Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Computed Tomography Angiography for Diagnosis of Stroke or Transient Ischemic Attack: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Stroke is a common cause of death and disability in Canada.[1,2] Stroke can be divided into two broad categories: ischemic and hemorrhagic. Differentiating between these two different underlying causes of stroke is important clinically as management differs substantially. Presentation of acute stroke, both ischemic and hemorrhagic, is a medical emergency requiring rapid diagnosis and intervention. Acute ischemic strokes or transient ischemic attacks (TIA) carry a significant risk of mortality and recurrent vascular events.[3] A TIA is a brief episode of focal neurological dysfunction that may lead to acute infarction, stroke or death.[3] Ischemic strokes arise from interruptions in cerebral blood flow as a result of large-artery atherosclerosis, cardioembolism, small-vessel occlusion or cryptogenic causes.[4] Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) are types of hemorrhagic stroke that may present as the initial stroke event.[2] Ischemic stroke may also be complicated by hemorrhagic transformation. Both SAH and ICH carry a very poor prognosis. The 30-day mortality is 40% for SAH and up to 50% for patients with an ICH. The type and timing of brain imaging in the initial diagnosis and management of stroke has evolved in recent years as interventions and treatments have become available.[2] The aim of the initial diagnostic imaging is to exclude stroke mimics, such as hypoglycemia or seizure, and to differentiate between ischemic and hemorrhagic stroke.[2]

The 2015 update of the Canadian Stroke Best Practice Guidelines and the 2013 Massachusetts General Hospital acute stroke imaging algorithm recommend that all patients who present with acute stroke or TIA undergo brain imaging consisting of a non-contrast computed tomography (NCCT) scan and concomitant non-invasive cerebral vascular imaging in the form of a computed tomography angiogram (CTA) or magnetic resonance angiogram (MRA) as an alternative.[3,5] The timing of these investigations depends the time since the onset of stroke or TIA symptoms and how the imaging results will affect subsequent interventions. Both NCCT and CTA are recommended as part of the diagnostic work-up of ischemic stroke as they assist the clinician in making treatment decisions regarding the use of intravenous thrombolysis (in the absence of hemorrhage on a NCCT), or endovascular therapy such as mechanical clot retrieval (in the case of proximal arterial occlusion).[1-3,6] The Canadian guidelines recommend that any patient presenting with a suspected SAH or ICH immediately receive a NCCT for diagnosis and vascular imaging with CTA, MRA or catheter angiography to potentially identify the cause of the hemorrhage.[3]

Cerebral angiography (including digital subtraction angiography [DSA]) is the gold standard for assessing blood flow through cerebral arteries.[7] However, cerebral angiography is invasive and associated with a risk of stroke, and is therefore rarely used in current clinical practice.[7] A CTA is a non-invasive alternative to cerebral angiography and uses intravenous contrast and timed helical CT images to assess the blood flow through the vasculature.[7] CTA is able to identify filling defects suggestive of intravascular occlusion through images captured during arterial phase of contrast flow.[1] Multi-phase CTA allows for visualization of collateral blood flow through images captured during the mid and late venous phases of contrast circulation.[7] Multi-phase CTA is useful in assessing a patients suitability for mechanical thrombectomy.[7] A potential risk associated with CTA is renal dysfunction, specifically contrast induced nephropathy (CIN). A recent CADTH Rapid Response report included two non-randomized studies which did not demonstrate an increased risk of CIN with CTA compared to NCCT.[8]

The National Institutes of Health Stroke Scale (NIHSS) is the recommended initial clinical assessment of patients who present with stroke.[5] The NIHSS is a clinical method for both diagnosing and determining the initial severity of stroke symptoms, with higher scores being associated with increased severity.[5]

The objective of this report is to review the evidence with respect to clinical effectiveness of CTA in the diagnosis of patients presenting with symptoms of stroke or TIA.

RESEARCH QUESTION

What is the clinical effectiveness of computed tomography angiography (CTA) for the diagnosis of patients presenting with symptoms of stroke or transient ischemic attack (TIA)?

KEY FINDINGS

One systematic review of patients presenting with acute ischemic stroke found that CTA-based selection of candidates to undergo endovascular therapy was associated with significantly better functional independence at 3 months compared to non-CTA based selection. A non-randomized study in patients with embolic stroke of undetermined source found that mean carotid plaque thickness was significantly greater on the ipsilateral compared to contralateral side as measured by CTA. Another non-randomized study found that CTA was significantly more reliable at detecting early ischemic changes (measured on the Alberta Stroke Program Early CT score [ASPECT score]) compared to non-contrast CT within 180 minutes of stroke symptom onset in patients with acute ischemic stroke.

Three systematic reviews found that CTA has a high sensitivity and specificity in detecting intracranial vascular lesions in patients with intracerebral hemorrhage and subarachnoid hemorrhage. One poor quality non-randomized study found that age younger than 65 years, female sex, non-smoking and absence of hypertension were associated with a higher likelihood of identifying a structural vascular lesion as the source of hemorrhage on CTA.

METHODS

Literature Search Methods

This report makes use of a literature search developed for a previous CADTH report.[9] The original literature search was conducted in July 2016 on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials; a very focused search was done for non-randomized studies. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2011 and July 14, 2016. For the current report, database searches were rerun on November 1, 2016 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since July 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies for the previous CADTH report.[9] In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. A second reviewer screened the potentially relevant articles selected for the previous CADTH report[9] and titles and abstracts from the updated literature search to identify additional potentially relevant articles. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients (age >18 years) presenting with possible stroke or TIA
Intervention	Computed tomography angiography (CTA)
Comparator	Non-contrast computed tomography (NCCT) Magnetic Resonance Imaging (MRI) Digital Ultrasonic System (DUS) Magnetic Resonance Angiography (MRA) No imaging No comparator
Outcomes	Diagnostic accuracy, subsequent stroke, mortality, repeat hospital or emergency department visits, disability
Study Designs	Health Technology Assessment, Systematic Reviews, Meta-Analyses Randomized Controlled Trials Non-Randomized Studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Articles were also excluded if they were reported as part of an included HTA or systematic review.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist,[10] articles evaluating diagnostic accuracy were assessed using the QUADAS tool.[11,12] The Newcastle-Ottawa Quality Assessment Scale[13,14] was used to assess non-randomized trials. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 31 potentially relevant reports were identified in the literature search of the initial CADTH report[9] and underwent full text screening. A total of 249 citations were identified in the updated literature search. Following screening of titles and abstracts, 236 citations were excluded and 13 potentially relevant reports from the electronic search were retrieved for full-text review. None of the publications retrieved from the grey literature search were potentially relevant. Of the 44 potentially relevant articles, 34 publications were excluded for various reasons, while 10 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included systematic reviews and non-randomized controlled studies are summarized below. Additional details can be found in Appendix 2.

