Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

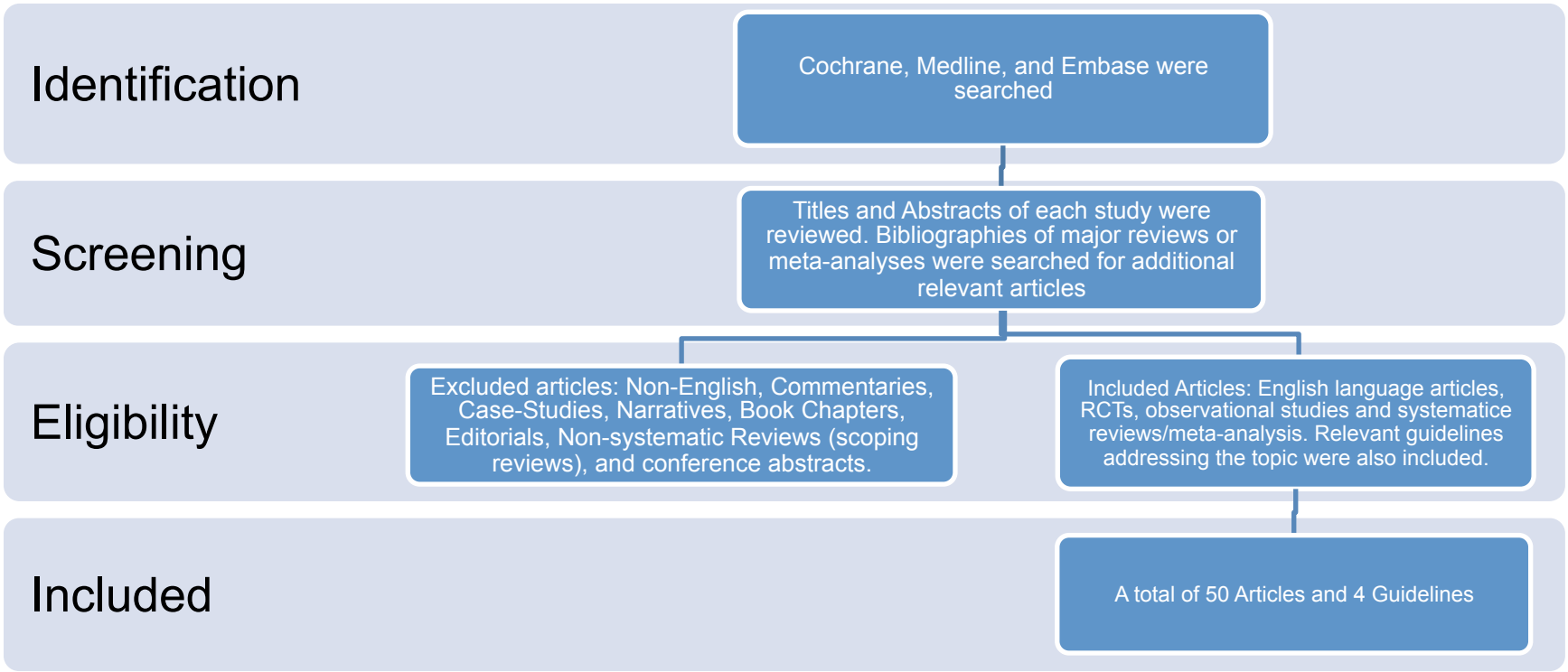
Acute Stroke Management Evidence Tables

Emergency Department Evaluation and Management of Patients with TIA and Acute Stroke

Jean-Martin Boulanger and Kenneth Butcher (Writing Group Chairs)
on Behalf of the Canadian Stroke Best Practice Recommendations
ACUTE STROKE MANAGEMENT Writing Group

Table of Contents

Search Strategy



Medline, Embase and the Cochrane Database were search using the terms ([Stroke OR Cerebrovascular Disorders] AND [Emergency Service, hospital OR Emergency Medicine OR Hyperacute]). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 50 articles and 4 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110** **(selected)**	**2. Emergency Evaluation & Treatment** **2.1. Stroke Scales** 1. The use of a stroke severity rating scale, preferably the NIHSS, is recommended. (Class 1; LOE B-NR). **2.2. Brain Imaging** 1. All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. In most cases, noncontrast CT (NCCT) will provide the necessary information to make decisions about acute management. (Class 1; LOE B-NR). 2. Systems should be established so that brain imaging studies can be performed within 20 minutes of arrival in the ED in at least 50% of patients who may be candidates for IV alteplase and/or mechanical thrombectomy. (Class 1; LOE B-NR). 3. There remains insufficient evidence to identify a threshold of acute CT hypoattenuation severity or extent that affects treatment response to IV alteplase. The extent and severity of acute hypoattenuation or early ischemic changes should not be used as a criterion to withhold therapy for such patients who otherwise qualify. (Class III: No benefit; LOW-B-R). 4. The CT hyperdense MCA sign should not be used as a criterion to withhold IV alteplase from patients who otherwise qualify. (Class III: No Benefit; LOE B-R) 5. Routine use of magnetic resonance imaging (MRI) to exclude cerebral microbleeds (CMBs) before administration of IV alteplase is not recommended. (Class III: No Benefit: LOE B-NR). 8. For patients who otherwise meet criteria for EVT, a noninvasive intracranial vascular study is recommended during the initial imaging evaluation of the acute stroke patient, but should not delay IV alteplase if indicated. For patients who qualify for IV alteplase according to guidelines from professional medical societies, initiating IV alteplase before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible. (Class I: LOE A) 12. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP, DW-MRI, or MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy. (Class I; LOE A). **2.3 Other Diagnostic Tests** 1. Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients. (Class I; LOE B-R). 2. Baseline ECG assessment is recommended in patients presenting with AIS, but should not delay initiation of IV alteplase. (Class I; LOE B-NR). 3. Baseline troponin assessment is recommended in patients presenting with AIS, but should not delay initiation of IV alteplase. (Class I; LOE B-NR).

	3. General Supportive Care and Emergency Treatment 3.1. Airway, Breathing, and Oxygenation 1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway. (Class I; LOE C-EO) 2. Supplemental oxygen should be provided to maintain oxygen saturation >94%. (Class I; LOE C-LD) 3.2. Blood pressure 1. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function. (Class I; LOE C-EO). 2. Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their systolic BP is <100 mm Hg before IV fibrinolytic therapy is initiated. (Class I; LOE B-NR). 3.3. Temperature 1. Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke. (Class I; LOE C-EO). 3.4 Blood glucose 1. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes than normoglycemia and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with AIS. (Class IIa; LOE C-LD). 2. Hypoglycemia (blood glucose <60 mg/dl) should be treated in patients with AIS. (Class I ; LOE C-LD).
Fuentes B, Ntaios G, Putaala J, Thomas B, Turc G, Díez-Tejedor E, European Stroke Organisation. **European Stroke Organisation (ESO) guidelines on glycaemia management in acute stroke.** ***Eur Stroke J* 2018, Vol. 3(1) 5–21.**	In patients with acute ischemic stroke, we suggest against the routine use of IV insulin to achieve a tight glycaemic control as a means to improve functional outcome, survival or infarct growth. Quality of evidence: Low; Strength of recommendation: Weak In patients with acute haemorrhagic stroke, we suggest against the routine use of IV insulin to achieve a tight glycaemic control as a means to improve functional outcome or survival. Quality of evidence: Very low; Strength of recommendation: Weak
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation.	Strong Recommendation All suspected stroke patients who have been pre-notified to the stroke or ED team, and who may be candidates for reperfusion therapy, should be met at arrival and assessed by the stroke team or other experienced personnel. Weak Recommendation The use of clinical screening tools to identify stroke by ED staff is recommended where an expert stroke team is unable to immediately assess a patient Strong Recommendation All patients with suspected stroke who are candidates for reperfusion therapies should undergo brain imaging immediately. All other suspected stroke patients should have an urgent brain CT or MRI ('urgent' being immediately where facilities are available and preferably within 60 minutes).

	Weak recommendation Updated In patients with suspected stroke and TIA, MRI is more sensitive and specific than non-contrast CT and is the preferred modality when diagnostic confirmation is required. Practice statement Consensus-based recommendation New Either CT or MRI are acceptable acute imaging options but these need to be immediately accessible to avoid delaying reperfusion therapies. Strong recommendation New If using CT to identify hyperdense thrombus, thin slice (< 2 mm) noncontrast CT should be used rather than the standard 5 mm slices to improve diagnostic sensitivity for vessel occlusion. Weak recommendation New CT perfusion imaging may be used in addition to routine imaging to improve diagnostic and prognostic accuracy. Strong recommendation Updated • All patients who would potentially be candidates for endovascular thrombectomy should have vascular imaging from aortic arch to cerebral vertex (CTA or MRA) to establish the presence of vascular occlusion as a target for thrombectomy and to assess proximal vascular access. • All other patients with carotid territory symptoms who would potentially be candidates for carotid re-vascularisation should have early vascular imaging to identify stenosis in the ipsilateral carotid artery. CT angiography (if not already performed as part of assessment for reperfusion therapies), Doppler ultrasound or contrast-enhanced MR angiography are all reasonable options depending on local experience and availability. Weak recommendation New Initial ECG monitoring should be undertaken for all patients with stroke. The duration and mode of monitoring should be guided by individual patient factors but would generally be recommended for at least the first 24 hours. Strong recommendation New For patients with embolic stroke of uncertain source, longer term ECG monitoring (external or implantable) should be used. Weak recommendation Updated Further cardiac investigations should be performed where clarification of stroke aetiology is required after initial investigations. In patients with ischaemic stroke, echocardiography should be considered based on individual patient factors. Transoesophageal echocardiography is more sensitive for suspected valvular, left atrial and aortic arch pathology.
Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of ischemic stroke. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2010 Jun. 70 p.	21.Emergency Department (ED) Diagnostic Evaluation Patients with a history of clinical TIA should be evaluated promptly [R]. The following diagnostic evaluations should typically be performed [C], [D], [R]. The speed and venue of the assessment described below will depend on the currency of the symptoms and the physician's assessment of risk of early recurrence of clinical TIA or the development of stroke. The work group recommends that patients presenting less than 24 hours since initial TIA with high risk symptoms (see Annotation #23, "High Risk for Stroke?") generally not leave the emergency department until the following are completed or scheduled within the next few hours on an inpatient basis. •Laboratory tests •Complete blood count

	•Electrolytes (sodium, potassium, chloride, CO2), blood urea nitrogen (BUN), creatinine, glucose •Prothrombin time/international normalized ratio •Activated partial thromboplastin time (aPTT) •Cardiac biomarkers (troponin) •Electrocardiogram •Brain and vascular imaging •MRI (preferred)/MRA •CT/CTA •CT/carotid ultrasound, if symptoms referable to carotid distribution **Brain Imaging** If the patient is not having symptoms at the time of presentation, a diffusion-weighted MRI (DW-MRI) is preferred, if available. Restricted proton diffusion in the setting of a clinical transient ischemic attack identifies higher risk of stroke. At this time, an MRA of the carotids and intracranial artery can be performed. If MRI is not available, a CT of the head would be indicated and, if feasible, a CTA of the head and neck can also be performed [B], [D], [R]. Another approach for patients with symptoms referable to a carotid territory would be CT of the brain followed by carotid ultrasound as vascular imaging.

