Bibliographic Cite	Literature Type	Level of Evidence	Purpose	Population	Intervention and Outcome Measures	Results/ Recommendations	Study Limitiations
Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378(8):708-18.	multi-center randomized open-label trial	moderate level of evidence	To determine the outcomes of patients with thrombectomy 6 to 16 hours after symptom onset	Patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less that 70 ml, and a ration of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more were included. randomly assigned to thrombectomy plus standard medical therapy or standard medical therapy alone. Patients has to have remaining ischmic brain tissue that was not yet infarcted to be included.	Patients were randomly assigned to endovascular therapy (thrombectomy) plus standard medical therapy (endovascular-therapy group) or standard medical therapy alone (medical-therapy group). The primary outcome was the ordinal score on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at day 90.	Endovascular therapy plus medical therapy, as compared with medical therapy alone, was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (odds ratio, 2.77; P < 0.001) and a higher percentage of patients who were functionally independent, defined as a score on the modified Rankin scale of 0 to 2 (45% vs. 17%, P < 0.001). The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group (P = 0.05), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; P = 0.75) or of serious adverse events (43% and 53%, respectively; P = 0.18). Authors conclude that endovascular thrombectomy for ischemic stroke 6 to 16 hours after a patient was last known to be well plus standard medical therapy resulted in better functional outcomes than standard medical therapy alone among patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion and a region of tissue that was ischemic but not yet infarcted.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled Single reader or no inter-reader reliability was calculated
Amarenco P, Lavallee PC, Labreuche J, et al. One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke. N Engl J Med. 2016;374(16):1533-42.	multi-center prospective	low level of evidence	To describe the comtemporary profile, etiologic factors, and outcomes in patients with TIA or minor ischemic stroke who receive care in health systems that now offer urgent evaluation by stroke specialists.	Patients who had a TIA or minor stroke within the previous 7 days at sites which had systems dedicated to urgent evaluation of patients with TIA. From 2009 through 2011, the authors enrolled 4789 patients at 61 sites in 21 countries.	Authors estimated the 1-year risk of stroke and of the composite outcome of stroke, an acute coronary syndrome, or death from cardiovascular causes. They also examined the association of the ABCD2 score for the risk of stroke (range, 0 [lowest risk] to 7 [highest risk]), findings on brain imaging, and cause of TIA or minor stroke with the risk of recurrent stroke over a period of 1 year.	Of the 4789 patients, 78.4% of the patients were evaluated by stroke specialists within 24 hours after symptom onset. A total of 33.4% of the patients had an acute brain infarction, 23.2% had at least one extracranial or intracranial stenosis of 50% or more, and 10.4% had atrial fibrillation. The Kaplan–Meier estimate of the 1-year event rate of the composite cardiovascular outcome was 6.2% (95% confidence interval, 5.5 to 7.0). Kaplan–Meier estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. In multivariable analyses, multiple infarctions on brain imaging, large-artery atherosclerosis, and an ABCD score of 6 or 7 were each associated with more than a doubling of the risk of stroke. The authors observed a lower risk of cardiovascular events after TIA than previously reported. The ABCD(2) score, findings on brain imaging, and status with respect to large-artery atherosclerosis helped stratify the risk of recurrent stroke within 1 year after a TIA or minor stroke.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled Non-consecutive recruitment Readers were not blinded or no comment was made about the blinding of the readers Single reader or no inter-reader reliability was calculated incomplete reporting This registry has important limitations. First, sites were not chosen at random but rather were chosen on the basis of the existence of a TIA clinic or dedicated care for patients with TIA, with at least 100 TIAs evaluated per year during the previous 3 years. Our registry was biased toward more specialized stroke physicians and possibly enrolled a cohort of patients that had characteristics that differed from those of patients in a population-based study but that probably represents patients whom clinical trials are recruiting. Second, owing to resource constraints, we were able to audit only 10% of the data for accuracy. Although primary outcome events and major bleeding events were adjudicated, primary outcome events may have been underreported in the registry. For this reason, our primary outcome included only hard end points, which are unlikely to be missed. Third, of 4583 patients analyzed, 4200 (91.6%) had 1-year follow-up data available at the time of this analysis. The fact that data were missing for more than 380 patients may have partially affected the 1-year event rate.