Systematic Reviews

In 2015, Zheng and colleagues[15] published a systematic review and meta-analysis in China. They included randomized controlled trials (RCT) that compared endovascular intervention plus standard care with standard care alone in patients over the age of 18 years with acute ischemic stroke. Standard care was use of intravenous tPA. Seven studies published between 2013 and 2015 with a total of 2217 participants were included. The mean (or median) age was 66 to 71 years and 48 to 58% of participants were male. The primary outcome was functional independence at 90 days. Authors also reported 90-day mortality. The analysis was stratified based on the use of CTA to select participants.

In 2014, Josephson and colleagues[16] published a systematic review in Canada. They included studies of single or comparative test accuracy for CTA, MRA or both compared to catheter intra-arterial digital subtraction angiography (IADSA) in patients with radiographically confirmed acute ICH. Eight studies published between 1998 and 2012 with 526 participants compared CTA with IADSA. Three studies with 401 participants compared MRA with IADSA. Studies took place in secondary and tertiary care centers in Asia, North America and Europe. Through an indirect comparison, authors compared the sensitivity and specificity of CTA and MRA.

In 2012, Ma and colleagues[17] published a systematic review and meta-analysis in India. They included studies that evaluated the effect of CTA compared to DSA or any other gold standard test in detecting underlying vascular abnormalities in otherwise healthy individuals with spontaneous intracerebral hemorrhage (SICH). They also undertook their own study that included 92 non-hypertensive participants with acute SICH not caused by trauma. Four studies published between 2009 and 2011 and the results of the authors' concurrent study representing a total of 544 participants were included. The authors did not report the study types. The studies took place in China, Korea, the USA and Canada. The mean age ranged from 31 to 50 years and 51 to 58% of participants were male. Some of the included studies did not report age or sex distribution. Reported outcomes were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CTA compared to a gold standard test.

In 2011, Westerlaan and colleagues[18] published a systematic review and meta-analysis in the Netherlands. They included studies that evaluated the utility of CTA in patients with proven SAH. Included studies used cerebral angiography, surgery, endovascular treatment or autopsy as the reference standard. Fifty studies with a total of 4097 participants were included; 40 to 100% of participants had ruptured aneurysms. No other baseline characteristics were reported. The primary outcome was sensitivity and specificity of CTA.

Non-randomized Studies

In 2016, Sundaram and colleagues[19] published a single center, retrospective study of all patients between 2011 and 2013 over the age of 18 with a TIA or stroke and underwent a CTA within 3 weeks of symptom onset in India. A total of 65 patients were included with a mean age of 57 years, 92% of patients were male, and the baseline NIHSS was 10. Mean time from symptom onset to CTA was 72 hours (range 2 to 504). Outcomes were functional status at 3 months measured by the modified Rankin scale (mRS) score, mortality, and recurrent ischemic events.

In 2016, Mukherjee and colleagues[20] published a prospective study of all consecutive patients who presented within 8 hours of onset of an acute ischemic stroke between April 2014 and May 2015 to a single center in India. A total of 105 patients were included. Their mean age was 58 years and 36% were female. Hypertension was present in 58%, diabetes in 47%, coronary artery disease in 30% and 23% were smokers. A cardioembolic source of stroke was reported in 44% of patients. Median baseline NIHSS was 11 (range 3 to 26). All patients underwent both a NCCT and CTA at initial presentation as part of the institutions standard stroke protocol. Patients then underwent repeat imaging (NCCT or diffusion-weighted MRI) at 24 hours to determine final infarct size. Outcomes were mortality, final infarct size, and functional ability based on the mRS score.

In 2016, Coutinho and colleagues[21] published a prospective study of all consecutive patients admitted with anterior circulation embolic stroke of undetermined source (ESUS) between January 1, 2012 and March 15, 2015 to a regional stroke center in Canada. A total of 85 patients were included. Their median age was 70 years and 52% were female. Hypertension was present in 60%, diabetes in 28%, coronary artery disease in 20% and 18% had a history of TIA or stroke. Intravenous thrombolysis was given in 47% of patients, endovascular reperfusion in 14% and carotid endarterectomy in 7%. Their median baseline NIHSS score was 7 (interquartile range 3 to 14). All patients underwent a CTA within 10 days of hospital admission. Outcomes were carotid artery stenosis, carotid plaque thickness and mortality.

In 2015, Bal and colleagues[22] published a retrospective study of patients presenting between August 2003 and January 2009 with acute ischemic stroke within 9 hours of symptom onset to a single stroke center in Canada. A total of 261 patients were included. Mean age was 67 years and 51% were male. Hypertension was present in 60%, diabetes in 17%, atrial fibrillation in 26% and 29% were smokers. All patients underwent both a NCCT and CTA as part of the institution's standard stroke protocol. Outcome was Alberta Stroke Program Early CT Score (ASPECTS). ASPECTS is a radiological grading of early ischemic changes seen on non-contrast CT to systematically evaluate the ischemic changes in the middle cerebral artery (MCA) territory.[22] The score grades attenuation, representing areas of ischemia, on a 10-point scale.[22] A score of 10 indicates a normal scan and a score of zero indicates completed MCA infarct.[22]

In 2014, Agarwal and colleagues[23] published a retrospective study of patients who presented to a single center in the USA between January 2009 and May 2012 with acute MCA stroke. A total of 35 patients were included. Baseline comorbidities were not reported. All patients received a CTA and magnetic resonance-susceptibility weighted imaging (MR-SWI) within 48 hours of symptom onset. The only study outcome relevant to this report was thrombus.