Evidence Tables

Initial Evaluation & Early Care

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Neurological Assessment					
Purroy et al. 2012 **Spain** **Prospective study**	NA	1137 patients presenting with symptoms of TIA from 30 centers. Mean age: 68.6 years. Patients with an mRS greater than 3 or non-TIA diagnosis, were excluded.	Patients were prospectively scored on the clinical variables included in the following tools: 1. ABCD 2. ABCD2 3. ABCD2I 4. ABCD (+brain infarction) 5. ABCD3 6. ESRS 7. SPI-II 8. California Scale Each of these tools are used to assess the likelihood of recurrent stroke in patients diagnosed with TIA.	**Primary outcome:** Stroke within 7 days, stroke within 90 days. **Secondary outcomes:** detection of large artery atherosclerosis on imaging.	**Prevalence of recurrent stroke:** 2.6% of patients had a recurrent stroke within 7 days; 3.9% within 90 days. **Stroke within 7 days of index TIA**: The ABCD3 and ABCD3V offered the ability to predict stroke within 7 days of TIA (p=0.004; p<0.001), all others were unable to predict stroke risk beyond chance alone (p>0.05). **Stroke within 90 days of index TIA**: The ABCD3 and ABCD3V offered the ability to predict stroke within 90 days of TIA (p=0.015; p=0.003). All others were unable to predict stroke risk beyond chance alone (p>0.05). **Clinical predictors of stroke within 7 days**: Prior TIA (p<0.001) and large artery atherosclerosis (p=0.003). **Clinical predictors of stroke within 90 days**: Prior TIA (p=0.006), large artery atherosclerosis (p=0.018), and motor weakness (p=0.035).
Giles et al. 2010 **UK** **Systematic Review & Meta-analysis**	NA	18 studies including patients presenting with TIA. Studies that provided non-continuous outcome scores, studies that included TIA mimics, were excluded.	All studies that assessed the ABCD or ABCD2 tools as predictors of recurrent stroke after TIA were included in the review. Sensitivity and specificity were calculated for each tool; AUCs were used to assess predictive ability.	**Outcomes**: Stroke within 7 days, stroke within 90 days.	**Stroke within 7 days**: The ABCD tool had an AUC of 0.72 (0.67 to 0.77); ABCD2 of 0.72 (0.63 to 0.80). **Stroke within 90 days**: the ABCD tool had an AUC of 0.63 (0.57 to 0.69), similar results for the ABCD2. **TIA vs. TIA mimic:** Pooled prediction using the ABCD2 tool, AUC was 0.73 (0.67 to 0.78).
Frankel et al. 2000	NA	312 patients from the placebo arm of the	Data collected at baseline, 2 hours, 24	**Primary outcome:** Poor outcome at 3 months	At 3 months, 47% of patients had a poor outcome at 3 months.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **Retrospective Study**		NINDS trial. Mean age was 65years, 59% were male. Median NIHSS score was 15.	hours, and at 7-10 days was used to identify variables associated with poor outcome (mRS>3 or death), 90-days post stroke		Using baseline data, 2 models were identified with specificity >90% 1) NIHSS>17+ atrial fibrillation: Sensitivity 16%, specificity 99%, + predicative value 96% 2) NIHSS > 17 and NIHSS item 1a (consciousness)>0: Sensitivity 35%, specificity 95%, + predictive value 86% Using 2-hour data, 2 models were identified with specificity >90% 1) NIHSS >26: Sensitivity 18%, specificity 99%, + predicative value 96% 2) NIHSS > 16 + NIHSS motor score total>9: Sensitivity 18%, specificity 99%, + predictive value 96%
Biomarkers					
Kisialiou et al. 2012 **Italy** **Prospective cohort study**	NA	105 patients with diagnosis of ischemic stroke within 24 hours. Mean age: 63.3 years.	Patient's biomarkers were collected on admission: glucose, albumin, TG, TC, LDL, HDL, INR, PTT, platelets, fibrinogen, erythrocyte sedimentation rate (ESR) and their values classified into quintiles (Q1, Q2, Q3 and Q4).	**Outcomes**: Size of ischemic lesion (D1 - <1.5cm; D2 – 1.5 to 3cm; D3 - > 3cm; D4 – non confluent dimensions), location (anterior or posterior), stroke severity (NIHSS). The independent contribution of biomarkers and lesion size and site on admission and with NIHSS scores at day 7 were assessed using regression models controlling for age and sex.	**Size of ischemic lesion:** The odds of having a D1 lesion were higher among patients in Q3 serum albumin (3.4-3.8g/L) vs Q1 (<2.9 g/L): OR= 5.25; 95% CI 1.351 to 20.39) and among patients in TG Q3 (111-162 mg/dL) vs. Q1 (<78 mg/dL), (OR= 9.00; 95% CI 2.48 to 32.56). The odds of having a D2 lesion were significantly lower among patients with serum albumin levels in Q2, Q3 and Q4 (i.e. 2.9->38 g/L) vs. Q1 (<29 g/L) and in TG Q3 (OR=0.132, 95% CI 0.004-0.04). The odds of having a D3 lesion were higher in patients in Q4 ESR (>30 mm) vs. Q1 (<10 mm) (OR= 5.25, 95% CI 1.00-27.5), and a fibrinogen level in Q3 (368-462 mg/dL) vs Q1 (<303 mg/dL) (OR= 5.50, 95% CI 0.003-29.5)). There were no independent predictors of D4 lesions. There were no significant association between lesion site and any blood markers. Higher INR and PTT values were associated with worse outcomes on the NIHSS (≥14; ≥7) (p=0.01; p=0.001). Better outcomes assessed using the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					NIHSS were associated with higher serum albumin levels (p=0.006).
Swallowing					
Lakshminarayan et al. 2010 **USA** **Audit of National Stroke Registry** **(Derived from Dysphagia and Malnutrition Rehabilitation section)**	NA	Records of 18,017 patients admitted and discharged for stroke from 222 hospitals in 6 states from March 1 to Dec 31, 2009, were reviewed.	Patients were identified and classified according to dysphagia screening status: Unscreened Screen/pass Screen/fail Associations between screening status and incidence of pneumonia were explored using adjusted logistic regression.	**Primary outcome:** Pneumonia	Number (%) of patients: Unscreened: 4509 (25%) Screened/pass: 8406 (46.6%) Screened/fail: 5099 (28.3%) Adjusting for age, gender, race, weakness, aphasia and altered level of consciousness, unscreened patients were at higher risk of developing pneumonia compared to patients who passed screening (OR=2.2, 95% CI 1.7 to 2.7).
Middleton et al. 2011 **Australia** **Cluster RCT** **(Derived from Dysphagia and Malnutrition Rehabilitation section)**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	19 large tertiary care facilities with acute stroke units. Patients were eligible if they had been admitted to one of these facilities with a diagnosis of stroke (ischemic or hemorrhagic) within 48 hours.	4,198 patients were randomized to receive care at institutions that had adopted treatment protocols to manage hyperglycemia, fever and swallowing dysfunction (FeSS intervention) or to a control facility. Clinicians at the participating control institutions received abridged guidelines only.	**Primary outcome:** Death or dependency at 90 days (mRS score of ≥2), BI, SF-36 (mental component summary score), physical component summary score. **Secondary outcomes:** Mean temperature for first 72 hours, proportion of swallowing screenings completed within the first 24 hours of admission, pneumonia diagnosis, LOS.	The outcomes of patients who were treated at institutions that had treatment protocols in place had significantly better outcomes (Intervention vs. control group). Death or dependency at 90 days: 42% vs. 585, p=0.002, BI scores ≥95: 69% vs. 60%, p=0.07, Mean SF-36 (physical health): 45.6 vs. 42.5, p=0.002 Swallowing screening was performed more frequently at care protocol sites: 46% vs. 7%, p<0.0001 There was no significant difference in pneumonia incidence: 2% vs. 3%, p=0.82
Seizures					
Procaccianti et al. 2012 **Italy** **Prospective, observational study**	NA	Patients with ischemic (n=1742) and hemorrhagic stroke (n=311) admitted acutely to a single hospital from 2004-2008. Mean age was 82 years, 49% were female. Patients with a history of epilepsy were excluded.	Seizure incidence and independent predictors of early seizures were evaluated	**Primary Outcome:** Occurrence of seizure within 7 days of stroke	The incidence of seizure was 3.2%. Seizures occurred more frequently during the first 24 hours (59%). Seizures occurred in 3.3% of patients with ischemic stroke and in 2.6% of patients with ICH. Seizures were tonic-clonic generalized in 27 patients (41%), focal with automatisms in 6 (9%) and focal motor in 33 (50%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Status epilepticus was diagnosed in 13 patients (0.6% of the entire sample, 19.6% of early seizures). Independent predictors of any seizures were total anterior circulation infarct (OR=2.95, 95% CI 1.67-5.21), hemorrhagic transformation (OR=2.69, 95% CI 1.38-5.24), hyperglycemia (>100 mg/dL, 2.07, 95% CI 1.14-3.78). However, the risk of seizure activity was significantly lower among diabetics presenting with hyperglycemia (OR=0.39, 95% CI 0.38-0.91).
Lamy et al. 2003 **France** **Prospective observational study**	NA	581 patients aged 18-55 with recent cryptogenic ischemic stroke included from 30 European neurology departments. Mean age was 42.5 years,	Seizure incidence and independent predictors of early seizures were evaluated	**Primary outcome:** Seizure occurrence (early-within 24 hours and recurrent)	Mean duration of follow-up was 38 months. Early seizures were documented in 14 patients (2.4%). Of these, 10 (71%) occurred during the first 24 hours of stroke. Two patients developed status epilepticus. Patients were treated with valproic acid (n=5), carbamazepine (n=2) and phenytoin (n=1). Baseline Rankin scale ≥3 (OR= 3.9, 95%, CI 1.2 to 12.7) and cortical involvement (OR= 7.7, 95% CI 1.0 to 61.1) were independently predictors of early seizure occurrence.
Van Tuijl et al. 2011 **UK** **RCT** **(Derived from acute seizure management section)**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑	16 stroke patients from a neurology department were enrolled in the study. Patients with lobar intracerebral hemorrhage or ischemic stroke, with a cortical syndrome and a mRS≥3 or National Institute of Health Stroke Severity (NIHSS) ≥6 were included. Participants with previous history of epilepsy or history of antiepileptic medication use were excluded.	Participants were randomized to receive levetiracetam (250-700mg BID, n=9) or placebo (n=6). The total treatment time was 14 weeks and 3 days. Follow up assessments took place at 1, 6, 16, and 52 weeks after enrollment in the study. Phone call follow ups were completed at weeks 26 and 39 to ask about seizure occurrence.	**Primary Outcome:** First late epileptic seizure (>1-week post stroke). **Secondary Outcome:** Time to event (time between stroke and seizure), occurrence of early seizure (<7 days' post stroke), seizure severity, neurological and neurocognitive function, handicap score, quality of life, and medication side effects.	The trial fell far short of its recruitment of goal of 200 participants per arm. No data analysis was conducted.