Andersen SD, Skjoth F, Yavarian Y, et al. Multiple Silent Lacunes Are Associated with Recurrent Ischemic Stroke. Cerebrovasc Dis. 2016;42(1-2):73-80.	single center cohort	low level of evidence	The authors aimed at investigating the association of silent lacunes and the risk of ischemic stroke recurrence, death, and cardiovascular events in a cohort of patients with incident ischemic stroke and no atrial fibrillation (AF).	The authors included 786 patients (mean age 59.5 (SD 14.0); 42.9% females) in a registry-based, observational cohort study on patients with first-ever ischemic stroke. On brain MRI the authors assessed the number of silent lacunes as none, single, or multiple and the authors calculated stratified incidence rates of the outcomes. Cox proportional hazard ratios (HRs) adjusted for age, gender, congestive heart failure, hypertension, diabetes, and vascular disease were calculated with no silent lacunes as reference. In additional analyses, the authors further adjusted for white matter hyperintensities. Patients were followed up until death or recurrence of ischemic stroke.	On brain MRI the authors assessed the number of silent lacunes as none, single, or multiple and we calculated stratified incidence rates of the outcomes. Cox proportional hazard ratios (HRs) adjusted for age, gender, congestive heart failure, hypertension, diabetes, and vascular disease were calculated with no silent lacunes as reference. In additional analyses, they further adjusted for white matter hyperintensities. Patients were followed up until death or recurrence of ischemic stroke.	In 168 (21.5%) patients, at least one silent lacune was present, and in 87 (11.1%) patients, multiple silent lacunes were found. Patients with at least one silent lacune were older (mean age 66.1 vs. 57.7, p < 0.001) and were more often hypertensive (60.1 vs. 43.4%, p < 0.001) compared to patients with no silent lacunes. During a median follow-up time of 2.9 (interquartile range 3.1) years, we observed 53 recurrent ischemic strokes, 76 deaths, and 96 cardiovascular events. Incidence rates per 100 person-years of ischemic stroke recurrence were 1.6, 2.5, and 5.0 for none, single, and multiple silent lacunes respectively. In this large cohort of patients with incident ischemic stroke and no AF, an increasing number of silent lacunes was associated with increasing incidence rates of ischemic stroke recurrence. In the adjusted Cox proportional hazard analyses, the presence of multiple silent lacunes was significantly associated with an increased risk of ischemic stroke recurrence. The risk of death or cardiovascular events was not significantly influenced by the presence of silent lacunes.	Non-consecutive recruitment There are also important limitations to consider. First, we did a registry-based study; thus, we cannot rule out misclassification of both the diagnosis of stroke and the comorbidities, but the validity of the Danish Stroke Registry is high. Second, we included only those patients who had done an MRI scan. Compared to the entire stroke cohort, these patients were younger and had minor strokes, and this selection may be a potential limitation to the generalizability of our findings. Third, MRI scans were rated only by a single stroke neurologist. Although a small validation sample was also rated by a consultant neuroradiologist and reproducibility was very high, we cannot rule out rater bias.