In 2012, Bekelis and colleagues[24] published a retrospective analysis of patients who presented to a single center in the USA between January 2000 and September 2008 with ICH. A total of 257 patients were included. The mean age was 66 years and 51% were male. All patients underwent a CTA. Outcomes were patient characteristics that increased the yield of CTA in detection of vascular sources of ICH.

Summary of Critical Appraisal

Strengths and limitations of the systematic reviews and non-randomized studies are provided in Appendix 3.

Systematic Reviews

Overall, two of the systematic reviews were of good quality[15,16] and two were of fair quality.[17,18] All four of the systematic reviews reported an *a priori* study design and clearly reported their research questions and inclusion criteria. Study selection was performed independently in duplicate in three of the systematic reviews.[16-18] Zheng and colleagues did not report whether study selection was completed in duplicate.[15] Data abstraction was reported to be completed independently in duplicate in three of the systematic reviews.[15-17] A comprehensive literature search was performed in all four systematic reviews.[15-18] One of the systematic reviews reported searching the grey literature.[16] One of the systematic reviews reported a comprehensive list of excluded studies[16] the other three did not.[15,17,18] All four systematic reviews reported a list of included studies and baseline study characteristics. The scientific quality of the trials included in each systematic review was assessed, reported and considered when the authors formulated their conclusions in three of the systematic reviews.[15,16,18] The included studies in the systematic review conducted by Zheng[15] were reported to have a low risk of bias. The included studies in the systematic review conducted by Josephson[16] were reported to vary substantially; many of the studies were small with incomplete reporting. The included studies in the systematic review conducted by Westerlaan[18] were reported to good methodological quality. The methods used to combine study results were appropriate in three of the systematic reviews.[15,17,25] The systematic review by Ma and colleagues[17] does not provide details regarding how accuracy of CTA was defined. The systematic review published by Josephson and colleagues[16] compared the diagnostic accuracy of CTA and MRA using an indirect comparison based on a likelihood ratio test. Publication bias was considered *a priori* as part of the statistical plan in three of the systematic reviews.[15,16,18] One of the systematic reviews detected the presence of publication bias.[18] Conflicts of interest were reported in three of the systematic reviews.[15,17,18] None of the systematic reviews reported conflict of interest for the included studies.

Diagnostic Accuracy Studies

Overall, two of the diagnostic accuracy studies were of fair quality[20,22] and one was of poor quality.[23] The included patients were representative of those seen in clinical practice in two of the studies.[20,22] Selection criteria was clearly described in two of the studies.[22,23] The study by Agarwal[23] reported clear selection criteria, but did not report the details of the included patients. The reference standard was NCCT in two studies[20,22] and MR in one study;[23] the index test was CTA in all three studies. Both NCCT and MR are likely to correctly classify the target lesion. Patients in all three studies received both the reference standard and index test, regardless of the reference standard result. The index test was independent from the reference standard in all three studies. The time period between the reference test and index test (CTA) was short enough that the underlying condition was unlikely to change in one of the studies,[22] the time delay was not reported in one study[20] and a long delay between imaging modalities was present in the third study, 4 to 41 hours.[23] The process of both the reference tests and index test were clearly reported in two of the studies.[20,22] The study by Agarwal did not describe the procedure of MR and CTA in enough detail to allow for duplication. The results of the CTA were interpreted without knowledge of the reference standard results in one study.[22] In the study by Mukherjee, the neuroradiologist was aware of the side of the stroke prior to interpreting the image. The neuroradiologists were aware of the results of the reference test (MR) when interpreting the CTA results in the study by Agarwal and colleagues.[23] Uninterpretable or intermediate test results and withdrawals or incomplete data were not reported in any of the studies.

Non-randomized Studies

Overall, one of the non-randomized studies was of good quality,[21] one was of fair quality[24] and one was of poor quality.[19] All three studies included patients who had similar comorbidities to those seen in clinical practice. One study included a very low number of individuals who had a cardioembolic source of stroke and did not report whether a patient had a prior history of strokes.[19] Non-radiographic outcomes were obtained from secure patient records in all three studies. Radiographic outcomes were ascertained by independent blinded stroke neurologist and neuroradiologist in two studies[19,21] and obtained from patient records in a third study.[24] In the study by Sundaram, it was unclear whether the outcome of interest (internal carotid artery occlusion) was present at the start of the study. In the study by Bekelis[24] it was clinically unlikely that ICH was present prior to the study, however, this was not specifically reported by the authors. Follow-up was long enough for the outcome to be seen on imaging in all three studies. None of the studies report the amount or type of missing data.

Summary of Findings

The overall findings are summarized below and details are available in Appendix 4.

Clinical effectiveness of computed tomography angiography for the diagnosis of patients presenting with symptoms of stroke or transient ischemic attack

<u>Ischemic Stroke</u>

Systematic Reviews

Zheng and colleagues[15] found that functional independence at 90 days was significantly increased when CTA was used to select candidates to undergo endovascular therapy compared to non-CTA based selection, relative risk (RR) 1.75, 95% confidence interval (CI) 1.48 to 2.06 vs. RR 0.99, 95% CI 0.85 to 1.14, P<0.001. No difference was found between CTA-based and non-CTA based candidate selection in 90-day mortality, RR 0.78, 95%CI 0.60 to 1.01 vs. RR 0.97, 95%CI 0.75 to 1.26, P=NR.

Non-randomized Studies

Mukherjee and colleagues[20] reported that final infarct size was overestimated in 49 patients (46.7%) who underwent CTA by an average of 3.8 ASPECTS points. NCCT was found to underestimate the final infarct size in 63 patients (60%) by an average of 3.67 ASPECTS points. Final infarct size was determined by NCCT (90 patients) or diffusion-weighted MRI (15 patients) at 24 hours. Coutinho and colleagues[21] reported that carotid artery stenosis of <30% was reported on the ipsilateral side to the stroke in 76 patients (89%) compared to contralateral in 78 patients (92%). Mean carotid plaque thickness was statistically thicker on the ipsilateral compared to the contralateral sides, 2.2mm vs. 1.8mm, P=0.009. Bal and colleagues[22] reported that early ischemic changes measured on ASPECTS were significantly more reliable with CTA compared to NCCT at early time points (0-90 minutes: 6 vs. 8, P<0.001, 91 to 180 minutes: 7 vs. 8, P=0.006). There was no significant difference in the ASPECT score in CTA compared to NCCT at later time points (181 minutes: 7 vs. 7, P=0.12, 360 to 540 minutes: 6 vs. 7, P=0.83). The CTA ASPECTS were closer to the final 24 hour ASPECTS compared to NCCT at all time points. Agarwal and colleagues[23] reported that the sensitivity of CTA was not significantly better compared to MR-SWI (89% vs. 86%, P>0.05). Thrombus was found in 2 patients with MR-SWI that were not found on CTA. MR-SWI detected 28 of the 31 clots seen on CTA.