Neurovascular Imaging

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Menon et al. 2015 **Canada** **RCT (Secondary analysis of IMS III trial)**	NA	185 patients who had an M1 MCA with/without intracranial internal artery occlusion, whose baseline collateral status could be measured. 59 patients had been randomized to t-PA and 126 to endovascular treatment.	Collateral status was assessed using 3 methods (Score 1: the Regional Collateral Scoring system, Score 2: the Sylvain Sulcus & Cerebral Convexity Collateral Score and Score 3: the MCA Territory Collateral Score). The scores from each system were classified as good, intermediate and poor. Multivariable modeling was conducted to determine predictors of a good outcome based on baseline collateral status and treatment type (t-PA vs. endovascular)	**Primary outcome:** Good outcome at 90 days (mRS 0-2) **Secondary outcomes:** mRS scores 0-1 at 90 days, shift in mRS scores	The percentages of patients with good outcomes by collateral status at 90 days were: Scoring system 1 Good 37.8%, Intermediate 32.4% Poor 29.7% Scoring system 2 Good 39.5% Intermediate 46.5% Poor 14.1% Scoring system 3 Good 47.5% Intermediate 25.4% Poor 27.0% Significant predictors of a good outcome at 90 days were collateral scores (all) and baseline NIHSS. Treatment type was not a significant predictor. Treatment type was a significant predictor of mRS score of 0-1 at 90 days using scoring systems 1 and 2.
Frolich et al. 2014 **Germany** **Retrospective study**	NA	82 patients who received endovascular treatment from 2009-2012 who had received a 4-dimensional CTA. Mean age was 73 years. 62% were women. Median NIHSS score was 17.	Collateral flow was measured using the regional leptomeningeal score (rLMC). Images from early, peak and late phases, temporally fused maximum intensity projections (tMIP) and single-phase CTA (spCTA) were obtained.	**Primary outcome:** To determine which acquisition phase best depicts collaterals and predicts outcome (good outcome at 90 days, mRS 0-2).	26 patients had a good outcome, 56 had a poor outcome. Collaterals were best visualized using 4D CTA tMIP (median rLMC score 19.0 vs. 14.0 for single phase CTA, 5.0 for 4D CTA [early phase] and 11.0 for 4D CTA [late phase]). There were no significant differences between groups (good vs. poor outcome) in the median rLMC scores based on 4D CTA early phase (5.0 vs. 4.5, p=0.144) or 4D CTA peak phase imaging (12.5 vs. 11.0, p=0.052). The median rLMC scores were significantly higher for patients with a good outcome based on 4D CTA

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					tMIP images (20.0 vs.18.8, p=0.011) and spCTA (15.0 vs. 13.0, p=0.012) Baseline NIHSS score and CBV-ASPECTS were the only significant predictors of good functional outcome.
Brunser et al. 2013 **Chile** **Observational study**	NA	842 patients admitted to the emergency department with a suspected ischemic stroke.	Diffusion-weighted imaging (DWI) examinations were performed for all patients using a 1.5-Tesla Signa whole-body scanner. Patients were diagnosed with ischemic stroke or as a stroke mimic on the basis of clinical examination and neuroimaging.	**Primary outcome:** Sensitivity and specificity of DWI in detecting ischemic stroke.	729 participants received a final diagnosis of ischemic stroke, whereas 113 were categorized as stroke mimics. Of the 609 stroke patients who underwent DWI, 551 (90.4%) had an image compatible with stroke, as compared to 3 of the 103 (2.9%) of the stroke mimics who underwent DWI. For patients with suspected stroke, the sensitivity of DWI in detecting ischemic stroke was 90% (95% CI 87.9 to 92.6), and specificity was 97% (95% CI 91.8 to 99.0).
Bal et al. 2012 **Canada** **Retrospective study**	NA	850 patients admitted to a single institution who had received thrombolytic therapy from 1996-2009.	2 cohorts were created, matched for age, sex and baseline serum glucose and compared. Cohort 1 included patients admitted from 1996-2002 (n=297) who received only non-contrast CT imaging and cohort 2, 504 patients admitted from 2004-2009 who received CTA.	**Outcomes:** Treatment times, independent predictors of door-to-needle times.	The median onset to-needle time was significantly longer in cohort 2 patients, 61 vs. 55 minutes, p<0.01. There were no significant differences in median door-to needle time or onset-to-needle times, 67 vs. 62.5 minutes and 139 vs. 141.5 minutes, respectively. Significant predictors of door-to-needle time were increasing age (decrease of 5.4 minutes/decade of age) and onset-to-door time (increase of 4.0 minutes/30 minute delay)
Brazzelli et al. 2009 **UK** **Cochrane Review**	NA	8 studies met the inclusion criteria (7 of the 8 evaluated CT and MRI (DWI – diffusion weighted) for ischemic stroke and 2 of the 8 studies evaluated MRI for hemorrhagic stroke). A total of 226 patients were included. Mean age was 65.1 yrs.	All studies that compared the diagnostic accuracy of MRI and CT for either ischemic or hemorrhagic stroke were included in the review.	**Outcomes**: Sensitivity and specificity of the diagnostic tests reported separately for diagnosing ischemic stroke and hemorrhagic stroke.	**Diagnosis of Ischemic stroke (DWI and CT):** **DWI**: Sensitivity 0.99 (95% CI 0.23 to 1.00); Specificity 0.92 (95% CI 0.83 to 0.97). **CT**: Sensitivity 0.39 (95% CI 0.16 to 0.69); Specificity 1.00 (95% CI 0.94 to 1.00). **Diagnosis of Hemorrhagic stroke (MRI – DWI and GRE):** **DWI**: (1 study) Sensitivity: 1.00 (95% CI 0.91 to 1.00); Specificity: 1.00 (95% CI 0.91 to 1.00).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					GRE/DWI: (1 study) Sensitivity: 0.83 (0.52 to 0.98); Specificity: 1.00 (95% CI 0.95 to 1.00). **GRE**: (1 study) Sensitivity: 1.00 (0.91 to 1.00); Specificity: 0.98 (0.87 to 1.00). Cautions: Authors indicate the presence of possible selection bias of patients. Most studies did not include patients who were "stroke mimics". This may explain the high specificity and question the usefulness of the findings.
Coutts et al. 2009 **Canada** **Retrospective study**	NA	457 patients who received a CT/CTA within the first 24 hours, with pre-morbid independence (mRS≤1), and sufficient neurological functioning at admission (NIHSS ≤3). Mean age: 63 years (79% of patients had a final diagnosis of minor stroke or TIA) who were referred to an acute stroke center for suspected minor stroke or TIA and had a CT/CTA performed.	Imagining interpretation: CT: presence of acute stroke (Y/N) CTA: intracranial occlusion (no/mild atherosclerosis or more than 50% occlusion), and extracranial occlusion (no/mild occlusion or more than 50% occlusion). A composite measure of CT/CTA status included the presence of any of the three aforementioned imaging results.	**Primary outcome**: Functional status at 90 days (mRS≥2). If functional status was not available, discharge destination was used to classify patients as good or poor functioning.	Patients had a greater risk of poor outcome if there was evidence of an acute stroke on CT (RR= 2.98, 95% CI 1.82-4.89; p=0.0001), had an intracranial vessel occlusion or greater than 50% stenosis (RR= 2.71; 95% CI 1.64-4.47; p=0.0006) or if they had any one or more positive CT/CTA parameters (RR= 2.92; 95% CI 1.81-4.71; p=0.0001). The presence of an extracranial occlusion was not statistically significant of poor outcome (p=0.054). Age > 60 years, having a positive indication on at least one of the CT/CTA parameters and an NIHSS score of 3 or less were all predictors of 90-day disability.
Oppenheim et al. 2005 **France** **Retrospective study**	NA	86 patients with known time of stroke onset, specific stroke severity (≥3 on the NIHSS), who had received an MRI as part of initial investigations. Mean age was 69 years.	5 different MR image sequences were reviewed by 3 specialists (2 radiologists and 1 neurologist): T_1, GRE, FLAIR, t_2-EPI and DWI for each patient. Before review by the specialists, images were arranged in random order. Each sequence was classified by each reviewer as either: ICH or non-ICH.	**Outcomes**: Sensitivity and specificity of each MR sequence; intra-observer and inter-observer agreement with respect to identifying sequences as ICH or non-ICH were calculated using kappa.	43 patients were diagnosed with ICH, 43 were non-ICH **Sensitivity and specificity:** GRE: Sensitivity 100%; Specificity: 95 to 97.5% T_1: Sensitivity 97.3% to 100%; specificity: 97.4% to 100% FLAIR: Sensitivity 100%; Specificity 100% t_2-EPI: Sensitivity 100%; Specificity 100% DWI: Sensitivity 100%; Specificity 100% **Intra-observer Agreement**: All 5 sequences: k=1 (perfect agreement) **Inter-observer Agreement**:

