiver operating characteristic curve (AUROC) and the Hosmer-Lemeshow test, respectively. With the Hosmer-Lemeshow test, a non-significant p-value reflects appropriate calibration. The aforementioned analyses were performed in R version 3.5.1.

Missing values

Missing NIHSS scores were retrospectively scored with a standardized score chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy for time of procedure duration.[24] In order to make unbiased estimates of associations between imaging and clinical parameters and the

development of space-occupying edema, multiple imputation was performed. The descriptive analyses included all patients without imputation of the data.

RESULTS

Of the 1628 patients, who were registered in the MR CLEAN Registry, 140 patients were excluded, mainly because of an occlusion in the posterior circulation or because the time from onset to EVT was longer than 6.5 hours. From the included 1488 patients, 82 (6%, 95% CI 4-7%) patients were classified as having a malignant infarction. Patients with an unknown cause of death (n=43) were excluded from further analysis (Figure 1).

Baseline characteristics

Patients who developed malignant infarction were younger and higher NIHSS at the time of presentation than patients who did not develop malignant infarction (Table 1). Furthermore, patients with malignant infarction less often had hypertension and used statin less frequently, and they had lower ASPECTS scores, more proximal occlusions (ICA or ICA-T) and lower collateral scores. Also, these patients had longer times of onset to groin puncture and onset to reperfusion/last contrast bolus, a longer duration of the procedure and more often unsuccessful reperfusion (Table 1).

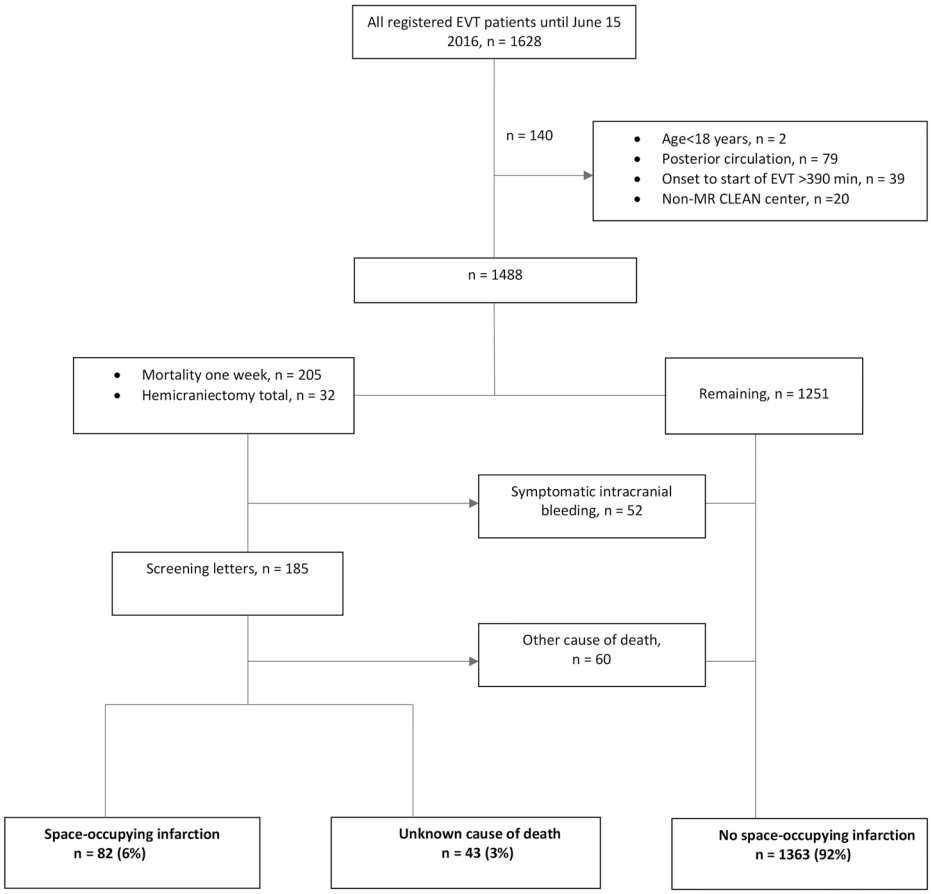

Figure 1. Flowchart of patient selection

Legend: EVT indicates endovascular treatment; MR CLEAN, Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands.

Table 1. Baseline characteristics

Characteristic, n (%)	**No malignant infarction** n=1363	**Malignant infarction** n=82	**P value**
Demographics			
Age, median (Q1-Q3)	70 (59-79)	61 (52-75)	<0.001
Male	718 (53)	47 (57)	0.428
NIHSS, median (Q1-Q3)	16 (11-20)	19 (16-22)	<0.001
Medical history			
Previous stroke	230 (17)	8 (10)	0.121
Myocardial infarction	212 (16)	9 (11)	0.343
Peripheral artery disease	127 (10)	4 (5)	0.232
Atrial fibrillation	306 (23)	13 (16)	0.172
Cardiovascular risk factors			
Hypertension	692 (51)	29 (36)	0.008
Hypercholesterolemia	397 (30)	19 (24)	0.258
Diabetes mellitus	230 (17)	12 (15)	0.651
Current Smoking	310 (23)	18 (22)	0.532
Medication			
Antiplatelet use	450 (34)	22 (5)	0.229
Statin	485 (36)	20 (24)	0.032
Stroke characteristics			
Treatment with IVT	1077 (79)	61 (74)	0.328
Glucose level, median (Q1-Q3)	7 (6-8)	7 (6-9)	0.159
ASPECTS subgroups			<0.001
- 0-4	73 (6)	17 (22)	
- 5-7	301 (23)	29 (37)	
- 8-10	932 (71)	33 (42)	
Most proximal level of occlusion			<0.001
- ICA/ICA-T	336 (25)	42 (55)	
- M1	774 (60)	31 (40)	
- M2	168 (13)	4 (5)	
- Other	18 (1)	0 (0)	

Table 1. Baseline characteristics (continued)

Characteristic, n (%)	No malignant infarction n = 1363	Malignant infarction n = 82	P value
Collateral score			<0.001
- 0=Absent collaterals	69 (6)	22 (29)	
- 1= Filling <50%	408 (32)	38 (50)	
- 2= >50% but less than 100%	514 (41)	8 (11)	
- 3=Filling 100%	274 (22)	8 (11)	
Workflow			
Onset to groin puncture in minutes, median (Q1-Q3)	205 (160-262)	220 (180-295)	0.009
Onset to reperfusion/last contrast bolus in minutes, median (Q1-Q3)	264 (214-326)	324 (261-353)	<0.001
Duration of procedure in minutes, median (Q1-Q3)	62 (40-89)	85(58-121)	<0.001
General anesthesia	339 (27)	28 (37)	0.063
Post EVT eTICI			0.048
- 0	226 (17)	19 (24)	
- 1	42 (3)	3 (4)	
- 2A	274 (20)	24 (30)	
- 2B	251 (19)	15 (19)	
- 2C	130 (10)	5 (6)	
- 3	421 (31)	14 (18)	
Successful reperfusion (eTICI 2B-3)	802 (60)	34 (43)	0.003

Q1 indicates first quartile; Q3, third quartile; NIHSS, National Institutes of Health Stroke Scale; IVT, intravenous trombolysis; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; MCA-M, middle cerebral artery segment; EVT, endovascular treatment; eTICI, expanded treatment in cerebral ischemia.

Model development

The following factors were independently associated with malignant infarction: lower age, higher baseline NIHSS, lower ASPECTS, proximal occlusion site (ICA or ICA-T), lower collateral score, longer time from onset to groin puncture and unsuccessful reperfusion (Table 2, Figure 2). The AUROC of a prediction model combining these

factors was 0.83 (95% CI 0.79-0.88). The Hosmer-Lemeshow test showed that the calibration of the model was appropriate (P=0.937).

Table 2. Associations between baseline characteristics and malignant infarction

	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Age, per 10 years older	0.8	(0.7-0.9)	0.7	(0.6-0.8)
NIHSS, per point higher	1.1	(1.1-1.2)	1.1	(1.0-1.1)
ASPECTS, per point lower	1.3	(1.2-1.4)	1.1	(1.0-1.3)
Proximal occlusion site (ICA/ICA-T)	3.2	(2.0-5.1)	2.2	(1.3-3.5)
Collateral score, per point lower	2.8	(2.1-3.8)	2.5	(1.8-3.4)
Onset to groin puncture, per 60 minutes longer	1.3	(1.1-1.5)	1.3	(1.1-1.6)
Unsuccessful reperfusion (eTICI 0-2A)	1.9	(1.2-3.0)	1.8	(1.1-2.9)

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; eTICI, expanded Treatment In Cerebral Ischemia.

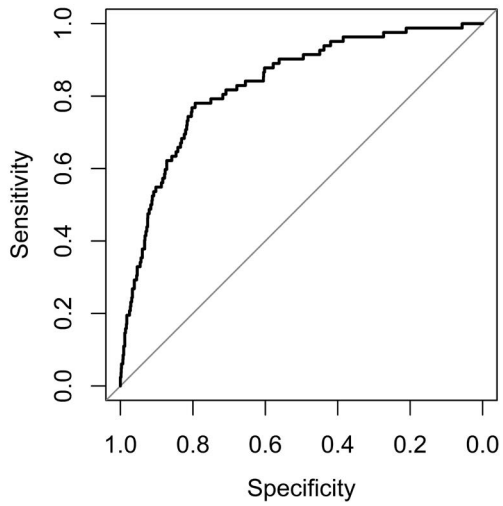

Figure 2. Receiver operating characteristic curve for the prediction of space occupying edema by the combined predictors (age, baseline NIHSS, ASPECTS, ICA/ICA-T occlusion, collateral score, time from onset to groin puncture and TICI 2B-3). The area under the curve is 0.83 (95%CI: 0.79-0.88).

DISCUSSION

In patients who had anterior circulation occlusions and received EVT, the risk of malignant infarction was 6%. This risk was higher with lower age, higher baseline NIHSS, lower ASPECTS, more proximal occlusion site, worse collateral filling, longer time from onset to groin puncture and unsuccessful reperfusion. A prediction model combining these factors had high discriminative ability and was well calibrated.

Before the implementation of EVT, the reported incidence of malignant infarction in patients with ischemic stroke ranged from 2% to 30%, with higher incidence in patients with larger infarcts.[3-5] In this study, we found a relatively low incidence of 6% in patients with large infarcts. This can partly be explained by the fact that all patients in this study received EVT resulting in higher rates of recanalization.[13,14]

Some previous studies have reported on associations between reperfusion therapies and malignant infarction.[5,25,26] In these studies, reperfusion injury was put forward as a possible causal factor. By contrast, Gauberti *et al*. showed no significant increase of edema after complete reperfusion in patients who received EVT for ischemic stroke.[27] We found a lower risk of malignant infarction in patients where successful reperfusion was achieved. Longer time from symptom onset to groin puncture was independently related to larger risk of malignant infarction. A large study, with more than 2000 patients treated over a course of 9 years, suggested that EVT reduces the risk of malignant middle cerebral artery infarctions considerably. The researchers reported an incidence of malignant infarction of 32% in patients who received IVT alone and an incidence of 24% in patients who received EVT.[28] Even lower rates of malignant infarction after EVT have been reported in the REVASCAT (11%) and ESCAPE (5%) trials. However, from these studies, patients with (extensive) signs of ischemia on baseline CT were excluded.[28,29]

Our predictors are in line with reports on malignant infarction in the absence of EVT. Lower age is a well-established predictor.[30] The ratio of the extracellular space to intracranial volume is lower in younger patients, probably providing less buffering capacity for brain swelling.[31] NIHSS is a measure of stroke severity and high NIHSS has also been associated with malignant infarction.[30] The presence of early ischemic changes on admission CT is a harbinger of malignant infarction and can be evaluated with ASPECTS, which is a widely used tool to assess early ischemic changes.[17] In our study, lower ASPECTS was indeed associated with malignant infarction. In line with other studies, ICA/ICA-T occlusions were associated with higher rates of malignant

infarction compared to more distal occlusions.[21] This is probably explained by infarct size, which is larger with more proximal occlusions.

Collateral pathways include the circle of Willis, leptomeningeal vessels, the ophthalmic artery, and connections between distal segments of the large cerebral arteries. In our study, a lower collateral score was associated with a larger probability of malignant infarction. With poor collateral status more tissue is subjected to hypoperfusion in an early phase, causing more extensive infarcts.[32] This is in line with previous reports, where poor collaterals were associated with malignant infarction.[2,18]

Several models have been developed for predicting malignant infarction, however these models predate the introduction of endovascular treatment and their validity in the setting of current standard care is unknown.[30] Most models include the following predictors: lower age, higher NIHSS, larger parenchymal hypoattenuation on CT (lower ASPECTS) and lack off revascularization.[30] Most of the earlier prediction models are based on relatively small numbers of patients.[22,33] Shimoyama *et al.* used MRI to assess ASPECTS, which is thought to be more accurate than using CT.[23] This was reflected in the observed c-statistic of 0.88. However, MRI is not routinely conducted in stroke care in most centers and, therefore, generalizability to other centers seems limited. The EDEMA score, consisting of basal cistern effacement, serum glucose, no intravenous thrombolysis or thrombectomy, midline shift, and prior stroke, showed an acceptable predictive value, which improved by adding baseline NIHSS (c-statistic 0.76).[33] Other than previous reports, we only included patients who received EVT. In this well-defined subgroup, our final prediction model was superior to most of the previously developed models, which makes it a promising prediction tool for future use.

Our prediction model shows good discrimination between patients who will develop malignant infarction after EVT and those who will not, by using easily retrievable parameters. The results from this study are generalizable for patients with an occlusion in the anterior circulation who received EVT. For reliable derivation of predictive values for individual patient outcomes, the model needs validation, preferably in an external cohort.

One of the strengths of this study is the prospective registry design minimizing the concern of several types of bias. Furthermore, a large group of patients was analyzed and we prevented bias, caused by missing data, by using multiple imputation.

The most important limitation of our study is the identification of patients with malignant infarction, which was done retrospectively. With our current definition of malignant infarction, and with the screening of discharge letters from selected patients, we are confident to have reached a high specificity for the final diagnosis of (severe) malignant infarction. Since we wanted to reduce the risk of "missing" patients with malignant infarction who died at day 6 or 7, we chose to select patients who died within 7 days. We also aimed to reduce the risk of misclassifying malignant infarction in case of death by other causes. For that reason, we limited ourselves to the first 7 days after symptom onset. However, we may have misclassified patients that survived malignant infarction without hemicraniectomy, leading to an underestimation of the incidence. Additionally, 43 patients were excluded from our analysis, because the cause of death was unclear.

Lower age, higher baseline NIHSS, more proximal occlusion, lower ASPECTS, worse collateral status, longer time from onset to groin puncture, and unsuccessful reperfusion are independent predictors of malignant infarction in patients who had anterior circulation occlusions and received EVT. A prediction model combining these easily retrievable parameters showed good discrimination between patients who developed malignant infarction and those who did not.

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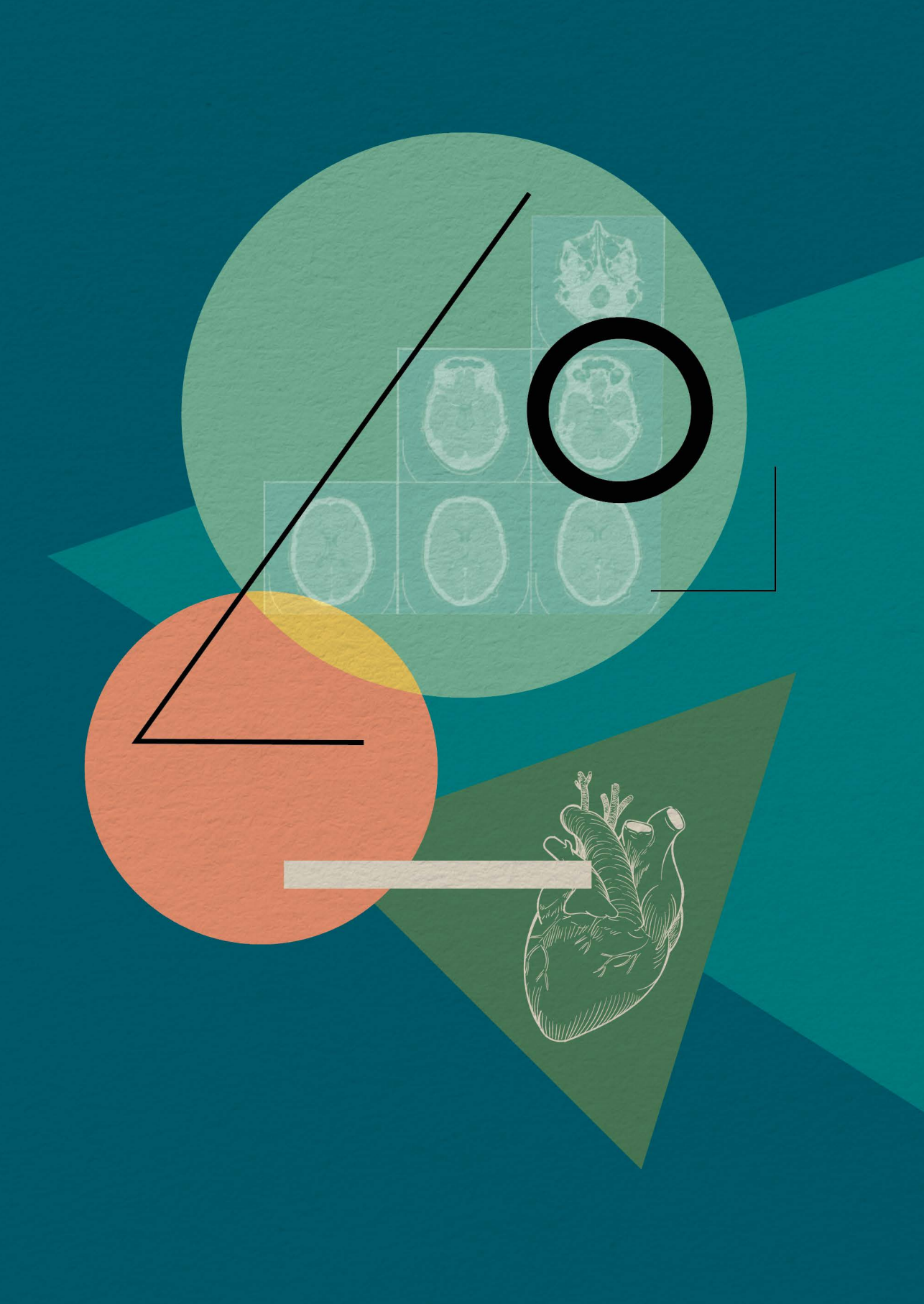

11

CEREBROSPINAL FLUID VOLUME IMPROVES PREDICTION OF MALIGNANT EDEMA AFTER ENDOVASCULAR TREATMENT OF STROKE

Based on:
Kauw* F, Bernsen* MLE, Dankbaar JW, de Jong HW, Kappelle LJ, Velthuis BK, van der Worp HB, van der Lugt A, Roos YB, Yo LS, van Walderveen MA, Hofmeijer J, Bennink E. Cerebrospinal fluid volume improves prediction of malignant edema after endovascular treatment of stroke. Int J Stroke. 2023 Feb;18(2):187-192.
*authors contributed equally as co-first authors

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ABSTRACT

Background

The ratio of intracranial cerebrospinal fluid (CSF) volume to intracranial volume (ICV) has been identified as a potential predictor of malignant edema formation in patients with acute ischemic stroke.

Aims

We aimed to evaluate the added value of the CSF/ICV ratio in a model to predict malignant edema formation in patients who underwent endovascular treatment.

Methods

We included patients from the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) Registry, a prospective national multicenter registry of patients who were treated with endovascular treatment between 2014 and 2017 because of acute ischemic stroke caused by large vessel occlusion. The CSF/ICV ratio was automatically measured on baseline thin-slice non-contrast CT. The primary outcome was the occurrence of malignant edema based on clinical and imaging features. The basic model included the following predictors: age, National Institutes of Health Stroke Scale, Alberta Stroke Program Early CT Score, occlusion of the internal carotid artery, collateral score, time between symptom onset and groin puncture, and unsuccessful reperfusion. The extended model included the basic model and the CSF/ICV ratio. The performance of the basic and the extended model was compared with the likelihood ratio test.

Results

Malignant edema occurred in 40 (6%) of 683 patients. In the extended model, a lower CSF/ICV ratio was associated with the occurrence of malignant edema (OR per percentage point, 1.2; 95% CI 1.1-1.3, P<0.001). Age lost predictive value for malignant edema in the extended model (OR 1.1; 95% CI 0.9-1.5, P=0.372). The performance of the extended model was higher than that of the basic model (P<0.001).

Conclusions

Adding the CSF/ICV ratio improves a multimodal prediction model for the occurrence of malignant edema after endovascular treatment.

INTRODUCTION

The occurrence of malignant edema may require timely decompressive surgery to prevent poor clinical outcomes in patients with acute ischemic stroke.[1,2] Accurate prediction of malignant edema formation may help in making prompt treatment decisions. Important factors that have been associated with malignant edema include lower age, higher National Institutes of Health Stroke Scale (NIHSS), more extensive early ischemic changes on non-contrast CT (NCCT), larger perfusion deficits on CT perfusion, more proximal thrombus location on CT angiography (CTA), and worse collateral filling in the affected area on CTA.[3] Incorporation of these factors in multivariable models has led to reasonable discrimination between groups of patients with and without malignant edema, but predictive values for individual patients remain moderate.[3]

In a previous study, we found the ratio of intracranial cerebrospinal fluid (CSF) volume to intracranial volume (ICV) to be of added value in models predicting malignant edema in patients with acute ischemic stroke.[4] Until now, this has not been validated in another cohort.

Recently, a prediction model for malignant edema after acute supratentorial ischemic stroke, for which endovascular treatment (EVT) was performed, has been developed based on the Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) Registry.[5] In the present study, we tested the additional predictive value of the CSF/ICV ratio.

METHODS

Study design

Patients were selected from the MR CLEAN Registry.[6] All patients undergoing EVT in the Netherlands were registered in this prospective national multicenter registry between March 16, 2014 and November 1, 2017. This study was reported according to the The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement.[7]

Patient selection

Inclusion criteria were age ≥18 years; clinical diagnosis of acute ischemic stroke due to large vessel occlusion of the anterior circulation (intracranial carotid artery, M1, M2, A1 or A2) visualized with CTA; EVT initiated within 6.5 hours of symptom onset or last seen well; and available thin-slice NCCT data on admission. As a result, 701 patients were included in our analysis (Figure 1).

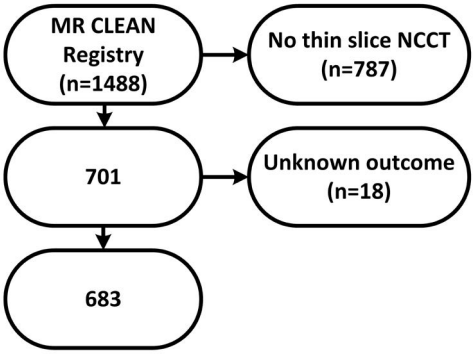

Figure 1. Flowchart of patient selection

Legend: MR CLEAN indicaties Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands; NCCT, non-contrast CT.

