CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Seventh Edition, Update 2022

Section 4: Emergency Department Evaluation and Management of Patients with Transient Ischemic Attack and Acute Stroke

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Acute Stroke Management Writing Group and in collaboration with the
Canadian Stroke Consortium

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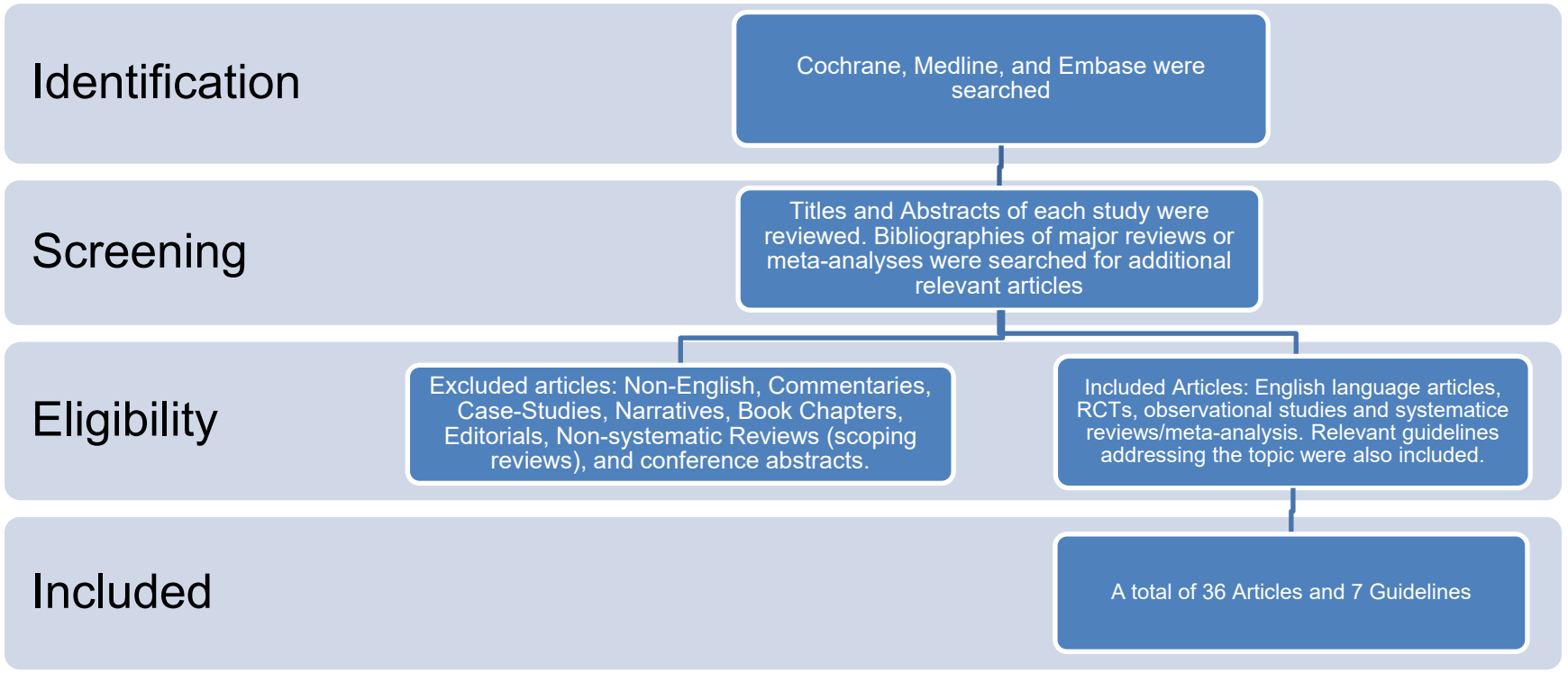
Search Strategy