Boulouis G, de Boysson H, Zuber M, et al. Primary angiitis of the central nervous system: Magnetic resonance imaging spectrum of parenchymal, meningeal, and vascular lesions at baseline. Stroke. 2017; 48(5):1248-1255.	multicenter cohort	low level of evidence	To report an overview and pictorial review of brain magnetic resonance imaging findings in adult primary angiitis of the central nervous system and to determine the distribution of parenchymal, meningeal, and vascular lesions in a large multicentric cohort.	A total of 60 adult patients from the French COVAC cohort (Cohort of Patients With Primary Vasculitis of the Central Nervous System), with biopsy or angiographically proven primary angiitis of the central nervous system and brain magnetic resonance imaging available at the time of diagnosis were included. Mean age was 45 years (±12.9). Patients initially presented focal deficit(s) (83%), headaches (53%), cognitive disorder (40%), and seizures (38.3%).	MR sequences from 23 centers were retrospectively reviewed using a standardized extraction form by 3 neuroradiologists with 5, 12, and 25 years of experience in stroke imaging, blinded to clinical, laboratory, and outcome data, and assessments were adjudicated by consensus when necessary.	The most common magnetic resonance imaging finding observed in 42% of patients was multiterritorial, bilateral, distal acute stroke lesions after small to medium artery distribution, with a predominant carotid circulation distribution. Hemorrhagic infarctions and parenchymal hemorrhages were also frequently found in the cohort (55%). Acute convexity subarachnoid hemorrhage was found in 26% of patients and 42% demonstrated pre-eminent leptomeningeal enhancement, which is found to be significantly more prevalent in biopsy-proven patients (60% versus 28%; P=0.04). Seven patients had tumor-like presentations. Seventy-seven percent of magnetic resonance angiographic studies were abnormal, revealing proximal/distal stenoses in 57% and 61% of patients, respectively.	Our study comes with limitations; the first being its retrospective design leading to incomplete imaging protocols and thus exclusions. Of note, approximately one fourth of patients were lacking post-gadolinium T1 sequences. An additional methodological drawback lies in the fact that it was not possible to analyze brain parenchyma apart from brain vessels with potential interactions in the ratings in either direction.
Coutts SB, Moreau F, Asdaghi N, et al. Rate and prognosis of brain ischemia in patients with lower-risk transient or persistent minor neurologic events. JAMA Neurol. 2019; 76(12):1439-1445.	prospective, observational, international, multicenter cohort study	moderate level of evidence	To establish the frequency of acute infarction defined by diffusion restriction detected on MRI scans among patientswith mild focal neurologic, but low-risk, symptoms.	1028 participants were prospectively enrolled from an outpatient clinic setting (732 [71.2%]) and the remainder from the emergency department. All had experienced nonmotor or nonspeech minor focal neurologic events of any duration or motor or speech symptoms of short duration (≤ 5 minutes), with no previous stroke. Median time from symptom onset to neurologic assessment was 50 hours (interquartile range [IQR], 15-106 hours). Median time from symptom onset to MRI was 102 hours (interquartile range, 53-144 hours). The mean (SD) age was 63.0 (11.6) years. Median National Institutes of Health Stroke Scale score was 0 (range, 0-3). Most patients (656 [63.8%]) reported that all symptoms related to the event had resolved at the time of assessment.	Participants were enrolled as soon as possible after their neurologic event, but no later than 8 days after symptom onset, and prior to undergoing MRI. Imaging was performed within 8 days to ensure capture of small restricted diffusion lesions. All participants were examined by stroke neurologists. Features of the medical history were self-reported. For each participant, a detailed standardized questionnaire describing the nature of the event was completed by the neurologist, the neurologic examination results were rated as normal or not, and a provisional diagnosis was recorded, all prior to the MRI. Follow-up at 1 year from symptom onset was completed by telephone to assess for recurrent strokes or death.	A total of 139 patients (13.5%) had an acute stroke as defined by diffusion restriction detected on MRI scans (DWI positive). The final diagnosis was revised in 308 patients (30.0%) after undergoing brain MRI. There were 7 (0.7%) recurrent strokes at 1 year. A DWI-positive brain MRI scan was associated with an increased risk of recurrent stroke (relative risk, 6.4; 95%CI, 2.4-16.8) at 1 year. Absence of a DWI-positive lesion on a brain MRI scan had a 99.8%negative predictive value for recurrent stroke. Factors associated with MRI evidence of stroke in multivariable modeling were older age (odds ratio [OR], 1.02; 95%CI, 1.00-1.04), male sex (OR, 2.03; 95%CI, 1.39-2.96), motor or speech symptoms (OR, 2.12; 95%CI, 1.37-3.29), ongoing symptoms at assessment (OR, 1.97; 95%CI, 1.29-3.02), no prior identical symptomatic event (OR, 1.87; 95%CI, 1.12-3.11), and abnormal results of initial neurologic examination (OR, 1.71; 95%CI, 1.11-2.65). This study suggested that patients with transient ischemic attack and symptoms traditionally considered low risk carry a substantive risk of acute stroke as defined by diffusion restriction (DWI positive) on a brain MRI scan. Early MRI is required to make a definitive diagnosis.	The results apply to a study population in which participantswere all referred to and evaluated by a stroke neurologistwith an initial suspicion of brain ischemiaas a potential diagnosis and all underwent an MRI within 8 days of symptom onset. Results do not necessarily apply to patients assessed differently or at later time points. The median time to MRI was 4 days, which is longer than assessment times in similar studies of patients with high-risk TIA or mildstroke. Most recurrent ischemic events in patients with high-risk TIA or mildstroke occur within the first 24 to 72 hours after symptom onset. It is plausible that a proportion of eligible participants were excluded owing to development of early recurrent infarcts by day 4, creating bias by selection. Authors did not include vascular imaging, which, when performed acutely, might identify more patients at risk for recurrent events. The low risk of long-term recurrent stroke may be an underestimate owing to the potential for telephone follow-up to miss outcome events.