Ethics Approval and Data Availability

The study protocol of the MR CLEAN Registry was approved by the central medical ethics committee of the Erasmus University Medical Center, Rotterdam, the Netherlands. The requirement for written informed consent was waived, but patients or their representatives were provided with information on the study and were given the opportunity to refuse participation. Source data will not be made available, since no patient approval was obtained for sharing anonymized data.

However, detailed analytic methods and study materials will be made available to other researchers upon reasonable request to the corresponding author.

Data collection

Baseline characteristics such as demographics, stroke characteristics, and imaging variables were available from the MR CLEAN Registry database. All patients underwent NCCT and CTA before EVT and digital subtraction angiography (DSA) as part of EVT. NCCT was performed after EVT in case of neurological deterioration.

Imaging analysis

Visual imaging assessments were performed independently by two of 21 core lab members (20 interventional neuroradiologists and one interventional neurologist). The observers were blinded to clinical information except for the side of symptoms. NCCT, CTA and DSA images were evaluated in separate sessions.

Early ischemic changes on NCCT were graded with the Alberta Stroke Program Early CT Score (ASPECTS).[8]

Intracranial occlusions were dichotomized into occlusion of the internal carotid artery (ICA) and occlusion of the middle cerebral artery (M1 or M2 segment) or anterior cerebral artery (A1 or A2 segment). Assessment of collateral filling on CTA was based on the extent of collateral filling in the territory of the occluded artery: 0 indicates 0% filling, 1 indicates >0% and ≤50% filling, 2 indicates >50% and <100% filling and 3 indicates 100% filling.[9] Collateral scores were dichotomized as poor (scores of 0 or 1) or good (scores of 2 or 3).

Reperfusion after EVT was evaluated with the expanded Thrombolysis in Cerebral Infarction (eTICI) scale on DSA.[10] A score was assigned for the degree of reperfusion in the occluded area: an eTICI score of 0 reflects no reperfusion; 1 reflects minimal reperfusion, but no filling of the distal branches; 2A reflects 1 to 49%; 2B50 50 to 66%; 2B67 67 to 89%; 2C 90 to 99% and 3 100% filling of the distal branches. Successful reperfusion was defined as an eTICI score of 2B50 or higher. If DSA images were only available in one plane, then the highest possible eTICI score was 2A.

The ratio of intracranial CSF volume to ICV was automatically determined on thin-slice NCCT, as described previously.[4] In short, the brain was coarsely segmented into three tissue regions (all intracranial CSF, gray matter, white matter) by registering the ICBM 152 nonlinear atlas.[11–13] Volume fractions were plotted against Hounsfield units resulting in a histogram for each coarse segmentation: one for gray matter,

one for white matter and one for CSF. Gaussian mixture models were subsequently fitted to these histograms. In this way, we acquired precise volume measures in noisy data without the need for precise segmentations. The areas under the three Gaussian mixture models combined reflect the ICV and the area under the CSF curve reflects the CSF volume.

Outcome measures

The primary outcome was malignant edema, which was based on clinical and radiological criteria. Malignant edema was defined as: 1) decompressive surgery or death within one week after stroke onset because of a clinical diagnosis of malignant edema or 2) clinical features of malignant edema (decreased consciousness, unilateral dilated pupil and severe neurological deficit) together with a midline shift greater than 5 millimeters on NCCT. Based on the available data, patients were categorized into three outcome groups: malignant edema, no malignant edema or death with unknown cause. Patients, who were assigned to the category of death with unknown cause, were excluded from the analysis (Figure 1).

The secondary outcome was functional outcome 90 days after the stroke, graded with the modified Rankin Scale (mRS).

Statistical analysis

Parametric and nonparametric tests, where appropriate, were used to compare the characteristics of the group with malignant edema and the group without.

For the prediction analyses, missing values were solved by using multiple imputation in SPSS version 24, as described previously.[5]

A previously developed multivariable model was used as the basic model, which included the following predictors: age, baseline NIHSS, ASPECTS, ICA occlusion, collateral score, time between symptom onset and groin puncture, and unsuccessful reperfusion (Table 1).[5] An extended model was developed by adding the CSF/ICV ratio to the basic model. The c-statistics were compared with the DeLong test.[14] The added value of the CSF/ICV ratio was assessed by comparing the goodness of fit of the two models using the likelihood ratio test. In addition, the predictive value of age and ASPECTS were evaluated in the extended model. The assumption of collinearity was not violated according to the calculated variance inflation factors. We report odds ratios (OR), c-statistics and 95% confidence intervals (CI).

RESULTS

Of the 701 patients, 18 died from an unknown cause and were excluded from the final analysis (Figure 1). Of the included 683 patients, 40 (6%) developed malignant edema. Mean age was 68±14 years and 372 (54%) patients were male (Supplemental table I). One patient without malignant edema underwent decompressive surgery because of symptomatic intracranial hemorrhage. The median mRS at 90 days was higher in the group with malignant edema than in the group without malignant edema (median 6 versus 3, respectively, P<0.001). The mean CSF/ICV ratio was lower in the group with malignant edema than in the group without malignant edema (9±5 versus 14±6 percent, respectively, P<0.001). In the extended model (Table 1), a lower CSF/ICV ratio was associated with the occurrence of malignant edema (OR per percentage point, 1.2; 95% CI 1.1-1.3, P<0.001). Age lost predictive value for malignant edema in the extended model (OR 1.1; 95% CI 0.9-1.5, P=0.372). Removing age from the extended model did not change the c-statistic of the model significantly (0.873). In addition, ASPECTS lost predictive value in the extended model (OR 1.1; 95% CI 1.0-1.3, P=0.070).

Table 1. Multivariable prediction models and the association with malignant middle cerebral artery infarction

	Basic model		**Extended model**	
Predictor	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age (per 10 years younger)	1.5 (1.2-1.9)	0.002	1.1 (0.9-1.5)	0.372
Baseline NIHSS (per point higher)	1.1 (1.0-1.2)	0.027	1.1 (1.0-1.2)	0.039
ASPECTS (per point lower)	1.2 (1.0-1.4)	0.022	1.1 (1.0-1.3)	0.070
ICA occlusion	2.2 (1.1-4.6)	0.027	1.9 (0.9-4.0)	0.074
Collateral score (per point lower)	2.5 (1.6-4.2)	<0.001	2.8 (1.7-4.8)	<0.001
Onset to groin (per 60 minutes)	1.3 (1.0-1.8)	0.074	1.3 (0.9-1.7)	0.133
Unsuccessful reperfusion	1.6 (0.8-3.2)	0.198	1.9 (0.9-3.9)	0.087
CSF/ICV ratio (per percent lower)	-	-	1.2 (1.1-1.3)	<0.001
C-statistic	*0.856*		*0.876*	*0.141*
Likelihood ratio test				*<0.001*

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; ICA, internal carotid artery; CSF: cerebrospinal fluid; ICV, intracranial volume.

The c-statistic of the extended model was slightly higher than the c-statistic of the basic model (0.88 versus 0.86, respectively, P=0.141), which is also reflected in the ROC curves (Figure 2). The goodness of fit of the extended model was superior to the basic model (P<0.001). An example case is shown in Supplemental figure I.

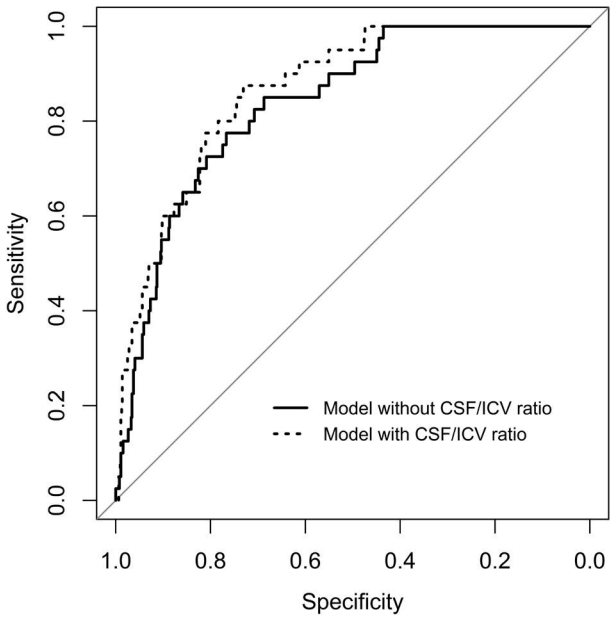

Figure 2. Receiver operating characteristic curves of the models with (dotted line) and without (solid line) the ratio of intracranial cerebrospinal fluid volume to intracranial volume.

Legend: CSF indicates cerebrospinal fluid; ICV, intracranial volume. The area under the curve of the basic model (solid line) was 0.86 and the area under the curve of the extended model (dotted line) was 0.88 (P=0.141).

DISCUSSION

This study shows that in patients with ischemic stroke, caused by large vessel occlusion, the CSF/ICV ratio on thin-slice NCCT is lower in patients who develop malignant edema after EVT than in those who do not, and that CSF/ICV ratio can improve a multimodal prediction model for malignant edema.

The predictive value of the CSF volume has been reported before.[4,15] In a previous multicenter study, we showed the added value of the CSF/ICV ratio to three prediction models.[4] In that study, we selected ischemic stroke patients independent of the treatment received. As a result, 70% received intravenous thrombolysis and 12%

received endovascular treatment, whereas in the current study, we assessed only patients who received endovascular treatment. The high proportion of reperfusion in the current cohort may explain the relatively low incidence of malignant edema in this study (6%) compared to the previous study (12%). Another explanation may be the applied definition of malignant edema. In previous studies, a single imaging parameter (midline shift >5 mm) was used, whereas in the current study we use both clinical information and imaging features to determine the occurrence of malignant edema.[4,16] Unfortunately, it was not feasible to perform a separate analysis with midline shift >5 mm as the outcome in this study. Despite these differences in methodology, the results regarding the added predictive value of the CSF/ICV ratio are similar.

The predictive value of age disappeared after the CSF/ICV ratio was added to our prediction model. In general, older patients have more CSF volume because of brain atrophy.[17] In addition, older patients may have had previous brain disease more often than younger patients such as stroke, which also results in more intracranial space. Consequently, older patients have a larger 'buffer' before brain swelling leads to midline shift or tissue herniation. In this study, previous ischemic stroke was more prevalent in the group without malignant edema than in the group with malignant edema. As age and the CSF/ICV ratio add similar predictive properties, one of the two predictors could be removed from the prediction model. Although age is readily available, and therefore more practical, the CSF/ICV ratio is a more direct reflection of the intracranial 'buffer' and adds more to the prediction model. This is supported by studies that showed that older patients can still develop malignant edema.[18]

An interaction between the CSF/ICV ratio and ASPECTS has been proposed.[19] Early signs of ischemia on non-contrast CT reflect early swelling of the brain.[8] As a result, it can be assumed that the CSF/ICV ratio is influenced by the degree of swelling in the acute phase. One might expect that the association between ASPECTS and malignant edema would weaken after adding the CSF/ICV ratio to the model, which was the case in this study. However, ASPECTS still had some predictive value in the extended model. The first possible explanation for this finding is that mixture model histograms were used to calculate the CSF and ICV volumes. This method is robust to noise, artefacts and early ischemic changes such as swelling. The second possible explanation is that the time window between symptom onset and CT was short (6.5 hours). The third possible explanation is that ASPECTS may involve only a (small) part of the brain, whereas the CSF/ICV ratio involves the whole brain.

Taken together with the previous study, in which the time window between symptom onset and CT was 9 hours, we did not find evidence for an interaction between ASPECTS and the CSF/ICV ratio. Still, (automated) calculations of both ASPECTS and CSF/ICV can help to identify patients at risk of developing malignant edema.

Several models have been proposed for the prediction of malignant edema.[3] Our analysis is in line with these studies with regard to the included predictors of malignant edema and the observed c-statistic of up to 0.88.[3] The c-statistic, which is equal to the area under the ROC curve, is often used to evaluate the discriminative performance of a prediction model, but it is not a sensitive measure for how well the model fits the data.[20] Discrimination is only one aspect of model performance, whereas goodness-of-fit is a more global measure of model performance, which can be evaluated with the likelihood ratio test.[20] This explains why the c-statistic of the extended model was slightly higher than the c-statistic of the basic model and the observed difference was insignificant, whereas the likelihood ratio test showed significant superiority of the extended model. This study is a step in finding the optimal prediction strategy for predicting malignant edema. Accurate prediction may lead to closer monitoring of patients at risk and timely decompressive surgery as warranted by the randomized controlled trials.[1]

Several strengths and limitations can be noted. A strength of this study was that a previously developed model, which was based on a cohort of 1445 patients, was used.[5] Although variables such as ICA occlusion and unsuccessful reperfusion were not significant in the extended model due to a lack of power, we were able to reliably compare the basic model to the extended model, which was the primary aim of this study. In addition, the prospective nature of this multicenter study resulted in only few missing values, which could be imputed. The second strength of this study was the determination of the CSF/ICV ratio, which was done automatically. The images can be analyzed within a few minutes and there is no risk of observer bias.

A limitation of this study was that we had to exclude many patients, because no thin-slice data were available. In our opinion, the risk of selection bias is limited as we do not expect that the availability of thin-slice data is related to either predictors or outcome. Nowadays, thin-slice NCCT data is available in almost every hospital in the Netherlands. In this study, all centers acquired thin-slice NCCT data, but not all the data were stored appropriately.

Another limitation of this study was the outcome assessment, which was done retrospectively. Although we believe that our definition of malignant edema was in

line with other studies, we may have missed some cases. Another limitation was the lack of validation of the extended prediction model, which can be done in an external cohort.

In conclusion, adding the CSF/ICV ratio improves a multimodal prediction model for the occurrence of malignant edema after endovascular treatment.

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SUPPLEMENTS

Supplemental table I. Patient characteristics

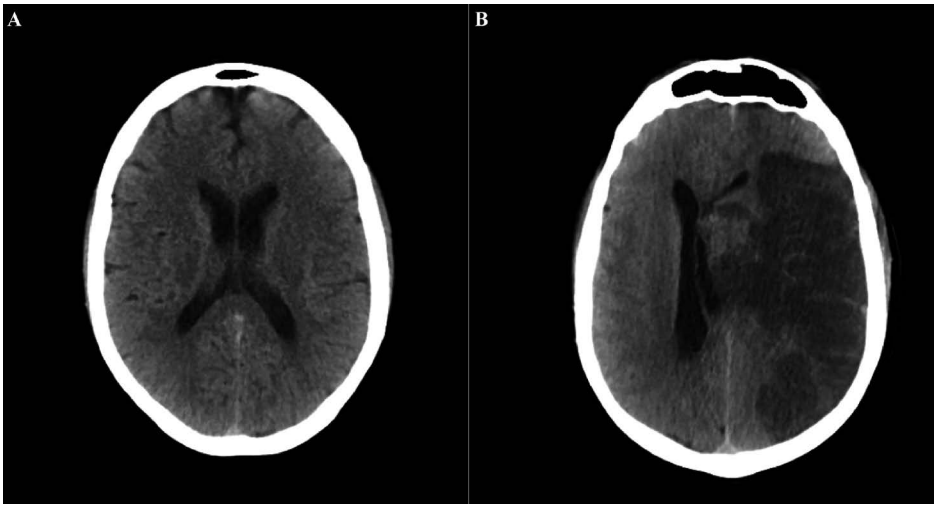
Characteristic, n (%)	**Total** n=683	**No ME** n=643	**ME** n=40	**P value***
Age, mean±SD	68±14	69±14	62±13	0.004
Male sex	372 (54)	347 (54)	25 (62)	0.293
Pre-stroke mRS, median (Q1-Q3)	0 (0-1)	0 (0-1)	0 (0-0)	0.010
Current smoking	156 (23)	149 (23)	7 (17)	0.268
Admission NIHSS, median (Q1-Q3)	15 (11-20)	15 (11-19)	20 (16-22)	<0.001
Intravenous thrombolysis	539 (79)	506 (79)	33 (82)	0.579
Medical history, n (%)				
Hypertension	333 (49)	319 (50)	14 (36)	0.080
Diabetes mellitus	112 (17)	104 (16)	8 (20)	0.544
Hyperlipidemia	185 (28)	175 (28)	10 (26)	0.754
Ischemic stroke	102 (15)	100 (16)	2 (5)	0.083
Myocardial infarction	110 (16)	105 (17)	5 (13)	0.527
Atrial fibrillation	135 (20)	131 (21)	4 (10)	0.113
Peripheral artery disease	50 (7)	50 (8)	0 (0)	0.071
Drug use, n (%)				
Antiplatelet	231 (34)	217 (34)	14 (35)	0.920
Coumarin	78 (12)	77 (12)	1 (2)	0.066
DOAC	15 (2)	14 (2)	1 (2)	0.902
Statin	231 (35)	221 (35)	10 (25)	0.189
Imaging findings, n (%)				
Occlusion site on CTA				<0.001
- Internal carotid artery	171 (25)	149 (23)	22 (55)	
- M1 segment of the MCA	392 (59)	376 (60)	16 (40)	
- M2 segment of the MCA	90 (14)	88 (14)	2 (5)	
- Other	10 (2)	10 (2)	0 (0)	
ASPECTS, median (Q1-Q3)	9 (7-10)	9 (7-10)	6 (5-9)	<0.001
Poor collateral score	276 (40)	245 (38)	31 (78)	<0.001
CSF volume, mL, mean±SD	171±78	174±77	112±61	<0.001
ICV, mL, mean±SD	1271±146	1274±146	1223±142	0.037

Supplemental table I. Patient characteristics (continued)

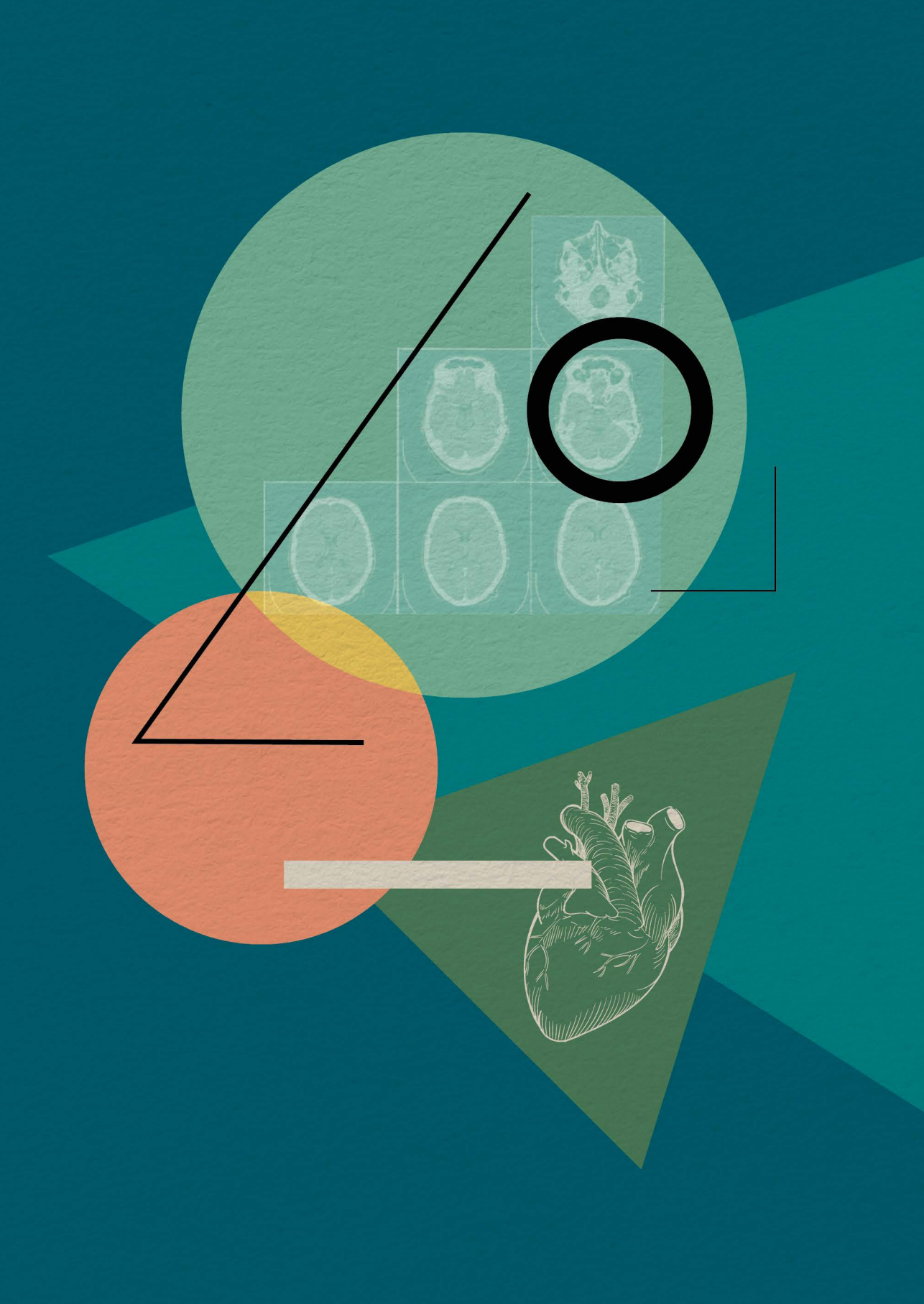
Characteristic, n (%)	**Total** n=683	**No ME** n=643	**ME** n=40	**P value***
CSF/ICV percentage, mean±SD	13±6	14±6	9±5	<0.001
Endovascular treatment, n (%)				
Time from onset to groin, minutes, mean±SD	209±73	208±73	230±70	0.058
Duration of procedure, minutes, mean±SD	66±35	65±34	87±41	0.002
General anesthesia	249 (40)	228 (39)	21 (58)	0.020
eTICI 2B50-3	405 (60)	387 (61)	18 (46)	0.065
Follow-up, n (%)				
Decompressive surgery	15 (2)	1 (0)	14 (35)	<0.001
mRS at 90 days, median (Q1-Q3)	3 (2-6)	3 (2-5)	6 (4-6)	<0.001

* Either parametric or nonparametric tests were performed depending on the variable distribution.

ME indicates malignant edema; SD, standard deviation; mRS, modified Rankin Scale; Q1, first quartile; Q3, third quartile; NIHSS, National Institutes of Health Stroke Scale; CTA, computed tomography angiography; MCA, middle cerebral artery; ASPECTS: Alberta Stroke Program Early CT Score; NCCT: non-contrast computed tomography; CSF: cerebrospinal fluid; mL, milliliter; ICV, intracranial volume; eTICI, expanded thrombolysis in cerebral infarction.



Supplemental figure I. Baseline (A) and follow-up non-contrast CT (B) of a 61-year-old male patient with an occlusion of the left internal carotid artery. Baseline NIHSS was 14. The intracranial cerebrospinal fluid (CSF) volume was 99 mL and the total intracranial volume (ICV) was 1504 mL resulting in a relatively small CSF/ICV ratio of 6.6 percent. The patient received intravenous thrombolysis and underwent endovascular treatment, but reperfusion was not achieved (eTICI 0). Almost five days after admission the patient developed malignant edema (B) and underwent hemicraniectomy. The clinical outcome after 3 months was poor with a modified Rankin Scale of 4.



12

CLINICAL AND IMAGING PREDICTORS OF RECURRENT ISCHEMIC STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Based on:
Kauw F, Takx RAP, de Jong HWAM, Velthuis BK, Kappelle LJ, Dankbaar JW. Clinical and Imaging Predictors of Recurrent Ischemic Stroke: A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2018;45(5-6):279-287.