Pubmed, EMBASE and the Cochrane Database were search using the terms (Stroke OR Cerebrovascular Disorders OR ischemic stroke), blood pressure lowering, Magnetic Resonance Imaging (OR MR OR NMR OR diffusion weighted OR T2-weighted OR Tomography, X-Ray Computed), blood glucose (OR hypoglycemia or hyperglycemia), Holter monitoring (OR electrocardiography or electrocardiogram). 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 36 articles and 7 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Dziewas R, Michou E, Trapl-Grundschober M, Lal A, Arsava EM, Bath PM, Clavé P, Glahn J, Hamdy S, Pownall S, Schindler A. **European Stroke Organisation and European Society for Swallowing Disorders guideline for the diagnosis and treatment of post-stroke dysphagia.** ***European Stroke Journal*. 2021, Vol. 6(3): LXXXIX–CXV** **(selected) Recommendations based on moderate quality of evidence or higher included**	20 PICO questions addressed. *PICO 1. Dysphagia Screening.* In patients with acute stroke does screening compared to no screening for dysphagia improve functional outcome and/or survival, reduce aspiration risk, reduce length of hospital stay, reduce adverse events and complications, have an effect on nutritional status and have an effect on quality of life? Recommendation 1: In all patients with acute stroke, we recommend a formal dysphagia screening test to prevent post-stroke pneumonia and decrease risk of early mortality. We recommend to screen the patients as fast as possible after admission. For screening, either water-swallow-tests or multiple-consistency tests may be used. Quality of evidence: Moderate, Strength of recommendation: Strong for intervention ↑↑ Recommendation 2: In patients with acute stroke, we recommend no administration of any food or liquid items, including oral medication, until a dysphagia screening has been done and swallowing was judged to be safe. Quality of evidence: Moderate, Strength of recommendation: Strong for intervention ↑↑ *PICO 1 Behavioral Interventions*. In patients with post-stroke dysphagia do behavioural swallowing exercises compared to no treatment improve functional outcome and/or survival, reduce aspiration risk, reduce length of hospital stay, reduce adverse events and complications, improve swallowing status/ability, have an effect on nutritional status and have an effect on quality of life? Recommendation 8: In patients with post-stroke dysphagia, we suggest behavioural swallowing exercises to rehabilitate swallowing function. Quality of evidence: Moderate, Strength of recommendation: Weak for intervention ↑? Recommendation 9: In patients with post-stroke dysphagia, we suggest that behavioural interventions should not be limited to one specific manoeuvre or training, but the treatment should be tailored to the specific swallowing impairment of the individual patient based on a careful assessment of dysphagia. Quality of evidence: Moderate, Strength of recommendation: Weak for intervention ↑? Recommendation 10: In patients with post-stroke dysphagia, we suggest that acupuncture may be used to rehabilitate swallowing function. Quality of evidence: Moderate, Strength of recommendation: Weak for intervention ↑? *PICO 1 Nutritional interventions.* In patients with post-stroke dysphagia does early initiation of oral nutritional therapy compared to late initiation of nutritional therapy improve functional outcome and/or survival, reduce aspiration risk, reduce length of hospital stay, reduce adverse events and complications, improve swallowing status/function, have an effect on nutritional status and have an effect on quality of life? Recommendation 11: In unselected stroke patients, we suggest to avoid routine use of oral nutritional supplementation. Quality of evidence: Moderate, Strength of recommendation: Weak against intervention ↓? Recommendation 13: In patients with post-stroke dysphagia and insufficient oral intake we suggest an early enteral nutrition via a nasogastric tube. Quality of evidence: Moderate, Strength of recommendation: Weak for intervention ↑?

Guideline	Recommendations
	PICO 1 Pharmacological treatment. In patients with post-stroke dysphagia, does pharmacological treatment compared to no treatment improve functional outcome and/or survival, reduce aspiration risk, reduce length of hospital stay, reduce adverse events and complications, improve swallowing status/ability, have an effect on nutritional status and have an effect on quality of life? Recommendation 16: We recommend that preventive antimicrobial treatment is not used in stroke patients. Quality of evidence: High, Strength of recommendation: Strong against intervention ↓↓ *PICO Neurostimulation treatment*. In patients with post-stroke dysphagia, do neurostimulation techniques compared to behavioural treatments improve functional outcome and/or survival, reduce aspiration risk, reduce length of hospital stay, reduce adverse events and complications, improve swallowing status/ ability, have an effect on nutritional status and have an effect on quality of life? Recommendation 20: In patients with post-stroke dysphagia, we suggest treatment with rTMS, TES, tDCS and PES as adjunct to conventional dysphagia treatments to improve swallowing function. Quality of evidence: Moderate, Strength of recommendation: Weak for intervention ↑? Recommendation 21: In tracheotomized stroke patients with severe dysphagia, we suggest treatment with pharyngeal electrical stimulation to accelerate decannulation. Quality of evidence: High, Strength of recommendation: Weak for intervention ↑?
Sandset EC, Anderson CS, Bath PM, et al. **European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage.** ***European Stroke Journal*. 2021 Jun;6(2):II.**	PICO 1: In patients with suspected acute stroke, does pre-hospital blood pressure lowering with any vasodepressor drug compared to no drug improve outcome? In patients with suspected stroke, we suggest against routine blood pressure lowering in the pre-hospital setting. Quality of evidence: Moderate, Strength of recommendation: Weak PICO 2: In hospitalised patients with acute ischaemic stroke not treated with reperfusion therapies (intravenous thrombolysis or mechanical thrombectomy), does blood pressure lowering with any vasodepressor drug compared to no drug improve outcome? In hospitalised patients with acute ischaemic stroke and blood pressure < 220/110 mmHg not treated with intravenous thrombolysis or mechanical thrombectomy, we suggest against the routine use of blood pressure lowering agents at least in first 24 hours following symptom onset, unless this is necessary for a specific comorbid condition. Quality of evidence: Moderate, Strength of recommendation: Weak PICO 3: In hospitalised patients with acute ischaemic stroke and undergoing intravenous thrombolysis (with or without mechanical thrombectomy), does blood lowering therapies compared to control improve outcome? In patients with acute ischaemic stroke undergoing treatment with intravenous thrombolysis (with or without mechanical thrombectomy) we suggest maintaining blood pressure below 185/ 110 mmHg before bolus and below 180/105 mmHg after bolus, and for 24 hours after alteplase infusion. No specific blood pressure-lowering agent can be recommended. Quality of evidence: Very low, Strength of recommendation: Weak In patients with acute ischaemic stroke undergoing treatment with intravenous thrombolysis (with or without mechanical thrombectomy) we suggest against lowering systolic blood pressure to a target of 130-140mmHg compared to <180mmHg during the first 72 hours following of symptom onset. Quality of evidence: Moderate Strength of recommendation: Weak