Kang DW, Han MK, Kim HJ, et al. Silent new ischemic lesions after index stroke and the risk of future clinical recurrent stroke. Neurology. 2016;86(3):277-85.	dual center prospective cohort	high level of evidence	To test whether a silent new ischemic lesion (SNIL) on MRI after stroke predicted future recurrent ischemic stroke or vascular events.	Patients presenting with acute ischemic stroke who underwent MRI <24 hours and 5 and 30 days after symptom onset. The mean (SD) age was 62.81 (11.56) years and 170 patients (63%) were male.	Authors analyzed data from patients presenting with acute ischemic stroke who underwent MRI < 24 hours and 5 and 30 days after symptom onset. The presence of a SNIL at 5 (5D-SNIL) and 30 (30D-SNIL) days was determined on diffusion-weighted and fluid-attenuated inversion recovery images. Patients were contacted every 3–6 months to identify recurrent clinical events. The log-rank test and Cox proportional hazard model were used to estimate the hazard ratio of recurrent ischemic stroke and composites of recurrent ischemic stroke, transient ischemic attack, acute coronary syndrome, and vascular death.	During the follow-up period (median of 47.9 months), clinical recurrent events occurred in 42 patients (15.6%): recurrent ischemic stroke (IS) in 25, TIA in 6, ACS in 5, and vascular death in 6. Of the 25 who developed recurrent IS, 11 (44%) had a silent new ischemic lesion at 5 days (5D-SNIL), 9 (36%) had a SNIL at 30 days (30D-SNIL), and 4 (16%) had both a 5D- and a 30D-SNIL. Cox proportional hazards model showed that 5DSNIL and 30D-SNIL were independent predictors of recurrent IS. Patients with a SNIL within the first few weeks after index stroke have an increased risk of recurrent ischemic stroke or vascular events. The presence of a SNIL on MRI could serve as a surrogate endpoint for clinical recurrence in secondary prevention clinical trials.	Readers were not blinded or no comment was made about the blinding of the readers Baseline characteristics of the control and experimental groups are different and/or there was no attempt to control for confounding effects High percentage (> 25%) of people who dropped out of the study Reference standard was inadequate (explain why in the box below) No reference standard for this study; large number of screened patients were excluded, and those that were included were not a representative sample of all screened patients. Patients receiving IV thrombolysis were excluded
Mokin M, Levy EI, Saver JL, et al. Predictive Value of RAPID Assessed Perfusion Thresholds on Final Infarct Volume in SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment). Stroke. 2017;48(4):932-8.	single center randomized trial	low level of evidence	To analyze the accuracy of various rCBV and rCBF thresholds for predicting the 27-hour infarct volume using RAPID automated analysis software from the SWIFT PRIME trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) data.	Patients from the SWIFT PRIME study who achieved complete reperfusion based on time until the residue function reached its peak > 6 s perfusion maps obtained at 27 hours were included.	Patients from both the intravenous tissue-type plasminogen activator only and endovascular groups were included in analysis. Final infarct volume was determined on magnetic resonance imaging (fluid-attenuated inversion recovery images) or computed tomography scans obtained 27 hours after symptom onset. The predicted ischemic core volumes on rCBV and rCBF maps using thresholds ranging between 0.2 and 0.8 were compared with the actual infarct volume to determine the most accurate thresholds.	The following CBV thresholds most accurately predicted the 27-hour infarct volume: rCBV=0.32, MAE=9 mL; and rCBV=0.34, MAE=9mL. The following CBF thresholds most accurately predicted the 27-hour infarct volume: rCBF=0.30, MAE=8.8 mL; rCBF=0.32, MAE=7 mL; and rCBF=0.34, MAE=7.3. Correlation of these thresholds between the baseline ischemic core volume and the 27-hour Tmax >6-s volume (predicted 27-hour volume) with the actual 27-hour infarct volume were as follows: rCBV=0.32, r=0.54, P<0.001; rCBV=0.34; r=0.52, P<0.001; rCBF=0.30, r=0.61, P<0.001; rCBF=0.32, r=0.62, P<0.001; and rCBF=0.34, r=0.62, P<0.001). Brain regions with rCBF 0.30 to 0.34 or rCBV 0.32 to 0.34 thresholds provided the most accurate prediction of infarct volume in patients who achieved complete reperfusion with MAEs of <=9 mL.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled Single reader or no inter-reader reliability was calculated Small sample size Limitations of the study include the fact that complete reperfusion was assessed at 27 hours. An earlier assessment would have allowed exclusion of patients with longer imaging to reperfusion times and would have potentially improved the accuracy of predicting the ischemic core. Even in the endovascular group, reperfusion typically did not occur for at least 60 minutes after imaging was obtained. Therefore, infarct growth between the time of imaging and reperfusion likely reduced the agreement between infarct core volumes and final infarct size.
Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med. 2018;378(1):11-21.	multi-center prospective randomized trial	low level of evidence	To determine the effect of endovascular thrombectomy performed more than 6 hours after the onset of ischemic stroke.	The authors enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age (<80 years or ≥ 80 years). A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group.	Patients were randomly assigned to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group). The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.	The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00). Among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care than with standard care alone.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled Single reader or no inter-reader reliability was calculated This trial has limitations. Randomization was stratified according to prognostic variables that the investigators determined to be most pertinent in the patient population; these variables were balanced between the two treatment groups. However, there were significant differences between the two groups in other baseline variables. In post hoc sensitivity analyses that adjusted for these differences, the benefit of thrombectomy remained.
Ottaviani M, Vanni S, Moroni F, et al. Urgent carotid duplex and head computed tomography versus ABCD2 score for risk stratification of patients with transient ischemic attack. Eur J Emerg Med. 2016;23(1):19-23.	single center prospective Observational	high level of evidence	To prospectively compare the prognostic value of ABCD score, urgent carotid ultrasound (CUS), and unenhanced head computed tomography (UHCT) in patients presenting to the emergency department with transient ischemic attack (TIA).	The authors carried out a prospective observational study including consecutive adult patients with TIA. The authors included 186 patients with a median age of 75 years and a prevalent male sex (57.5%).	Each patient underwent ABCD score assessment, urgent CUS, and UHCT within 24 h from presentation. The primary outcome was the occurrence of ischemic stroke within 30 days. Follow-up was extended to 30 days after emergency department presentation by a researcher physician blinded to admission data, with clinical evaluation during hospitalization or calling back patients after discharge.	The mean ABCD2 score was 4 ± 1; 130 (69.5%) patients had a score of at least 4. Of 12 total strokes, four (7.1%) occurred in the group with ABCD2 score less than 4 and eight (6.2%) in the group with ABCD2 of at least 4 (P = 0.755). The accuracy of ABCD2 score estimated by C-statistic did not reach statistical significance (0.53, 95% CI 0.35–0.71). An internal carotid stenosis of at least 50% consistent with the neurological deficit was found in 15 patients (8.1%), four (7.1%) with ABCD2 score less than 4 and 11 (8.4%) with ABCD2 score of at least 4. Patients with internal carotid stenosis of at least 50% consistent with the neurological deficit were at higher stroke risk (20%) than patients without (5.3%), with an OR of 4.5 (95% CI 1.1–18.8) An ischemic lesion consistent with the neurological deficit was revealed by UHCT in 15 patients (8.1%), five (8.9%) with ABCD2 score less than 4 and 10 (7.7%) with ABCD2 score of at least 4. Patients with such lesions showed a higher trend for stroke risk (13.3%) than patients without (5.8%) (OR 2.5, 95% CI 0.5–12.5) Patients with neither critical stenosis nor ischemic lesion at UHCT (159 patients) had low incidence of stroke (5%) at 30 day follow-up, whereas patients with at least one (24 patients) or both positive imaging tests (three patients) showed increasing risk for stroke (12.5 and 33.3%, respectively, P =0.047). Simple imaging tests showed added prognostic value to ABCD score in TIA patients. Urgent CUS together with UHCT should be performed in all TIA patients regardless of ABCD score.	Single reader or no inter-reader reliability was calculated.