DOI: 10.1159/000490422

ABSTRACT

Background

Predictors of recurrent ischemic stroke are less well known in patients with a recent ischemic stroke than in patients with transient ischemic attack (TIA). We identified clinical and radiological factors for predicting recurrent ischemic stroke in patients with recent ischemic stroke.

Methods

A systematic search in PubMed, Embase, Cochrane Library and CINAHL was performed with the terms 'ischemic stroke' and 'predictors/determinants' and 'recurrence'. Quality assessment of the articles was performed and level of evidence was graded before the meta-analysis. Pooled risk ratios (RR) with 95% confidence intervals (CI) and heterogeneity were calculated using inverse variance random effects models.

Results

Ten articles with high quality results were included for the meta-analysis. Past medical history of stroke or TIA was a predictor of recurrent ischemic stroke (pooled RR 2.5; 95% CI 2.1-3.1). Small vessel strokes were associated with a lower risk of recurrence than large vessel strokes (pooled RR 0.3; 95% CI 0.1-0.7). Patients with stroke of an undetermined cause had a lower risk of recurrence than patients with large artery atherosclerosis (pooled RR 0.5; 95% CI 0.2-1.1). The following MRI findings were predictors of recurrent ischemic stroke: multiple lesions (pooled RR 1.7; 95% CI 1.5-2.0), multiple stage lesions (pooled RR 4.1; 95% CI 3.1-5.5), multiple territory lesions (pooled RR 2.9; 95% CI 2.0-4.2), chronic infarcts (pooled RR 1.5; 95% CI 1.2-1.9) and isolated cortical lesions (pooled RR 2.2; 95% CI 1.5-3.2). We found no studies using CT or ultrasound for the prediction of recurrent ischemic stroke.

Conclusions

In patients with a recent ischemic stroke, a history of stroke or TIA and the subtype large artery atherosclerosis are associated with an increased risk of recurrent ischemic stroke. Predictors evaluated with MRI include multiple ischemic changes and isolated cortical lesions. Predictors of recurrent ischemic stroke concerning CT or ultrasound have not been published.

INTRODUCTION

Patients with a recent ischemic stroke are at risk for a second ischemic stroke with reported 1-year-incidence rates ranging from 8% to 14%.[1–3] In contrast to patients with TIA, predictors of recurrent ischemic stroke in patients with a recent ischemic stroke are less well known. Clinical factors such as stroke subtype and past medical history of stroke have been reported to be associated with recurrent ischemic stroke.[4,5] Over the last decade, radiological findings have gained more interest in predicting recurrent stroke. For instance, several studies that were based on findings of transesophageal echocardiography or cardiac CT angiography have reported associations between certain aortic plaque characteristics and recurrent hemorrhagic or ischemic stroke.[6–8] However, most imaging studies investigated different study populations and used different definitions for outcome, which makes it difficult to extract generalizable conclusions. The current knowledge gap concerns predictors of recurrent ischemic stroke in the general ischemic stroke population. We conducted a systematic review of both clinical and imaging predictors of recurrent ischemic stroke and performed a meta-analysis of the current literature.

METHODS

Search strategy and selection

We performed a systematic search in PubMed, Embase, Cochrane Library and CINAHL up to September 2017 by using synonyms of 'ischemic stroke' and 'predictors/determinants' and 'recurrence' (Supplemental table I). One author (FK) screened articles on title and abstract for relevance by using the following inclusion criteria: unselected study population of patients with acute ischemic stroke, outcome was recurrent ischemic stroke, and effect estimates (risk ratio, odds ratio or hazard ratio) including 95% confidence intervals were reported or could be calculated (Supplemental Figure I). Animal studies, studies with other language than English, Dutch, German, French or Spanish, case series, reviews, conference abstracts and editorials were excluded for further review. Full-text screening was done independently by two authors (FK and RT). In case of disagreement between authors on the selected studies, consensus was achieved by discussion. Additional relevant papers were retrieved with cross-reference checks. To obtain comparable series of patients, series including patients with TIA and series that were selected on age or stroke subtype were excluded. All supporting data are available within this article and its online supplements. This review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[9]

Critical appraisal

The relevance and validity of the included studies were appraised by two authors (FK and RT). A quality assessment score was formulated, which was based on the Newcastle Ottawa Quality Assessment Scale.[10] Furthermore, we added additional topics to the quality assessment score including study design, analyses and outcome definition as has been done before in other systematic reviews (Supplemental table II).[11–13] If the quality assessment score was below 10, the study was excluded for the primary meta-analysis.

Level of evidence

The reported determinants were deemed as predictive, non-predictive or inconsistent based on consistency of the reported estimates and clinical relevance (Figure 1).[12] In addition, every predictive or non-predictive determinant was given a level of evidence based on the amount of studies with (non-) significant estimates.

Data extraction

Baseline characteristics of the included studies were collected such as sample size and follow-up duration. Risk Ratios (RR), odds ratios (OR) and hazard ratios (HR) on relevant outcome measures with corresponding 95% confidence intervals (CI) were extracted. In absence of the relevant effect estimates, RRs were calculated using crude data. Two-by-two tables were formed and the RR was calculated using the following formula: RR=(a/(a+b))/(c/(c+d)).

Statistical analysis

The weighted incidence rate with 95% CI and weighted mean follow-up duration were calculated by weighing the studies on sample size. When two or more RRs were present per predictor, the pooled RRs with 95% CIs were computed by using inverse variance random effects models in Review Manager (Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was quantified by calculating I^2 as a percentage. A low level of heterogeneity was present when I^2 was 25%, a moderate level when I^2 was 50% and a high level when I^2 was 75%.[14] Determinants were only included for analysis if multiple univariable RRs were available. A p-value smaller than 0.05 was considered significant. To check for differences between low and high quality studies we performed a second meta-analysis including all the studies that were assessed for quality.

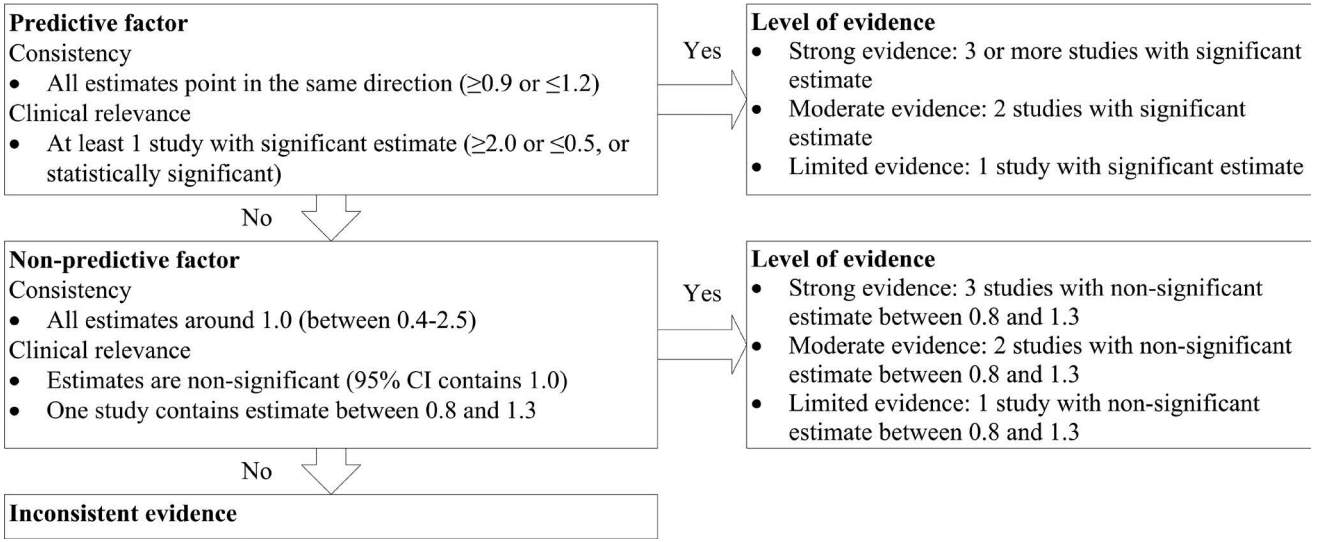


Figure 1. Criteria for level of evidence

Legend: CI indicates confidence interval.

RESULTS

Out of 2,173 unique articles, we included 16 studies for quality assessment (Supplemental Figure I). Most studies were excluded because of selected study populations and deviating definitions of outcome. Six studies were excluded due to low quality scores (Table 1).[15–20] Two studies used the same study population, but investigated different determinants for the recurrence of ischemic stroke: one study investigated multiple predictors while the other specifically focused on diabetes mellitus.[21,22] We included both studies, because each study provides additional information for this review. Finally, ten studies remained for meta-analysis including six prospective cohort and four retrospective cohort studies.[3–5,21–27] The included studies investigated a total of 212,864 patients with ischemic stroke. The weighted incidence rate of recurrent ischemic stroke was 99 (95% CI 98-101) per 1000 person-years with a weighted mean follow-up duration of 13 months.

Predictive factors

Clinical and imaging predictors of recurrent ischemic stroke are reported in Table 2 and visualized in Figure 2. A strong level of evidence for the prediction of recurrent ischemic stroke was found for previous history of stroke or TIA with significant RRs ranging from 1.8 to 3.4 in four studies. Small vessel disease as compared to large artery atherosclerosis was associated with a lower chance of recurrence (pooled RR 0.3, 95% CI 0.1-0.7). This was similar for an undetermined cause of the stroke as compared to large artery atherosclerosis (pooled RR 0.5, 95% CI 0.2-1.1), but with a moderate level of evidence.

Table 1. Characteristics of the studies included for quality assessment

Study *Country*	**Study design**	**Sample size total n**	**Sample size eligible n**	**Recurrences n (%)**	**Follow-up duration**	**Determinants**	**Estimate**	**Quality score**
Alter 1997† *USA*	Prospective	621	621	77 (12)	24 months	DM	uv RR‡	12
Ay 2010 *USA*	Retrospective*	1458	1458	60 (4)	90 days	Demographics, CVRF, stroke subtype, medication, imaging	uv RR‡; uv HR; mv β-coefficient	11
Bergström 2017 *Sweden*	Retrospective*	196,765	196,765	22,198 (13)§	1 year	Demographics, CVRF, medication	mv HR	11
Buenaflor 2017 *Philippines*	Retrospective	1155	1155	280 (24)	3 years	Demographics, CVRF	uv OR; uv RR‡	10
Grau 2001 *Germany*	Prospective	5017	5017	216 (4)	7 days	Stroke subtype	uv RR‡	9
Hankey 1998 *Australia*	Prospective	343	250	33 (13)	5 years	Stroke subtype	uv RR‡	9
Hillen 2003 *UK*	Prospective	1626	1166	80 (7)	5 years	LACI vs. non-LACI	uv RR‡	9
Hirayama 2010 *Japan*	Case control	374	374	72 (19)	3.1 years	Demographics, CVRF	uv RR‡	8

Table 1. Characteristics of the studies included for quality assessment (continued)

Study *Country*	**Study design**	**Sample size total n**	**Sample size eligible n**	**Recurrences n (%)**	**Follow-up duration**	**Determinants**	**Estimate**	**Quality score**
Kim 2014 *USA*	Retrospective	2378	2378	106 (4)	90 days	Demographics, CVRF, stroke subtype, medication, imaging	uv RR‡; uv and mv HR	11
Kuwashiro 2012 *Japan*	Prospective	260	260	25 (10)	12 months	Demographics, CVRF, biometry, laboratory, stroke subtype, medication	uv RR‡; mv OR	11
Lai 1994† *USA*	Prospective	621	621	77 (12)	24 months	Hypertension, atrial fibrillation	mv HR	10
Lee 2004 *Australia*	Retrospective	7816	7816	743 (10)	4 years	Demographics, CVRF, carotid endarterectomy	mv HR	11
Nam 2017 *South Korea*	Retrospective	959	959	63 (7)	31 months	Demographics, CVRF, stroke subtype, medication, imaging	uv RR‡; uv and mv HR	11

Table 1. Characteristics of the studies included for quality assessment (continued)

Study *Country*	**Study design**	**Sample size total n**	**Sample size eligible n**	**Recurrences n (%)**	**Follow-up duration**	**Determinants**	**Estimate**	**Quality score**
Omori 2015 *Japan*	Retrospective*	1087	991	232 (21)	704 days	Demographics, family history, stroke subtype, mRS at discharge	uv RR‡; mv OR	8
Soda 2004 *Japan*	Prospective	831	831	65 (8)	12 months	Demographics, CVRF, medication	uv RR‡ , adjusted RR	12
Suanprasert 2011 *Thailand*	Case control	234	234	67 (29)	13 months	Demographics, CVRF, stroke subtype, medication	uv RR‡; mv OR	7

* Data were retrieved from a prospective database.
† The study populations were identical, but different predictors were assessed.
‡ Estimates were calculated by using crude data.
§ Estimate indicates cumulative 1-year incidence.
USA: United States of America, DM: diabetes mellitus, CVRF: cardiovascular risk factors, uv: univariable, RR: risk ratio, HR: hazard ratio, mv: multivariable, OR: odds ratio, UK: United Kingdom, LACI: lacunar infarcts, RR: relative risk

Table 2. Predictive factors for recurrent ischemic stroke

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv RR (95% CI)	mv HR (95% CI)
Clinical factors							
Strong level							
Prior stroke/TIA	Ay 2010	1458	-	8%	90 days	3.4 (2.1-5.6)	
I^2=0%	Bergström 2017	196,765	Prior ischemic stroke	15%	1 year		1.3 (1.2-1.4)
	Kim 2014	2378	Within last month	14%	90 days	2.6 (1.9-3.4)	
	Kuwashiro 2012	260	Prior ischemic stroke	24%	12 months	1.8 (1.1-3.1)	OR 2.0 (0.8-5.0)
	Soda 2004	713	Prior stroke/TIA	27%	12 months	2.3 (1.5-3.8)	
	Pooled					**2.5 (2.1-3.1)**	
Small vessel disease vs. LAA	Ay 2010	1458	CCS	10%	90 days	0.1 (0.0-0.7)	
	Kim 2014	2378	CCS	12%	90 days	0.1 (0.0-0.3)	
I^2=67%	Kuwashiro 2012	260	TOAST	31%	12 months	0.3 (0.1-0.9)	
	Nam 2017	959	TOAST	31%	31 months	0.5 (0.3-1.0)	
	Soda 2004	745	NINDS	26%	12 months	0.8 (0.4-1.7)	
	Pooled					**0.3 (0.1-0.7)**	
Moderate level							

Table 2. Predictive factors for recurrent ischemic stroke (continued)

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv RR (95% CI)	mv HR (95% CI)
Undetermined cause vs. LAA	Ay 2010	1458	CCS	36%	90 days	0.4 (0.2-0.7)	
	Kim 2014	2378	CCS	12%	90 days	0.2 (0.1-0.5)	
I^2=76%	Soda 2004	745	NINDS: Uncertain cause	22%	12 months	1.1 (0.5-2.2)	
	Pooled					**0.5 (0.2-1.1)**	
Imaging factors (MRI)							
Moderate level							
Multiple lesions I^2=0%	Ay 2010	1458	*	40%	90 days	1.8 (1.5-2.1)	
	Nam 2017	959	*	39%	31 months	1.6 (1.3-2.0)	
	Pooled					**1.7 (1.5-2.0)**	
Multiple stage lesions I^2=13%	Ay 2010	1458	*	11%	90 days	3.5 (2.4-5.2)	
	Nam 2017	959	*	11%	31 months	4.7 (3.3-6.7)	6.0 (3.5-10.1)
	Pooled					**4.1 (3.1-5.5)**	
Multiple territory lesions I^2=0%	Ay 2010	1458	*	10%	90 days	2.7 (1.7-4.4)	
	Nam 2017	959	*	6%	31 months	3.2 (1.8-5.8)	
	Pooled					**2.9 (2.0-4.2)**	

Table 2. Predictive factors for recurrent ischemic stroke (continued)

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv RR (95% CI)	mv HR (95% CI)
Chronic infarcts I^2=0%	Ay 2010	1458	*	30%	90 days	1.4 (1.1-2.0)	
	Kim 2014	2378	*	15%	90 days	1.6 (1.1-2.3)	1.4 (0.9-2.3)
	Pooled					**1.5 (1.2-1.9)**	
Isolated cortical lesion	Ay 2010	1458	*	9%	90 days	2.2 (1.3-3.8)	
	Nam 2017	959	*	9%	31 months	2.1 (1.2-3.8)	2.5 (1.3-5.0)
I^2=0%	**Pooled**					**2.2 (1.5-3.2)**	
Limited level							
White matter lesions I^2=79%	Kim 2014	2378	*	44%	90 days	1.2 (1.0-1.5)	1.5 (1.0-2.3)
	Nam 2017	959	*	25%	31 months	2.0 (1.5-2.7)	1.9 (1.1-3.4)
	Pooled					**1.5 (0.9-2.6)**	

* See Supplemental table III for definitions of imaging factors.

Uv indicates univariable; RR, risk ratio; CI, confidence interval; mv, multivariable; HR, hazard ratio; TIA, transient ischemic attack; OR, odds ratio; LAA, large artery atherosclerosis; CCS, Causative Classification System for Ischemic Stroke; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NINDS, National Institute of Neurological Diseases and Stroke; MRI, magnetic resonance imaging.

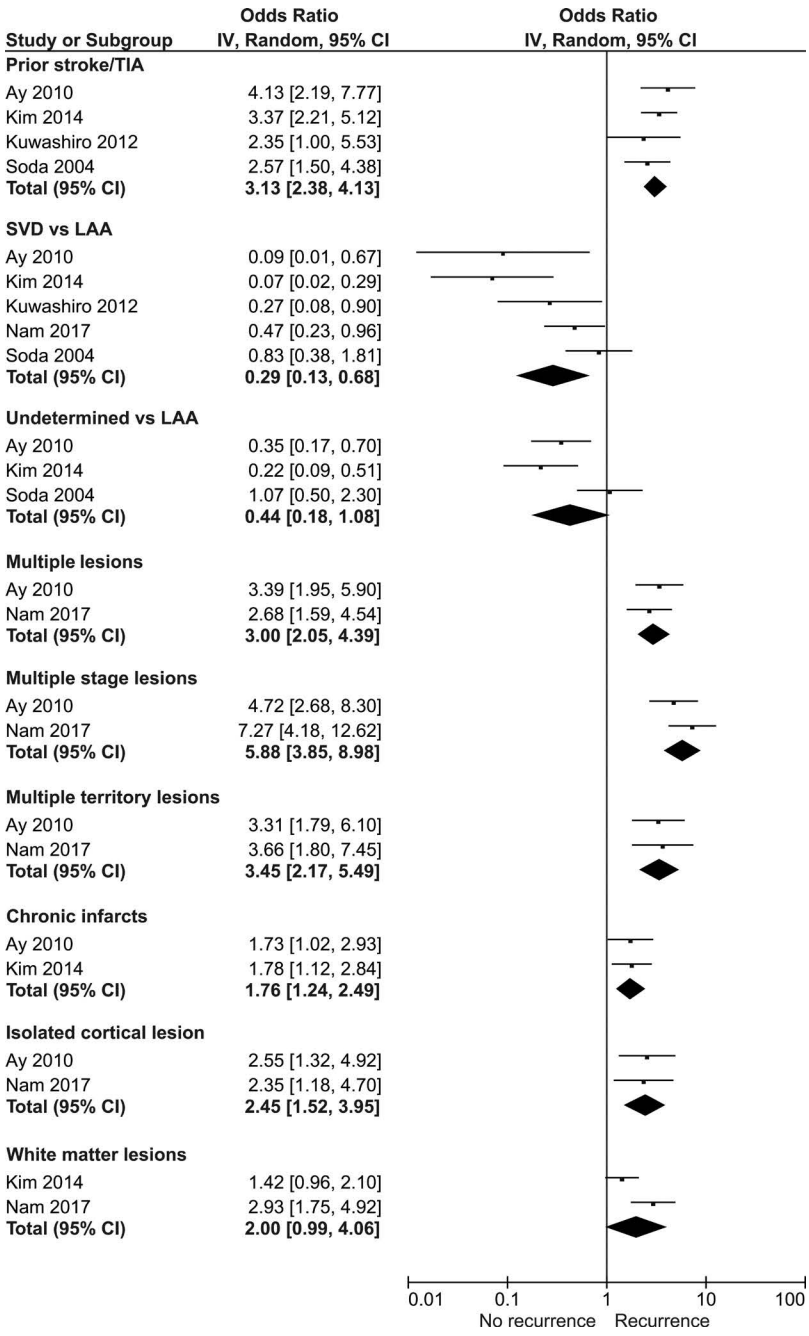


Figure 2. Forest plot of predictors of recurrent ischemic stroke

Legend: IV indicates inversed variance; CI, confidence interval; TIA, transient ischemic attack; SVD, small vessel disease; LAA, large artery atherosclerosis.

A moderate level of evidence for the prediction of recurrent ischemic stroke was found for MRI based predictors such as multiple lesions, multiple stage lesions, multiple territory lesions, chronic infarcts and isolated cortical lesions, which are defined in Supplemental table III. A limited level of evidence was present for the association between white matter lesions and recurrence of ischemic stroke (pooled RR 1.5, 95% CI 0.9-2.6). No predictive imaging factors based on CT or ultrasound were found. A second meta-analysis including all the studies that were assessed for quality (Table 1) did not provide substantial different results compared to the analysis of the high quality studies (Supplemental table IV).

A single large (n=196,765) Swedish study[4] reported the following positive and negative predictors of recurrent ischemic stroke during a one-year follow-up: age 76-85 years versus age 18-65 years (HR 1.1, 95% CI 1.1-1.2), prior ischemic stroke (HR 1.3, 95% CI 1.2-1.4), prior myocardial infarction (HR 1.3, 95% CI 1.2-1.3), diabetes mellitus (HR 1.2, 95% CI 1.1-1.3), atrial fibrillation without warfarin treatment (HR 1.6, 95% CI 1.5-1.7), atrial fibrillation with warfarin treatment (HR 0.8, 95% CI 0.7-0.9), use of acetylsalicylic acid (HR 0.9, 95% CI 0.9-1.0), use of acetylsalicylic acid in combination with dipyridamole (HR 0.9, 95% CI 0.6-0.9) and use of lipid lowering medication (0.9, 95% CI 0.8-0.9). The reported predictors were further adjusted for female sex (HR 1.0, 95% CI 0.9-1.0) and medication use including clopidogrel (HR 1.1, 95% CI 1.0-1.2), calcium channel blockers (HR 1.0, 95% CI 1.0-1.1), beta-blockers (HR 1.2, 95% CI 1.2-1.3), diuretics (HR 1.1, 1.0-1.1) and angiotensin converting enzyme inhibitors (HR 1.0, 95% CI 1.0-1.0).

Non-predictive factors

Factors that were not predictive of recurrent ischemic stroke in at least 3 studies (strong level of evidence) were male sex, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, use of anticoagulant medication, use of antiplatelet medication and statin use (Supplemental table V). Furthermore, no association was found for alcohol use and use of antihypertensive medication with a moderate level of evidence.

Inconsistent factors

Conflicting evidence was found for the association between smoking and recurrent ischemic stroke (Supplemental table VI). Two out of six studies reported that smoking at baseline is significantly protective for recurrence of ischemic stroke. However, the remaining four studies provided neutral RRs. Conflicting evidence was also found for cardiac embolism as cause of the ischemic stroke compared to large artery atherosclerosis and for presence of prior cardiovascular disease. Only two studies provided univariable RRs for carotid intervention with broad confidence intervals.