Guideline	Recommendations
	PICO 4: In patients with acute ischaemic stroke caused by large vessel occlusion and undergoing mechanical thrombectomy (with or without intravenous thrombolysis), does blood pressure lowering with any vasodepressor drug compared to no drug improve outcome? In patients with acute ischaemic stroke due to large vessel occlusion undergoing mechanical thrombectomy (with or without intravenous thrombolysis) we suggest keeping blood pressure below 180/105 mmHg during, and 24 hours after, mechanical thrombectomy. No specific blood pressure-lowering agent can be recommended. Quality of evidence: Very low, Strength of recommendation: Weak In patients with acute ischaemic stroke due to large vessel occlusion we suggest against actively reducing systolic blood pressure <130mmHg during the first 24 hours following successful mechanical thrombectomy Quality of evidence: Moderate, Strength of recommendation: Weak In patients with acute ischaemic stroke due to large vessel occlusion undergoing treatment with mechanical hrombectomy (with or without intravenous thrombolysis) systolic blood pressure drops should be avoided. Quality of evidence: Very low, Strength of recommendation: Strong PICO 6: In patients with acute ischaemic stroke, does continuing versus temporarily stopping previous oral blood pressure lowering therapy improve outcome? In patients with acute ischaemic stroke, there is continued uncertainty over the benefits and risks (advantages/disadvantages) of continuing versus temporarily stopping previous blood pressure lowering therapy. Quality of evidence: Moderate, Strength of recommendation: -
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.**	**Emergency Assessment and Diagnosis of Patients with Ischaemic Stroke** 1. It is recommended that patients suspected of having an ischaemic stroke should complete brain imaging within 30min of arrival at the emergency department (class I, level of evidence B). 2. Emergency assessment of blood glucose, renal function, electrolytes, complete blood count (including platelet count), blood coagulation (including international normalised ratio (INR)), cardiac injury markers and a bedside 12-lead ECG is recommended, but should not delay the initiation of intravenous recombinant tissue plasminogen activator (IV rtPA). For most patients, only the assessment of blood glucose must precede the initiation of IV rtPA (class I, level of evidence B). 3. If feasible, patients with AIS within 6–24hours of last known normal who have large vessel occlusion (LVO) in the anterior circulation, obtaining CT perfusion (CTP) or diffusion -weighted imaging (DWI) with MRI perfusion is recommended to aid in patient selection for endovascular therapy. Patient selected for endovascular therapy should follow the same eligibility criteria of the two major RCTs (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3)) (class IIa, level of evidence B). 4. It is unclear whether using multimodal imaging criteria to select patients with ischaemic stroke who have unclear time of symptom onset for treatment with IV rt-PA is beneficial or not, therefore is not recommended outside a clinical trial (class III, level of evidence B). 5. If needed, multimodal imaging should be obtained as quickly as possible, to not delay administration of IV rt-PA (class IIb, level of evidence B). 6. It is unclear whether using perfusion imaging (CTP or perfusion weighted imaging) for selecting patients for endovascular treatment last known normal time, < 6hours is beneficial (class IIb, level of evidence B).

Guideline	Recommendations
	7. It is recommended for patients with AIS meeting the eligibility criteria of the two major RCTs (DAWN and DEFUSE 3) within 6–24hours of last known normal who have LVO in the anterior circulation to obtain CTP or DWI with MRI perfusion for subsequent endovascular therapy (class IIa, level of evidence B). 8. It is recommended that the Alberta Stroke Program Early CT Score (ASPECTS) based on head CT be considered when evaluating for endovascular treatment. However, the decision-making doctor must have received the training in the assessment of National Institutes of Health Stroke Scale (NIHSS) and ASPECTS scores and been verified for consistency (class IIa, level of evidence B). 9. For patients with acute presentation of neurological dysfunction, medical history record and physical examination must be performed rapidly. Medical history includes onset characteristics, predisposing factors, last known normal time, past medical history and current medication list. Physical examination includes vital signs and general physical examination. The use of NIHSS as a stroke severity rating scale is recommended (class I, level of evidence A). **Assessment of blood pressure** 1. Hypertension after AIS should be moderated strictly and lowered moderately, controlling the blood pressure in 140~160/80~99mm Hg within 24~48hours is reasonable (class I, level of evidence A). 2. Blood pressure variation and pulse pressure should be monitored closely after AIS. Blood pressure correlates the prognosis (class IIa, level of evidence B). **Blood pressure management** 1. For patients with blood pressure <220/120mm Hg, who do not receive IV rt-PA or endovascular treatment and do not have complications requiring emergency antihypertensive treatment, starting or restarting antihypertensive therapy within the first 48–72hours after AIS is not effective in preventing death or severe disability (class III, level of evidence A). 2. For patients with blood pressure ≥220/120mm Hg, who do not receive IV rt-PA or endovascular treatment and do not have complications requiring emergency antihypertensive treatment, the effect of starting or restarting antihypertensive therapy within the first 48–72hours after AIS is uncertain. It may be reasonable to reduce blood pressure by 15% within the first 24hours after a stroke attack (class IIb, level of evidence C). **Assessment of abnormal glucose metabolism** 1. High blood sugar level and blood sugar fluctuation after AIS is closely related to the prognosis. Clinical monitoring and strict glycaemic control are recommended (class I, level of evidence A). 2. Blood glucose should be strictly monitored after AIS and insulin should be recommended for stable hyperglycaemic control, it is reasonable to control the blood glucose concentration to 5~8mmol/L (class IIa, level of evidence B). 3. For patients with AIS with other complications (such as simultaneous acute coronary events, acute heart failure, aortic dissection, bleeding transformation after thrombolysis or pre-eclampsia/eclampsia), early antihypertensive therapy is indicated. At the initial stage, a 15% reduction in blood pressure may be safe (class I, level of evidence C).
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; on behalf of the American Heart Association Stroke Council. **Guidelines for the early**	**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. Head & Neck Imaging**