Provost C, Soudant M, Legrand L, et al. Magnetic resonance imaging or computed tomography before treatment in acute ischemic stroke. Stroke. 2019; 50(3):659-664.	multi-center sub-group analysis of a RCT	low level of evidence	To compare workflow and functional outcome in acute ischemic stroke patients screened by magnetic resonance imaging (MRI) or computed tomography (CT) before treatment in the THRACE trial (Thrombectomie des Artères Cérébrales), with emphasis on the duration of the imaging step.	Patients with acute ischemic stroke were eligible for inclusion if they were aged 18 to 80 years, had a National Institutes of Health Stroke Scale (NIHSS) score of 10 to 25, had a proximal cerebral artery occlusion confirmed by CT or MRI, could receive intravenous tPA (tissue-type plasminogen activator) within 4 hours of symptom onset, and if thrombectomy could be initiated within 5 hours of symptom onset. Among 414 randomized patients in the THRACE trial, 401 patients were included in the present study (2 patients withdrew consent, screening imaging modality was unknown in 8 patients, and imaging time information was not available for 2 MRI-selected patients and 1 CT-selected patient).	The THRACE trial was a RCT. Patients were randomized to receive either intravenous tPA and mechanical thrombectomy or intravenous tPA alone. The choice of screening imaging modality was left to each enrolling center. Differences between MRI and CT groups were assessed using univariable analysis and the impact of imaging modality on favorable 3-month functional outcome (modified Rankin Scale score of ≤2) was tested using multivariable logistic regression.	Of the 401 participating patients, 299 were MRI-selected and 102 CT-selected patients. Median baseline National Institutes of Health Stroke Scale score was 18 in both groups. MRI scan duration (median [interquartile range]) was longer than CT (MRI: 13 minutes [10–16]; CT: 9 minutes [7–12]; P<0.001). Stroke-onset-to imaging time (MRI: median 114 minutes [interquartile range, 89–138]; CT: 107 minutes [88–139]; P=0.19), onset-to intravenous tPA time (MRI: 150 minutes [124–179]; CT: 150 minutes [123–180]; P=0.38) and onset-to-angiography suite time (MRI: 200 minutes [170–250]; CT: 213 minutes [180–246]; P=0.57) did not differ between groups. Imaging modality was not significantly associated with functional outcome in the multivariable analysis. The authors conclude that, although MRI scan duration is slightly longer than CT, MRI-based selection for acute ischemic stroke patients is accomplished within a timeframe similar to CT-based selection, without delaying treatment or impacting functional outcome. This should help to promote wider use of MRI, which has inherent imaging advantages over CT.	The study has several limitations. The THRACE trial was not designed for the purpose of the current study and randomization was not stratified on imaging modality. As a consequence, the choice of imaging modality may have depended on confounding variables. For instance, in centers using MRI as a prime screening imaging modality in stroke patients, the most severely ill patients might be directed towards CT. However, in THRACE, stroke clinical severity did not differ between the CT and MRI groups, likely because the majority of patients medically ineligible for MRI suffer from intracerebral hemorrhage, whereas THRACE focused on ischemic stroke. Next, there was no synchronization across all clocks and imagers, which may have led to some degree of inaccuracy in the times recorded. Finally, some of the workflow times were not recorded in the case report form of the THRACE trial (arrival to hospital door and groin puncture), therefore preventing a comprehensive evaluation of the workflow, as well as comparisons with others and current guidelines for door-to-imaging and door-to-groin puncture times.