DISCUSSION

Strong evidence was found for past medical history of stroke or TIA and large rather than small vessel disease as predictors of recurrent ischemic stroke. There is a moderate level of evidence that patients with an undetermined cause of stroke had a more benign prognosis with respect to recurrent ischemic stroke than patients with large artery atherosclerosis. Negative associations were found for atrial fibrillation with warfarin treatment, use of acetylsalicylic acid, use of acetylsalicylic acid in combination with dipyridamole and use of lipid lowering medication. When considering imaging predictors, strong level of evidence was absent, but a moderate level of evidence was found for the association between recurrent ischemic stroke and the load of ischemic lesions on MRI.

No other systematic review focusing on prediction of recurrent ischemic stroke after recent ischemic stroke was found. We had to exclude several studies that studied clinical and imaging predictors of ischemic stroke, because these studies investigated heterogeneous stroke populations or subgroups of the general stroke population. For instance, several studies studied both patients with ischemic stroke and patients with TIA. Since predictors of ischemic stroke recurrence differ between subgroups of the general stroke population and the general stroke population, the need for studying unselected study populations should be emphasized. Other studies that were excluded investigated predictors of recurrent stroke including hemorrhagic stroke. Several studies used recurrence of both hemorrhagic and ischemic stroke as outcome and they found that white matter lesions on MRI are associated with stroke recurrence, while in our meta-analysis, in which only recurrent ischemic stroke was used as outcome, only two studies provided evidence for this association.[28,29]

We chose to exclude hemorrhagic recurrences as outcome, because causative mechanisms differ between ischemic and hemorrhagic stroke, which, in turn, may be related to recurrence. Similarly, causative mechanisms may differ between early and late recurrences of ischemic stroke. In our study, we could not analyze early and late recurrences separately, because longitudinal data on recurrences were not provided. Future studies need to elucidate whether early and late recurrences of ischemic stroke indeed differ in causative mechanisms, how these outcomes should be defined and whether prediction models of recurrent ischemic stroke need to be adjusted for those differences.

It remains difficult to evaluate a possible association between the clinical predictors and the imaging findings. In this review, the prognostic imaging factors seem compatible with the reported clinical predictors. Previous ischemic events may lead to brain damage that can be seen on MRI. Furthermore, atherosclerosis of large arteries such as the internal carotid artery has been associated with multiple white matter lesions on MRI.[30] We think that the combination of baseline clinical and imaging factors remains vital for predicting recurrent ischemic stroke. If prior cardiovascular events are absent based on history taking, imaging studies may elucidate 'silent' cerebrovascular disease, which has been associated with future stroke.[31,32] To improve prediction models, the role of imaging needs to be established and, more specifically, future imaging studies should focus on determining the cause of stroke and previous ischemic brain damage.

Atrial fibrillation was not of predictive value according to our pooled findings. In the Swedish stroke registry study, patients with atrial fibrillation were divided in two groups: one group receiving anticoagulant treatment and one group not receiving anticoagulant treatment.[4] In multivariable analysis, anticoagulant treatment was associated with decreased risk of ischemic stroke recurrence, while no treatment was predictive for recurrence. Based on clinical risk scores, anticoagulant therapy is only indicated when the risk of ischemic stroke outweighs the risk of hemorrhagic complications.[33] In the other included studies, treatment was not addressed when assessing atrial fibrillation as a predictor, which may be the reason of atrial fibrillation not being a predictor of recurrent ischemic stroke according to our review. These results indicate that future studies should address treatment strategies in atrial fibrillation as distinct predictors of ischemic stroke recurrence. Ideally, the effect of anticoagulant treatment on ischemic stroke recurrences in patients with recent ischemic stroke and atrial fibrillation should be investigated in a randomized placebo-controlled manner. The same goes for treatment of other risk factors, but ethical objections may be raised.

A strong point of this study was the fact that we used strict criteria for study domain and outcome and that we analyzed the selected studies according to the well-established PRISMA criteria. Because we only included unselected study populations of ischemic stroke and only studies with ischemic stroke recurrence as outcome, heterogeneity between studies was low and generalizability was high. Despite the fact that we had to exclude several studies because of our strict selection criteria, a sufficient number of studies were found to provide strong level of evidence for certain predictors of recurrent ischemic stroke. Furthermore, the gaps in current literature concerning recurrent ischemic stroke are highlighted and thereby encourage investigators to fill those gaps.

A drawback of this study was the possible existence of publication bias. Studies that did not find significant estimates may have been averted from publication. We could not formally test publication bias, because the amount of studies was too low. No funnel plots were generated, since they may not detect publication bias as less than 10 studies were available per category.[34] Heterogeneity between studies may have been an issue, because differences were present across studies with respect to number of study participants, follow-up durations and definitions of predictors. Furthermore, patients may have been treated differently across studies, because treatment protocols have been improved over the years. However, within the single studies, all patients received the same treatment. Hence, considering the limitations of this study, we anticipate that the mentioned sources of heterogeneity will have limited impact on our pooled results as most heterogeneity percentages were low, strict selection procedures were followed and inverse variance random effects models were applied to adjust for variations across studies. Future studies should anticipate on these heterogeneity issues by using similar follow-up durations and similar definitions of cardiovascular risk factors, stroke subtypes and imaging variables.

In conclusion, clinical predictors of ischemic stroke recurrence have been well established. The role of imaging predictors is less well established and only investigated for MRI, which emphasizes the need for further investigation of imaging to visualize characteristics and causes of (recurrent) ischemic stroke.

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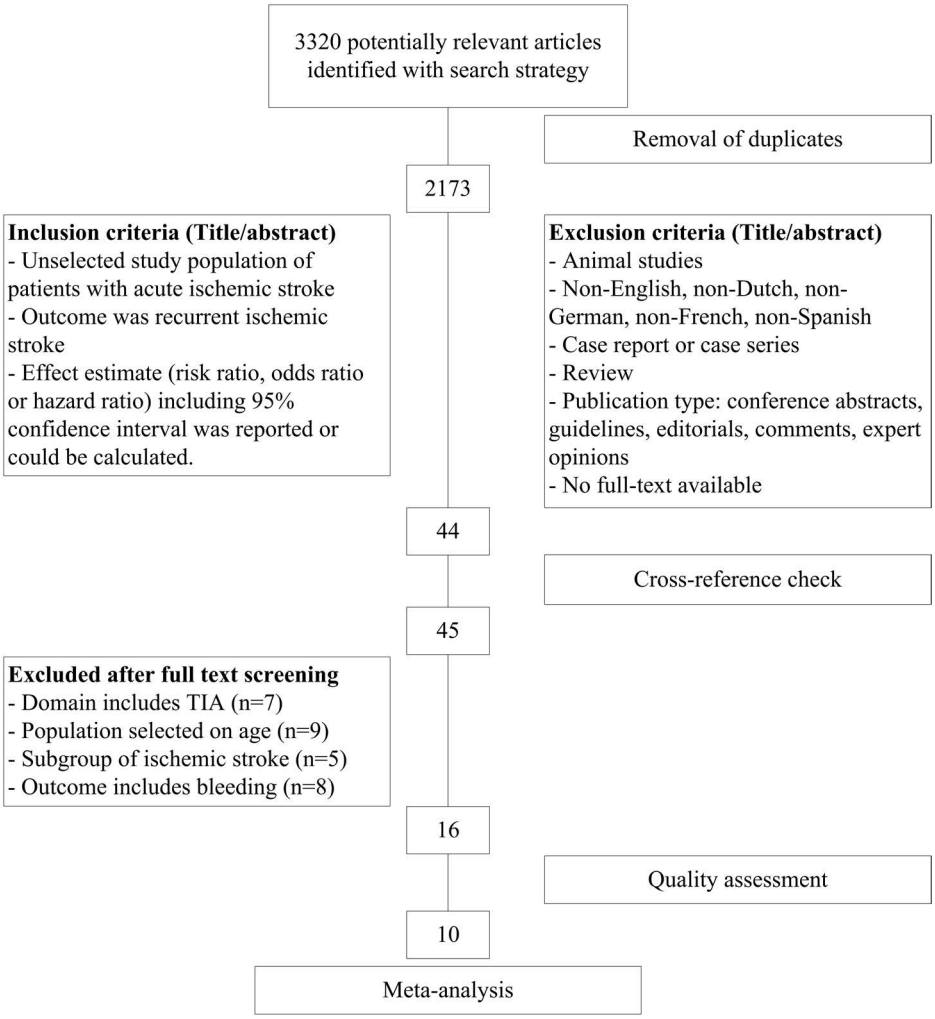
SUPPLEMENTS



Supplemental Figure I. Flowchart of systematic literature search

Legend: TIA indicates transient ischemic attack.

Supplemental table I. Search syntax

Database	Search term
PubMed	((“ischemic stroke”[Title/Abstract] OR “ischaemic stroke”[Title/Abstract] OR “brain infarct”[Title/Abstract]) AND (“determinant”[Title/Abstract] OR “determinants”[Title/Abstract] OR “risk factor”[Title/Abstract] OR “risk factors”[Title/Abstract] OR “predictor”[Title/Abstract] OR “predictors”[Title/Abstract]) AND (“recurrence”[Title/Abstract] OR “recurrent”[Title/Abstract]))
EMBASE	Replaced [Title/Abstract] with :ti,ab
Cochrane Library	Removed [Title/Abstract]
CINAHL	Removed [Title/Abstract]

Supplemental table II. Quality assessment score

Characteristic		Points
Design		
Study design	Prospective	3
	Retrospective from prospective database	2
	Retrospective	1
	Case control	0
Selection		
Representativeness of the exposed cohort	Representative of the average ischemic stroke population	1
	Selected group of the ischemic stroke population	0
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	1
	Drawn from a different source	0
Ascertainment of exposure	Secure record or structured interview	1
	Self-report or no description	0
Outcome was not present at study start	Yes	1
	No	0
Comparability		
Univariable analysis	Both crude data and estimates* with 95% CI were provided	2
	Crude data or estimates* with 95% CI were provided	1
	No crude data or estimates* were provided	0

Supplemental table II. Quality assessment score (continued)

Characteristic		**Points**
Multivariable analysis and confounding	Contained important potential confounders and rule of ten events per variable was respected	2
	Contained important potential confounders or rule of ten events per variable was respected	1
	Did not contain important potential confounders and rule of ten events per variable was not respected	0
Outcome		
Outcome definition	Recurrent ischemic stroke was defined	1
	Unclearly defined or other definition than recurrent ischemic stroke	0
Assessment of outcome	Independent blind assessment or record linkage	1
	Self-report or no description	0
Adequate follow-up duration (≥90 days)	Yes	1
	No	0
Adequacy of follow-up of cohorts	≤10% or description of those lost	1
	>10% or no description of those lost	0
Maximum score		**15**

* Estimates included odds ratios or hazard ratios.

Supplemental table III. Predictive factors for recurrent ischemic stroke including low quality studies

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
Clinical factors							
Strong level							
Prior stroke/TIA	Ay 2010	1458	-	8%	90 days	4.1 (2.2-7.8)	
I^2=0%	Bergström 2017	196,765	Prior ischemic stroke	15%	1 year		HR 1.3 (1.2-1.4)
	Kim 2014	2378	Within last month	14%	90 days	3.4 (2.2-5.1)	
	Kuwashiro 2012	260	Prior ischemic stroke	24%	12 months	2.4 (1.0-5.6)s	2.0 (0.8-5.0)
	Soda 2004	713	Prior stroke/TIA	27%	12 months	2.6 (1.5-4.4)	
	Pooled					**3.4 (2.4-4.7)**	
Small vessel disease vs LAA	Ay 2010	1458	CCS	10%	90 days	0.1 (0.0-0.7)	
	Grau 2001	5017	TOAST	20%	7 days	0.4 (0.2-0.5)	
I^2=81%	Hankey 1998	250	Lacunar syndrome	10%	7 days	1.5 (0.5-4.4)	
	Nam 2017	959	TOAST	31%	31 months	0.5 (0.2-1.0)	
	Kim 2014	2378	CCS	12%	90 days	0.1 (0.0-0.3)	
	Kuwashiro 2012	260	TOAST	31%	12 months	0.3 (0.1-0.9)	
	Omori 2015	991	Clinical subtype	32%	704 days	1.3 (0.9-1.9)	
	Soda 2004	745	NINDS	26%	12 months	0.8 (0.4-1.8)	
	Pooled					**0.5 (0.3 – 0.9)**	

Supplemental table III. Predictive factors for recurrent ischemic stroke including low quality studies (continued)

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
Moderate level							
Undetermined cause vs LAA	Ay 2010	1458	CCS	36%	90 days	0.3 (0.2-0.7)	
	Grau 2001	5017	TOAST	23%	7 days	0.4 (0.3-0.6)	
I^2=64%	Kim 2014	2378	CCS	12%	90 days	0.2 (0.1-0.5)	
	Soda 2004	745	NINDS: Uncertain cause	22%	12 months	1.1 (0.5-2.3)	
	Pooled					**0.4 (0.3-0.7)**	
Imaging factors (MRI)							
Moderate level							
Multiple lesions I^2=0%	Ay 2010	1458	Hyperintense on DWI and hypointense on ADC maps	40%	90 days	3.4 (2.0-5.9)	
	Nam 2017	959	On DWI	39%	31 months	2.7 (1.6-4.54)	
	Pooled					**3.0 (2.1-4.4)**	
Multiple stage lesions I^2=13%	Ay 2010	1458	Multiple infarcts of different ages on ADC/ FLAIR	11%	90 days	4.7 (2.7-8.3)	
	Nam 2017	959	On DWI	11%	31 months	7.3 (4.2-12.6)	HR 6.0 (3.5-10.1)
	Pooled					**5.9 (3.9-9.0)**	

Supplemental table III. Predictive factors for recurrent ischemic stroke including low quality studies (continued)

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
Multiple territory lesions I^2=0%	Ay 2010	1458	(sub)acute in right and left anterior circulations or in anterior and posterior	10%	90 days	3.3 (1.8-6.1)	
	Nam 2017	959	On DWI	6%	31 months	3.7 (1.8-7.5)	
	Pooled					**3.5 (2.2-5.5)**	
Chronic infarcts I^2=0%	Ay 2010	1458	Hyperintense on FLAIR and hypo-/isointense on DWI	30%	90 days	1.7 (1.0-2.9)	
	Kim 2014	2378	On MRI	15%	90 days	1.8 (1.1-2.8)	HR 1.4 (0.9–2.3)
	Pooled					**1.8 (1.2-2.5)**	
Isolated cortical lesion	Ay 2010	1458	-	9%	90 days	2.6 (1.3- 4.9)	
	Nam 2017	959	On DWI	9%	31 months	2.4 (1.2-4.7)	HR 2.5 (1.3-5.0)
I^2=0%	**Pooled**					**2.5 (1.5-4.0)**	

Limited level

Supplemental table III. Predictive factors for recurrent ischemic stroke including low quality studies (continued)

Predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
White matter lesions I^2=79%	Kim 2014	2378	FLAIR: Fazekas <2 vs ≥2	44%	90 days	1.4 (1.0-2.1)	HR 1.5 (1.0–2.3)
	Nam 2017	959	FLAIR: Fazekas ≤2 vs >2	25%	31 months	2.9 (1.8-4.9)	HR1.9 (1.1-3.4)
	Pooled					**2.0 (1.0-4.1)**	

Uv indicates univariable; CI, confidence interval; mv, multivariable; OR, odds ratio; TIA, transient ischemic attack; LAA, large artery atherosclerosis; CCS, Causative Classification System for Ischemic Stroke; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NINDS, National Institute of Neurological Diseases and Stroke; MRI, magnetic resonance imaging; FLAIR, fluid attenuation inversion recovery; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient.

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
Strong level							
Male sex	Ay 2010	1458	-	54%	90 days	1.1 (0.7-1.9)	
I^2=0%	Bergström 2017	196,765	-	50%	1 year		HR 1.0 (1.0-1.1)
	Buenaflor 2017	1155	-	53%	3 years	1.1 (0.8-1.4)	
	Kim 2014	2378	-	54%	90 days	1.0 (0.6-1.4)	
	Kuwashiro 2012	260	-	58%	12 months	1.6 (0.7-3.9)	1.7 (0.7-4.7)
	Lee 2004	7816	-	51%	4 years		HR 1.2 (1.0–1.3)
	Nam 2017	959	-	62%	31 months	0.9 (0.5-1.5)	
	Soda 2004	745	-	58%	12 months	0.7 (0.4-1.2)	
	Pooled					**1.0 (0.8-1.2)**	
Hypertension	Ay 2010	1458	-	70%	90 days	1.2 (0.7-2.1)	
I^2=56%	Buenaflor 2017	1155	Medication; persistent blood pressure >140/90 mmHg	95%	3 years	0.6 (0.4-1.1)	
	Kim 2014	2378	Medication; repeated ≥140/9mmHg	69%	90 days	1.9 (1.2-3.1)	
	Kuwashiro 2012	260	Medication; SBP≥140;DBP≥90	80%	12 months	0.9 (0.4-2.2)	
	Nam 2017	959	-	66%	31 months	0.8 (0.5-1.4)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Soda 2004	736	Medication; >140/90 mmHg; also at two following occasions after index stroke	68%	12 months	1.7 (0.9-3.1)	
	Lai 1994	621	Medical history of hypertension	59%	24 months		HR 2.0 (1.2-3.2)
	Lee 2004	7816	-	62%	4 years		HR 1.1 (0.9–1.2)
	Pooled					**1.1 (0.8-1.6)**	
Dyslipidemia I^2=0%	Buenaflor 2017	1155	Medication; total chol≥240mg/dl;LDL≥160mg/dl	36%	3 years	1.1 (0.8-1.5)	
	Kuwashiro 2012	260	Medication; total chol≥220mg/dL	41%	12 months	0.8 (0.3-1.9)	
	Lee 2004	7816	-	15%	4 years		HR 0.9 (0.7–1.1)
	Nam 2017	959	-	31%	31 months	0.8 (0.5-1.5)	
	Soda 2004	709	Fasting total cholesterol >5.7 mmol/l, fasting triglycerides >1.70 mmol/l, or HDL cholesterol <1.04 mmol/l	39%	12 months	1.5 (0.9-2.5)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Pooled					**1.1 (0.9-1.4)**	
DM I^2=36%	Alter 1997	621	History of DM; medication; diet; elevated HbA1c (>6.2%)	32%	24 months	1.2 (0.7-1.9)	
	Ay 2010	1458	-	24%	90 days	0.9 (0.5-1.6)	
	Bergström 2017	196,765	-	21%	1 year		HR 1.2 (1.1-1.3)
	Buenaflor 2017	1155	Medication; fasting glucose≥7mmol/L; symptoms plus random glucose≥11.1mmol/L; HbA1c>6.5%)	25%	3 years	0.7 (0.5-1.0)ns	
	Kim 2014	2378	Medication; repeated fasting glucose ≥126 mg/dL	23%	90 days	1.0 (0.6-1.6)	
	Kuwashiro 2012	260	Medication; fasting glucose≥126mg/dL; positive 75g oral glucose tolerance test result	34%	12 months	1.9 (0.8-4.3)	
	Nam 2017	959	-	30%	31 months	1.6 (0.9-2.6)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Soda 2004	742	Fasting glucose >7.0 mmol/l, positive 75g oral glucose tolerance test result, or HbA1c >6.5%	34%	12 months	1.2 (0.7-2.0)	
	Lee 2004	7816	-	22%	4 years		HR 1.27 (1.1–1.5)
	Pooled					**1.1 (0.8-1.4)**	
AF	Ay 2010	1458	-	30%	90 days	0.7 (0.4-1.3)	
I^2=13%	Buenaflor 2017	1155	By ECG or 24h Holter	17%	3 years	0.9 (0.6-1.3)	
	Lai 1994	621	AF by ECG	16%	24 months		HR 1.8 (1.0-3.1)
	Lee 2004	7816	-	23%	4 years		HR 1.0 (0.9–1.2)
	Kim 2014	2378	-	25%	90 days	0.8 (0.5-1.3)	
	Kuwashiro 2012	260	-	20%	12 months	2.0 (0.8-4.9)	
	Nam 2017	959	-	14%	31 months	1.3 (0.7-2.5)	
	Pooled					**1.0 (0.7-1.2)**	
Anticoagulant	Ay 2010	1458	-	41%	90 days	1.0 (0.6-1.8)	
I^2=0%	Kim 2014	2378	-	37%	90 days	1.2 (0.8-1.8)	
	Kuwashiro 2012	260	-	23%	12 months	1.1 (0.4-2.8)	
	Nam 2017	959	-	13%	31 months	0.9 (0.4-1.9)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Soda 2004	745	1 year after index or during recurrence stroke	18%	12 months	1.1 (0.6-2.2)	
	Pooled					**1.1 (0.9-1.4)**	
Antiplatelet	Ay 2010	1458	-	67%	90 days	1.1 (0.6-1.8)	
I^2=0%	Kim 2014	2378	-	70%	90 days	1.0 (0.7-1.6)	
	Kuwashiro 2012	260	-	76%	12 months	1.3 (0.5-3.5)	
	Nam 2017	959	-	90%	31 months	1.1 (0.4-2.5)	
	Pooled					**1.1 (0.8-1.4)**	
Statin	Ay 2010	1458	-	56%	90 days	0.8 (0.5-1.3)	
I^2=0%	Kim 2014	2378	-	66%	90 days	1.1 (0.7-1.7)	
	Nam 2017	959	-	71%	31 months	1.0 (0.5-1.7)	
	Pooled					**1.0 (0.7-1.3)**	
Moderate level							
Alcohol I^2=0%	Buenaflor 2017	1155	≥5 drinks on same occasion on each of 5 or more days in the past 30 days	8%	3 years	0.7 (0.4-1.2)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Kuwashiro 2012	260	Consumption (including occasional drinking)	38%	12 months	0.9 (0.4-2.2)	
	Nam 2017	959	-	40%	31 months	0.9 (0.6-1.6)	
	Soda 2004	592	Heavy: >43g/day	17%	12 months	0.6 (0.2-1.4)	
	Pooled					**0.8 (0.6-1.1)**	
Antihypertensive medication	Kim 2014	2378	-	28%	90 days	0.9 (0.6-1.4)	
I^2=0%	Kuwashiro 2012	260	-	45%	12 months	0.5 (0.2-1.3)	
	Nam 2017	959	-	49%	31 months	0.9 (0.6-1.6)	
	Pooled					**0.9 (0.6-1.2)**	
Limited level							
Other cause vs LAA	Ay 2010	1458	CCS	6%	90 days	2.3 (1.1-4.8)	
I^2=35%	Kim 2014	2378	CCS	8%	90 days	1.2 (0.7-2.1)	
	Kuwashiro 2012	260	TOAST	27%	12 months	0.5 (0.2-1.5)	
	Nam 2017	959	TOAST	9%	31 months	1.4 (0.6-3.0)	

Supplemental table IV. Non-predictive factors of recurrent ischemic stroke (continued)

Non-predictive factor	Study	Sample size, n	Variable definition	Factor prevalence	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Pooled					**1.3 (0.8-2.0)**	

Uv indicates univariable; CI, confidence interval; mv, multivariable; OR, odds ratio; HR, hazard ratio; TIA, transient ischemic attack; LAA, large artery atherosclerosis; CCS, Causative Classification System for Ischemic Stroke; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NINDS, National Institute of Neurological Diseases and Stroke.