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			The diagnostic standard used was multisequence MRI		GRE: k=0.98 to 1 T_1: k=0.95 to 1 FLAIR: k=1 t_2-EPI: k=1 DWI: k=1 **Study limitations:** Comparison diagnostic was multisequence MRI, not compared to CT. Only the diagnostic accuracy of the tools for diagnosis of ICH patterns was studied.
Wardlaw et al. 2004 **UK** **Cost-effectiveness analysis**	NA	1000 patients aged 70-74 years (repeated using data from other age groups: 60-64 years and 80-84 years).	A comparison of 12 imaging strategies was conducted in the form of a cost-effectiveness analysis with the comparator strategy being scanning all patients within 48 hours of admission.	**Costs**: Derived from National Health Service Data from 2000. These data included cost of CT scan and cost of inpatient stay. **QALYs**: According to being independent, dependent or dead at 6, 12, and 24 months after stroke: Number of life years (derived from the stroke registry – mean survival based on stroke classification and age) X Weights (derived from the EQ5D of the stroke registry based on age and functional status at 18 months).	**Dominant Imaging Strategy**: "CT Scan for all patients immediately" An immediate scan results in the lowest length of stay in hospital and therefore outweighs the additional cost of off-hour CT scans.
Douglas et al. 2003 **US** **Retrospective study**	NA	322 patients with a diagnosed TIA and a completed CT scan within 48 hours were included. 81% of patients were older than 60 years	Patient charts were reviewed for the presence of abnormal findings on the CT scan at admission (old or new infarct, periventricular white-matter disease, atrophy, vascular calcification) and for any events occurring within 90 days.	**Primary outcome**: Occurrence of stroke within 90 days of admission to emergency department for TIA.	Incidence of stroke following a TIA: 52 patients (10.9%). Adjusted Analysis: (adjusted for age, length of TIA, symptoms in the emergency room). **Risk of stroke:** CT scan indicated the presence of a new infarct in 13 (4%) of patients and an old infarct in 69 (21%) of patients. For those patients indicated as having a new infarct, there was a greater chance of subsequent stroke within 90 days (OR= 4.06, 95% CI 1.16-14.14, p=0.028). For patients with an old infarct on CT scan, the change of having a stroke within 90-days was not statistically significant (p=0.58). Likewise, other abnormal CT findings such

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					as periventricular white-matter disease, atrophy and vascular calcification were not found to be statistically significantly associated with stroke within 90 days (p=0.92; p=0.79; p=0.97).

Cardiovascular Investigations

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sposato et al. 2015 **Canada** **Systematic review & meta-analysis**	NA	50 studies, estimating the proportion of patients diagnosed with atrial fibrillation following stroke or TIA, using 8 diagnostic methods: admission ECG, serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, Holter monitoring, mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording. Mean age of included patients was 67 years, 57% were men.	Sub groups of studies were formed based on 4 phases of cardiac monitoring: emergency room, in-hospital, first ambulatory period and second ambulatory period.	**Primary outcome:** Proportion of patients diagnosed with post-stroke AF	The results from the 11 studies (n=2,896) that initiated investigations during the Emergency room (phase 1), which an ECG, reported an estimated 7.7% (95% CI 5.0-10.8%) of patients were diagnosed with AF.
Grond et al. 2013 **Germany** **Cohort Study**	NA	1135 consecutively admitted patients with stroke or TIA with no known atrial fibrillation.	All patients underwent 72-hour Holter ECG monitoring using a 3-lead Holter device. Monitoring was initiated within 12 hours of hospital admission.	Diagnosis of atrial fibrillation (defined as one or more 30 second periods of absolute arrhythmia without detectable P-waves or patterns more consistent with another diagnosis).	Of the 1135 participants, 49 (4.3%, 95% CI 3.4% to 5.2%) were diagnosed with atrial fibrillation, corresponding to a number needed to screen to detect 1 patient with silent AF of 23 (95% CI 15 to 31). The rate of detection did not differ significantly between the first 24 hours and the last 48 hours (2.6% vs. 1.8%). The number needed to screen for 25 to 78 hours to detect 1 patient with silent AF not detected during 24-hour monitoring was 55 (95% CI 35 to 123).
Lazzaro et al. 2012	NA	133 consecutively admitted patients with	All participants underwent ECG at admission, during	Detection of atrial fibrillation.	Holter monitoring and CCT was performed for a mean of 29.8 and 73.6 hours per patient,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
US **Observational study**		stroke or TIA who underwent concurrent Holter and continuous cardiac telemetry (CCT) evaluation during hospitalization with no previous history of AF.	which AF was not detected. CCT was performed throughout hospitalization. Holter monitoring was used for at least 24 hours (except for 3 patients who were evaluated for 7, 16, and 22 hours).		respectively. A significantly higher rate of AF was detected by Holter monitoring than be CCT (6 vs. 0%, p=0.008). AF was diagnosed by Holter monitoring in 5 out of 53 (9.4%) patients initially diagnosed with cryptogenic stroke.
Suissa et al. 2012 **France** **Prospective cohort study**	NA	946 patients with ischemic stroke without history of AF were included (354 in conventional stroke unit care; 592 in intensive stroke unit care). Mean age was 62.6 years	Patients were enrolled into either intensive stroke unit care (with continuous cardiac monitoring initiated on admission) or conventional stroke unit care (baseline ECG, 24-hour Holter monitor and additional ECGs when necessary) (admission to either unit were based on neurologist's evaluation).	Detection of atrial fibrillation.	New cases of AF were identified more often in the continuous cardiac monitoring group (14.9% vs. 2.3%). Patients in the continuous cardiac monitoring group were more likely to be identified with AF (adj OR= 5.29; 95% CI 2.43 to 11.55). The odds of detection were greatest within the first 24 hours (OR= 9.82; 95% CI 3.01 to 32.07). Key points: Continuous monitoring for potential AF diagnosis is important, as not all cases are evident at baseline. The greatest detection was within the first 24 hours after stroke.
Douen et al. 2008 **Canada** **Retrospective study**	N/A	144 patients admitted to a single institution over a 8.5-month period with acute ischemic stroke	Rates of AF detection were compared between the use of serial ECGs (up to 72 hours after admission) and a Holter monitor in an inpatient stroke unit setting.	Detection of atrial fibrillation.	143 studies were performed. 126 patients who received both ECG and Holter studies. AF was detected in 24 (16.8%) cases. Of these, there were 9 cases (6.3%) in which there was a baseline history of AF. Therefore, 15 new cases of AF were found. Seven new cases were detected based on admission ECG, and 8 more cases were detected by ECGs conducted over the next 72 hours. Holter monitoring detected AF in 50% (6 of 12) of ECG-positive AF cases. (3 patients did not receive Holter monitoring), while ECG detected AF in 67% (6/9) Holter monitoring positive AF cases. There was no significant difference in detection rates between cardiac monitoring groups. AF was identified in 15 new patients using serial ECG and in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					9 new patients using a Holter monitor. The majority of these cases were identified within 72 hours (83%).
Liao et al. 2007 **Canada** **Systematic Review**	NA	5 studies including 736 patients without a previous diagnosis of atrial fibrillation (AF), diagnosed with ischemic stroke or TIA, who received cardiac monitoring for at least 12 hours.	All studies that evaluated noninvasive cardiac monitoring in patients post stroke.	Detection of atrial fibrillation.	No RCTs were identified for the review. Cardiac monitoring was initiated at variable time points, but ranged between admission to a ward, and 55 days after admission to hospital. All cardiac monitoring involved the use of a Holter monitor. Some studies also used an event loop recorder. Combined detection of AF in 4.6% (95% CI 0% to 12.7%) of patients.
de Bruijn et al. 2006 **Netherlands** **Prospective study**	NA	231 patients with recent stroke (all types) or TIA were enrolled. Only patients who after initial ECG, ultrasound assessments and blood tests were performed still had an unknown cause. 192 patients were greater than 45 years; 39 patients were less than or equal to 45 years.	All patients had a transesophageal echocardiography (TEE) followed by a transthoracic echocardiography (TTE). Identification of major and minor cardiac sources of embolism were compared between the two diagnostic tools.	**Outcomes**: Potential and major cardiac sources of embolism.	**Prevalence of potential sources of embolism**: A potential cardiac source of embolism was found in 55% (127/231) of patients and a major risk factor; was identified in 20% (46/231). **Comparison of TTE and TEE:** The detection of possible cardiac sources of embolism was significantly greater using TEE compared to TTE. Among all patients, a potential cardiac source was identified in 16% of patients (TTE+, TEE+) and a major risk factor was identified in 3% of patients (TTE+, TEE+). Significantly more abnormalities were identified using TEE Cardiac source: 39% (90/231) where TEE +, TTE- Major risk factor: 16% (38/231) where TEE +, TTE- The identification of major risk factors was independent of age (≤45 years vs. >45 years, p=0.224).