Guideline	Recommendations
management of patients with acute ischemic stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association ***Stroke.* 2019;50:e344–e418.** **(selected)**	1. All patients with suspected acute stroke should receive emergency brain imaging evaluation on first arrival to a hospital before initiating any specific therapy to treat AIS (Class 1; LOE A). 2. Systems should be established so that brain imaging studies can be performed as quickly as possible in patients who may be candidates for IV fibrinolysis or mechanical thrombectomy or both. (Class 1; LOE B-NR). 3. Noncontrast CT (NCCT) is effective to exclude ICH before IV alteplase administration. Class 1; LOE A 4. Magnetic resonance (MR) imaging (MRI) is effective to exclude ICH before IV alteplase administration. Class 1. LOE-B-NR. 5. CTA with CTP or MR angiography (MRA) with diffusion-weighted magnetic resonance imaging (DW-MRI) with or without MR perfusion is recommended for certain patients. (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-NR). 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). 4. 4. Usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of IV alteplase. (Class IIb; 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-LD). 3.4 Blood glucose 1. Hypoglycemia (blood glucose <60 mg/dl) should be treated in patients with AIS. (Class I ; LOE C-LD). 2 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).

Guideline	Recommendations
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
Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, Harris KC, Nakhla M, Cloutier L, Gelfer M, et al; Hypertension Canada. **Hypertension Canada's 2018 Guidelines for diagnosis, risk assessment,** **prevention, and treatment of hypertension in adults and children.** ***Can J Cardiol*. 2018;34:506–525.**	***A***. *BP management in acute ischemic stroke (onset to 72 hours)* 1. For patients with ischemic stroke not eligible for thrombolytic therapy, hypertension in the setting of acute ischemic stroke or transient ischemic attack should not be routinely treated (Grade D; revised wording). Extreme BP increases (eg, SBP > 220 mm Hg or DBP > 120 mm Hg) may be treated to reduce the BP by approximately 15% (Grade D), and not more than 25%, over the first 24 hours with gradual reduction thereafter (Grade D). Avoid excessive lowering of BP because this might exacerbate existing ischemia or might induce ischemia, particularly in the setting of intracranial or extracranial arterial occlusion (Grade D; revised wording). Pharmacological agents and routes of administration should be chosen to avoid precipitous decreases in BP (Grade D). 2. For patients with ischemic stroke who are eligible for thrombolytic therapy, very high BP (> 185/110 mm Hg) should be treated concurrently with thrombolysis to reduce the risk of hemorrhagic transformation (Grade B; revised guideline). BP should be lowered to < 185/110 mm Hg before tissue plasminogen activator therapy and to < 180/105 for the next 24 hours (Grade D; revised guideline). **B**. *BP management after acute ischemic stroke* 1. Strong consideration should be given to the initiation of antihypertensive therapy after the acute phase of a stroke or transient ischemic attack (Grade A). 2. After the acute phase of a stroke, BP-lowering treatment is recommended to a target of consistently < 140/90 mm Hg (Grade C). 3. Treatment with an ACE inhibitor and thiazide/ thiazide-like diuretic combination is preferred (Grade B). 4. For patients with stroke, the combination of an ACE inhibitor and ARB is not recommended (Grade B).
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

Guideline	Recommendations
	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. Weak recommendation Against Intensive blood pressure lowering in the acute phase of care to a target SBP of < 140 mmHg is not recommended for any patient with stroke Strong recommendation All stroke patients should have their blood glucose level monitored for the first 72 hours following admission, and appropriate glycaemic therapy instituted to treat hyperglycaemia (glucose levels greater than 10 mmol/L), regardless of their diabetic status.