Sundaram[19] reported that recurrent vascular events occurred in 2 patients (3.1%) at 3 months' follow-up.

Mortality was reported in 3 of the studies (Table 2). Sundaram and colleagues reported that a total of 4 patients (6.2%) had died at 3 months follow up. Mukherjee and colleagues reported 5 deaths during hospital admission and 2 during follow up. Coutinho and colleagues reported that 2 (2%) patients died during hospital admission.

Table 2. Mortality

Study	Mortality outcome	
Sundaram,[19] 2016	3 months	4 (6.2%)
Mukherjee,[20] 2016	During hospital admission	5
	During follow-up	2
Coutinho,[21] 2016	In-hospital mortality	2 (2%)

Sundaram and colleagues[19] reported that 33 patients (50.8%) had poor functional outcomes (mRS≥3) at 3 months. In the study by Mukherjee[20] baseline median mRS was 4, improved to 3 at discharge and was 2 at 90 days follow-up.

<u>Hemorrhagic Stroke</u>

Systematic Reviews

Diagnostic accuracy of CTA in detecting vascular lesions in patients with ICH or SAH was reported in three of the systematic reviews (Table 3).[16-18] Josephson and colleagues[16] conducted an indirect comparison of CTA and MRA in the detection of intracranial vascular malformation as a cause of ICH. The likelihood ratio test found no statistically significant difference in the sensitivity or specificity in CTA compared to MRA (P=0.6). Ma[17] and colleagues reported that the PPV of CTA was 96.6% (95%CI 93.4% to 98.6%), the NPV was 97.4% (95%CI 95.3% to 98.6%) and the accuracy was 97.2% (95%CI 95.5% to 98.3%) compared to a gold standard test such as DSA.

Table 3. Diagnostic Accuracy for detecting intracranial lesions in ICH or SAH

Study	Type of stroke	Sensitivity (95%CI)	Specificity (95%CI)
Josephson,[16] 2014	ICH	0.95 (0.90 to 0.97)	0.99 (0.95 to 1.00)
Ma,[17] 2012	ICH	0.95 (0.92 to 0.98)	0.98 (0.96 to 0.99)
Westerlaan,[18] 2011	SAH	0.98 (0.97 to 0.99)	1.00 (0.97 to 1.00)

Non-randomized Studies

Bekelis and colleagues[24] found that CTA was negative (unable to identify a source of ICH) in 223 patients and positive (underlying vascular origin of the ICH was identified) in 34 (13.2%) patients. Factors associated with a higher likelihood of identifying a structural vascular lesion as a source of hemorrhage were age <65 years (odds ratio [OR] 16.36, 95%CI 2.45 to 109.26), female sex (OR 14.90, 95%CI 1.79 to 124.46), non-smokers (OR 103.80, 95%CI 6.98 to >999.999), presence of intraventricular hemorrhage (OR 9.42, 95%CI 1.13 to 78.36), and absence of comorbid hypertension (OR 515.78, 95%CI 30.21 to >999.999).

Limitations

One systematic review[15] and five non-randomized studies[19-23] evaluated the role of CTA in ischemic stroke. The systematic review was of good quality, mainly limited by the lack of reporting of details such as duplicate study selection, searching of the grey literature and reporting excluded studies. The five non-randomized studies were all single center studies with small sample sizes. Findings from the non-randomized studies such as mortality and recurrent vascular events should be interpreted cautiously. The lack of control group makes drawing conclusions as to how CTA compares to other imaging modalities with respect to these outcomes difficult. None of the non-randomized trials in ischemic stroke patients reported withdrawals. Sundaram and colleagues[19] included a very low number of patients with cardioembolic sources and did not report prior strokes in the included patients. Both issues affect the generalizability of the study findings. Interpretation of the clinical outcomes in the non-randomized study by Agarwal[23] was limited by the fact that the neuroradiologists interpreting the CTA were aware of the findings of the reference test (MR).

Three systematic reviews and one non-randomized study evaluated the role of CTA in hemorrhagic strokes, specifically acute ICH[16,17,24] and SAH.[18] Interpretation and application of the findings of two of the systematic reviews is limited by the lack of description of included study types[17] and baseline patient characteristics.[18] The systematic review by Josephson[16] and colleagues was limited by the variable quality of the included studies, small sample sizes and incomplete reporting. The systematic review by Westerlaan[18] and colleagues detected a significant risk of publication bias. This could mean that unpublished studies may affect the results of their systematic review.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Both Canadian and American practice guidelines for the use of imaging in patients with stroke recommend CTA as part of the initial diagnostic investigations.[3,5] Both NCCT and CTA were undertaken as part of the standard stroke protocol in two of the included studies,[20,22] one of which was conducted at the Calgary Stroke Program in Canada.[22] One of the studies found that CTA had the potential to overestimate the final infarct size in almost half the patients.[20] However, the Canadian study[22] demonstrated that CTA was more reliable at determining early ischemic changes (based on the ASPECT score) soon after the onset of stroke symptoms (180 minutes or less). This may be of clinical importance as the ASPECT score can assist in determining patient suitability for both thrombectomy and thrombolytic therapy.

One of the strengths of the systematic review by Zheng and colleagues[15] was the use of CTA in a manner similar to one of its established roles in the work-up of stroke, to determine the location of an intracerebral clot and select candidates for endovascular therapy. Overall, they demonstrated significantly improved functional outcomes at 90 days when CTA was used to select candidates for endovascular therapy compared to a non-CTA based selection. As endovascular therapy for the treatment of ischemic stroke becomes available at more stroke centers, these findings indicate that patient selection using CTA may be increasingly required.