Acute Blood Pressure Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews					
Bath & Krishnan	NA	26 trials with 17,011	Studies evaluating single	**Primary Outcome**:	**Blood Pressure Lowering**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2014 **UK** **Cochrane Review**		participants, 18 years of age or older, diagnosed with either ischemic or hemorrhagic stroke, excluding SAH.	or multiple agents of deliberate blood pressure lowering or elevation in acute stroke, regardless of dosage or route of treatment, compared against placebo or open control. The most commonly used agents used to lower blood pressure were: Angiotensin receptor antagonist (ARA), n=6 trials; Angiotensin converting enzyme-inhibitor (ACE-I), n=5 trials, Nitric oxide (NO) donor, n= 5 trials; Calcium channel blocker (CCB), n=3 trials. A single trial aimed to raise blood pressure. The timing of interventions: within 4 hours of stroke onset, n=2 trials, < 6 hours post stroke, n=2 trials, <48 hours, n=11 trials, <168 hours, n=10 trials. Participants were treated for varying lengths of time, ranging from 1 day to 2.5 years. Treatment for 7-12 days was most frequently reported (n=13 trials)	Death or dependency (mRS> 2 (or >3, when available) at least one month after stroke **Secondary outcomes:** Early and late case fatality, neurologic deterioration, blood pressure and heart rate. Assessment time points: 24 hours after randomization (blood pressure and heart rate), within 7 days (blood pressure) within one month (mortality, neurologic deterioration), after one month.	When the results of all trials were combined, there was no significant reduction in the risk of death or dependency within one month (OR= 0.98, 95% CI 0.92 to 1.05). The reductions in risk were not significant in stratified analysis of type of agent, timing of initiation of treatment, stroke type, stroke location. Blood pressure lowering did not reduce the risk of early or late case fatality, or early neurological deterioration The use of antihypertensive agents was associated with significant reductions in SBP and DBP at first measurement post randomization, day 1, day 7 and the end of treatment. **Blood Pressure Elevation** Only a single trial using Phenylephrine examined the effects of increasing blood pressure. There were no significant changes in SBP or DSP observed.
Greganage & Bath 2009 **UK**	NA	37 trials, including 9008 patients aged ≥18 yrs, with ischemic stroke and intracerebral	All randomized controlled trials assessing an intervention that is expected to modify blood	**Outcomes:** Mortality, dependency (Barthel Index score 0 to 55; Rankin Score 3 to 5), blood	A decrease in blood pressure of 8mm Hg resulted in the lowest odds of death within one month (OR= 0.87; 95% CI 0.54 to 1.23).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Meta regression		hemorrhage, excluding SAH.	pressure within one week of acute stroke were included. Analysis involved the use of meta regression to explore the relationship between outcome and changes in blood pressure and define the most optimal level of change. **Drug classes:** 1. ACE inhibitors; 2. ARAs; 3. B receptor agonists; 4. Calcium channel blockers; 5. Basic fibroblast growth factor; 6. Hemoglobin analogue; 7. Magnesium sulfate; 8. Naftidrofuryl; 9. NO donors; 10. Piracetam; 11. Prostacyclin; 12. Phenylephrine; 13. Mixed antihypertensive therapy.	pressure. Assessment time points: Baseline (blood pressure), during treatment (blood pressure), within 1 month (mortality), end of trial (mortality and dependency).	A decrease in blood pressure of 14.4mm Hg resulted in the lowest odds of death at the end of follow-up (OR=0.96; 95% CI 0.31 to 1.65). A decrease in blood pressure of 14.6mm Hg resulted in the lowest odds of death or dependency at the end of follow-up (OR= 0.95; 95% CI 0.11 to 1.72). “U and J shaped relationships” were seen between change in blood pressure and all outcomes (mortality within one month, mortality at the end of follow-up and death or dependency at follow-up).
Geeganage & Bath 2010 **UK** **Cochrane Review**	NA	43 trials, which included 7649 patients, aged ≥18 yrs, with either ischemic or hemorrhagic stroke, excluding SAH.	All randomized and quasi-randomized trials that included the use of a vasoactive drug used within one week of an acute stroke were included.	**Outcomes**: Mortality, dependency (BI or 0-55 or mRS 3-5), blood pressure, heart rate, length of hospital stay, discharge destination, presence of hypotension. Assessment time points: End of trial (mortality, dependency), within one month (mortality), less than 24 hours and 24-72 hours (blood pressure and heart rate).	**Blood pressure lowering therapy** The use of vasoactive drugs was not associated with the reduced risk of early death, death at the end of follow-up, early death or deterioration, or death or dependency at the end of the trial. Treatment was associated with significant early and late reductions in SBP and DBP **Blood pressure elevation therapy** The use of vasoactive drugs was not associated with the reduced risk of death, but for patients receiving diaspirin cross-linked hemoglobin (DCLHb), there was a significant increase in the odds of death or disability at the end of the trial (OR= 5.41; 95% CI 1.87 to 15.64).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Treatment was associated with early increases in SBP (MD= 15.82, 95% CI 5.10- 26.54 mm Hg), but not DBP.
Clinical Trials					
Oh et al. 2015 **Korea** **RCT** ***Valsartan Efficacy oN modest blood pressure Reduction in acute ischemic stroke (VENTURE)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	393 patients with acute ischemic stroke presenting to hospital within 24 hours of symptom onset with SBP 150-185 mm Hg were included. Patients undergoing thrombolytic treatment and those with contraindications to ARBs, were excluded. Mean age was 65 years, 59% were male, median NIHSS score was 3.	Patients were randomized 1:1 to undergo blood pressure reduction with valsartan (starting dose of 80 mg/day with modifications, as required) with a target decrease of 15% or 145 mm Hg, or to a no treatment control condition, for 7 days. All patients were treated according to current guidelines.	**Primary outcome:** Death or dependency (mRS>3) at day 90. **Secondary outcomes:** Composite outcome of nonfatal stroke, nonfatal MI and vascular death at 90 days, NIHSS sore and BI scores at 90 days **Safety outcome:** Early neurological deterioration during 7-day treatment period.	There was no significant difference between groups in the risk of the primary outcome (24.6% valsartan vs. 22.6% control; OR=1.11, 95% CI 0.69-1.79, p=0.67). There was no significant difference between groups in the risk of the composite secondary outcome (3.7% valsartan vs. 2.7% control; OR=1.41, 95% CI 0.44-4.49, p=0.77). There were no differences between groups in the risks of recurrent stroke, MI, vascular death or death from any cause. Patients in the valsartan group were significantly more likely to experience early neurological worsening within the treatment period (16.6% vs. 7.6%; OR=2.43, 95% CI 1.25-4.73, p=0.008). Complete follow-up was available for 372 (95%) patients.
Bath et al. 2015 **UK** **RCT** ***Efficacy of Nitric Oxide in Stroke (ENOS)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	4011 patients with recent ischemic or hemorrhagic stroke, >18 years, with a motor deficit in the arm or leg or both with a SBP of 140-220 mm Hg who could be treated within 48 hours of stroke onset. (Patients who received treatment with t-PA, were eligible to participate). Mean age: 70 years.36% of patients were men.	Patients were randomized to receive transdermal glycerin trinitate (5 mg, n=2000), or no glycerin trinitate (n=2011) for 7 days. A subset of 2097 patients who had been taking antihypertensive medications prior to stroke were also randomized to continue taking their BP meds (n=1057) or to discontinue them (n=1044) for 7 days.	**Primary outcome:** Distribution of mRS scores at day 90. **Secondary outcomes (day 7):** Mortality, recurrent stroke, neurological deterioration, symptomatic ICH, headache, hypotension, hypertension, serious adverse event **Secondary outcomes (day 90):** Poor outcome (mRS 0-2), mortality, death or institutionalization, Barthel Index, EQ-VAS	Mean baseline blood pressure was similar between groups (167/90 mm Hg). At day 1, the mean BP of patients in the intervention group was significantly lower by 7 (systolic) and 3.5 (diastolic) mm Hg compared with the control group (p<0.0001). The differences between groups disappeared by day 3. The distribution of mRS scores did not differ significantly between groups (OR for worse outcome for treatment group=1.01, 95% CI 0.91-1.13, p=0.83). In sub-group analysis, the intervention was associated with significantly increased odds of improvement in functional outcome at day 90 among women and in those treated <6 hours. Age (≤ 70 vs. > 70 years), a history of hypertension, stroke, stroke type, atrial fibrillation, treatment with

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					t-PA stroke severity and use of pre-stroke antihypertensive medications were not significantly associated with outcome. The odds of headache or hypotension at day 7 were significantly increased among patients in the intervention group. At day 90, there were no significant differences between groups on any of the secondary outcomes. Among the subgroup of patients who continued their medications, the odds of being dead or institutionalized at discharge and being dependent at day 90 (BI score <60) were significantly higher. Among the subgroup of patients who stopped taking their antihypertensive medication, the odds of hypertension occurring during the study period were significantly higher. The number of serious adverse events did not differ significantly between groups at days 7 or 90.
Berge et al. 2015 **International** **Additional analysis from *International Stroke Trial (IST*)**	NA	3,035 patients (53% >80 years), symptoms and signs of clinically definite acute stroke; the time of stroke onset was known; treatment could be started within 6 hours of onset, CT/MRI confirmation.	For all patients, blood pressures were measured at randomization, at the start of treatment and at 30 minutes, 1 hour and 24 hours. The association between change in SBP and blood pressure-lowering treatment within the first 24 hours and early adverse events was examined.	**Early adverse events:** Symptomatic infarct swelling, symptomatic ICH, neurological deterioration not due to swelling or ICH, early ischemic stroke, any early adverse event and early death **6-month outcome:** Poor functional outcome (Oxford Handicap Scale score 3-6)	Median SBP were 155 and 156 mm Hg in the t-PA and control groups, respectively. The mean SBP of patients who experienced a symptomatic ICH (4.0%) or any early adverse event (19.3%) within 24 hours was significantly higher compared to those within any adverse events (162 vs. 159 mm Hg, OR per 10 mm Hg increments =1.10, 95% CI 1.02-1.19, p=0.015, and 162 vs. 159 mm Hg, OR per 10 mm Hg increments =1.05, 95% CI 1.01-1.09, p=0.016). Patients who experienced greater blood pressure variability (expressed as standard deviation units) were more likely to suffer an early ischemic stroke or early death (14.7 vs. 13.4 mm Hg; OR per 10 mm Hg increments =1.22, 95% CI 1.07-1.38, p=0.003 and 15.4 vs. 13.5 mm Hg, OR per 10 mm Hg increments =1.36, 95% CI 1.15-1.61, p=0.001, respectively). Patients who experienced a greater mean change