Streifler JY, den Hartog AG, Pan S, et al. Ten-year risk of stroke in patients with previous cerebral infarction and the impact of carotid surgery in the Asymptomatic Carotid Surgery Trial. Int j. 2016;11(9):1020-7.	multi-center sub-group analysis of a RCT	low level of evidence	To evaluate the impact of prior cerebral infarction in patients enrolled in the Asymptomatic Carotid Surgery Trial, a large trial with 10-year follow-up in which participants whose carotid stenosis had not caused symptoms for at least six months were randomly allocated either immediate or deferred carotid endarterectomy.	The first Asymptomatic Carotid Surgery Trial included 3120 patients. Of these, 2333 patients with baseline brain imaging were identified and divided into two groups.	Previous cerebral infarction was defined as a history of ischemic stroke or TIA in any territory occurring > 6 months prior to randomization or radiological evidence of an asymptomatic or "silent" brain infarct. Patients fitting this definition were included in group 1 and those without previous cerebral infarction were included in group 2. Patients with prior stroke or TIA were included in group 1 even if their imaging was reported as normal.Stroke and vascular deaths were compared during follow-up, and the impact of carotid endarterectomy was observed in both groups.	At 10 years follow-up, stroke was more common among participants with cerebral infarction before randomization (absolute risk increase 5.8% (1.8–9.8), p=0.004), and the risk of stroke and vascular death was also higher in this group (absolute risk increase 6.9% (1.9–12.0), p=0.007). On multivariate analysis, prior cerebral infarction was associated with a greater risk of stroke (hazard ratio=1.51, 95% confidence interval: 1.17–1.95, p=0.002) and of stroke or other vascular death (hazard ratio=1.30, 95% confidence interval: 1.11–1.52, p=0.001). At 10 years, greater absolute benefits from immediate carotid endarterectomy were seen in those patients with prior cerebral infarction (6.7% strokes immediate carotid endarterectomy vs. 14.7% delayed carotid endarterectomy; hazard ratio 0.47 (0.34–0.65), p ¼ 0.003), compared to those lower risk patients without prior cerebral infarction (6.0% vs. 9.9%, respectively; hazard ratio 0.61 (0.39–0.94), p=0.005), though it must be emphasized that the first Asymptomatic Carotid Surgery Trial was not designed to test this retrospective and non-randomized comparison. Asymptomatic carotid stenosis patients with prior cerebral infarction have a higher stroke risk during long-term follow-up than those without prior cerebral infarction. Evidence of prior ischemic events might help identify patients in whom carotid intervention is particularly beneficial.	Readers were not blinded or no comment was made about the blinding of the readers Single reader or no inter-reader reliability was calculated. A significant number of patients did not have CT scan prior to randomization; their baseline characteristics, however, were broadly similar, and the presence or lack of baseline imaging was largely determined by center location rather than individual participants' features.
Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset. N Engl J Med. 2018; 379(7):611-622.	multi-center RCT	high level of evidence	To determine whether treatment with alteplase would improve functional outcomes in patients with an unknown time of stroke onset and a mismatch between diffusion-weighted imaging and FLAIR findings on MRI.	Patients were eligible if they presented with clinical signs of acute stroke, were 18 to 80 years of age, and had been able to carry out usual activities in their daily life without support before the stroke. The patient either recognized stroke symptoms on awakening or could not report the timing of the onset of symptoms (e.g., as a result of aphasia or confusion). All had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. Patients with planned thrombectomy were excluded. A total of 503 patients were enrolled.	Patients were randomly assigned to receive either IV alteplase or placebo. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis).	The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P = 0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P = 0.003). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P = 0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P = 0.15). The authors conclude that, in patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days.	Approximately two thirds of the patients who were screened in the trial did not undergo randomization, mainly because they did not have the mismatch pattern of recent stroke on MRI required for enrollment. The exclusion of patients who planned to undergo thrombectomy limits the generalization of the findings. It is possible that some patients with severe stroke from large vessel occlusion in the anterior circulation were not enrolled in the trial and were treated with thrombectomy outside the trial.