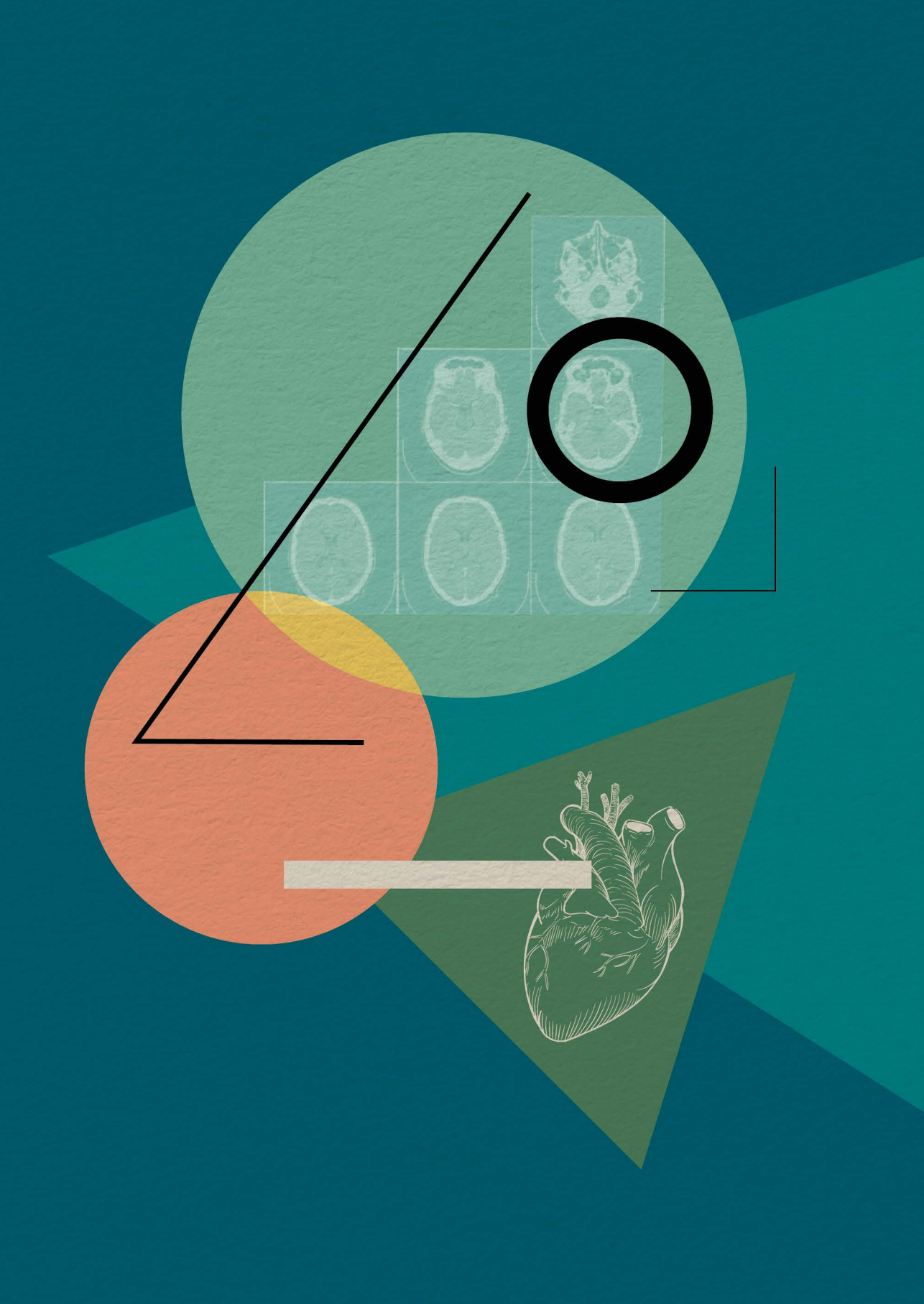
Supplemental table V. Factors with inconsistent evidence

Factor	Study	Sample size (n)	Definition variable	Patients with predictor (%)	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
Smoking	Ay 2010	1458	-	21%	90 days	1.3 (0.7-2.3)	
I^2=17%	Buenaflor 2017	1155	Current pipe/cigar or cigarette smoking during index stroke	15%	3 years	0.7 (0.5-1.0)	
	Kim 2014	2378	Current smoking	19%	90 days	1.0 (0.6-1.6)	
	Kuwashiro 2012	260	Smoking habit: previous and current	44%	12 months	0.8 (0.4-2.0)	
	Soda 2004	606	Currently or quit <12 months	32%	12 months	0.5 (0.2-0.9)	
	Pooled					**0.8 (0.6-1.1)**	
CE vs LAA	Ay 2010	1458	CCS	25%	90 days	0.5 (0.2-1.0)	
I^2=84%	Kim 2014	2378	CCS	45%	90 days	0.3 (0.2-0.5)	
	Kuwashiro 2012	260	TOAST	18%	12 months	0.6 (0.2-2.0)	
	Nam 2017	959	TOAST	17%	31 months	1.1 (0.6- 2.1)	
	Soda 2004	745	NINDS	22%	12 months	2.1 (1.1-4.1)	
	Pooled					**0.7 (0.3-1.6)**	
Prior CVD I^2=NA	Bergström 2017	196,765	Prior myocardial infarction	12%	1 year		HR 1.3 (1.2-1.3)
	Kuwashiro 2012	260	Ischemic heart disease	15%	12 months	0.5 (0.1-2.0)	
	Lee 2004	7816	Other cardiac conditions	49%	4 years		HR 1.2 (1.0–1.4)

Supplemental table V. Factors with inconsistent evidence (continued)

Factor	Study	Sample size (n)	Definition variable	Patients with predictor (%)	Follow-up duration	uv OR (95% CI)	mv OR (95% CI)
	Pooled					**NA**	
Carotid intervention	Ay 2010	1458	Carotid endarterectomy/ angioplasty/stent	5%	90 days	1.1 (0.3-3.6)	
I^2=0%	Lee 2004	7816	Carotid endarterectomy	1%	4 years		HR 0.6 (0.3–1.3)
	Nam 2017	959	Carotid endarterectomy/stent	1%	31 months	2.6 (0.6-12.2)	
	Pooled					**1.5 (0.6-3.9)**	

Uv indicates univariable; CI, confidence interval; mv, multivariable; OR, odds ratio; CE, cardioembolic; LAA, large artery atherosclerosis; CCS, Causative Classification System for Ischemic Stroke; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; NINDS, National Institute of Neurological Diseases and Stroke; CVD, cardiovascular disease; NA, not applicable; HR, hazard ratio; MRI, magnetic resonance imaging.



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PREDICTION OF LONG-TERM RECURRENT ISCHEMIC STROKE: THE ADDED VALUE OF NON-CONTRAST CT, CT PERFUSION AND CT ANGIOGRAPHY

Based on:

Kauw F, Greving JP, Takx RAP, de Jong HWAM, Schonewille WJ, Vos JA, Wermer MJH, van Walderveen MAA, Kappelle LJ, Velthuis BK, Dankbaar JW; Dutch Acute Stroke Study (DUST) investigators. Prediction of long-term recurrent ischemic stroke: the added value of non-contrast CT, CT perfusion, and CT angiography. Neuroradiology. 2021 Apr;63(4):483-490.

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ABSTRACT

Introduction

Prediction of stroke recurrence risk has conventionally been based on demographic, stroke subtype, risk factor and medical history variables. The aim of this study was to evaluate whether the addition of brain CT imaging data to a model incorporating clinical risk factors improves prediction of ischemic stroke recurrence over 5 years of follow-up.

Methods

A total of 638 patients with ischemic stroke from three centers were selected from the Dutch Acute Stroke Study (DUST). CT derived candidate predictors included findings on non-contrast CT, CT perfusion and CT angiography. Five-year follow-up data were extracted from medical records. We developed a multivariable Cox regression model containing clinical predictors and an extended model including CT derived predictors by applying backward elimination. We calculated net reclassification improvement and integrated discrimination improvement indices. Discrimination was evaluated with the optimism-corrected c-statistic, and calibration with a calibration plot.

Results

During 5 years of follow-up, 56 patients (9%) had a recurrence. The c-statistic of the clinical model, which contained male sex, history of hyperlipidemia and history of stroke or transient ischemic attack, was 0.61. Compared with the clinical model, the extended model,

which contained previous cerebral infarcts on non-contrast CT and Alberta Stroke Program Early CT Score greater than 7 on mean transit time maps, derived from CT perfusion, had higher discriminative performance (c-statistic 0.65, P=0.01). Inclusion of these CT variables led to a significant improvement in reclassification measures by using the net reclassification improvement and integrated discrimination improvement indices.

Conclusion

Data from CT imaging significantly improved the discriminatory performance and reclassification in predicting ischemic stroke recurrence beyond a model incorporating clinical risk factors only.

BACKGROUND

Recurrent stroke accounts for approximately a quarter of all strokes that occur and has important implications for the long-term outcome of patients.[1] The 1-year incidence of recurrent ischemic stroke has been estimated to range from 8% to 14%.[2,3] The risk estimation of recurrent ischemic stroke can be achieved by using prediction models.

Many clinical predictors for recurrent ischemic stroke have been investigated. Strong evidence was established for a limited number of factors, which include stroke prior to the index stroke and stroke subtype.[4] Other factors such as age, sex, hypertension, diabetes mellitus, hyperlipidemia, smoking, history of myocardial infarction, history of atrial fibrillation and history of peripheral artery disease have been suggested as predictors of recurrent ischemic stroke in some studies, but not in others.[4]

CT is often the imaging modality of choice for diagnosing acute ischemic stroke because of high availability and lack of contra indications.[5] Previously identified imaging predictors for recurrent ischemic stroke include acute ischemia on non-contrast CT (NCCT), occlusion or stenosis on CT angiography (CTA) and poor collateral supply on CTA.[6,7] In addition, magnetic resonance imaging (MRI) derived predictors such as multiple ischemic lesions are shown to have added value to clinical models.[4,8,9]

Clinical prediction models have been summarized in a systematic review and meta-analysis.[10] The discriminative performance of these models was moderate.[10] Most models are developed for predicting recurrences of ischemic stroke not longer than 90 days or 1 year after the initial stroke, whereas ischemic stroke may recur up to 5 years after the initial stroke and beyond.[11] To our knowledge, the only model that was developed to predict 5-year ischemic stroke recurrence was developed in young stroke patients. Prediction of 5-year recurrent stroke in adult patients has not been studied before and the added value of CT derived predictors is unknown. Therefore, we sought to develop a model incorporating clinical risk factors for predicting 5-year recurrent ischemic stroke in patients with ischemic stroke and we aimed to evaluate whether adding CT derived predictors improved this model.

METHODS

Study population

All patients participated in the Dutch Acute Stroke Study (DUST), a prospective multicenter observational cohort study in the Netherlands. The DUST was designed to assess the prognostic value of CT perfusion (CTP) and CTA in predicting clinical outcome after 90 days, in addition to patient characteristics and NCCT findings. A detailed description of the design and baseline characteristics of the participants has been described elsewhere.[12,13] The study was approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands.

The current study is based on the three largest DUST centers: University Medical Center Utrecht, Leiden University Medical Center and St. Antonius Hospital Nieuwegein. Patients were enrolled between 2009 and 2013. Additional 5-year follow-up data were collected by evaluating medical records in June 2018. From the original 766 patients enrolled in the three selected DUST centers, imaging data were incomplete for 38 patients. Additionally, we excluded 90 patients without a diagnosis of ischemic stroke at baseline. The remaining sample included 638 patients.

Baseline assessments

The following baseline data were collected: demographics, pre-stroke modified Rankin Scale (mRS), characteristics of the index event (National Institutes of Health Stroke Scale [NIHSS], Trial of ORG 10172 in Acute Stroke Treatment [TOAST] classification), time from symptom onset to CT scan, intravenous thrombolysis, endovascular treatment and vascular risk factors.[14] Imaging data included NCCT findings such as hyperdense vessel sign and Alberta Stroke Program Early CT Score (ASPECTS) of either the anterior or posterior circulation. CTA findings included the presence of occlusion, clot burden score (CBS), collateral score (CS) and symptomatic arterial stenosis >70%.[15–17] Furthermore, ASPECTS was determined on cerebral blood volume and mean transit time maps, which were derived from CTP.[18]

Candidate predictors

All candidate predictors were selected based on the results of two systematic literature reviews.[4,10] Demographic factors included age and sex. Clinical characteristics included the NIHSS score on admission and the TOAST classification. Other variables included hypertension, diabetes mellitus, hyperlipidemia, smoking, history of myocardial infarction, history of atrial fibrillation, history of peripheral artery disease, and history of transient ischemic attack (TIA) or ischemic stroke.

Imaging characteristics included previous cerebral infarcts on NCCT, hyperdense vessel sign on NCCT, symptomatic arterial stenosis >70% on CTA, collateral score (poor versus good) on CTA and ASPECTS (>7 versus ≤7) on cerebral blood volume and mean transit time maps.[17,19,20]

Recurrent ischemic stroke

Follow-up data were based on hospital visits (follow-up visits or admissions) or communications (telephone or correspondence) and were extracted from medical records. If follow-up data were missing, the patient was censored at the time of the last visit or communication.

The primary outcome was recurrent ischemic stroke, which was defined as a clinical event of sudden onset with new neurological deficits that persisted for more than 24 hours and was not caused by another diagnosis than ischemic stroke.

Statistical analysis

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for candidate predictors of recurrent ischemic stroke by performing multivariable Cox regression analyses. We plotted Schoenfeld residual plots to check the proportional hazards assumption, which was not violated.

Two models were developed: model 1 included clinical predictors and model 2 included clinical and imaging predictors. First, the clinical model was developed applying backward elimination to the model with all the clinical candidate predictors. The full model containing all candidate predictors was then simplified by performing backward elimination based on a p-value threshold of 0.1. For model 2, the candidate imaging predictors were added to the final clinical model and the described process of backward elimination was repeated. To prevent removal of the clinical predictors, the clinical predictors were forced into the model. Model improvement was evaluated by calculating the continuous net reclassification improvement (NRI) and 95% CI using the Kaplan Meier method and 1,000 bootstrap samples.[21,22] NRI is based on reclassification of patients with or without the outcome and increases as the patients with the outcome are reclassified as having a high risk or the patients without the outcome are reclassified as having a low risk.[21] The improvement in discrimination slopes was evaluated with the measure of integrated discrimination improvement (IDI).[21] Model improvement was also evaluated with the likelihood ratio test.

Optimism of the clinical and extended models was evaluated with 1,000 bootstrap samples. Global shrinkage of the model was done with the jackknife method.[23] Finally, discrimination and calibration of the optimism-corrected model were assessed with the c-statistic and the calibration plot and its slope. Statistical analysis was performed with packages *survival*, *rms*, *nricens*, and *survIDINRI* in R version 3.5.0. This study was performed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Checklist for Prediction Model Development and Validation.[24]

RESULTS

Of the 638 patients with stroke at baseline, 56 (9%) had a recurrent ischemic stroke over the 5 years of follow-up. Baseline characteristics are shown in Table 1. Comparison of the baseline characteristics of our study population with all remaining DUST participants is shown in Supplemental table I.

Table 1. Baseline characteristics stratified by recurrence of ischemic stroke over 5 years of follow-up

Characteristic	**Recurrence** n=56	**No recurrence** n=582
Age, mean±SD	68±12	67±14
Male sex, n (%)	41 (73)	324 (56)
mRS ≥3 before stroke, n (%)	1 (2)	43 (7)
Admission NIHSS, median (Q1-Q3)	4 (3-7)	6 (3-12)
Posterior circulation infarct, n (%)	11 (20)	79 (14)
Intravenous thrombolysis, n (%)	30 (54)	360 (62)
Endovascular treatment, n (%)	1 (2)	40 (7)
Medical history		
Hypertension, n (%)	34 (62)	285 (49)
Diabetes mellitus, n (%)	10 (18)	74 (13)
Hyperlipidemia, n (%)	29 (52)	161 (28)
Smoking currently, n (%)	15 (29)	178 (33)
Former smoking, n (%)	22 (42)	154 (28)
Never smoked, n (%)	15 (29)	213 (39)
Atrial fibrillation, n (%)	8 (15)	79 (14)
Anticoagulant medication, n (%)	12 (21)	82 (14)

Table 1. Baseline characteristics stratified by recurrence of ischemic stroke over 5 years of follow-up (continued)

Characteristic	**Recurrence** n=56	**No recurrence** n=582
History of stroke or TIA, n (%)	22 (39)	114 (20)
History of MI, n (%)	10 (18)	65 (11)
History of PAD, n (%)	4 (7)	30 (5)
Imaging findings		
Previous cerebral infarcts on NCCT, n (%)	24 (43)	170 (29)
Hyperdense vessel sign, n (%)	5 (9)	123 (21)
Early signs of ischemia on NCCT, n (%)	13 (23)	160 (27)
Perfusion deficit present on CTP, n (%)	27 (51)	383 (68)
CBV ASPECTS, median (Q1-Q3)	10 (9-10)	10 (7-10)
CBV ASPECTS ≤7, n (%)	5 (9)	143 (25)
MTT ASPECTS, median (Q1-Q3)	10 (8-10)	8 (4-10)
MTT ASPECTS ≤7, n (%)	10 (19)	251 (45)
Symptomatic arterial stenosis >70% on CTA	12 (22)	125 (22)
Occlusion on CTA, n (%)	22 (39)	329 (57)
Clot burden score, median (Q1-Q3)	10 (9-10)	10 (7-10)
Poor collateral score, n (%)	6 (11)	102 (18)
TOAST classification		
Large artery atherosclerosis, n (%)	18 (32)	185 (32)
Cardioembolism, n (%)	5 (9)	114 (20)
Small vessel disease, n (%)	11 (20)	54 (9)
Other, n (%)	4 (7)	49 (8)
Unknown, n (%)	18 (32)	180 (31)

SD indicates standard deviation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; TIA, transient ischemic attack; MI, myocardial infarction; PAD, peripheral artery disease; NCCT, non-contrast CT; CTP, CT perfusion; CBV, cerebral blood volume; ASPECTS, Alberta Stroke Program Early CT Score; MTT, mean transit time; ICA, internal carotid artery.

Model building

The main clinical predictors of ischemic stroke recurrence were male sex, history of hyperlipidemia, and history of either stroke or TIA (Table 2). The c-statistic of the clinical model, which contained male sex, history of hyperlipidemia and history of stroke or TIA, was 0.61. Compared with the clinical model, the extended model, which contained previous cerebral infarcts on non-contrast CT and ASPECTS greater than 7 on mean transit time maps had higher discriminative performance (c-statistic 0.65, P=0.01).

The NRI for the recurrence group was 0.40 (95% CI -0.04-0.73) and 0.04 (95% CI -0.13-0.54) for the non-recurrence group. Taken together, the total NRI was significant (0.44, 95% CI 0.14-0.74). The discrimination slope also improved significantly (IDI 0.03, 95% CI 0.01-0.09).

The calibration plots are shown in Figure 1. According to the slopes of the clinical (0.70) and the extended (0.72) models, the models were reasonably calibrated.

Table 2. Effect estimates of the full and simplified clinical model and the extended model for predicting recurrent ischemic stroke

Candidate predictor	Full clinical HR (95% CI)	Simplified HR (95% CI)	Full extended HR (95% CI)	Simplified HR (95% CI)
Age>65	1.5 (0.8-2.8)	1.3 (0.7-2.3)	1.2 (0.7-2.2)	-
Male sex	1.7 (0.9-3.2)	1.9 (1.1-3.5)	1.7 (0.9-3.2)	1.8 (0.98-3.3)
Hypertension	1.0 (0.5-1.8)	-	-	-
Diabetes	0.9 (0.4-2.0)	-	-	-
Current smoking	0.7 (0.4-1.5)	-	-	-
History of hyperlipidemia	2.0 (1.01-3.9)	1.7 (0.98-3.0)	1.6 (0.9-2.9)	1.8 (1.03-3.2)
History of stroke/TIA	2.1 (1.1-3.9)	2.4 (1.3-4.1)	2.1 (1.1-3.8)	2.0 (1.1-3.6)
History of MI	0.9 (0.4-2.1)	-	-	-
History of AF	0.9 (0.4-2.0)	-	-	-
History of PAD	1.0 (0.3-3.3)	-	-	-
NIHSS ≥7	0.7 (0.4-1.4)	-	-	-
Lacunar stroke (TOAST)	0.6 (0.3-1.2)	0.6 (0.3-1.1)	0.6 (0.3-1.3)	-
Previous cerebral infarct on NCCT			1.5 (0.9-2.7)	1.5 (0.9-2.7)
Hyperdense vessel sign on NCCT			0.7 (0.2-2.3)	-
CBV ASPECTS >7			1.1 (0.3-4.2)	-
MTT ASPECTS >7			2.8 (0.97-8.0)	2.3 (1.2-4.7)
Symptomatic arterial stenosis >70% on CTA			1.8 (0.9-3.8)	-
Occlusion on CTA			0.8 (0.4-1.6)	-
Poor collateral score			0.6 (0.2-1.7)	-
C-statistic		0.67		0.70
Optimism-corrected c-statistic		0.61		0.65
Calibration slope		0.70		0.72

HR indicates hazard ratio; CI, confidence interval; TIA, transient ischemic attack; MI, myocardial infarction; AF, atrial fibrillation; PAD, peripheral artery disease; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NCCT, non-contrast CT; CBV, cerebral blood volume; ASPECTS, Alberta Stroke Program Early CT Score; MTT, mean transit time; CTA, CT angiography.

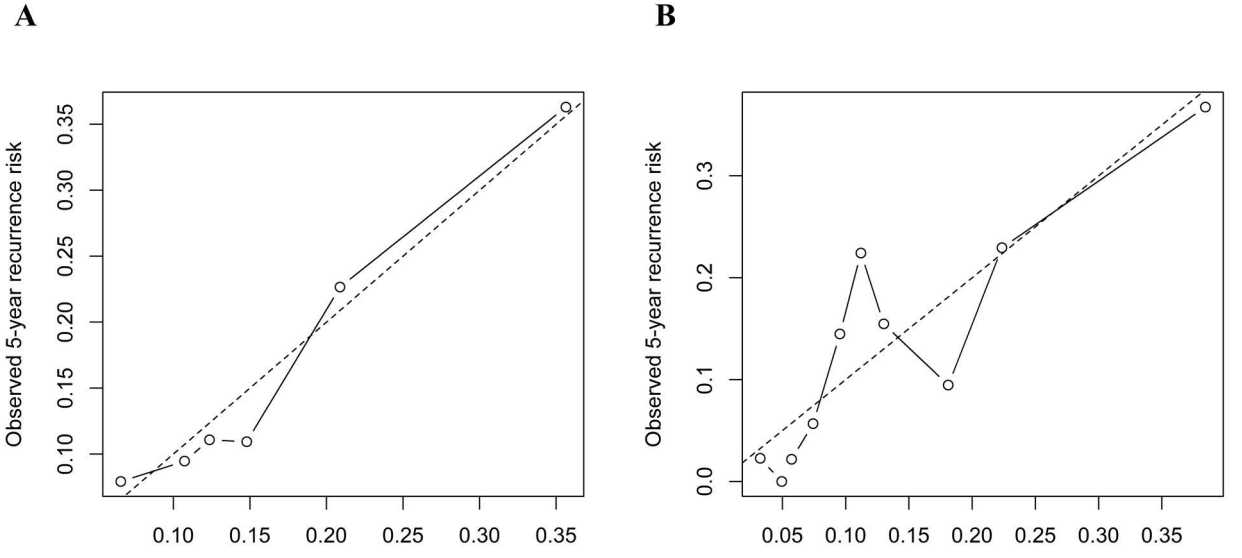

Figure 1. Calibration plot for the clinical model (A) and the extended model (B) containing clinical and CT derived predictors. A calibration slope of 1.0 indicates perfect calibration (dotted line).