Guideline	Recommendations
Harris D, Hall C, Lobay K, McRae A, Monroe T, Perry JJ et al. **Canadian Association of Emergency Physicians Position Statement on Acute Ischemic Stroke.** ***CJEM* 2015; 17(02):217-226**	1. While in the Emergency Department, patients should have continuous cardiac monitoring to assess for atrial fibrillation. Ideally, continuous cardiac monitoring should continue for at least 24 hours post intravenous thrombolysis (STRONG RECOMMENDATION, MODERATE QUALITY EVIDENCE). 2. Evidence about the optimal management of blood pressure in the hyperacute phase of stroke, or in the immediate post-thrombolysis period is limited. A consensus view, based on blood pressure treatment parameters prior to and during thrombolysis administration, would suggest that blood pressure be lowered if >185 systolic or >105 diastolic. Blood pressure should be lowered only by 15% acutely and no more than 25% over the first 24 hours. Using easily titrated agents (labetolol, nitroprusside, etc) tocontrol blood pressure in the first 24 hours is reasonable (WEAK RECOMMENDATION, LOW QUALITY EVIDENCE). 3. All patients with acute stroke should have a swallowing assessment undertaken prior to administration of any medication or nutrition by mouth. The use of nasogastric (NG) tubes should be avoided for up to 24 hours after intravenous thrombolysis administration, but could be inserted after 12 hours if necessary for medications that cannot be provided using another route. Hydration with IV fluids (normal saline) should be instituted (BEST PRACTICE STATEMENT). 4. Maintenance of euglycemia has been associated with better neurological outcomes in stroke. Routine, repeated measurement of blood glucose while in the Emergency Department is recommended, as is avoidance of glucose containing IV fluids (STRONG RECOMMENDATION, MODERATE QUALITY EVIDENCE). 5. Urinary catheters should not be placed following tPA administration, and should be generally avoided in all patients with stroke, as they are a potential source of infection (STRONG RECOMMENDATION, MODERATE QUALITY EVIDENCE). 6. Temperature should be monitored as part of routine vital sign assessments, every four hours for first 48 hours. For temperature greater than 37.5° Celsius, increase frequency of monitoring, initiate temperature reducing measures, investigate possible infection such as pneumonia or urinary tract infection (BEST PRACTICE STATEMENT)

Evidence Tables

Initial Evaluation & Early Care

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Assessment of Stroke Severity using NIHSS Scale					
Fonarow et al. 2012 **USA** **Retrospective study**	NA	33,102 patients with acute ischemic stroke treated at 404 hospitals from 2003-2006, included in GWTG. Mean age was 79.0 years, 58% were women.	The association between NIHSS scores and 30-day mortality was examined. NIHSS scores were grouped as 0-7, 8-13, 14-21 and 22-42.	**Primary outcome:** 30-day mortality	There were 4,496 deaths (13.6%). 30-day mortality by NIHSS categories was: 0 to 7, 4.2%; 8 to 13, 13.9%; 14 to 21, 31.6%; and 22 to 42, 53.5%. The median NIHSS score was significantly higher among patients who died compared with those who were alive at 30 days (17 versus 4, p<0.0001). A model with NIHSS alone provided excellent discrimination when included as a continuous variable (c-statistic 0.82, 95% CI 0.81 to 0.83]),
Frankel et al. 2000 **USA** **Retrospective Study**	NA	312 patients from the placebo arm of the NINDS trial. Mean age was 65years, 59% were male. Median NIHSS score was 15.	Data collected at baseline, 2 hours, 24 hours, and at 7-10 days was used to identify variables associated with poor outcome (mRS>3 or death), 90-days post stroke	**Primary outcome:** Poor outcome at 3 months	At 3 months, 47% of patients had a poor outcome at 3 months. 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	NA	105 patients with diagnosis of ischemic stroke within 24 hours.	Patient's biomarkers were collected on admission: glucose,	**Outcomes**: Size of ischemic lesion (D1 - <1.5cm; D2 – 1.5 to 3cm; D3	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Italy **Prospective cohort study**		Mean age: 63.3 years.	albumin, TG, TC, LDL, HDL, INR, PTT, platelets, fibrinogen, erythrocyte sedimentation rate (ESR) and their values classified into quintiles (Q1, Q2, Q3 and Q4).	- > 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.	(<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 NIHSS were associated with higher serum albumin levels (p=0.006).
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%). Status epilepticus was diagnosed in 13 patients (0.6% of the entire sample, 19.6% of early seizures).

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

Cardiac 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.	Subgroups 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.

Acute Blood Pressure Management

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Systematic Reviews					
Bath & Krishnan 2014 **UK** **Cochrane Review**	NA	26 trials with 17,011 participants, 18 years of age or older, diagnosed with either ischemic or hemorrhagic stroke, excluding SAH.	Studies evaluating single 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	**Primary Outcome**: 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.	**Blood Pressure Lowering** 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

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			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)	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.	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.
Geeganage & Bath 2009 **UK** **Meta regression**	NA	37 trials, including 9008 patients aged ≥18 years, with ischemic stroke and intracerebral hemorrhage, excluding SAH.	All randomized controlled trials assessing an intervention that is expected to modify blood pressure within one week of acute stroke were included. Analysis involved the use of meta regression to explore the relationship between outcome and	**Outcomes:** Mortality, dependency (Barthel Index score 0 to 55; Rankin Score 3 to 5), blood 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 8mm Hg resulted in the lowest odds of death within one month (OR= 0.87; 95% CI 0.54 to 1.23). 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).