Yoo AJ, Berkhemer OA, Fransen PSS, et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). Lancet neurol. 2016;15(7):685-94.	multi-center a subgroup analysis of a randomised phase 3 trial	low level of evidence	To examine the effect of the baseline Alberta Stroke Program Early CT Score (ASPECTS) on the safety and efficacy of intra-arterial treatment in a subgroup analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).	MR CLEAN was a randomized, controlled, open-label, phase 3 trial of intra-arterial treatment in patients (aged ≥ 18 years from the Netherlands) with proximal arterial occlusion of the anterior circulation, given intra-arterial treatment within 6 h of stroke onset. Imaging criteria for inclusion were a CT or MRI scan ruling out hemorrhage and CT, magnetic (MR), or digital subtraction angiography showing occlusion of the intracranial internal carotid artery, middle cerebral artery (M1 or M2 segments), or anterior cerebral artery (A1 or A2 segments). No imaging exclusion criteria based on ASPECTS or the extent of early ischemic changes on non-contrast CT were used.	The primary outcome was 90 day modified Rankin Scale (mRS) score. The authors estimated the intra-arterial treatment effect for all patients in MR CLEAN who had ASPECTS graded by using multivariable ordinal logistic regression analysis (a proportional odds model) to calculate the adjusted common odds ratio for a shift towards a better functional outcome according to the mRS for intra-arterial treatment and usual care than for usual care alone. The authors entered an interaction term into the model to test for interaction with prespecified ASPECTS subgroups: 0-4 (large infarct) versus 5-7 (moderate infarct) versus 8-10 (small infarct).	Of the 496 patients—232 (47%) in the intra-arterial treatment and usual care group and 264 (53%) in the usual care alone group, there was no significant difference in intra-arterial treatment effect between the ASPECTS subgroups according to 90 day ordinal mRS (adjusted common odds ratio interaction term relative to ASPECTS 8–10: ASPECTS 0–4: 0·79 [95% CI 0·20–3·19], p=0·740; and ASPECTS 5–7: 1·02 [0·44–2·35], p=0·966). Intra-arterial treatment did not cause a significant increase in the proportion of patients with at least one serious adverse event in any of the ASPECTS subgroups (ASPECTS 0–4: eight [73%] of 11 patients in treatment and usual care group vs 11 [58%] of 19 in usual care alone group, p=0·42; ASPECTS 5–7: 32 [59%] of 54 vs 19 [49%] of 39, p=0·31; ASPECTS 8–10: 70 [42%] of 167 vs 82 [40%] of 206; p=0·68). For death within 7 days or within 30 days and hemicraniectomy, the differences between the intra-arterial treatment and usual care versus usual care alone groups were not significant by ASPECTS subgroups. A significantly higher proportion of patients had recurrent ischaemic stroke in the intra-arterial treatment plus usual care group than in the usual care alone group in the ASPECTS 8–10 subgroup (eight [5%] vs one [<1%]; p=0·007). Contrary to findings from previous studies suggesting that only patients with non-contrast CT ASPECTS of more than 7 benefit from intra-arterial treatment, data from this study suggest that patients with ASPECTS 5-7 should be treated. Further evidence is needed for patients with ASPECTS 0-4, for whom treatment might yield only marginal absolute benefit.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled Single reader or no inter-reader reliability was calculated The main limitation of this analysis is the small number of patients in the ASPECTS 0–4 category, which probably resulted in an underpowered test for interaction between ASPECTS and treatment allocation. However, because MR CLEAN was the only intra-arterial treatment trial that did not have an explicit imaging exclusion criterion based on the extent of parenchymal ischaemic changes, our study population was the largest with ASPECTS 0–4 among the recent randomised trials of intra-arterial therapy.