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					in SBP were less likely to suffer a symptomatic ICH (-14.2 vs. -12.2 mm Hg, OR per 10 mm Hg increments =0.90, 95% 0.82-0.99, p=0.037) CI 1.07-1.38) and were less likely to have a poor outcome at 6 months (-17.5 vs. -12.2 mm Hg, OR per 10 mm Hg increments =0.93, 95% 0.89-0.97, p=0.001). The use of blood-pressure lowering agents during the first 24 hours was associated with reduced odds of a poor outcome at 6 months (OR=0.78, 95% CI 0.65-0.78, p=0.007).
He et al. 2014 **China** **RCT** ***China Antihypertensive Trial in Acute Ischemic Stroke (CATIS)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	4071 patients with acute ischemic stroke (within 48 hrs, aged >22 yrs, with systolic blood pressure between 140 and 220 mg Hg.	Participants were randomized to either receive (n=2038) or not receive (n=2033) antihypertensive therapy during hospitalization. Target blood pressure for the treatment condition was a reduction of 10-25% within 24 hours and a target level of 140/90 mm Hg within 7 days, which was to be maintained throughout hospitalization.	**Primary outcome**: Combined death or major disability (modified Rankin Scale >2) at 14 days post-study entry or hospital discharge (whichever came first). **Secondary outcome**: Combined death or major disability, and vascular disease events at 3-month follow-up.	At 7 days post-randomization, mean systolic blood pressure was significantly lower among patients in the intervention group (137.3 vs. 146 mm, p<0.001). Target blood pressure was achieved by 65.7% and 72.0% of those in the active treatment group at 7- and 14-days post-randomization, respectively. Treatment was not associated with significant reduction in the risk of death or major disability at either 14-days (OR= 1.00, 95% CI 0.88 to 1.14) or 3-months (OR= 0.99, 95% CI 0.86 to 1.15) following study entry. **Lost to follow-up**: Treatment=50 (2.5%); control=46 (2.0%).
Sandset et al. 2011 **Hornslien et al. 2015 (Long-term follow-up)** **Norway** **Multicenter RCT** ***Scandinavian Candesartan Acute Stroke Trial (SCAST)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,029 patients admitted to hospital within 30 hours of acute stroke (either ischemic or hemorrhagic), with systolic blood pressure (SBP) of ≥ 130 mmHg. Mean age was 71 years. Mean baseline blood pressure was 171/90mmHg	Patients were allocated to either intervention (candesartan, n=1017) or control (placebo, n-1012). Treatment was administrated for 7 days on a specified dosing regimen (with gradual increase in dose). Blood pressure was measured two times before randomization (within 10 minutes of each other) and then once daily thereafter for a	**Primary outcome**: Composite endpoint of vascular death or non-fatal MI, non-fatal stroke during the first 6 months; and functional status at 6 months (mRS) **Secondary outcomes**: All-cause mortality, vascular death, stroke, MI, neurological status at day 7 (SSS) and performance on ADL (BI)	During the 7-day treatment period, mean blood pressures were significantly lower in patients in the candesartan group (147/82 vs. 152/84 mm Hg, p<0.0001). The risk of the composite vascular endpoint did not differ between (candesartan, 120 events, vs placebo, 111 events; adjusted HR=1.09, 95% CI 0.84–1.41; p=0.52). There was a shift in mRS suggesting that the risk of a poor outcome was significantly higher in the candesartan group (adjusted common HR=1.01, 95% CI 1.00-1.38, p=0.048. There were no significant differences in the risk of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			period of 7 days.		any of the secondary outcome with the exception of stroke progression, which was significantly higher in the candesartan group (RR=1.47, 95% CI 1.01-2.13, p=0.040. Adverse events: There were no significant differences between groups during follow-up in the numbers of episodes of symptomatic hypotension (9 vs. 5) or renal failure (18 vs. 13). **Long-term follow-up** Data were available for 1,256/1,286 patients (98%). At the end of 3-year of follow-up, there was no significant difference between groups in the risk of the primary outcome (28% vs. 33%, HR=0.87, 95% CI 0.71-1.07, p=0.19). There was no significant difference between groups in the risk of stroke (16.9% vs. 20.5%, HR=0.83, 95% CI 0.64-1.07, p=0.15) or the severity of stroke (adjusted common OR=0.78, 95% CI 0.59-1.04, p=0.09). There was no significant difference between groups in the risk of all-cause mortality (17.9% vs. 18.8%, HR=1.00, 95% CI 0.77-1.30, p=1.00).
Ahmed et al. 2009 **Sweden** **Retrospective study**	NA	11,080 patients included in the SITS-ISTR study with ischemic stroke and treated with thrombolysis. Median age was 70 years	Patients were classified into one of four groups according to pre-morbid hypertension and use of antihypertensive therapy within 7 days of receiving thrombolysis. **Group 1**: Hx of hypertension and antihypertensive therapy **Group 2**: Hx of hypertension and no antihypertensive therapy **Group 3**: No Hx of hypertension and antihypertensive therapy	**Outcomes**: Symptomatic intracerebral hemorrhage (defined as: ≥4 points on the NIHSS or death within 24 hours); any symptomatic hemorrhage (defined as: any decrease in NIHSS score or death within 7 days); death (mRS=6); dependence (mRS=0-2). Blood pressure was measured at 2 hours, and 24 hours post-thrombolysis. Change in blood pressure taken as an average of the 2	*Adjusted analysis: (blood pressure as a continuous variable). Symptomatic intracerebral hemorrhage, symptomatic hemorrhage, mortality at 3 months and dependence at 3 months were all associated with high SBP, 2-24 hours after thrombolysis (p<0.0001) For patients with a history of hypertension, mortality was higher for patients not treated with antihypertensives (p<0.0001) and independence was lower (p=0.0002). For patients with no history of hypertension, mortality was higher for patients not treated with antihypertensives (p<0.0001). No significant difference was found with respect to independence

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			Group 4: No Hx of hypertension and no antihypertensive therapy. Analysis was based on comparing outcomes between Group 1 and 2 and between Groups 3 and 4.	and 24-hour readings. Assessment time points: variable time points after thrombolysis (imaging for hemorrhage), 2 hours (NIHSS), 24 hours (NIHSS), 7 days (NIHSS), 3 months (mRS).	at 3 months (p=0.29).
Schrader et al. 2003 **Germany** **RCT** ***Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☒	342 patients admitted with acute disabling stroke, excluding intracranial hemorrhages, with hypertension requiring treatment. Mean age was 68.3 years (treatment group) & 67.8 years (placebo group)	Patients were randomized to receive either 4 mg/day candesartan cilexetil (n=175) or a placebo (n=167) on day one post-stroke. On day 2, dosages in the treatment group were increased targeting a blood pressure reduction of 10 – 15% in 24 hours. After 7 days, patients exhibiting a hypertensive profile were given either more candesartan or an additional hypertensive drug. Members of the placebo group exhibiting hypertension were given candesartan targeted to lower blood pressure to beginning on day 7 following admission.	**Primary outcome:** Death or disability 3 months post stroke **Secondary outcomes:** Combined secondary end point included overall mortality and cerebrovascular and cardiovascular events occurring within the study period	Trial was stopped prematurely (planned recruitment was 500) Follow-up examinations were undertaken at 3, 6 and 12 months. At outset, during the first 7 days (placebo-controlled phase) and throughout the subsequent 12 months, there was no significant difference in blood pressure between the two groups. Over the 12-month follow-up, there were significantly fewer vascular events in the intervention group (9.8% vs. 18.7%, p=0.026) and fewer deaths (2.9% vs. 7.2%, p=0.07). The odds of death or vascular events were significantly lower in the intervention group (OR=0.48, 95% CI 0.52-0.90). There were 13 cerebrovascular events in the treatment group vs. 19 in the placebo group.
Hypertension and Thrombolysis					
NCT01422616 ***ENCHANTED (Blood pressure-lowering arm)*** **International** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,300 (planned) patients ≥18 years, with acute ischemic stroke, eligible to received t-PA within 4.5 hours of stroke onset, who have SBP ≤185 mmHg. Additional criteria specific to BP arm of trial	Patients were randomized to an intensive SBP lowering group, with target BPs of 130– 140 mmHg, achieved within 60-minutes of randomization, which were to be maintained for ≥ 72 hrs, or hospital discharge, or	**Primary outcome:** Death or disability (mRS 2-6) at 90 days **Secondary outcome:** Any ICH	TBA

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		included patients who will (or have) received intravenous t-PA, with a sustained SBP ≥150 mm Hg, and able to begin intensive treatment within 6 hours of stroke onset.	death; or guideline-recommended BP lowering group with target SBP < 180 mmHg, after commencement of thrombolysis treatment		

Neuroprotection with Magnesium Sulpahte

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Muir et al. 2004 **UK** **RCT** ***Intravenous Magnesium Efficacy in Stroke (IMAGES)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2589 patients, aged ≥18 years, previously independent, conscious, with a clinical diagnosis of stroke, with onset of <12 hours, presenting with limb weakness.	Patients were randomized to receive $MgSO_4$ (16 mmol bolus) with 65 mmol given over 24 hours (n=1292) or placebo (n=1297)	**Primary outcome:** Death or disability (BI score <95 or mRS ≥2) at 90 days **Secondary outcomes:** Death, disability at 90 days	The risk of death or disability was not significantly reduced in the $MgSO_4$ group (OR=0.95, 95% CI 0.80-1.12, p=0.53). The risk of death was not reduced (OR=1.22, 95% CI 0.98-1.53, p=0.073). In planned sub group analyses of the primary outcome, no treatment effects were noted for timing of treatment (≤6 vs. >6 hrs) or stroke type (ischemic vs. non-ischemic). A benefit of treatment was noted for patients with non-cortical strokes (OR=0.75, 95% CI 0.58-0.97, p<0.011).