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			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.		"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). Treatment was associated with early increases in SBP (MD= 15.82, 95% CI 5.10- 26.54 mm Hg), but not DBP.
Clinical Trials					
Yuan et al. 2020	Concealed Allocation: ☑	483 patients with acute severe stroke and	Patients were randomized 1:1 to	**Primary outcome:** Poor outcome (mRS 3-5) or	During the first 24 h, the mean SBP was 144.0 mm Hg in the individualized treatment group and 148.2

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China **RCT** ***Controlling Hypertension After Severe Cerebrovascular Event (CHASE)***	Blinding: Patient ☑ Assessor ☑ ITT: ☑	elevated BP (150-210 mmHg) were recruited from 26 Chinese hospitals. Mean age was 66.7 years, 44.3% were women. Median baseline NIHSS was 16.	receive an individualized blood pressure lowering group (with 10–15% reduction in SBP from admission level, achieved within 2 hours and sustained for 1 week) or standard blood pressure lowering group (with a target SBP of <200 mm Hg in acute ischemic stroke and <180 mm Hg in ICH, sustained for 1 week)	all-cause death), at 90 days, **Secondary outcomes:** Poor outcome at hospital discharge, neurological deficits at hospital discharge, Barthel Index (BI) at 90 days, serious adverse events	mm Hg in the standard treatment group. At day 7, the mean SBP was 138.1 mm Hg (20.5% reduced from baseline) in the individualized treatment group and 139.7 mm Hg (18.1% reduced from baseline) in the standard treatment group. The odds of a poor outcome were not reduced significantly in the individualized group (71.1% vs. 73.4%, with adjustment for age, sex, and baseline GCS: OR=0.89, 95% CI 0.47 to 1.19; p=0.222). The odds of a poor outcome at hospital discharge were not reduced significantly in the individualized group (91.3% vs. 92.1%, OR=0.79, 95% CI 0.40 to 1.56; p=0.495). There were no significant differences between groups in the median BI score at discharge (50 vs. 49, p=0.92). There were no significant differences between groups in the percentages of patients who died within 90 days or any serious adverse events (16.5% vs. 19.6% and 27.7% vs. 28.2%, respectively). Individualized BP-lowering treatment had a significant effect on reducing the neurological deficits at hospital discharge as evaluated by NIHSS (β estimate=0.13; 95%CI -0.2 to -0.03; p= 0.009).
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.	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	**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	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.

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		Mean age was 65 years, 59% were male, median NIHSS score was 3.	according to current guidelines.	deterioration during 7-day treatment period.	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 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.

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					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 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	Concealed	4071 patients with acute	Participants were	**Primary outcome**:	At 7 days post-randomization, mean systolic blood

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China **RCT** ***China Antihypertensive Trial in Acute Ischemic Stroke (CATIS)***	Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	ischemic stroke (within 48 hrs, aged >22 yrs, with systolic blood pressure between 140 and 220 mg Hg.	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.	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.	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 period of 7 days.	**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 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**

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					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**: History (Hx) of hypertension and antihypertensive therapy **Group 2**: Hx of hypertension and no antihypertensive therapy **Group 3**: No Hx of hypertension and antihypertensive therapy **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.	**Primary 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 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).	*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 at 3 months (p=0.29).
Schrader et al.	Concealed	342 patients admitted	Patients were	**Primary outcome:**	Trial was stopped prematurely (planned recruitment

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2003 **Germany** **RCT** ***Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS)***	Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☒	with acute disabling stroke, excluding intracranial hemorrhages, with hypertension requiring treatment. Mean age was 68.3 years (treatment group) & 67.8 years (placebo group)	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.	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	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					
Anderson et al. 2019 **International** **RCT** ***ENCHANTED (Blood pressure-lowering arm)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,227 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 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. Mean age was 67 years,	Patients were randomized to an intensive SBP lowering group, with target BPs of 130– 140 mmHg, achieved within 60-minutes of randomization, which was to be maintained for ≥ 72 hours, or hospital discharge, or death; or guideline-recommended BP lowering group with target SBP < 180 mmHg, after commencement of thrombolysis treatment	**Primary outcome:** Death or disability (mRS 2-6) at 90 days **Secondary outcome:** Any intracranial hemorrhage (ICH)	Median time from stroke onset to randomization was 3·3 hours. Median baseline NIHSS scores were 7 (intensive) and 8 (guideline) Mean SBP over 24 h was significantly lower in the intensive group (144·3 vs. 149·8 mm Hg, p<0·0001). The distribution of mRS score at 90 days did not differ between groups (OR=1·01, 95% CI 0·87–1·17, p=0·8702). No interactions were identified. The percentage of patients who experienced death or disability at 90 days did not differ significantly between groups (46·5% vs. 48·0%, adj OR=0·94, 95% CI 0·78–1·14, p=0·55). The percentage of patients with major disability