DISCUSSION

In this study, addition of two CT imaging variables (previous cerebral infarcts on NCCT and ASPECTS on mean transit time maps derived from CTP) to the clinical model resulted in an improved model for predicting 5-year recurrence of ischemic stroke.

CT is often performed in patients with ischemic stroke as CT has some advantages over MRI in the acute stroke setting such as the short acquisition time, patient compatibility, costs, and availability. Besides diagnostic purposes, findings on admission CT can be used for prognostic purposes in patients with acute ischemic stroke. For instance, several studies investigated the value of CT findings on predicting clinical outcome after ischemic stroke.[13,25] The added value of predictors derived from CTP and CTA for predicting clinical outcome after 3 months was limited in the DUST dataset.[13] A previous study showed that prediction of recurrent ischemic stroke at 90 days was significantly improved by adding MRI derived predictors such as multiple infarcts and involvements of multiple vascular territories to a clinical model.[8] In addition, similar MRI derived predictors were identified as being predictive of recurrent ischemic stroke during a 2-year follow-up.[9] However, the added value of CT derived predictors has never been investigated for predicting recurrent ischemic stroke beyond 2 years. In this study, we showed that recurrence risk estimation can be significantly improved by adding CT derived predictors to a model incorporating clinical predictors.

Although stroke subtype was a significant predictor of recurrent ischemic stroke in previous studies, this predictor did not have added value to the clinical prediction model in our study population.[4] The stroke etiology was determined using the TOAST classification.[14] Determination of the stroke etiology often requires extensive diagnostic work-up and can sometimes only be accurately determined during a follow-up period after the stroke, whereas immediate recurrence prediction after the index event is desirable.[26] In this study, the TOAST classification was determined during the initial admission phase. As follow-up studies for determining the final stroke etiology were not routinely taken into account, the cause of the stroke remained unknown for 31% of the cases. Therefore, we feel that we should be careful with drawing conclusions from this particular analysis. Future studies should elucidate whether stroke subtype has added value to long-term prediction of recurrent stroke.

The added value of previous cerebral infarcts on NCCT to a history of either stroke or TIA can be explained by the fact that brain ischemia may occur without the patient noticing, which is called a silent brain infarction. The association between silent brain infarction and future stroke has been established before, but it has never been related to recurrent ischemic stroke.[27] Whether the patient has had a previous ischemic stroke or TIA is usually evaluated by history taking. However, it is possible that ischemic brain damage is present, although the patient has not experienced any stroke symptoms. This is a typical example of how CT imaging has added prognostic value to clinical assessments such as history taking.

In this study, poor collateral score was less prevalent in the recurrence group compared to the group without recurrence, but no significant association was observed. In previous studies, poor collateral score was associated with recurrent stroke.[6,7] An explanation for this finding is the lack of power due to the small number of patients with poor collaterals. This finding needs verification in a more balanced population.

The observed association between higher ASPECTS on mean transit time maps derived from CTP and increased recurrence risk is surprising, because it implies that patients with smaller areas of ischemia and/or involvement of less ASPECTS regions face a higher risk of recurrence compared with patients with greater areas of ischemia and/or involvement of more ASPECTS regions. We were not able to distinguish between the infarct size and the multiplicity of the infarct as these data were not routinely collected in the DUST. Additional studies are warranted to confirm this remarkable association and to assess its relation to infarct size, multiplicity and etiology. An advantage of using ASPECTS is that it can be graded in the acute stroke phase and that it can be instantly used for prediction purposes. Although ASPECTS has been initially developed for NCCT assessments, it can also be applied to other CT modalities such as CTP.[15,28] In this study, the dichotomized measure of ASPECTS had added value to the clinical prediction, model making it a promising tool for recurrence prediction purposes. This finding however needs verification in a larger study with prospective outcome evaluation.

In this study, we showed that recurrence prediction after ischemic stroke can be improved by using imaging information in addition to clinical information. However, even after the model was improved, the performance was still moderate. A few steps need to be taken before a model that predicts recurrent ischemic stroke can be used in routine stroke care. First, studies need to look for more predictors to see if a clinically relevant improvement can be achieved. Second, once a model with a

sufficiently high performance is developed, it needs to be validated in other cohorts. Third, the impact of the model needs to be quantified ideally in a randomized controlled trial. In this way, the prognostic model may guide treatment decisions and therefore affect patient outcomes. This study contributes to the process of finding an optimal model for recurrence prediction.

A strength of this study was the selection of candidate predictors, which was based on literature. In this way, we avoided selecting predictors purely on significant p-values. In addition, predictor information was collected prospectively, leading to a minimal number of missing values.

A limitation of this study was the retrospective collection of follow-up data, which could have induced underestimation of the outcome prevalence. This could have influenced our results in case certain associations are related to the loss of follow-up. For instance, recurrences, which were recorded in another hospital than the hospital of the index stroke, were missed. We do not believe that this has happened often, as most patients return to their own hospital for follow-up visits. Although the observed prevalence is in line with previous results, studies with prospective follow-up are needed to verify our findings.

The number of outcomes was relatively small, which was also a limitation of this study. Heart failure was not collected as a potential predictor in this study, whereas it showed to be of predictive value in previous studies.[29,30] However, with less than sixty recurrences, we were not allowed to add more than 5 predictors to our extended model. Selecting only three out of fourteen DUST centers contributed to this limitation, but acquiring follow-up data from the other DUST centers was not deemed feasible. Studying larger cohorts may allow more predictors into the final model.

Instead of improving a previously developed model, we had to create our own clinical model that best fitted our data. A drawback of this method is that our clinical model needs validation in other studies, whereas a previously developed model has already been validated.

In conclusion, clinical models for predicting long-term recurrence after ischemic stroke have moderate performance and can be improved by adding CT derived predictors.

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SUPPLEMENTS

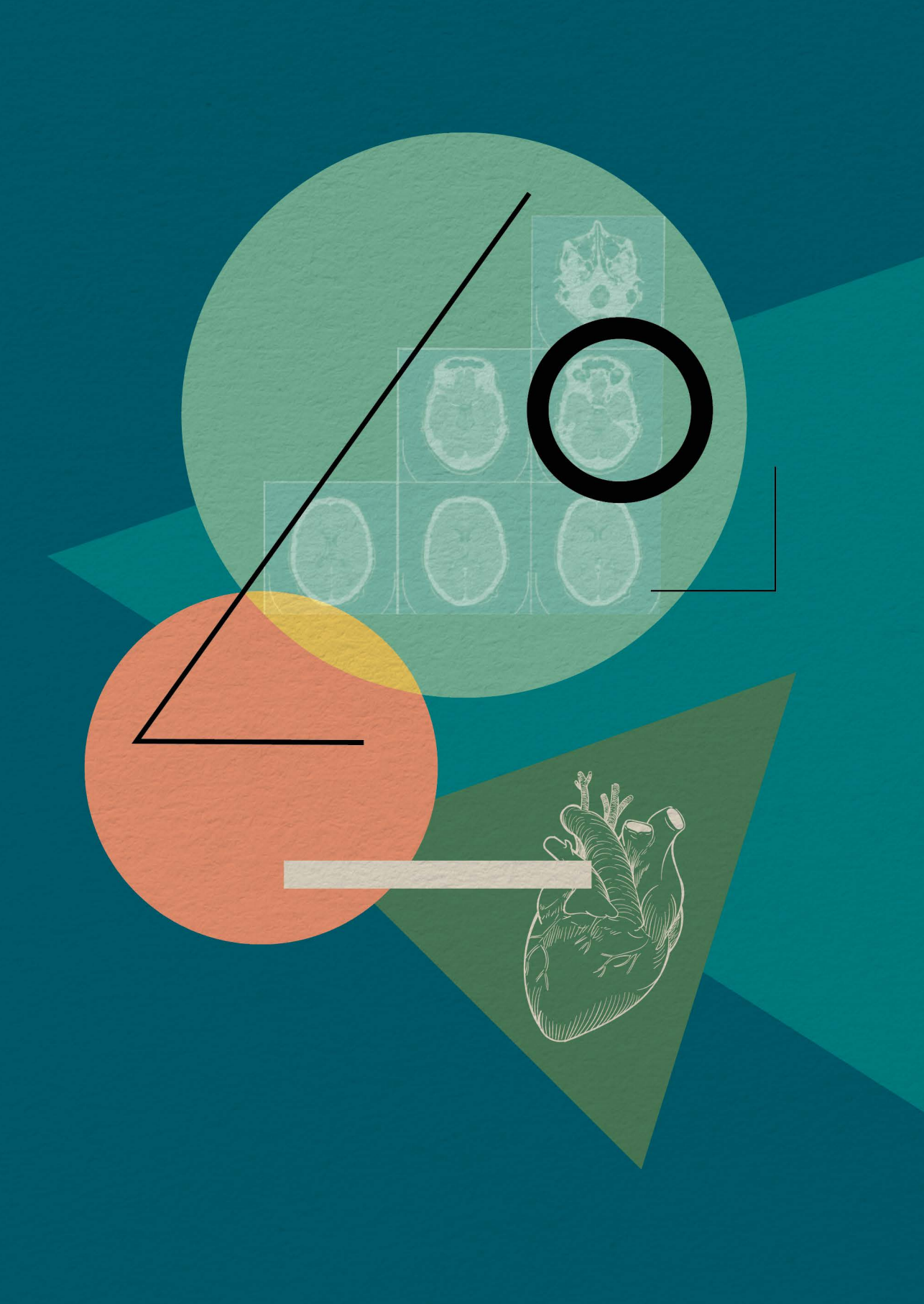
Supplemental table I. Patient characteristics stratified by included and excluded centers, which participated in the Dutch Acute Stroke Study

Characteristic	**Included** n=638	**Excluded** n=755
Age, mean±SD	67±14	67±14
Male sex, n (%)	365 (57)	431 (57)
mRS ≥3 before stroke	44 (7)	39 (5)
Admission NIHSS, median (Q1-Q3)	6 (3-12)	6 (3-12)
Intravenous thrombolysis, n (%)	390 (61)	479 (63)
Endovascular treatment, n (%)	41 (6)	40 (5)
Medical history		
Hypertension, n (%)	319 (50)	408 (54)
Diabetes mellitus, n (%)	84 (13)	129 (17)
Hyperlipidemia, n (%)	190 (30)	267 (35)
Smoking currently, n (%)	193 (32)	188 (25)
Former smoking, n (%)	176 (29)	237 (31)
Never smoked, n (%)	228 (38)	245 (33)
Atrial fibrillation, n (%)	87 (14)	90 (12)
Anticoagulant medication, n (%)	94 (15)	72 (10)
History of stroke/TIA, n (%)	136 (21)	206 (27)
History of MI, n (%)	75 (12)	95 (13)
History of PAD, n (%)	34 (5)	48 (6)
Imaging findings		
Old infarcts on NCCT, n (%)	194 (30)	214 (28)
Hyperdense vessel sign, n (%)	128 (20)	155 (21)
Early signs of ischemia on NCCT, n (%)	173 (27)	170 (23)
Perfusion deficit present on CTP, n (%)	410 (66)	387 (51)
CBV (pc)ASPECTS, median (Q1-Q3)	10 (8-10)	10 (8-10)
CBV (pc)ASPECTS ≤7, n (%)	148 (24)	138 (18)
MTT (pc)ASPECTS, median (Q1-Q3)	9 (4-10)	9 (5-10)
MTT (pc)ASPECTS ≤7, n (%)	261 (42)	249 (33)
ICA stenosis >70% or occlusion on CTA	137 (22)	108 (14)

Supplemental table I. Patient characteristics stratified by included and excluded centers, which participated in the Dutch Acute Stroke Study (continued)

Characteristic	**Included** n=638	**Excluded** n=755
Occlusion on CTA, n (%)	351 (55)	362 (48)
Clot burden score, median (Q1-Q3)	10 (8-10)	10 (8-10)
Poor collateral score, n (%)	108 (17)	64 (9)
TOAST classification		
LAA, n (%)	203 (32)	217 (29)
CE, n (%)	119 (19)	116 (15)
SVD, n (%)	65 (10)	118 (16)
Other, n (%)	53 (8)	50 (7)
Unknown, n (%)	198 (31)	254 (34)
Follow-up		
Poor clinical outcome at 90 days*, n (%)	254 (40)	247 (33)

* Poor clinical outcome was defined as modified Rankin scale equal or greater than 3.
SD indicates standard deviation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; TIA, transient ischemic attack; MI, myocardial infarction; PAD, peripheral artery disease; NCCT, non-contrast CT; CBV, cerebral blood volume; pc, posterior circulation; ASPECTS, Alberta Stroke Program Early CT Score; MTT, mean transit time; ICA, internal carotid artery; CTA, CT angiography.



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SUMMARY AND GENERAL DISCUSSION

SUMMARY

Acute ischemic stroke (AIS) is one of the most prevalent causes of death and the leading cause of long-term disability in the world. Patients with suspected stroke or transient ischemic attack (TIA) usually undergo CT imaging including non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA). NCCT is used to exclude hemorrhage and evaluate early ischemic changes. CTA can show arterial occlusion(s) and possible causes of the stroke. CTP maps are used to identify salvageable brain tissue at risk for infarction (penumbra) and dead brain tissue (infarct core). The acute stroke imaging protocol is essential for guiding treatment decisions and predicting outcomes. This protocol can be improved by using advanced CT imaging techniques such as dual-energy or spectral CT. The aim of this thesis was to improve diagnostic and prognostic aspects of stroke care with advanced CT imaging.

In **part I** of this thesis, we explored advanced CT imaging variables in patients with AIS. **Chapter 2** describes the comparison between virtual NCCT, reconstructed from dual-energy CTA, and standard linearly blended NCCT, the dual-energy surrogate of conventional 120 kVp NCCT, regarding the detection of early ischemic changes with the Alberta Stroke Program Early CT Score (ASPECTS) in patients with suspected AIS. Of the 193 included patients, 100 patients (52%) had ischemia on diffusion weighted imaging MRI. Compared to the MRI reference standard, the ASPECTS concordance correlation coefficient for conventional and virtual NCCT was 0.23 (95% CI 0.15-0.32) and 0.44 (95% CI 0.33-0.53), respectively. The difference in concordance correlation coefficient between virtual and conventional NCCT was 0.20 (95% CI 0.01-0.39) and did not cross the pre-specified non-inferiority margin of -0.10. In conclusion, dual-energy virtual NCCT was noninferior to conventional NCCT for the detection of early ischemic changes.

In **Chapter 3**, pitfalls of automated post-processing CTP data were evaluated. Automated post-processing of raw CTP data is routinely used in stroke care as it simplifies the application of CTP and may improve reproducibility, however, it is also prone to failure. In reviewing 176 consecutive AIS patients, failures occurred in 20 (11%) patients during automated post-processing by the RAPID software. The most common cause of failure was motion and, to a lesser extent, streak artifact and poor arrival of contrast bolus. Higher stroke severity was associated with failure.

Chapter 4 describes several methods including single phase CTA, CTP derived three-phase CTA, multiphase CTA and temporal maximum intensity projection images, and digital subtraction angiography (DSA) to assess the collateral circulation and

to predict the clinical outcome in patients with AIS patients who underwent CTP, CTA, and DSA prior to thrombectomy with occlusion of the internal carotid artery or the M1 or M2 segments of the middle cerebral artery. Concordance correlation coefficient (n=80) was 0.08 (three-phase CTA), 0.09 (standard single-phase CTA) and 0.23 (multiphase CTA) for static assessments and 0.10 (three-phase CTA) and 0.27 (multiphase CTA) for dynamic assessments. Adjusted for recanalization, higher static collateral scores on multiphase CTA (OR 1.7; 95% CI 1.1-2.7) and temporal maximum intensity projection images (OR 2.0; 95% CI 1.1-3.4) were associated with good clinical outcome (modified Rankin Scale ≤2) as were higher dynamic collateral scores (modified American Society of Interventional and Therapeutic Neuroradiology score) on three-phase CTA (OR 1.5; 95% CI 1.1-2.2) and multiphase CTA (OR 1.7; 95% CI 1.1-2.6). This study showed that the concordance between assessments on CT and DSA was poor. The collateral status evaluated on CTP-derived CTA, but not on standard single-phase CTA or DSA, was associated with clinical outcome.

In **Chapter 5**, the rationale and design of the "Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke" (ENCLOSE) study was described. ENCLOSE is a prospective observational cohort study, which was conducted in two Dutch stroke centers, University Medical Center Utrecht and Amsterdam University Medical Center. The aim of ENCLOSE was to improve early detection of small volume stroke and thromboembolic sources and to improve prediction of recurrence in patients with AIS. To improve detection of small volume stroke and thromboembolic sources, dual-energy thin-slice CTP and cardiac CTA were used, respectively. Clinical and imaging predictors of recurrent ischemic stroke were evaluated in multivariable models.

Chapter 6 describes an AIS patient with two intracardiac thrombi as possible cardioembolic sources on dual-energy cardiac CTA. Repeated imaging after early recurrence of ischemic stroke demonstrated a diminished left ventricular thrombus. This case emphasizes the potential benefit of: 1) cardiac evaluation through CTA in the acute stroke setting and 2) use of dual energy CT angiography for detection of thrombus and differentiating between thrombus, myocardial wall and slow flow of contrast.

In **Chapter 7**, the results from the ENCLOSE study regarding early detection of cardioembolic sources in acute ischemic stroke are described. Patients with TIA or AIS underwent non-gated head-to-heart CTA. Forty-four (12%) of 370 included patients had a cardiac thrombus on admission CTA: 35 (9%) in the left atrial appendage (LAA) and 14 (4%) in the left ventricle. Patients with cardiac thrombus

had more severe strokes (median National Institutes of Health Stroke Scale [NIHSS], 10 versus 4, P=0.006), higher clot burden (median clot burden score 9 versus 10, P=0.004) and underwent endovascular treatment more often (43% versus 20%, P<0.001) than patients without cardiac thrombus. LAA thrombus was present in 28% and 6% of the patients with and without atrial fibrillation, respectively (P<0.001). The diagnostic certainty for LAA thrombus was higher for spectral iodine maps compared with the conventional CTA (P<0.001). The presence of cardiac thrombus on CTA increased the likelihood of a cardioembolic source according to an expert panel (P<0.001). In conclusion, extending the stroke CTA to cover the heart increases the chance of detecting cardiac thrombi and helps to identify cardioembolic sources in the acute stage of ischemic stroke with more certainty. Spectral iodine maps provide additional value for detecting LAA thrombus.

In **part II** of this thesis, we evaluated CT imaging predictors of treatment effect, malignant infarction and recurrent stroke.

In **Chapter 8**, the association between intravenous thrombolysis and several outcomes were evaluated across different patterns of intracranial internal carotid artery calcification (ICAC) in patients from the Dutch Acute Stroke Study (DUST). Of 982 patients, 609 (62%) received intravenous thrombolysis and 381 (39%) had a 90-day modified Rankin Scale of 3-6. Intravenous thrombolysis was associated with a lower 90-day modified Rankin Scale in the group without ICAC (adjusted OR 0.3; 95% CI 0.1-0.9) and in the group with a medial ICAC pattern (adjusted OR 0.5; 95% CI 0.3-0.8), but not in the groups with intimal (adjusted OR 0.9; 95% CI 0.5-1.5) or indistinguishable patterns (adjusted OR 0.6; 95% CI 0.2-1.8). Intravenous thrombolysis was only associated with recanalization in the group with a medial ICAC pattern (adjusted OR 3.5; 95% CI 1.2-11.0). Compared to an intimal ICAC pattern, a medial ICAC pattern was associated with good collateral status (adjusted OR 2.6; 95% CI 1.1-6.0). In conclusion, intravenous thrombolysis was associated with favorable clinical outcome and successful recanalization in the group with a medial ICAC pattern, but not in the group with an intimal ICAC pattern.

Chapter 9 describes the association between the ratio of intracranial cerebrospinal fluid (CSF) volume to intracranial volume (ICV), measured on thin-slice NCCT, and the occurrence of malignant middle cerebral artery infarction in patients with intracranial large vessel occlusion from the DUST study. Of the 286 included patients, 35 (12%) developed malignant MCA infarction. CSF/ICV was independently associated with malignant MCA infarction in three multivariable models: 1) with age and admission NIHSS (OR 3.3; 95% CI 1.1-11.1), 2) with admission NIHSS and poor

collateral score (OR 7.0; 95% CI 2.6-21.3) and 3) with terminal ICA or proximal M1 occlusion and poor collateral score (OR 7.7; 95% CI 2.8-23.9). The performance of model 1 (AUROC 0.795 versus 0.824, P=0.033), model 2 (AUROC 0.813 versus 0.850, P<0.001) and model 3 (AUROC 0.811 versus 0.856, P<0.001) improved significantly after adding CSF/ICV. In conclusion, the CSF/ICV ratio was associated with the risk of malignant medial cerebral artery infarction and had added value to small clinical and imaging prediction models.

In **Chapter 10**, incidence and predictors of malignant middle cerebral artery infarction were evaluated in patients with large vessel occlusion who received endovascular treatment. Data from the "Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands" (MR CLEAN) Registry were used. Of the 1445 included patients, 82 (6%) developed malignant infarction. Independent predictors were lower age, higher NIHSS, lower ASPECTS, internal carotid artery occlusion, lower collateral score, longer times from onset to groin puncture, and unsuccessful reperfusion. The AUROC of a prediction model combining these features was 0.83 (95% CI: 0.79-0.88) and the Hosmer-Lemeshow test indicated appropriate calibration (P=0.937).

In conclusion, successful reperfusion decreases the risk of malignant infarction after endovascular treatment started within 6.5 hours of stroke onset. A prediction model combining easily retrievable measures of age, ASPECTS, collateral status, and reperfusion shows good discrimination between patients who will develop malignant infarction and those who will not.

Chapter 11 describes the added value of the CSF/ICV ratio to the model described in Chapter 10. Patients with a middle cerebral artery occlusion and available thin-slice NCCT were selected from the MR CLEAN Registry. A basic prediction model including age, NIHSS, ASPECTS, occlusion of the internal carotid artery, collateral score, time between symptom onset and groin puncture, and unsuccessful reperfusion was compared to an extended model (basic model and the CSF/ICV ratio). Malignant edema occurred in 40 (6%) of 683 patients. In the extended model, a lower CSF/ICV ratio was associated with the occurrence of malignant edema (OR per percentage point, 1.2; 95% CI 1.1-1.3, P<0.001). Age lost predictive value for malignant edema in the extended model (OR 1.1; 95% CI 0.9-1.5, P=0.372). The performance of the extended model was higher than that of the basic model (P<0.001). In conclusion, adding the CSF/ICV ratio improves a multimodal prediction model for the occurrence of malignant edema after endovascular treatment.