All three systematic reviews[16-18] of patients with hemorrhagic stroke found that CTA had a high sensitivity and specificity for accurately detecting intracranial vascular lesions in patients with ICH or SAH. These findings could have significant clinical implications for patients with hemorrhagic stroke as early diagnosis of a culprit lesion may expedite appropriate intervention.

What remains unknown is the utility of CTA in patients who present with symptoms of stroke or TIA but are outside the time window for thrombolysis or endovascular therapy. One of the included non-randomized studies evaluated the role of CTA within 10 days of hospital admission.[21] Investigators found that carotid plaque thickness was more common on the ipsilateral rather than contralateral side in patients with ESUS. This finding may have implications in the investigation of patients who present with stroke of unclear etiology. Another of the included non-randomized studies evaluated the role of CTA within 3 weeks of symptom onset in ischemic stroke and found that CTA may have a predictive role in functional outcomes after stroke.

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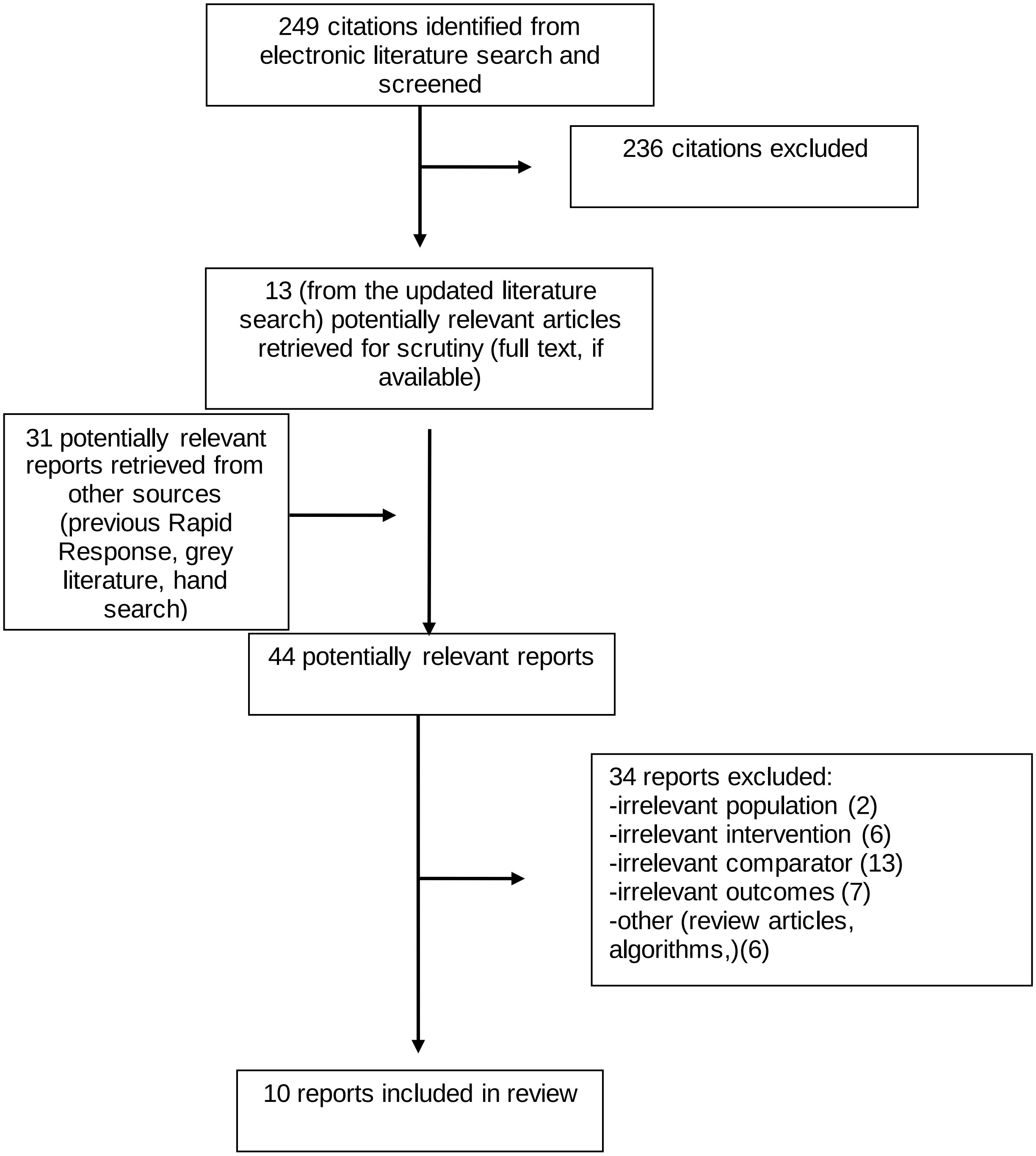
ABBREVIATIONS

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ASPECTS	Alberta Stroke Program Early CT score
CIN	Contrast Induced Nephropathy
CTA	Computed Tomography Angiography
DUS	Digital Ultrasonic System
DSA	Digital Subtraction Angiography
ESUS	Embolic Stroke of Undetermined Source
ICH	Intracerebral Hemorrhage
MCA	Middle Cerebral Artery
NCCT	Non-contrast Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
MR-SWI	Magnetic Resonance-Susceptibility Weighted Imaging
NPV	Negative Predictive Value
PPV	Positive Predictive Value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
SAH	Subarachnoid Hemorrhage
TIA	Transient Ischemic Attack

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Zheng,[15] 2015, China	7 included studies All RCT	n=2217 Acute ischemic stroke Male: 48-58% Mean (or median) age: 66-71 years NIHSS score (IQR): 9-26	Endovascular therapy (stent) + standard care (tPA) Comparison stratified based on use of CTA to select patients	Standard care (tPA)	Functional independence at 90 days Mortality at 90 days
Josephson,[16] 2014, Canada	CTA = 8 studies MRA = 3 studies	CTA: n=526 MRA: n=401 Acute ICH Secondary and Tertiary centers in Asia, NA, Europe	CTA	MRA	Sensitivity Specificity Indirect comparison
Ma,[17] 2012, India	5 included studies (4 previously published + author data) Study type NR	n=544 cases SICH Gender and age NR for some studies	CTA	None	Sensitivity Specificity PPV NPV Accuracy
Westerlaan,[18] 2011, Netherlands	50 included studies Majority (31 studies) used a consecutive design	n=4097 Acute SAH Ruptures aneurysm: 40-100%	CTA	None	Sensitivity Specificity