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		38% were women.			(mRS of 3-6), death or neurological deterioration or death within 90 days did not differ significantly between groups. Significantly fewer patients in the intensive groups had an ICH (14.8% vs. 18.7%, OR= 0·75, 0·60–0·94, p=0·0137). The number of serious adverse events did not differ significantly between groups (19·4% vs.22·0%; OR= 0·86,95% CI 0·70–1·05, p=0·1412).
Teng et al. 2019 **Singapore** **Systematic review & meta-analysis**	Most studies were of moderate to high quality	26 studies (n=38,937) in which patients received thrombolysis treatment and pretreatment SBP/DBP values and functional outcome and ICH data were reported.	The difference in mean baseline SBP and DBP was calculated between patients who experienced a good vs. poor functional outcome.	**Primary outcome:** mRS scores at 90 days, sICH	The mean SBP of patients who had a good functional outcome defined as mRS of 0-1 or 0-2 was significantly lower compared with patients with poor functional outcome (mean difference=3.87 mmHg, 95% CI 1.18-6.56; p=0.005). The mean DBP of patients who had a good functional outcome was not significantly lower compared with patients with poor functional outcome (mean difference=-0.91; 95% CI -2.85-1.03; P=0.3). Higher baseline SBP was associated with increased risk of developing sICH. The mean difference in baseline SBP between those with and without sICH was 5.31 mm Hg (95% CI 2.22-8.40, p=0.0004).

Blood Glucose Abnormalities

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Johnston et al. 2019 **USA** **RCT** ***Stroke Hyperglycemia Insulin Network***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,151 patients ≥18 years with hyperglycemia following acute ischemic stroke, presenting within 12 hours with NIHSS scores of 3-22. Persons with type 1 diabetes were excluded. Mean age was 66 years, 46% women.	Patients were randomized (1:1) to receive intensive or standard glucose-lowering treatment during hospital stay. Patients in the intensive treatment group received a continuous intravenous	**Primary outcome:** Favourable outcome (mRS 0, 0-1 or 0-2 depending on baseline NIHSS scores) at 3 months **Secondary outcomes:** NIHSS score, Barthel Index score and Stroke Specific QoL	Trial was halted prematurely due to futility. During treatment mean blood glucose level was significantly lower in the intensive group (6.6 vs. 9.9 mmol/L) 20.5% of patients in the intensive groups had a favourable outcome at 90 days vs. 21.6% in the standard group (adj RR=0.97, 95% CI 0.87 to

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Effort (SHINE)		80% had diabetes. 17.5% had a previous ischemic stroke.	insulin infusion as needed to maintain a blood glucose concentration of (4.44-7.22 mmol/L). Patients in the standard treatment group received insulin on a sliding scale that was administered subcutaneously every 6 hours as needed to maintain a blood glucose concentration of 4.44-9.93 mmol/L).	**Safety outcome:** Severe hypoglycemia (<2.2 mmol/L)	1.08, p=0.55). There were no differences between groups for any of the secondary outcomes. A significantly higher percentage of patients in the intensive group experienced severe hypoglycemia (2.2% vs. 0%, p<0.01).
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: 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.	**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 number of deaths.	**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). 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:	180 patients with ischemic stroke (within the carotid area) diagnosed using MRI within 5 hours of stroke,	Patients were randomized to receive intravenous administration of insulin (IIT) on a continuous	**Primary outcome**: Capillary glucose test (CGT) (% patients with <7mmol/L CGT in each group).	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%)

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	Patient ☒ Assessor ☒ ITT: ☑	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.	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.	**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).	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.
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	**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

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			and patients with no pre-morbid diabetes.		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 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).

Additonal Considerations

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Emergent Chest Radiographs					
Saber et al. 2016 **USA** **Retrospective study**	NA	615 patients from IMS III study who had a completed chest radiograph (CXR) completed. Mean age was 65 years, 51% were men.	The features of patients who had a CXR done before vs. after IV, were compared.	**Primary outcome:** Door-to-needle time	Patients with CXR done before treatment (n=243) had a significantly longer mean door-to-needle times than those who had x-rays completed after thrombolysis treatment (n=372); 75.8 vs 58.3 minutes, P=0.0001. CXR before thrombolysis was an independent predictor of door-to-needle time ≥60 minutes (OR=2.78, 95% CI 1.97–3.92, p< 0.00001).
Swallowing					
Boaden et al. 2021 **UK** **Cochrane review**	Using the QUADAS-2 tool, the quality of the studies was generally considered to be of poor quality – only 6 studies were at low risk across all 4 risk of bias domains, and 2 studies were at low risk of bias for 3 domains	25 studies including 3,953 participants with acute stroke. 4 included studies did not contain quantitative data and were excluded from analyses.	The test characteristics of 37 screening tests were evaluate. The reference criterion included the results from the Mann Assessment of Swallowing Ability (MASA, n=20) fibreoptic endoscopic evaluation of swallowing (FEES, n=6), and videofluoroscopy (VF, n=11). 24 (65%) tests used water only, 6 (16%) used a combination of water and other consistencies, and 7 (19%) used other methods	**Primary outcomes:** Diagnostic accuracy, sensitivity, specificity	Statistical pooling of diagnostic accuracy data was not possible. The best performing test using water only was the Toronto Bedside Swallowing Screening Test with a sensitivity of 1.00 (95% CI, 0.75–1.00) and specificity of 0.64 (95% CI, 0.31–0.89). The best performing test that used water, semisolids, and solid trials and management plan was the Gugging Swallowing Screen with a sensitivity of 1.00 (95% CI, 0.77–1.00) and specificity of 0.69 (95% CI, 0.41–0.89). The best performing test that combined water swallow test with an instrumental assessment was the Bedside Aspiration test (combined) with a sensitivity of 1.00 (95% CI, 0.87–1.00) and specificity of 0.71 (95% CI, 0.49–0.87). Screening tools that used a combination of water and other consistencies as testing materials were more accurate than screening tests that used only water. Test that used methods other than water only and water and other consistencies had mixed results; some performed as well as the water-only tests, while others performed worse.