Chapter 12 concerns a systematic review and meta-analysis of clinical and radiological predictors of recurrent ischemic stroke in patients with recent ischemic stroke. Ten studies were included. Past medical history of stroke or TIA was a predictor of recurrent ischemic stroke (pooled RR 2.5; 95% CI 2.1-3.1). Small vessel strokes were associated with a lower risk of recurrence than large vessel strokes (pooled RR 0.3; 95% CI 0.1-0.7). Patients with stroke of an undetermined cause had a lower risk of recurrence than patients with large artery atherosclerosis (pooled RR 0.5; 95% CI 0.2-1.1). A moderate level of evidence was found for the association between recurrent ischemic stroke and the load of ischemic lesions on MRI. Strong level of evidence was absent for imaging predictors.

In **Chapter 13**, the added value of NCCT, CTP and CTA for predicting long-term recurrent ischemic stroke in patients with AIS, participating in DUST, was evaluated. During 5 years of follow-up, 56 (9%) of the 638 included patients had a recurrence. The c-statistic of the clinical model, which contained male sex, history of hyperlipidemia and history of stroke or TIA, was 0.61. Compared to the clinical model, the extended model, which contained previous cerebral infarcts on NCCT and ASPECTS greater than 7 on mean transit time (MTT) maps derived from CTP had higher discriminative performance (c-statistic 0.65, P=0.01). Inclusion of these CT variables led to a significant improvement in reclassification measures, by using the net reclassification improvement and integrated discrimination improvement indices. In conclusion, data from CT imaging significantly improved the discriminatory performance and reclassification for predicting recurrent ischemic stroke recurrence beyond a model incorporating clinical risk factors.

GENERAL DISCUSSION

Part I: Advanced CT imaging in stroke

Non-contrast CT

CT of the head is the most commonly utilized modality in the evaluation of stroke.[1] NCCT is generally the first imaging study in the evaluation of suspected stroke to exclude intracranial hemorrhage and to evaluate early ischemic changes with ASPECTS.[2] ASPECTS is predictive of functional outcome after intravenous thrombolysis and endovascular thrombectomy, and is therefore widely used to make treatment decisions.[3–5] To determine the ASPECTS, maximal contrast between gray and white brain matter is crucial. The applications of DECT, also known as spectral CT, to improve tissue contrast are becoming increasingly apparent.[6] In this thesis, we have demonstrated that virtual NCCT, which is reconstructed from CTA, is non-inferior to standard linearly blended NCCT, the dual-energy surrogate of conventional NCCT, for the detection of early ischemic changes with ASPECTS.[7] Previous studies have shown that virtual NCCT also enables reliable detection of intracranial hemorrhage and the hyperdense vessel sign.[8–10] Ultimately, virtual NCCT has the potential to replace the conventional NCCT, which would also result in less radiation exposure for the patient. Whether dual-energy virtual NCCT saves time in the acute stroke work-up is uncertain as dual-energy reconstructions also take a little extra time, and NCCT needs to be acquired first to exclude intracranial hemorrhage. As the dual-energy virtual NCCT images need to be reconstructed from the CTA, it is difficult to omit the conventional NCCT in clinical practice. Therefore, this study does not directly impact patients with acute stroke but it does show possible future applications of dual-energy CT.

CT perfusion

In acute stroke, CTP is often used to identify the infarct core and penumbra (tissue at risk for infarction) to determine treatment eligibility, especially in the time window beyond six hours after symptom onset or with unknown time of onset, such as wake-up stroke. Perfusion maps are generated by post-processing the CTP source images, but failures may occur. We evaluated prevalence of automated CTP post-processing failures and associated patient factors. Failures were mostly caused by motion and, to a lesser extent, by streak artifact and poor arrival of contrast bolus. The patient factor significantly associated with failures was higher stroke severity, probably because such patients are more likely to be agitated and to move during the CTP scanning. The software was successful in 89% of the cases, but 11% of CTP scans showed artifacts leading to erroneous ischemic core volume estimations that

might have affected patient management in 3% of the cases. Therefore, stroke experts should be aware of the pitfalls of post-processing CTP data especially in patients with severe strokes.

CTP has good sensitivity (80%) and specificity (95%) for brain infarct detection.[11,12] However, accurate detection of small volume infarcts is still difficult with CTP, because of noise and limited spatial resolution.[13] In addition, evaluation of the posterior fossa is often hampered by streak artefacts.[14] In case no stroke is visualized with CT, MRI may be indicated to ascertain the diagnosis. Future studies need to show how the acute CTP stroke protocol can be improved further. Post-processing failures of CTP should be avoided, or, at least, recognized to prevent erroneous treatment decisions. Ideally, future studies should focus on preventing post-processing failures, for instance with help from artificial intelligence. In addition, acquisition and post-processing techniques may further improve over the years and may result in improvement of small volume stroke detection with CTP. In a previous study, we showed that monoenergetic reconstructions can help to improve infarct detection with CTP, but this needs to be clinically validated.[15]

Until then, small volume stroke will largely remain a clinical diagnosis, where MRI can be used to guide acute stroke therapies such as intravenous thrombolysis.

CT angiography

Collateral circulation

Patients with AIS routinely undergo CTA from head to the aortic arch to evaluate the presence of a large vessel occlusion and a possible stenosis or dissection of the carotid or vertebral arteries. In addition, CTA enables the evaluation of the collateral circulation, which can help to predict infarct volume and functional outcome after treatment.[16–18] Several grading systems and imaging modalities can be used to assess the collateral circulation. In current guidelines, DSA is recommended as the reference standard for assessing collaterals as it is the ultimate dynamic study of the cerebral vessels.[19] However, in clinical practice, collaterals are assessed with CTA, because DSA is not routinely performed in patients who do not undergo endovascular treatment. CTP source images can also be used to reconstruct a multiphase CTA or temporal maximum intensity projection CTA to evaluate the collateral circulation over time instead of using a single snapshot (standard single-phase CTA). In this thesis, we compared single-phase CTA and CTP derived three-phase CTA, multiphase CTA and temporal maximum intensity projection images with DSA, with respect to their ability to reliably grade collateral circulation in AIS.

We evaluated two scoring systems: a static collateral score entailing four categories, and a dynamic collateral score entailing five categories.[20–22] Agreement between the two systems was moderate to good. Collateral assessment achieved similar interobserver agreement for all imaging modalities, but concordance with DSA was, in general, poor. An explanation for this poor concordance may be the fact that the contralateral ICA or the posterior circulation are usually not visualized with DSA in anterior circulation stroke. As a result, the DSA assessment of collateral filling is likely to be incomplete relative to information from CTA and CTP. Also, the collateral scales on each modality and technique may be too different to correlate well. CTA lacks the temporal resolution of DSA, and CTA scales cannot capture the time resolved blood flow into the collateral circulation. For instance, if one looks at time point 1 and time point 2, which are separated by 20 seconds on a multiphase CTA, the collateral score might be good on the CTA scale. However, the DSA scale might show that it takes much longer for the collateral vessels to fill, which might result in a poor collateral score.

Associations with favorable outcome were significant for CTP derived CTA, but not for single-phase CTA or DSA assessments. Our study showed added value of multiple phase CTA images derived from CTP for the prediction of clinical outcomes. This implies that CTP derived CTA or multiple phase CTA should be considered as the reference standard for assessing collateral circulation instead of DSA, which is not acquired if endovascular treatment is not indicated.

The advantage of multiple phase CTA created with CTP images is that CTP images are often routinely acquired as part of the stroke imaging protocol. Multiphase CTA would require additional radiation exposure to the patient and longer scan duration in a setting where “time is brain”. In the future, artificial intelligence algorithms may be helpful in assessing the collateral circulation of CTP derived multiphase CTA images in a standardized manner and may contribute to treatment decision making and prediction of functional outcome in stroke patients.[23] Ultimately, all the required NCCT and CTA images may be extracted from one dynamic CTP scan in patients with suspected ischemic stroke. In addition, the stroke imaging protocol may be personalized, for instance by using different protocols for patients who present within the regular treatment window (6 hours) and who present beyond this window. Beyond the 6-hour time window treatment decisions are currently based on the collateral circulation and infarct volumes (penumbra and infarct core), whereas this is not the case for patients who present within the 6-hour time window. Future studies with selected patients should indicate how the stroke imaging protocol could be tailored to individual stroke patients.

Cardiac imaging

In current clinical practice, the heart and thoracic aorta are not routinely covered with CTA in patients with TIA or AIS.[24] The presence of a cardioembolic source of the stroke is currently evaluated in the subacute stage with electrocardiogram, 72-hour telemetry or Holter, and transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE).[25] However , the sensitivity of echocardiography for detecting cardiac thrombus is limited, especially using TTE to rule out LAA thrombus.[26] In addition, echocardiography is often performed one to several days after stroke onset, which may influence the chance of detecting cardiac thrombus, especially after intravenous thrombolysis.[27] Current guidelines recommend TTE or TEE for the detection of cardiac thrombi. TEE has a higher sensitivity than TTE, but is time-consuming, uncomfortable for the patient and has a negative influence on swallowing for at least the first 24 hours in acute stroke patients.[28,29] Both TTE and TEE do not outperform CTA.[30] The case report in this thesis illustrated the potential yield of admission non-gated spectral cardiac CTA. In this case, a patient with AIS and two cardiac thrombi in the left atrial appendage and the left ventricular apex had a recurrent ischemic stroke, which was most likely caused by the thrombus in the left ventricle as this diminished on follow-up imaging. To prospectively evaluate the yield of non-gated spectral cardiac CTA in acute stroke, we initiated the ENCLOSE study. In our study, cardiac thrombi were detected with non-gated cardiac CTA in 12% of the patients with TIA or AIS. Iodine maps were the most useful spectral reconstructions for the observers to detect LAA thrombus. The presence of a cardiac thrombus was associated with higher stroke severity and higher intracranial clot burden resulting in a higher rate of endovascular treatment. According to an expert panel, the additional information provided by the admission non-gated cardiac CTA significantly increased the certainty of a cardioembolic cause of the stroke in patients with cardiac thrombus.

These results show that the routine non-gated stroke CTA can be extended to detect cardioembolic sources in TIA or AIS in <5 seconds extra scan time, without extra iodine contrast material and with an acceptable increase of the radiation dose of 2 millisievert. Different scanner types including conventional scanners were used and therefore the results from ENCLOSE seem largely generalizable to other centers. In a recent Dutch ECG-gated CTA study, cardiac thrombus was detected in 7% of the patients with AIS.[31,32] Similar to ENCLOSE, patients with cardiac thrombus had higher clot burden and more severe strokes than patients without cardiac thrombus. Whether the diagnostic value of non-gated cardiac CTA is equivalent to ECG-gated CTA in AIS is unknown. Technical improvements of CT scanners allow faster acquisition times, which should improve image quality and reduce motion artifacts

without increasing the radiation dose in non-gated cardiac CTA.[33] Compared to non-gated cardiac CTA, ECG-gated CTA requires a separate scan with extra iodine contrast agent, radiation dose and time in a situation where "time is brain" in AIS.[33] Therefore, implementation of non-gated cardiac CTA seems more feasible than ECG-gated cardiac CTA in acute stroke care.

Besides cardiac thrombi, admission non-gated cardiac CTA also enables detection of other cardiac abnormalities such as a left ventricular aneurysm, myocardial ischemia and cardiomyopathy which were associated with the presence of left ventricular thrombus in ENCLOSE. Plaque in the ascending aorta or aortic arch may be the cause of the stroke in patients with cryptogenic stroke.[34] We found more low attenuation plaque (lipid-rich core), irregular surface or ulceration in the aortic arch than in the ascending aorta. These plaque characteristics are associated with an increased risk of stroke.[35] More extensive plaque characterization in the aorta and carotid arteries can be useful to assess the risk of recurrence and may be done by using advanced CT techniques such as dual-energy/spectral CT or photon counting CT, a new technology in CT in which X-rays are detected using a photon-counting detector.[36–38] These studies should relate these characteristics with stroke recurrence and the impact of prevention strategies.

Early detection of a cardioembolic source of stroke can help to initiate proper prophylactic treatment. Both patients with TIA and AIS, and also patients with and without known AF or oral anticoagulation use, had cardiac thrombi. This implies that all these patients may benefit from early detection of cardiac thrombus with non-gated cardiac CTA. Future studies need to evaluate the impact of cardiac imaging in acute stroke on prevention strategies and stroke recurrence, and also which group of patients will benefit the most from early detection of cardiac thrombus. In my opinion, the benefits of extending the stroke CTA to the heart outweigh the disadvantages of increased radiation dose and extra seconds of scan duration, and therefore cardiac CTA should be widely implemented in stroke care. In the Netherlands, non-gated cardiac CTA has already been implemented in several stroke centers.

Part II: CT imaging predictors of treatment effect, malignant infarction and recurrent stroke

Treatment effect

In this thesis, we evaluated the association between intravenous thrombolysis and 90-day functional outcome in a large cohort of consecutive patients with ischemic stroke stratified by the ICAC pattern. ICAC pattern evaluation may contribute to understanding why certain patients with ischemic stroke benefit from acute treatment and why certain patients do not. We found that intravenous thrombolysis was significantly associated with favorable functional outcome and successful recanalization in the group with a medial ICAC pattern, but not in the group with an intimal ICAC pattern. The pathophysiological mechanism behind this finding is not yet fully understood. One theory is that the ICAC pattern is related to the characteristics of the occluding thrombus influencing treatment effects.[39] However, thrombus characteristics are related to the stroke etiology, which did not differ between the intimal and medial ICAC groups in our study. Another explanation is that ICAC pattern may be related to the collateral circulation. It is hypothesized that calcification of the medial layer leads to arterial stiffening and, consequently, to higher pulse pressures distal to the calcification site. Consequently, the possible impaired distal microcirculation of the brain may trigger the pathway of collateral vessel formation. In this study, we found a relation between medial ICAC pattern and presence of collateral vessels in the brain supporting this hypothesis. On the contrary, MR CLEAN Registry data showed that intimal ICAC, and not medial ICAC, was associated with good collateral status.[40,41] It is hypothesized that higher pulse pressure caused by arterial stiffening may actually impair collateral blood flow and that stenosis of the vessel lumen, as seen in intimal ICAC, may trigger collateral vessel formation. These studies show that the eventual modifying effect of ICAC patterns on treatment effects are not yet fully understood.

Before ICAC pattern evaluation can be implemented in routine clinical practice, studies are needed to investigate the exact mechanisms causing the effect modification of intravenous thrombolysis or endovascular treatment. The generalizability of these findings also need to be explored in different non-Dutch stroke populations.

Malignant infarction

Three studies were performed to evaluate predictors of malignant edema (ME) in stroke. In the first study, the ratio of cerebrospinal fluid volume to intracranial volume (CSF/ICV) had added value to three small prediction models in a population with

wide inclusion criteria. In the second study, all patients had undergone endovascular treatment of the anterior circulation as part of the MR CLEAN Registry, and the developed basic prediction model of ME included younger age, higher baseline NIHSS, proximal occlusion, lower ASPECTS, poor collateral status, longer time from onset to groin puncture, and unsuccessful reperfusion. In the third study, we showed that CSF/ICV had added value to the basic model described in the second study. The CSF/ICV was based on mixture models, which allow for volume measurements in noisy data, without the need for precise segmentation. Since this is an entirely automated technique for quantifying brain volumes, neither observation bias nor interrater reliability is an issue for this measurement. Furthermore, this method can be done quickly, and is robust to CT noise, loss of gray-white differentiation or other early ischemic changes on NCCT.

In general, older patients have more CSF volume because of brain atrophy.[42] Therefore, it is not surprising that patients who develop ME are typically younger than patients who do not develop ME as there is less space for the brain to swell without causing herniation.[43] In addition, with higher age, patients generally have suffered from more brain disease such as stroke than patients with lower age, contributing to more intracranial space in the elderly. Consequently, older patients have a larger 'buffer' before brain swelling leads to midline shift or tissue herniation. The predictive value of age disappeared after the CSF/ICV ratio was added to our prediction model. As age and the CSF/ICV ratio add similar predictive properties, one of the two predictors could be removed from the prediction model. Although age is readily available, and therefore more practical, the CSF/ICV ratio is a more direct reflection of the intracranial 'buffer' and adds more to the prediction model. This is supported by studies that showed that older patients can still develop malignant edema.[44] Therefore, the CSF/ICV ratio should be used as a predictor of malignant edema instead of age.

Early and accurate prediction of ME is important to make prompt treatment decisions and achieve better functional outcomes.[45] Accurate prediction may lead to closer monitoring of patients at risk and timely decompressive surgery as warranted by the randomized controlled trials.[45] CSF/ICV can be acquired with fully automated measurements in the early phase of the stroke. Software could be developed to easily acquire the volume estimations. This finding is a step in the development of a clinically usable prediction model. Future studies should look for additional predictors and externally validate our findings. Artificial intelligence algorithms may also contribute to optimizing prediction in the future. Although the risk of malignant infarction is an important parameter to decide whether decompressive surgery

should be performed, comorbidity and preferences of the patient, relatives and physicians will remain essential for the final decision outcome.

Recurrent stroke

In a systematic review of the literature and meta-analysis of predictors of recurrent ischemic stroke, we found strong evidence for clinical predictors such as stroke etiology and a medical history of previous stroke or TIA. A strong level of evidence was absent when considering imaging predictors, but a moderate level of evidence was found for the association between recurrent ischemic stroke and the load of ischemic lesions on MRI. As there was little evidence for CT imaging predictors, we investigated CT imaging predictors in the DUST study. Previous cerebral infarcts on NCCT and ASPECTS greater than 7 on MTT maps derived from CTP had added value to a clinical prediction model for recurrence. These findings, however, need verification in a larger study with prospective outcome evaluation before it can be implemented in future prediction models.

In this thesis, we showed that prediction of recurrence after ischemic stroke can be improved by using imaging information in addition to clinical information. However, even after the clinical model was improved, the performance was still moderate. A few steps need to be taken before a model that predicts recurrent ischemic stroke can be used in routine stroke care. First, studies need to look for more predictors (e.g. derived from cardiac CT) to see if a clinically relevant improvement can be achieved, preferably in a prospective cohort study such as ENCLOSE. Second, once a model with a sufficiently high performance is developed, it needs to be validated in other cohorts. The impact of a new model on prevention strategies and outcomes needs to be quantified, ideally in a randomized controlled trial. In this way, the prognostic model may guide treatment decisions and therefore affect patient outcomes. Whether patient outcomes will truly be affected by the prediction models remains to be seen as secondary prevention is already quite rigorous in patients who have had TIA or AIS.

General conclusions

In conclusion, this thesis showed that advanced CT imaging techniques have diagnostic and prognostic value in patients with AIS. Future studies need to evaluate whether the results from this thesis impact treatment strategies and outcomes after TIA or AIS. In combination with upcoming advanced CT techniques and artificial intelligence applications, stroke physicians will be aided in the future by advanced hardware and software for determining the diagnosis and prognosis in patients with TIA or AIS.

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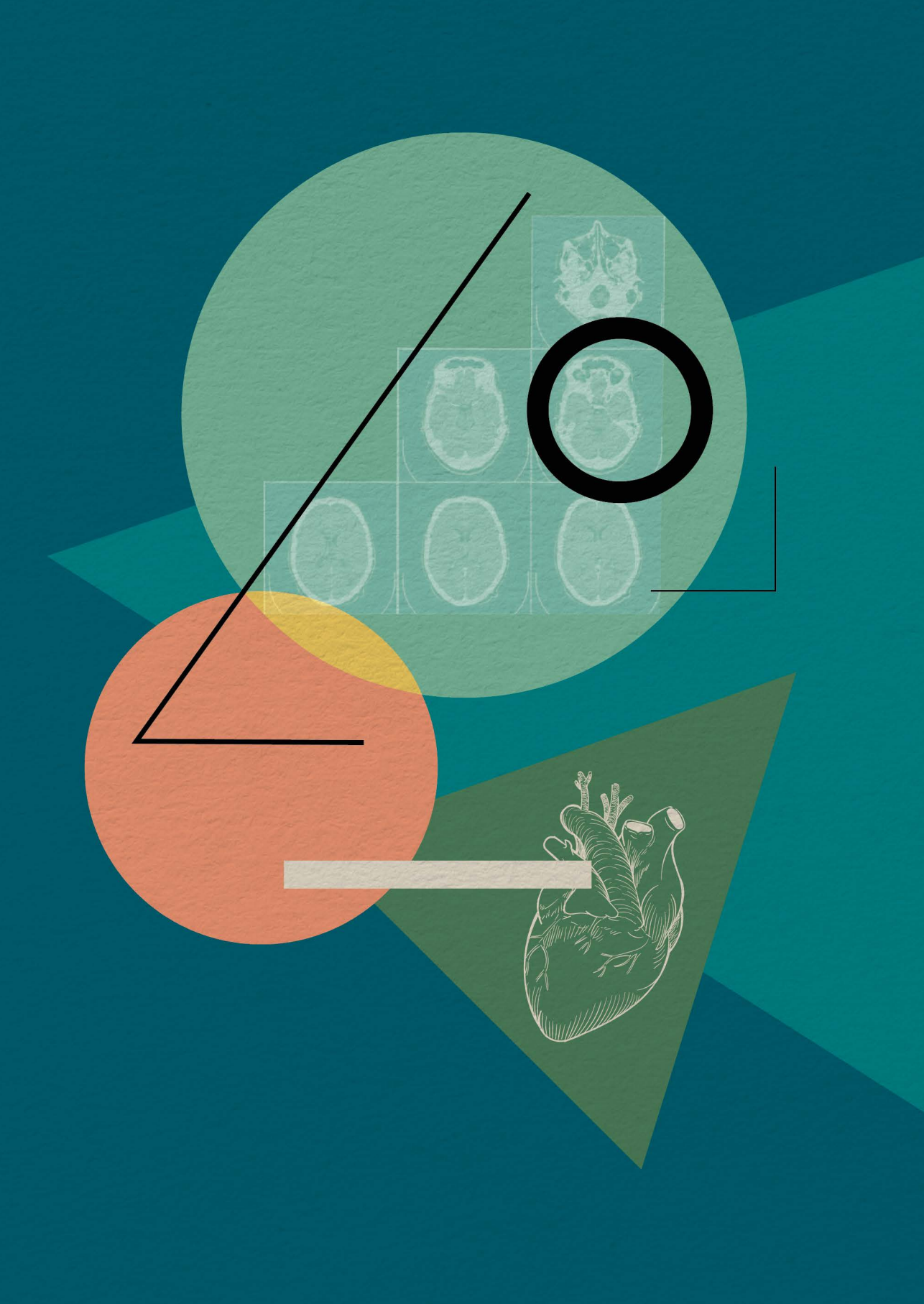

APPENDICES

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Beroerte is één van de meest voorkomende oorzaken van overlijden en de meest voorkomende oorzaak van langdurige invaliditeit in de westerse wereld. Een beroerte kan een herseninfarct of een hersenbloeding zijn. Bij een herseninfarct raakt een aanvoerend bloedvat (slagader) naar de hersenen verstopt, meestal door een bloedprop (stolsel). Indien de klachten binnen 24 uur hersteld zijn dan wordt dit een transient ischemic attack (TIA) genoemd. Bij een hersenbloeding scheurt een bloedvat in de hersenen open, waardoor bloed direct de hersenen instroomt en schade veroorzaakt. Het herseninfarct is onderwerp van dit proefschrift.