Blood Glucose Abnormalities

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bellolio et al. 2014 **US** **Cochrane Review**	NA	11 RCTs including 1583 adult patients with blood glucose level of > 6.1mmol/L measured within 24 hours of acute stroke.	Treatment contrasts for blood glucose control included insulin vs. placebo, low dose vs. high dose insulin and close vs. loose monitoring. Secondary (subgroup and sensitivity) analysis:	**Primary outcome:** Death, dependency (Barthel Index ≤ 60 or mRS 3-6). **Secondary outcomes:** Neurological deficit (National Institute of Health Stroke Scale - NIHSS, European Stroke Scale - ESS), Hypoglycemia (glucose < 3mmol/L), and	**Primary outcome:** Blood-glucose-lowering treatment was not associated with reductions in death or dependency (OR=0.99, 95% CI 0.79-1.23). **Secondary outcomes:** Blood-glucose-lowering treatment was not associated with reductions in death (OR= 1.09, 95% CI 0.85-1.41), or final neurological deficit (SMD= -0.09, 95% CI -0.19 to 0.01).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			outcomes compared separately for patients diagnosed with diabetes vs. not, at 60 vs. 90 days, and separately for studies that included patients with a presumed diagnosis of stroke (not confirmed with CT), where controls may have received insulin, with inadequate methodology and the largest study.	number of deaths.	Treatment was associated with a significant increase in the risk of symptomatic hypoglycemia events (OR= 14.6, 95% CI 6.62-32.21) and asymptomatic hypoglycemia events (OR= 18.4, 95% CI 9.09-37.3).
Rosso et al. 2012 **France** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	180 patients with ischemic stroke (within the carotid area) diagnosed using MRI within 5 hours of stroke, and the initiation of imaging within 6 hours of stroke. NIHSS score 5-25. The median age of patients in the subcutaneous group was 76.9 years and 69.6 years in the intravenous group.	Patients were randomized to receive intravenous administration of insulin (IIT) on a continuous basis or subcutaneous administration (every 4 hours) for 24 hours (SIT). The stop point for treatment was <5.5 mmol/L in the IIT group and 8 mmol/L in the SIT group.	**Primary outcome**: Capillary glucose test (CGT) (% patients with <7mmol/L CGT in each group). **Secondary outcomes**: Infarct growth, good outcome (mRS 0-2) at 3 months, hypoglycemia events (CGT <3.0mmol/L), death, serious adverse events (NIHSS increase >3 points).	The median admission serum glucose levels of patients in the SIT and IIT groups were 6.3 mmol/L and 6.7 mmol/L, respectively. Median baseline HBA1C: (SIT=6%; IIT=5.9%) A significantly higher number of patients in the IIT group achieved and maintained a mean CGT of <7mmol/L (95.4% vs. 67.4%; p<0.0001). The mean size of infarct growth was significantly higher among patients in the IIT group (27.9 vs. 10.8 cm^3, p=0.04). There was no significant difference in the number of patients who experienced a good outcome (45.6% vs. 45.6%) or death (15.6% vs. 10.0%) There were significantly more asymptomatic hypoglycemia events among patients in the IIT group (8 vs. 0, p=0.02). There were no significant differences in the number of adverse events or number of deaths between the two groups.
McCormick et al. 2010 **UK**	Concealed Allocation: ☑	40 adult patients, >18 years with hemispheric stroke, onset within 24 hours, and capillary	Patients were randomized to either control group that received normal saline	**Outcomes**: Blood glucose, lesion volume; recanalization of occlusion), functional outcome (mRS).	Mean baseline blood glucose was 7.33 mmol/L (control group) and 8.31mmol/L (intervention group)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	Blinding: Patient ☑ Assessor ☒ ITT: ☒	glucose >7mmol/L. The mean age of patients was 75 years. 30% of patients had a preadmission diagnosis of diabetes	(n=15) or to one of three groups that received glucose potassium insulin (GKI) for varying periods of time (24, 48 or 72 hours). Insulin dose was based on maintaining patient blood-glucose levels between 4-7mmol/L.	Assessment time points: Days 1, 3 and 7 for stroke severity and MRI results; 1 month for functional outcome.	Mean HbA1c: 6.51% (control group) and 6.89% (intervention group). There were 42 episodes of hypoglycemia (4mmol/l) in 19/25 (76%) patients receiving GKI and 1 episode in the control group. The mean blood glucose was significantly lower for patients in the GKI groups from 6 hours (5.4 vs. 6.9 mmol/l, p< 0.001) to 12 hours (5.8mmol/l] vs 7.0 mmol/l, p= 0.008), compared with control. There were no significant differences in infarct growth between the two groups over 72 hours. The distribution of mRS scores at 30 days did not differ between GKI and control groups
Yong & Kaste 2008 **Germany** **Additional analysis from ECASS II trial**	NA	748 patients with completed glucose measurements were available (21.5% with pre-morbid diabetes). As per ECASS II protocol, patients aged 18-80 years admitted acutely to hospital for ischemic stroke were eligible and their candidacy for t-PA was assessed. Patients with blood glucose measures of <2.75 or > 22.0 mmol/L., history of recent seizure, hypertension, or recent brain injury, were excluded.	Patients were classified as having one of four hyperglycemic patterns: 1. Hyperglycemia present only at baseline (n=100) 2. Hyperglycemia present only at 24 hours (n=70) 3. Persistent hyperglycemia (present at baseline and at 24 hours) (n=146) 4. Persistent normoglycemia (n=432) Outcomes were compared between these four groups. Analyses were performed separately for patients with pre-morbid diabetes and patients with no pre-morbid diabetes.	**Outcomes:** Neurological improvement (NIHSS≥4) at day 7, hemorrhagic infarction at day 7, 30-day good functional outcome (Barthel Index score 95-100), minimal disability (mRS 0-2) and all-cause mortality at 90 days. Multivariate analysis results: (controlled for age, gender, tPA treatment, baseline neurologic status, history of hypertension and congestive heart failure).	**Patients with pre-morbid diabetes** The odds of 7-day neurological improvement, good functional outcome at 30 days, minimal disability or death at 90 days were not significantly increased/decreased for patients with persistent hyperglycemia, or among patients with 24-hour hyperglycemia (category 2), compared with patients with persistent normoglycemia. **Patients without pre-morbid diabetes** Patients with persistent hyperglycemia experienced significantly worse outcomes compared to those with persistent normoglycemia: Neurological improvement: OR= 0.31, 95% CI 0.16 to 0.60 Hemorrhagic infarctions: OR= 0.30, 95% CI 0.13 to 0.71 30-day Barthel Index score of 95-100: OR=0.27, 95% CI 0.12 to 0.62 Minimal disability at day 90:: OR=0.36, 95% CI 0.17 to 0.73 90-day mortality: OR= 7.61, 95% CI 3.23 to 17.90

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Compared with patients with persistent normoglycemia, patients with 24-hour hyperglycemia (category 2) were less likely to have minimal disability at 90 days (OR= 0.40, 95% CI 0.20 to 0.78) and more likely to be dead at 90 days (OR=5.99, 95% CI 2.51 to 14.20).
Gray et al. 2007 **RCT** ***UK Glucose Insulin in Stroke Trial (GIST-UK)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	899 patients with acute stroke (symptom onset within 24 hours) and plasma glucose levels of 6.0-17.0mmol/L. Mean age was 75 years.	Patients were randomized to receive variable-dose-insulin glucose potassium insulin (GKI) to maintain blood glucose concentration between 4-7mmol/L or saline (control) as a continuous intravenous infusion for 24 hours. For patients in the control group, if capillary glucose was > 17 mmol/L, insulin therapy could be started, at the discretion of the treating physician.	**Primary outcome:** All-cause mortality at 90 days. **Secondary outcome:** Avoidance of severe disability (mRS score 4-6) and severe functional impairment (Barthel Index <9), at 90 days.	Median blood glucose was 7.6 mmol/L (control group) and 7.8mmol/L (intervention group). The trial was stopped early due to slow enrolment Treatment with GKI was not associated with a significant reduction in 90-day mortality (OR= 1.14; 95% CI 0.86 to 1.51; p=0.37). Treatment with GKI was not associated with avoidance of severe disability (OR= 0.96; 95% CI 0.70 to 1.32) or severe functional impairment (OR= 0.84; 95% CI 0.59 to 1.20), or neurological deficits (MD=1.1; p=0.6). Earlier treatment (within 6 hrs was also not associated with a decreased risk of 90-day death or disability) Rescue dextrose was given to 73/464 GKI-treated patients as per protocol for asymptomatic prolonged hypoglycaemia (blood glucose <4 mmol/L for >30 min) Patients in the intervention group experienced a greater decrease in mean systolic blood pressure compared to the control group (MD=9.03mmHg; 95% CI 5.3-12; p<0.0001).

Mobile Stroke Units

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Kunz et al. 2016 **Germany** **Retrospective study**	NA	Patients who were living independently prior to stroke, who received thrombolysis following acute stroke. Mean age was 70.5 years, 42% male, Median baseline NIHSS score was 8.	The outcomes of patients who received thrombolysis therapy using the mobile stroke unit, STEMO from 2011-2015 (n=305) were compared with patients who received thrombolysis but arrived to hospital via EMS (n=353). Patients from the EMS group were only included if they were treated during the hours that STEMO operated (0700-2300 h)	**Primary outcome:** Excellent functional outcome at 3 months (mRS 0-1) **Secondary outcomes:** Proportion of patients living without severe disability, or able to ambulate independently (mRS 0-3) at 3 months, 3-month mortality **Safety outcomes:** Intracranial hemorrhage, 7-day mortality	The median time from stroke onset to thrombolysis was significantly shorter in the STEMO group (73 vs. 115 minutes, p<0.0005. A significantly higher proportion of patients in the STEMO group were treated ≤ 90 minutes of stroke (62% vs. 35%, p<0.0005). There was no significant difference in the number of patients who achieved an excellent outcome at 3 months (53% STEMO vs. 47% conventional, p=0.14). A significantly higher proportion of patients in the STEMO group were living without severe disability at 3 months (83% vs. 74%, p=0.004). 3-month mortality was significantly lower in the STEMO group (6% vs. 10%, p=0.022). There were no significant differences in the safety outcomes between the 2 groups (sICH 3% vs. 5%, p=0.27 and 7-day mortality 2% vs. 4%, p=0.23) Adjusting for baseline characteristics, STEMO was an independent predictor of living without severe disability at 3 months (OR=1.86, 95% CI 1.20-2.88, p+0.006), but was not an independent predictor of the primary outcome (OR=1.40, 95% CI 1.00-1.97, p=0.052).
Ebinger et al. 2014 ***PHANTOM-S*** **Germany** **Open-label RCT**	CA: ☒ Blinding patient: ☒ assessor: ☒ ITT: ☒	7,986 patients, who lived within 16 minutes' travel time from the fire station were STEMO was based, within symptom onset <4 hours. Treated at one of 14 hospitals. Mean age was 74 years, 44.5% were male.	Patients were randomized to receive response from a Stroke Emergency Mobile (STEMO) ambulance, equipped with a CT scanner, point-of-care-lab and a specialized pre-hospital stroke team including a paramedic, neurologist and neuroradiologist or to routine care (n=2,969) on	**Primary outcome:** Time from alarm to t-PA treatment **Secondary outcomes:** Thrombolysis rate, in-hospital mortality, symptomatic ICH, adverse events	Of 3,213 patients who suffered a stroke during an on- STEMO week, STEMO was deployed in 1,804 cases. In most of the cases when STEMO was not deployed, it was already in use and was not available. Of the patients with ischemic stroke, t-PA was used in 32.6% of STEMO deployment cases, 29% during STEMO weeks, and 21.1% during control weeks. Mean alarm to treatment time was significantly shorter in the STEMO deployed group compared with the control weeks (51.8 vs. 76.3 min, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			alternating weeks.		The proportions of patients treated with t-PA within 90 minutes of stroke were significantly higher when STEMO was deployed (58%), compared with 48% during STEMO weeks (i.e., STEMO not deployed) and 37% during control weeks. There were no significant differences among groups in hospital mortality, sICH or LOS.
Walter et al. 2012 **Germany** **RCT**	CA: ☑ Blinding patient: ☒ assessor: ☒ ITT: ☑	100 patients 18-80 years with ≥1 stroke symptoms using the modified ROSIER criteria, beginning within the previous 2-5 hours. Median age was 71 years, 62% were male. Median baseline NIHSS scores were 5 (MSU) and 6 (control)	Patients were randomized to a mobile stroke unit (MSU) group (n=53) or a control group (n=47). The MSU response consisted of a paramedic, neurologist and neuroradiologist and the ambulance was equipped with a portable CT scanner, a telemedicine system and a point-of-care laboratory. Patients in the control group received optimised conventional stroke management in hospital, which included point-of-care laboratory	**Primary outcome:** Time from alarm to treatment decision **Secondary outcomes:** Number of patients treated with t-PA, time from alarm to t-PA, number of patients with t-PA or intra-arterial recanalization, time from alarm to t-PA or to intra-arterial recanalization. NIHSS, BI and mRS scores at days 1 and 7.	The trial was stopped early after interim analysis, which demonstrated pre-specified superiority of the MSU. 200 patients were planned. 29 MSU patients (55%) and 25 (53%) control patients were diagnosed with ischemic stroke. Median time from alarm to treatment decision was significantly shorter in the MSU group (35 vs. 76 min, p<0.0001). Median time from stroke onset to treatment decision was significantly shorter in the MSU group (56 vs. 104 min, p<0.0001). Similar proportions of patients were treated with t-PA (23% vs. 17%, p=0.30). Median times from alarm and symptom onset to treatment with t-PA were significantly shorter in the MSU group (38 vs. 73 min, p<0.0001, and 73 vs. 153, p=0.0011, respectively). 23% of patients in both groups were treated with t-PA or endovascular therapy. Median times from alarm and symptom onset to therapy were significantly shorter in the MSU group. There were no significant differences in neurological outcomes between groups, assessed using NIHSS, BI or mRS at either day 1 or 7. Survival at day 7 was 89% (MSU) and 96% (control). CT scanning was unavailable for 8 patients in the MSU group due to technical problems.