PPV=positive predictive value; NPV=negative predictive value; NR=not reported; SICH=spontaneous intracranial hemorrhage; CTA=Computed Tomography Angiography; SAH=subarachnoid hemorrhage; MRA=magnetic resonance angiography; NA=North America; RCT=Randomized Controlled Trial; NIHSS=National Institutes of Health Stroke Scale; IQR=interquartile range; tPA=tissue plasminogen activator; CTA=computed tomography angiography; MRA=magnetic resonance angiography; ICH=intracerebral hemorrhage

Table A2: Characteristics of Included Non-randomized Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Sundaram,[19] 2016, India	Retrospective study	n=65 TIA or Ischemic Stroke Age (mean): 57 yrs (+/- 11.6 yrs) Male: 92% NIHSS: 10 (IQR: 4-18) Mean time from symptom onset to CTA: 74 hours (range 2 to 504)	CTA within 3 weeks of symptom onset	No comparator	Functional outcome at 3 months Mortality Recurrent vascular events
Mukherjee,[20] 2016, India	Prospective study	n=105 Acute ischemic stroke (presenting within 8 hours of symptom onset) Age (mean):58 (range 19 to 84) Female: 38 (36.2%) HTN: 61 (58.1%) DM: 49 (46.7%) CAD: 31 (29.5%) Smokers: 24 (22.8%) Cardioembolic source: 44.2% NIHSS, median: 11 (range 3-26)	CTA all patients also had a NCCT IV thrombolysis: 50 (77%) intra-arterial thrombolysis: 2 (3%) mechanical thrombectomy: 5 (8%) bridging thrombolysis to mechanical thrombectomy: 8 (12%)	NCCT	Functional outcomes Mortality Final Infarct Size

Table A2: Characteristics of Included Non-randomized Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Coutinho,[21] 2016, Canada	Prospective study	n=85 Acute ischemic stroke secondary to ESUS Age (median): 70 (IQR 58-79) Female: 52% NIHSS, median: 7 (IQR 3-14) HTN: 51 (60%) DM: 24 (28%) CAD: 17 (20%) Previous stroke/TIA: 15 (18%)	CTA within 10 days of hospital admission IV thrombolysis: 40 (47%) Endovascular reperfusion therapy: 12 (14%) Carotid endarterectomy: 6 (7%)	No comparator	Carotid artery stenosis Carotid plaque Mortality
Bal,[22] 2015, Canada	Retrospective Study	n=261 Acute ischemic stroke presenting within 9 hours of symptom onset Proximal anterior occlusions ICA=34 (13%) MCA M1=143 (54.8%) proximal M2=84 (32.2%) Age (mean): 66.8 yrs (+/- 15.1 yrs) Male: 51% HTN: 261 (60.1%) AF:69 (26.4%)	CTA	NCCT	ASPECTS

Table A2: Characteristics of Included Non-randomized Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		DM: 46 (17%) Smokers: 76 (29%)			
Agarwal,[23] 2014, USA	Retrospective Study	n=35 Acute MCA stroke	CTA	MR-SWI	Thrombus
Bekelis,[24] 2012, USA	Retrospective Study	n=257 ICH Age (mean): 66.1 yrs (9 to 93 yrs) Male: 51%	CTA	No comparator	RF that increase yield of CTA

NCCT=Non-contrast computed tomography; ICA=Internal Carotid Artery; MR-SWI=magnetic resonance susceptibility weighted imaging; MCA=middle cerebral artery; EVT=endovascular treatment; ESUS=embolic stroke of undetermined source; TIA=transient ischemic attack; NIHSS=National Institutes of Health Stroke Scale; CTA=computed tomography angiography; HTN=hypertension; DM=diabetes mellitus; CAD=coronary artery disease; AF=atrial fibrillation; RF=risk factors; ICH=intracerebral hemorrhage; USA=United States of America; IQR=interquartile range; ASPECTS=Alberta Stroke Program Early CT score

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[10]	
Strengths	**Limitations**
Zheng,[15] 2015	
• Authors reported an *a priori* study design • Data abstraction was completed independently and induplicate by two reviewers • Authors report a comprehensive literature search • A list of included studies, with patient characteristics was provided • Quality of the included studies was assessed and documented. Overall, the included studies had a low risk of bias • Quality of included studies was considered when formulating conclusions • Methods to combine study results was appropriate • Publication bias was investigated. No evidence of publication bias was found by the authors • Authors clearly report that they have no conflicts of interest. Funding was received from the National Natural Science Foundation of China	• Authors do not report whether study selection was completed in duplicate • Authors do not report whether the grey literature was searched • A list of excluded studies was not provided • Conflict of interest of included studies was not reported
Josephson,[16] 2014	
• Authors reported an *a priori* study design • Full text study selection was completed in duplicate • Data abstraction was completed in duplicate • Authors report a comprehensive literature search and reported searching the grey literature • A list of both included and excluded studies was provided • Characteristics of included studies was clearly reported • Quality of the included studies was assessed using the QUADAS tool by two independent reviewers. Overall, the quality of the included studies varied substantially. Studies were small with incomplete reporting • Authors reported a plan to investigate	• Screening of titles and abstracts was completed by one reviewer • Conflict of interest (for both the systematic review and included studies) was not reported • Authors used an unadjusted indirect comparison to compare CTA and MRA