Door de afsluiting van een slagader in de hersenen krijgt een deel van de hersenen geen bloed, waardoor hersenweefsel afsterft. Afhankelijk van welk deel van de hersenen is aangedaan, ontstaan er uitvalsverschijnselen zoals onverstaanbaar spreken (dysartrie), stoornis in taal of begrip (afasie), gezichtsvelduitval, afhangende mondhoek of uitval van één of meer ledematen. Bij het ontstaan van neurologische uitval is het belangrijk snel te handelen. Eenmaal op de spoedeisende hulp zal de hulpverlener een korte anamnese afnemen en neurologisch onderzoek verrichten. De ernst van het herseninfarct kan worden ingeschat met de National Institutes of Health Stroke Scale (NIHSS). Na de opvang op de spoedeisende hulp zal beeldvorming worden verricht.

Beeldvorming

In de meeste ziekenhuizen ondergaan patiënten met het vermoeden op een herseninfarct een CT scan. Het voordeel van CT ten opzichte van bijvoorbeeld MRI is de 24/7 beschikbaarheid, de hoge snelheid en het relatief lage aantal contra-indicaties. Een nadeel van CT is dat het gepaard gaat met ioniserende (Röntgen) straling, welke geassocieerd is met een subtiel verhoogd risico op het ontwikkelen van kanker gedurende het leven. Het scan protocol voor patiënten met het vermoeden op een acuut herseninfarct bevat een blanco CT, een CT perfusie en een CT angiografie.

Met de blanco CT scan kan een bloeding worden uitgesloten en kunnen soms al vroege tekenen van een herseninfarct zichtbaar worden gemaakt. De mate van vroege tekenen van een herseninfarct kan worden bepaald met de Alberta Stroke Program Early CT Score (ASPECTS). De doorbloeding van de hersenen kan worden gemeten met CT perfusie, waarbij jodiumhoudend contrast wordt gegeven. De instroom en uitstroom van het contrast in de hersenen wordt vastgelegd,

waarmee perfusie waarden kunnen worden berekend (post-processing). Met de CT perfusie waarden kunnen ook de penumbra (gebied van het infarct wat nog te redden is) en de infarctkern (niet meer te redden weefsel) worden berekend. De grootte van de penumbra en de infarctkern zijn belangrijk voor het beslissen omtrent vroege behandelingen, met name bij patiënten die zich buiten de standaard behandeltermijn (binnen 6 uur na ontstaan van klachten) presenteren of als het tijdstip van ontstaan van de klachten onbekend is (bijvoorbeeld na ontwaken). Betrouwbare CT perfusie waarden zijn hiervoor essentieel. De CT angiografie wordt gebruikt om de bloedvaten af te beelden met jodiumhoudend contrast. Een afsluiting in de hersenslagader of andere vaatafwijkingen kunnen hiermee zichtbaar gemaakt worden. Bij een afsluiting zijn er soms bloedvaten aanwezig die een omweg kunnen vormen voor de bloedstroom naar het infarctgebied, de zogenoemde collateralen. Met CT angiografie kunnen ook oorzaken van een herseninfarct zichtbaar gemaakt worden zoals vernauwingen ten gevolge van slagaderverkalking (atherosclerose) in de halsslagaders.

Het hart

Ongeveer een derde van de herseninfarcten wordt veroorzaakt door een stolsel dat is ontstaan in het hart. Het vaststellen van de oorzaak van een herseninfarct is belangrijk, zodat adequate behandeling gestart kan worden om een herhaling (recidief) van een herseninfarct te voorkomen. In de huidige klinische praktijk is het soms moeilijk om een oorzaak vanuit het hart vast te stellen. Vaak wordt een hartfilmpje (ECG) en langdurige ritme monitoring gedaan om een hartritmestoornis zoals boezemfladderen (atriumfibrilleren) op te sporen. Van atriumfibrilleren is bekend dat er een stolsel in het hart kan ontstaan en een herseninfarct kan veroorzaken. Tevens wordt een echo van het hart (echocardiografie) verricht om een stolsel in het hart op te sporen. De gevoeligheid (sensitiviteit) voor het aantonen van een stolsel in het hart met echocardiografie is echter beperkt. Daarnaast wordt een echo vaak pas enkele dagen na een herseninfarct verricht, waardoor de pakkans van een stolsel afneemt.

Patiënten met een herseninfarct ondergaan standaard een CT angiografie van hoofd tot aan de grote lichaamsslagader. Hiermee kunnen vernauwingen door bijvoorbeeld slagaderverkalking worden vastgesteld. Het hart wordt niet standaard gescand. Kleine retrospectieve studies hebben aangetoond dat het mee scannen van het hart een veelbelovend alternatief is voor echocardiografie.

Dual-energy CT

Spectrale of dual-energy CT (DECT) is een relatief nieuwe CT techniek waarbij informatie op meerdere energieniveaus wordt verkregen in plaats van op één energieniveau zoals bij standaard CT. Er zijn verschillende manieren om DECT beelden te verkrijgen. Bij spectrale CT wordt een detector gebruikt die de CT (Röntgen) stralen van één bron op meerdere energieniveaus kan vastleggen. Deze techniek levert aanvullende informatie op en kan bijvoorbeeld gebruikt worden om typen weefsels beter van elkaar te onderscheiden. Zo is het bijvoorbeeld mogelijk om bloed van kalk en jodiumhoudend contrast te onderscheiden, terwijl dit met standaard CT niet goed mogelijk is. De toepassingen van DECT in de beroertezorg zijn nog beperkt onderzocht.

Behandelingen

Er zijn twee behandelingen die in de vroege fase van een acuut herseninfarct gegeven kunnen worden: intraveneuze trombolyse (IVT) en intra-arteriële trombectomie (IAT). Bij IVT wordt een infuus gegeven met het medicijn alteplase, een tissue-type plasminogeen activator, met als doel om het stolsel in de hersenen op te lossen. Bij IAT wordt via de lies- of polsslagader een katheter opgevoerd naar de hersenslagader om daar het stolsel te verwijderen. IAT wordt voornamelijk uitgevoerd bij een afsluiting van een grote hersenslagader. De behandelingen blijken vooral in de vroege fase na een herseninfarct effectief: binnen 4,5 uur voor IVT en binnen 6 uur voor EVT. Studies hebben echter aangetoond dat deze behandelingen ook na deze termijnen nog effectief kunnen zijn als de verhouding tussen penumbra en infarctkern op de CT perfusie gunstig is. Het doel van de behandelingen is om de prognose van de patiënten met een herseninfarct ten gunste te beïnvloeden. Er zijn variabelen die het effect van de behandelingen beïnvloeden zoals de aanwezigheid van collateralen en het patroon van kalkafzettingen in de halsslagader (intracraniële calcificaties van de arteria carotis interna, afgekort ICAC).

De aanwezigheid van collateralen zorgt er voor dat het infarct proces wordt vertraagd en is geassocieerd met beter herstel na een herseninfarct vergeleken met afwezigheid van collateralen. De aanwezigheid van collateralen kan met verschillende soorten beeldvorming en schalen geclassificeerd worden. Vaak worden de collateralen beoordeeld met een enkele fase CT angiografie, waarbij maar één enkel beeld van de collateralen wordt verkregen op één tijdsmoment. Het vullen van de collateralen na contrast toediening is echter een dynamisch proces en daarom wordt het gebruik van digitale subtractie angiografie (DSA) aanbevolen voor het beoordelen van de collateralen in de huidige richtlijnen. Met DSA worden live beelden verkregen van de vullende bloedvaten met behulp

van Röntgenstralen en jodiumhoudend contrast. Het is ook mogelijk om een CT angiografie met meerdere fasen te scannen of te reconstrueren uit CT perfusie beelden, maar de verglijkbaarheid met DSA en de relatie met het functionele herstel na een herseninfarct is niet goed bekend.

De aanwezigheid van ICAC is geassocieerd met het optreden van een herseninfarct. ICAC kan worden vastgesteld en getypeerd met behulp van een blanco CT scan met dunne plakken (coupes). Een ICAC patroon waarbij de kalk zich voornamelijk in de middelste (tunica media) of binnenste elastische (lamina elastica interna) lagen van de slagaderwand bevindt (mediaal patroon), kan onderscheiden worden van een ICAC patroon waarbij de kalk zich met name in de binnenste laag (tunica intima) bevindt (intimaal patroon). Eerdere studies hebben uitgewezen dat de prognose en het effect van IAT kan verschillen tussen de patiënten met verschillende ICAC patronen. Het is niet bekend of dit ook voor de IVT behandeling geldt.

Complicaties

Na een herseninfarct kunnen een aantal complicaties optreden die de functionele uitkomst na het herseninfarct kunnen beïnvloeden. Tussen de tweede en de vijfde dag na een groot herseninfarct kan er bijvoorbeeld maligne oedeem ontstaan. Hierbij wordt er zoveel vocht bij het herseninfarct gevormd dat er geen ruimte meer binnen de schedel is voor de hersenen om te zwellen (inklemming). Indien dit niet behandeld wordt, is de kans groot dat de patiënt hieraan komt te overlijden. De behandeling bestaat uit een operatie waarbij de schedel wordt geopend, zodat er weer ruimte ontstaat voor de hersenen om te zwellen. De huidige richtlijnen geven aan dat deze operatie binnen 48 uur na het herseninfarct moet worden uitgevoerd. Hierom is het belangrijk om deze complicatie in een vroege fase te kunnen voorspellen. Er zijn reeds klinische en radiologische voorspellers beschreven.

Het doel van de behandelingen bij patiënten met een herseninfarct is om een zo goed mogelijke functionele uitkomst te behalen voor de patiënt. De mate van invaliditeit kan worden gescoord met de modified Rankin Scale (mRS). Deze schaal bestaat uit zeven (0-6) categorieën waarbij 0 geen symptomen betekent en 6 overlijden.

Ongeveer een kwart van alle beroertes betreft een recidief en kan grote gevolgen hebben voor het functioneren van de patiënt. De kans op een recidief binnen een jaar na een herseninfarct wordt geschat tussen de 8% en 14%. Het voorspellen van een recidief is belangrijk, omdat behandelingen ter voorkoming van een recidief daarop kunnen worden aangepast.

Het proefschrift

In dit proefschrift worden studies beschreven die zijn gericht op geavanceerde CT technieken en het voorspellen van uitkomsten na een herseninfarct met behulp van CT. Het doel van dit proefschrift was om de diagnostische en prognostische aspecten van de beroertezorg te verbeteren. Dit proefschrift bestaat uit twee delen: CT beeldvorming bij het acute herseninfarct (deel 1) en CT voorspellers van het effect van IVT, het ontstaan van maligne oedeem en het recidief herseninfarct (deel 2).

Deel 1: CT beeldvorming bij het acute herseninfarct

In het eerste deel van dit proefschrift worden geavanceerde CT technieken bij het acute herseninfarct beschreven.

In **Hoofdstuk 2** wordt het onderzoek beschreven naar DECT. DECT werd gebruikt om (virtuele) blanco CT beelden te reconstrueren uit CT angiografie beelden. Deze beelden werden vergeleken met de standaard blanco CT, waarbij detectie van een infarct op de diffusie gewogen MRI als gouden standaard werd gebruikt. De aanwezigheid en uitgebreidheid van het infarct werd gemeten met behulp van ASPECTS. Van de 193 geïncludeerde patiënten met verdenking op een acuut herseninfarct hadden er 100 (52%) een infarct op de diffusie gewogen MRI scan. In deze studie werd aangetoond dat de virtuele blanco CT beelden vergelijkbaar zijn met de standaard blanco CT voor het aantonen van vroege tekenen van een herseninfarct. Deze toepassing van DECT kan in de toekomst mogelijk gebruikt worden om de standaard blanco CT weg te laten (indien er al een CT angiografie wordt verricht) en daardoor de stralingsdosis voor de patiënt te verlagen.

In **hoofdstuk 3** worden fouten beschreven die kunnen optreden tijdens het automatisch verwerken (post-processing) van ruwe CT perfusie beelden tot bruikbare perfusie maps. Deze fouten kwamen in 20 (11%) van de 176 patiënten met een herseninfarct voor. Deze fouten werden veroorzaakt door beweging van de patiënt, streepvormige artefacten en slechte aankomst van jodiumhoudend contrast in de hersenen. De fouten traden vooral op bij patiënten met ernstige herseninfarcten. Indien deze fouten niet herkend worden, zou dit de beslissingen rondom de behandelingen kunnen beïnvloeden, aangezien deze beslissingen op basis van de CT perfusie waarden worden genomen in de late behandeltermijn of als het tijdstip van ontstaan onduidelijk is. De behandelaar dient zich daarom bewust te zijn van deze mogelijke fouten van CT perfusie bij het maken van behandelbeslissingen.

In **hoofdstuk 4** worden verschillende manieren beschreven voor het afbeelden en classificeren van de collateralen. Volgens de richtlijnen is DSA de gouden standaard voor het afbeelden van collateralen, maar dit kan ook met CT angiografie of CT perfusie. Verschillende manieren van beeldvorming werden onderzocht in deze studie: enkele fase CT angiografie, drie-fasen en multipele fasen CT angiografie gereconstrueerd uit CT perfusie beelden, en DSA. Tachtig patiënten met een groot herseninfarct van de voorste circulatie (occlusie van de arteria carotis interna of M1-M2 segment van de arteria cerebri media) die voorafgaand aan IAT een CT scan ondergingen werden geïncludeerd. Er bleek een slechte mate van overeenstemming (concordantie) te bestaan tussen de collateralen die gescoord waren op CT en DSA. De multipele fasen CT angiografie was voorspellend voor de functionele uitkomst, maar dit was niet het geval voor de enkele fase CT angiografie en DSA. Deze resultaten impliceren dat CT angiografie meer van waarde is dan DSA, de gouden standaard, voor het afbeelden van de collateralen in patiënten met een herseninfarct.

In **hoofdstuk 5** wordt de rationale en de opzet van de 'Improved Prediction of Recurrent Stroke and Detection of Small Volume Stroke' (ENCLOSE) studie beschreven. ENCLOSE is een prospectieve observationele studie in het Universitair Medisch Centrum Utrecht en het Amsterdam Universitair Medisch Centrum, waarbij patiënten met een TIA of een acuut herseninfarct werden geïncludeerd. De hoofddoelstellingen van ENCLOSE zijn (1) het verbeteren van de detectie van kleine herseninfarcten met geavanceerde CT perfusie, (2) het verbeteren van de detectie van de oorzaak van een herseninfarct, onder andere door het mee scannen van het hart met CT angiografie en (3) het verbeteren van het voorspellen van recidief herseninfarcten met behulp van CT beeldvorming.

In **hoofdstuk 6** wordt een casus beschreven van een patiënt die een herseninfarct heeft doorgemaakt en twee stolsels in het hart blijkt te hebben op de CT angiografie, een stolsel in het linker hartoor en een stolsel in de linker hartkamer. Een dag later heeft deze patiënt een recidief herseninfarct en is het stolsel in de linker hartkamer aanzienlijk kleiner geworden. Mogelijk is een deel van dit stolsel omhoog geschoten naar de hersenen. Deze casus toont de mogelijke meerwaarde van het mee scannen van het hart met de CT angiografie in de vroege fase van het herseninfarct.

In **hoofdstuk 7** worden de resultaten van het mee scannen van het hart binnen ENCLOSE beschreven. Van de 370 patiënten hadden 44 (12%) een stolsel in het hart. Er werden verschillende soorten reconstructies gemaakt met behulp van spectrale CT, waaronder jodium maps, waarbij de concentratie jodiumhoudend contrast kan

worden gemeten op de beelden. De jodium maps verhoogden de diagnostische zekerheid van een trombus in het linker hartoor. De aanwezigheid van een stolsel in het hart was geassocieerd met een medische voorgeschiedenis van een hartinfarct en met een voorgeschiedenis van boezemfladderen. De aanwezigheid van een stolsel in het hart was tevens geassocieerd met ernstigere herseninfarcten. Volgens een expert panel waren de CT angiografie beelden van het hart bruikbaar om een oorzaak van het herseninfarct vanuit het hart met meer zekerheid vast te kunnen stellen. Deze studie toont aan dat scannen van het hart met (spectrale) CT angiografie van waarde is in de vroege fase na een herseninfarct. Deze techniek kan makkelijk geïmplementeerd worden in huidige scanprotocollen zonder dat het veel extra tijd, jodiumhoudend contrast of veel extra straling voor de patiënt kost. Vroege detectie van de oorzaak vanuit het hart kan helpen om de preventie te optimaliseren en recidiverende herseninfarcten te voorkomen.

Deel 2: CT voorspellers voor het effect van intraveneuze trombolyse, het maligne herseninfarct en het recidief herseninfarct

Het tweede deel van dit proefschrift beschrijft het voorspellen van het effect van IVT, het ontstaan van maligne oedeem en het recidief herseninfarct.

In **hoofdstuk 8** wordt het behandeleffect van IVT beschreven voor de verschillende ICAC patronen. Van de 982 geïncludeerde patiënten met een herseninfarct kregen 609 (62%) IVT. Patiënten met een mediaal ICAC patroon bleken vaker een gunstige functionele uitkomst na 90 dagen te hebben na IVT, maar dit was niet het geval voor de patiënten met een intimaal ICAC patroon. Het mediale ICAC patroon was tevens geassocieerd met betere collateralen, wat deze bevinding mogelijk kan verklaren. Deze studie draagt bij aan het begrijpen van het behandeleffect van IVT in patiënten met een acuut herseninfarct.

In **hoofdstuk 9** wordt een nieuwe voorspeller van maligne oedeem beschreven binnen de Dutch Acute Stroke Study (DUST). De ratio tussen het volume van het hersenvocht in de hersenen en het totale volume binnen de schedel (CSF/ICV) werd automatisch gemeten op dunne coupes van de blanco CT. Deze voorspeller is een surrogaat voor de 'buffer' binnen de schedel en de ruimte voor het brein om te zwellen. Van de 286 geïncludeerde patiënten met een herseninfarct ontwikkelden 35 (12%) maligne oedeem. De CSF/ICV bleek van toegevoegde waarde in drie multivariabele modellen: 1) met leeftijd en NIHSS, 2) met NIHSS en collateraal score en 3) met proximale occlusie (arteria carotis interna of proximale M1 segment van de arteria cerebri media) en collateraal score. Op basis van deze studie werd

geconcludeerd dat de CSF/ICV toegevoegde voorspellende waarde heeft in kleine voorspelmodellen van het maligne herseninfarct.

In **hoofdstuk 10** worden voorspellers van maligne oedeem beschreven bij patiënten met een acuut herseninfarct die IAT hebben ondergaan (MR CLEAN Registry). Van de 1445 geïncludeerde patiënten ontwikkelden 82 (6%) een maligne herseninfarct. Er werd een voorspelmodel ontwikkeld met de volgende voorspellers van maligne oedeem: jongere leeftijd, ernstiger herseninfarct (hogere NIHSS), proximale occlusie (arteria carotis interna), meer vroege veranderingen op de blanco CT (ASPECTS), slechte collateralen, langere tijd tussen ontstaan van klachten en start IAT en niet succesvolle IAT behandeling. Het voorspelmodel bleek goed in staat om onderscheid te maken tussen patiënten met een hoog risico en een laag risico op het ontwikkelen van maligne oedeem.

In **hoofdstuk 11** werd de toegevoegde waarde van CSF/ICV aan het voorspelmodel in hoofdstuk 10 onderzocht. Patiënten van de MR CLEAN Registry, waarbij blanco CT beelden met dunne coupes beschikbaar waren, werden onderzocht. Van de 683 geïncludeerde patiënten ontwikkelden 40 (6%) een maligne herseninfarct. De voorspellende waarde van het model uit hoofdstuk 10 werd significant verbeterd na het toevoegen van CSF/ICV. Deze studies geven richting voor het vinden van een optimaal voorspelmodel voor maligne oedeem in patiënten met een groot herseninfarct.

In **hoofdstuk 12** wordt een systematische evaluatie en meta-analyse van de literatuur beschreven van voorspellers van een recidief herseninfarct. Er werden 10 studies geïncludeerd. Er bleek sterk bewijs te bestaan voor sommige klinische voorspellers zoals een medische voorgeschiedenis van een herseninfarct of transient ischemic attack (TIA) en de oorzaak van het herseninfarct. Er bleek matig bewijs te bestaan voor MRI voorspellers en er waren geen studies die CT voorspellers hebben onderzocht. Deze studie toont aan dat er hiaten zijn in de literatuur ten aanzien van CT voorspellers voor het voorspellen een recidief herseninfarct.

In **hoofdstuk 13** werd de aanvullende waarde van CT voorspellers voor het voorspellen van een recidief herseninfarct onderzocht. Van de 638 geïncludeerde DUST patiënten kregen 56 (9%) een recidief herseninfarct tijdens een periode van 5 jaar. Er werd een klinisch voorspelmodel ontwikkeld, waaraan CT voorspellers werden toegevoegd. De aanwezigheid van oude infarcten op de blanco CT bleek van aanvullende waarde voor het klinische voorspelmodel. Hetzelfde gold voor de uitgebreidheid (ASPECTS) van de afwijkingen op de CT perfusie. Deze studie

toont aan dat CT voorspellers voor het voorspellen van een recidief herseninfarct toegevoegde waarde hebben bovenop klinische voorspellers.

Conclusie

Concluderend worden in dit proefschrift geavanceerde CT technieken beschreven die diagnostische en prognostische waarde hebben bij patiënten met een acuut herseninfarct of TIA. Met behulp van geavanceerde CT technieken kan de beroertezorg verder worden geoptimaliseerd om complicaties te voorkomen en functionele uitkomsten te verbeteren. In combinatie met kunstmatige intelligentie toepassingen zullen hulpverleners geholpen worden door geavanceerde hard- en software voor het bepalen van de diagnose en de prognose in patiënten met een acuut herseninfarct.

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Lieve Lidewij, jij bent mijn steun en toeverlaat. Ik ben blij dat ik in dezelfde tijd leef als jij. Met jou wil ik de toekomst ontdekken.

Boek af!

LIST OF PUBLICATIONS

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Awards

2020 Paul Dudley White award (best Dutch abstract), International Stroke Conference, Los Angeles, United States of America

2020 Junior Investigator Travel award, International Stroke Conference, Los Angeles, United States of America

CURRICULUM VITAE

Frans Kauw was born on June 28, 1992 in Zwijndrecht, the Netherlands. He grew up in Sliedrecht with his parents, Marieke and Frans, and his twin brother, Dirkjan. In 2010, Frans graduated from the gymnasium at the Willem de Zwijger College, Papendrecht, and in the same year he moved to Utrecht to start medical school at the Utrecht University.

As a medical student, Frans followed senior internships focusing on neurology, vascular medicine, radiology and research. In 2016, he received his medical degree and started working as a resident (ANIOS) at the neurology department of the St. Antonius Hospital, Nieuwegein. In 2017, he started his PhD trajectory at the radiology and neurology departments of the University Medical Center Utrecht and, in 2018, he worked at Stanford University as a research visiting scholar for seven months. The research subjects mainly included stroke, CT imaging and outcome prediction. As a PhD candidate, Frans performed ad hoc reviews for international peer-reviewed journals such as *Circulation* and *Stroke*. In 2019, Frans finished the post-graduate Epidemiology Master at Utrecht University. In 2019, he paused his PhD trajectory to work as a resident (ANIOS), and from 2020, as a neurologist in training (AIOS) at the neurology department of the University Medical Center. In 2023, Frans finished his PhD trajectory, which resulted in this thesis.