Reference List

The ENOS Trial Investigators (ENOS). Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* 2015;385:617-628.

Ahmed, N., Wahlgren, N., Brainin, M., Castillo, J., Ford, G. A., Kaste, M. et al. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis: retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke* 2009;40: 2442-2449.

Bath PMW, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database of Systematic Reviews 2014*, Issue 10. Art. No.: CD000039. DOI: 10.1002/14651858.CD000039.pub3.

Bal S, Menon BK, Demchuk AM, Hill MD. Routine CT angiography in acute stroke does not delay thrombolytic therapy. *Can J Neurol Sci 2012*; 39(4):499-501.

Bellolio, M. F., Gilmore, R. M., & Stead, L. G. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev;* 2014, Issue 1. Art. No.: CD005346

Berge E, Cohen G, Lindley RI, et al. Effects of Blood Pressure and Blood Pressure-Lowering Treatment During the First 24 Hours Among Patients in the Third International Stroke Trial of Thrombolytic Treatment for Acute Ischemic Stroke. *Stroke 2015*;46(12):3362-3369.

Brazzelli, M., Sandercock, P. A., Chappell, F. M., Celani, M. G., Righetti, E., Arestis, N. et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. Cochrane.*Database.Syst.Rev.* 2009, Issue 4. Art. No.: CD007424

Brunser AM, Hoppe A, Illanes S, et al. Accuracy of diffusion-weighted imaging in the diagnosis of stroke in patients with suspected cerebral infarct. *Stroke* 2013;44:1169-1171.

Christoforidis GA, Mohammad Y, Kehagias D, Avutu B, Slivka AP. Angiographic assessment of pial collaterals as a prognostic indicator following intra-arterial thrombolysis for acute ischemic stroke. American Journal of *Neuroradiol* 2005;26(7):1789-97.

Coutts, S. B., O'Reilly, C., Hill, M. D., Steffenhagen, N., Poppe, A. Y., Boyko, M. J. et al. Computed tomography and computed tomography angiography findings predict functional impairment in patients with minor stroke and transient ischaemic attack. *Int J Stroke* 2009;4: 448-453.

de Bruijn, S. F., Agema, W. R., Lammers, G. J., van der Wall, E. E., Wolterbeek, R., Holman, E. R. et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006; 37:2531-2534.

Douen, A. G., Pageau, N., & Medic, S. Serial electrocardiographic assessments significantly improve detection of atrial fibrillation 2.6-fold in patients with acute stroke. Stroke *2008*;39: 480-482.

Douglas, V. C., Johnston, C. M., Elkins, J., Sidney, S., Gress, D. R., & Johnston, S. C. Head computed tomography findings predict short-term stroke risk after transient ischemic attack. *Stroke* 2003;34: 2894-2898.

Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. *JAMA* 2014; 311(16):1622-1631.

Frolich AM, Wolff SL, Psychogios MN, Klotz E, Schramm R, Wasser K et al. Time-resolved assessment of collateral flow using 4D CT angiography in large-vessel occlusion stroke. *Eur Radiol 2014*; 24(2):390-396.

Geeganage, C. & Bath, P. M. Vasoactive drugs for acute stroke. *Cochrane Database Syst Rev* 2010, Issue 7. Art. No.: CD002839

Geeganage, C. M. & Bath, P. M. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension* 2009;54: 775-781.

Giles, M. F. & Rothwell, P. M. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores. Stroke 2010;41:667-673.

Goyal N, Tsivgoulis G, Male S, Metter EJ, Iftikhar S, Kerro A, Chang JJ, Frey JL, Triantafyllou S, Papadimitropoulos G, Abedi V. FABS: an intuitive tool for screening of stroke mimics in the emergency department. *Stroke.* 2016;47(9):2216-20.

Gray, C. S., Hildreth, A. J., Sandercock, P. A., O'Connell, J. E., Johnston, D. E., Cartlidge, N. E. et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007;6: 397-406.

Grond M, Jauss M, Hamann et al. Improved detection of silent atrial fibrillation using 72-hour holter ECG in patients with ischemic stroke: A prospective multicenter cohort study. *Stroke* 2013;44:3357-3364.

He J, Zhang Y, Xu T, Zhao Q, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke. *JAMA* 2014;311:479-489.

Hornslien AG, Sandset EC, Igland J, et al. Effects of candesartan in acute stroke on vascular events during long-term follow-up: results from the Scandinavian Candesartan Acute Stroke Trial (SCAST). *Int J Stroke* 2015;10(6):830-835.

Karliński M, Gluszkiewicz M, Członkowska A. The accuracy of prehospital diagnosis of acute cerebrovascular accidents: an observational study. Archives of medical science: *Arch Med Sci* 2015;11(3):530.

Kisialiou, A., Pelone, G., Carrizzo, A., Grillea, G., Trimarco, V., Marino, M. et al. (2012). Blood biomarkers role in acute ischemic stroke patients: higher is worse or better? *Immun Ageing* 2012;9: 22.

Kunz A, Ebinger M, Geisler F, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: an observational registry study. *Lancet Neurol.* 2016; 15(10):1035-43.

Lakshminarayan, K., Tsai, A. W., Tong, X., Vazquez, G., Peacock, J. M., George, M. G. et al. Utility of dysphagia screening results in predicting poststroke pneumonia. *Stroke* 2010;41: 2849-2854.

Lamy C, Domigo V, Semah F, et al. Early and late seizures after cryptogenic ischemic stroke in young adults. *Neurol* 2003;60:400-04.

Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. *J Stroke Cerebrovas Dis* 2012;21:89-93.

Lee W, Frayne J. Transient ischaemic attack clinic: An evaluation of diagnoses and clinical decision making. *J Clin Neuro* 2015;22(4):645-8.

Liao, J., Khalid, Z., Scallan, C., Morillo, C., & O'Donnell, M. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke* 2007;38: 2935-2940.

McCormick, M., Hadley, D., McLean, J. R., Macfarlane, J. A., Condon, B., & Muir, K. W. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol* 2010;67: 570-578.

Menon BK, Demchuk AM. Computed Tomography Angiography in the Assessment of Patients with Stroke/TIA. *Neurohospitalist 2011*;1:187-199.

Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. *Radiology 2015*. 275(2):510-20.

Menon BK, Qazi E, Nambiar V, Foster LD, Yeatts SD, Liebeskind D et al. Differential Effect of Baseline Computed Tomographic Angiography Collaterals on Clinical Outcome in Patients Enrolled in the Interventional Management of Stroke III Trial. *Stroke 2015*. 46(5):1239-44.

Merino JG, Luby M, Benson RT, Davis LA, Hsia AW, Latour LL, et al. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. *J Stroke Cerebrovasc Dis.* 2013;22(8):e397–403.

Middleton, S., McElduff, P., Ward, J., Grimshaw, J. M., Dale, S., D'Este, C. et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet* 2011;378:1699-1706.

Morris, J. G., Duffis, E. J., & Fisher, M. Cardiac workup of ischemic stroke: can we improve our diagnostic yield? *Stroke* 2009;40: 2893-2898.

Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet 2004; 363(9407):439-445.

Oh MS, Yu KH, Hong KS, et al. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. *Int J Stroke* 2015;10(5):745-751.

Oppenheim, C., Touze, E., Hernalsteen, D., Peeters, A., Lamy, C., Mas, J. L. et al. Comparison of five MR sequences for the detection of acute intracranial hemorrhage. *Cerebrovasc Dis* 2005;20: 388-394.

Procaccianti G, Zaniboni A, Rondelli F, et al. Seizures in acute stroke: incidence, risk factors and prognosis. *Neuroepidemiology* 2012;39:45-50.

Purroy, F., Jimenez Caballero, P. E., Gorospe, A., Torres, M. J., Alvarez-Sabin, J., Santamarina, E. et al. Prediction of early stroke recurrence in transient ischemic attack patients from the PROMAPA study: a comparison of prognostic risk scores. *Cerebrovasc Dis* 2012;33:182-189.

Rosso, C., Corvol, J. C., Pires, C., Crozier, S., Attal, Y., Jacqueminet, S. et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized INSULINFARCT trial. *Stroke* 2012;43: 2343-2349.

Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet.* 2011;377(9767):741-750.

Schrader J, Luders S, Kulschewski A, Berger J, Zidek W, Treib J, et al. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke; 2003;34(7):1699-703.

Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol 2015*; 14(4):377-387.

Suissa, L., Lachaud, S., & Mahagne, M. H. Optimal Timing and Duration of Continuous Electrocardiographic Monitoring for Detecting Atrial Fibrillation in Stroke Patients. *J Stroke Cerebrovasc Dis* 2012;22:991-995.

van Tuijl, J. H., van Raak, E. P., de Krom, M. C., Lodder, J., & Aldenkamp, A. P. Early treatment after stroke for the prevention of late epileptic seizures: a report on the problems performing a randomised placebo-controlled double-blind trial aimed at anti-epileptogenesis. *Seizure* 2011;20: 285-291.

Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol 2012*; 11(5):397-404.

Wardlaw, J. M., Murray, V., Berge, E., del, Z. G., Sandercock, P., Lindley, R. L. et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012; 379: 2364-2372.

Wardlaw, J. M., Seymour, J., Cairns, J., Keir, S., Lewis, S., & Sandercock, P. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke* 2004;35: 2477-2483.

Yong, M. & Kaste, M. Dynamic of hyperglycemia as a predictor of stroke outcome in the ECASS-II trial. *Stroke* 2008;39: 2749-2755.