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[10]	
Strengths	**Limitations**
publication bias, but were unable as the studies were too small • Quality of included studies was considered when formulating conclusions	
Ma,[17] 2012	
• Authors reported an *a priori* study design • Authors report a comprehensive literature search • Study selection and data abstraction was completed in duplicate • Methods to combine study results was appropriate • A list of included studies, with patient characteristics was provided • Authors clearly report that they have no conflicts of interest	• Only published studies were included; authors did not search the grey literature • Quality of included studies was not assessed • A list of excluded studies was not provided • Likelihood of publication bias was not assessed • Conflict of interest of included studies was not reported
Westerlaan,[18] 2011	
• Authors reported an *a priori* study design • Authors report a comprehensive literature search • Study selection was completed in duplicate • A list of included studies, with minimal patient characteristics was provided • Quality of the included studies was assessed using the QUADAS tool by two independent reviewers. Overall, the included studies had good methodological quality. Their QUADAS scores ranged from 8 to 14 (maximum score is 14) • Quality of included studies was considered when formulating conclusions • Methods to combine study results was appropriate • Authors report that they have no financial relationships to disclose	• Authors do not report whether data abstraction was completed in duplicate • Authors do not report whether the grey literature was searched • A list of excluded studies was not provided • Authors reported the presence of publication bias in the included studies potentially leading to overestimation of the results of the meta-analysis • Conflict of interest of included studies was not reported

Table A4: Strengths and Limitations of Diagnostic Accuracy Studies using QUADAS[11,12]	
Strengths	**Limitations**
Mukherjee,[20] 2016	
• Patients were representative of those seen in practice • Reference standard (NCCT) is likely to correctly classify the target condition • All patients received both the reference standard (NCCT) and the index test (CTA),	• Poor quality images (motion artifact or technical difficulties) were excluded • Study inclusion criteria not well defined • Time delay between NCCT and CTA was not described • Neuro-radiologists were aware of the side

Table A4: Strengths and Limitations of Diagnostic Accuracy Studies using QUADAS[11,12]	
Strengths	**Limitations**
regardless of the results of the NCCT • Both NCCT and CTA were described in sufficient detail to allow for replication •	of the stroke prior to image interpretation • Uninterpretable / intermediate test results and withdrawals or incomplete data were not clearly reported in the study
Bal,[22] 2015	
• Patients were representative of those seen in practice • Clear selection criteria were used • Reference standard (NCCT) is likely to correctly classify the target condition and there was minimal time delay between NCCT and CTA • All patients received both the reference standard (NCCT) and the index test (CTA), regardless of the results of the NCCT • Both NCCT and CTA were described in sufficient detail to allow for replication • Interpretation of NCCT and CTA was blinded and completed in multiple by both stroke neurologists and neuroradiologists	• Unclear whether the same clinical data would be available in practice that was available when either the NCCT or CTA were interpreted • Uninterpretable / intermediate test results and withdrawals or incomplete data were not clearly reported in the study
Agarwal,[23] 2014	
• Clear selection criteria were used • Reference standard (MR) is likely to correctly classify the target condition • All patients received both the reference standard (MR) and the index test (CTA), regardless of the results of the MR • The reference test (MR) was independent of the index text (CTA)	• Details about the included patients were not reported • There was a long delay (4 to 41 hours) between the two imaging modalities, during which time the clinical condition may have changed • The clinical procedure of the reference test (MR) and index test (CTA) were not reported in sufficient detail to allow for duplication • When the index test (CTA) was interpreted, the neuroradiologists knew the results of the reference test (MR) • Unclear whether the same clinical data would be available in practice that was available when either the MR or CTA were interpreted • Uninterpretable / intermediate test results and withdrawals or incomplete data were not clearly reported in the study

Table A5: Strengths and Limitations of Non-randomized studies using Newcastle-Ottawa Quality Assessment Scale[13,14]	
Strengths	**Limitations**
Sundaram[19] 2016	
• The patients had similar comorbidities to patients in clinical practice • The study was retrospective and non-radiographic outcomes were obtained from patient records • Radiographic outcomes were ascertained by independent blind stroke neurologist and neuro-radiologist • Timeframe was long enough for outcomes to have occurred	• There were fewer patients with a cardio-embolic source of stroke (3%) compared to what would be expected in clinical practice • Authors did not report the proportion of patients with a previous stroke • It is unclear whether ICA occlusion was present at the start of the study • Amount and type of missing data from patient records was not described
Coutinho,[21] 2016	
• The patients were representative of those seen in clinical practice • Radiographic outcomes were ascertained by independent blind stroke neurologist and neuro-radiologist • Non-radiographic outcomes were obtained from patient records collected in a prospective manner • Patients were enrolled prospectively after admission for stroke and the authors report history of prior strokes in the baseline data • All CTAs were reviewed by a blinded neuro-radiologist • Timeframe was long enough for outcomes to have occurred (CTA was completed within 10 days of hospital admission for stroke)	• Amount and type of missing data from patient records was not described
Bekelis,[24] 2012	
• The patients were representative of those seen in clinical practice • The study was retrospective and non-radiographic outcomes were obtained from patient records (radiological, diagnosis-related group and operative procedure codes) • It is unlikely that ICH was present prior to presenting to hospital, although it is not specifically reported • Timeframe was long enough for outcomes to have occurred	• The authors do not report the type of physician interpreting the imaging studies, or whether this physician was blinded • Amount and type of missing data from patient records was not described

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Systematic Reviews	

Zheng,[15] 2015

Main Study Findings:

Outcome	Intervention	RR (95%CI)	P-value
Functional independence at 90 days	CTA-based	1.75 (1.48,2.06)	<0.001
	Non-CTA-based	0.99 (0.85,1.14)	
90-days mortality	CTA-based	0.78 (0.60,1.01)	NR
	Non-CTA-based	0.97 (0.75,1.26)	

Author's Conclusions:

- Demonstrated the effect of vascular imaging on patients with acute ischemic stroke who would benefit from endovascular therapy

Josephson,[16] 2014

Main Study Findings:

Diagnostic accuracy for detection of intracranial vascular malformations as a cause of ICH

Test	Studies	Cases	Patients	Sensitivity (95%CI)	Specificity (95%CI)
CTA	8	180	526	0.95 (0.90 to 0.97)	0.99 (0.95 to 1.00)
MRA	3	122	401	0.98 (0.80 to 1.00)	0.99 (0.97 to 1.00)

Likelihood ratio to compare differences in sensitivity and specificity between the two tests, P=0.6

Author's Conclusions:

- No evidence of a significant difference in sensitivity or specificity between CTA or MRA
- CTA and MRA are probably of comparable accuracy to IADSA in diagnosing intracranial vascular malformations in patients with ICH

Ma,[17] 2012

Main Study Findings:

Detecting vascular lesions in SICH

Outcome	%	95% CI
Sensitivity	95.4	91.6 to 97.6
Specificity	98.3	96.3 to 99.2
PPV	96.9	93.4 to 98.6
NPV	97.4	95.3 to 98.6
Accuracy	97.2	95.5 to 98.3

Author's Conclusions:

- CTA has a high PPV and NPV for vascular lesions and should be the initial investigation in patients with acute SICH

Westerlaan[18] 2011

Main Study Findings:

Diagnostic accuracy of CTA in the diagnosis of cerebral aneurysms in patients with acute SAH

Sensitivity (42 studies): 98% (95%CI: 97% to 99%)

Specificity (42 studies): 100% (95%CI: 97% to 100%)

Author's Conclusions:

- CTA can be used as the primary tool for diagnosing patients with a SAH

Retrospective Cohort Studies

Sundaram,[19] 2016

Main Study Findings:

Functional Outcomes at 3 months

Poor outcome (mRS≥3): 33 (50.8%)

Mortality: 4 (6.2%)

Author's Conclusions:

- Assessment of collateral circulation by CTA is an important tool in predicting 3

<table>
<tr><th colspan="2">Table A6: Summary of Findings of Included Studies</th></tr>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td>Recurrent vascular event: 2 (3.1%)</td><td>month outcomes in patients with symptomatic ICA occlusion</td></tr>
<tr><td colspan="2">Mukherjee,[20] 2016</td></tr>
<tr><td>Median modified Rankin Scale (mRS)
Baseline: 4
Discharge: 3
90 days (n=99): 2
Death: 7 (5 during hospital admission, 2 during follow-up)
Final Infarct Size
CTA overestimated in 49 (46.7%) of patients
NCCT underestimated in 63 (60%) of patients</td><td>• Final infarct size may be overestimated using CTA because of the ischemic penumbra and should be considered when interpreting CTA images</td></tr>
<tr><td colspan="2">Coutinho,[21] 2016</td></tr>
<tr><td>In-hospital mortality: 2 (2%)
Carotid artery stenosis <30%:
Ipsilateral: 76/85 (89%)
Contralateral: 78/85 (92%)
Mean carotid plaque thickness
Ipsilateral: 2.2mm
Contralateral: 1.8mm
P=0.009</td><td>• Carotid artery plaque is more common on ipsilateral compared to contralateral carotid arteries in patients with cryptogenic stroke
• Findings suggest that non-stenotic plaque, measured by CTA, may be a cause of stroke</td></tr>
<tr><td colspan="2">Bal,[22] 2015</td></tr>
<tr><td>ASPECT Scores
<table>
<tr><th>Time (stroke onset to CT)</th><th>N</th><th>ASPECTS, Median (IQR)</th><th>P-value (NCCT vs. CTA)</th></tr>
<tr><td>0-90 minutes</td><td>69</td><td>NCCT: 8 (6-10)
CTA: 6 (4-7)
Final: 5 (2-8)</td><td><0.001</td></tr>
<tr><td>91-180 minutes</td><td>88</td><td>NCCT: 8 (6-9)
CTA: 7 (5-8)
Final: 6 (3-8)</td><td>0.006</td></tr>
<tr><td>181-360 minutes</td><td>46</td><td>NCCT: 7 (6-9)
CTA: 7 (5-9)
Final: 5 (3-9)</td><td>0.12</td></tr>
<tr><td>360-540 minutes</td><td>58</td><td>NCCT: 7 (5-9)
CTA: 6 (5-9)
Final: 6 (4-8)</td><td>0.83</td></tr>
</table>
Both NCCT and CTA ASPECT are significantly higher than final ASPECT score at each time point, P≤0.02.</td><td>• Based on ASPECTS, CTA is more reliable at early time points after symptom onset compared to NCCT
• CTA should be used as baseline imaging in acute stroke protocols to identify patients with extensive early ischemic changes</td></tr>
<tr><td colspan="2">Agarwal,[23] 2014</td></tr>
<tr><td>Thrombus seen on 2 patients with MR-SWI that were not seen on CTA.
MR-SWI detected 28 of the 31 thrombi on CTA
Sensitivity of CTA vs. MR SWI: 89% vs. 86%, P>0.05</td><td>• MR-SWI has high sensitivity for detection of thrombus in acute MCA stroke and can estimate clot burden which is challenging on CTA</td></tr>
<tr><td colspan="2">Bekelis,[24] 2012</td></tr>
<tr><td>Negative CTA for source of hemorrhage: n=223
Positive CTA for source of hemorrhage: n=34(13.2%)

Characteristics associated with higher likelihood of identifying</td><td>• In patients with acute ICH, individual factors should be considered before pursuing CTA (most importantly the</td></tr>
</table>

<table>
<tr><th colspan="2">Table A6: Summary of Findings of Included Studies</th></tr>
<tr><th>Main Study Findings</th><th>Author's Conclusions</th></tr>
<tr><td>a structural vascular lesion as source of hemorrhage
<table>
<tr><th>Variable</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>Age (<65 yrs vs. >65 yrs)</td><td>16.36 (2.45 to 109.26)</td><td>0.0039</td></tr>
<tr><td>Sex (female vs. male)</td><td>14.90 (1.79 to 124.46)</td><td>0.0126</td></tr>
<tr><td>Smoking (non-smoker vs. smoker)</td><td>103.80 (6.98 to >999.999)</td><td>0.0008</td></tr>
<tr><td>Intraventricular Hemorrhage (yes vs. no)</td><td>9.42 (1.13 to 78.36)</td><td>0.0379</td></tr>
<tr><td>Hypertension (no vs. yes)</td><td>515.78 (30.21 to >999.999)</td><td><0.0001</td></tr>
</table>
</td><td>presence of hypertension)
• Patients >65 with hypertension, and hemorrhage in the basal ganglia or cerebellum have a very low likelihood of a vascular lesion and can be managed without CTA
• Younger patients (<45 years), non-smokers not on anticoagulation have a high likelihood of a vascular lesion and are best managed with DSA initially
• Patients who do not fit into either of these groups can be safely and effectively screen with CTA</td></tr>
</table>

mRS=modified Rankin Score