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					Screening tests with dysphagia as the primary outcome generally performed better than screening tests for which the primary outcome was aspiration. Screening tools carried out by nurses performed consistently better than those carried out by other healthcare providers.
Middleton et al. 2019 **Australia** **Cluster RCT** ***Triage, treatment and transfer of patients with stroke in emergency department trial (the T^3 Trial)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,242 patients aged ≥18 years, admitted to the stroke unit via the Emergency Department (ED) with a clinical diagnosis of ischemic stroke or ICH, and presented to ED within 48 hours from symptom onset (time the person was last seen/known to be well by patient or relative/carer).	26 EDs were randomized 1:1 to intervention or control group. The intervention EDs. focused on eligibility screening and appropriate administration of t-PA; implementing clinical protocols for managing fever, hyperglycemia, and swallowing; and prompt transfer to the stroke unit. Protocols related to swallowing included ensuring patients remain NPO until screened for dysphagia and that all patients who fail the screen be assessed by a SLP. EDs randomized to the control group did not receive the clinical protocols or additional support.	**Primary outcome:** 90-day death or dependency (mRS score ≥2) **Secondary outcomes:** Barthel Index (BI) score ≥95 at 90 days	Among 918 patients in the intervention group, 840 (91.5%) remained NPO until they received a swallowing screen or assessment, compared with 591 patients (87.8%) in the control group (p=0.29). The percentage of patients who received a swallow screen or assessment within 24 hours of ED admission did not differ between groups (81.5% vs. 81.3%, p=0.88). 16.6% of patients in the intervention group failed a swallowing screen vs. 12.2% in the control group (p=0.07). 90.8% of patients in the intervention group received a swallowing assessment after a failed screen compared with 82.9% of patients in the control group (p=0.41). There was no significant difference between groups in the percentage of patients with the primary outcome (53.5% vs. 48.7%, p=0.24).
Middleton et al. 2011 **Australia** **Cluster RCT**	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	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	**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:**	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		(ischemic or hemorrhagic) within 48 hours.	a control facility. Clinicians at the participating control institutions received abridged guidelines only.	Mean temperature for first 72 hours, proportion of swallowing screenings completed within the first 24 hours of admission, pneumonia diagnosis, LOS.	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
Indwelling Urinary Catheterization					
Ouyang et al. 2020 **Australia/UK** **Prospective study**	NA	11,093 patients with acute stroke included in the HeadPoST trial, which examined the effect of head position (flat vs. elevated) on stroke outcome. Patients were recruited from 114 hospitals in 9 countries. Mean age was 68 years, 40% were women. Median NIHSS score was 4.	The outcomes of patients who received an indwelling urinary catheter (IUC) within the 7 days of randomization (n=1,167, 12%) and those who did not (n=9,829, 88%), were compared	**Primary Outcome:** Poor outcome (mRS score of 3–6) at 90 days **Secondary outcome:** Urinary tract infection (UTI) at 90 days	Compared to patients without an IUC, those with IUC had a greater likelihood of a poor outcome (76.6% vs. 34.7%; P < 0.0001). IUC was an independent predictor of a poor outcome adjusting for treatment group, region, age, sex, premorbid mRS, baseline NIHSS, history of heart disease, diabetes mellitus or stroke, and pathological stroke type, stroke unit admission, and antibiotic use (OR=1.40, 95% CI 1.13–1.74, p=0.002). Compared to patients without an IUC, those with IUC had a greater likelihood of a UTI (1.5% vs. 0.6%; P = 0.0002). The median time to diagnosis of UTI was 17 days. IUC was not an independent predictor of UTI after multiple adjustment (OR=1.13, 95% CI: 0.59–2.18, p=0.71).
Wu et al. 2013 **Taiwan** **Prospective study**	NA	2,803 patients admitted to a single facility with acute ischemic (n=2,253) or intracerebral hemorrhagic stroke (n=550) within 10 days of symptom onset, from August 2006 to December 2008.	The outcomes of patients who received an indwelling urinary catheter (IUC) (n=697, 25%) and those who did not, were compared	**Primary Outcome:** Poor outcome (mRS score of 3–6) at 90 days	IUC during acute hospitalization was significantly associated with unfavorable 3-month outcome (OR=2.09, 95% CI 1.39–3.13, p<0.001). Catheterization was usually carried out within 1–2 days of admission (86%), with estimated cumulative incidence of 13% at 2 days in patients with ischemic stroke and 57% in patients with ICH.
Hyperthermia					
De Ridder et al. 2017 **Netherlands**	CA: ☑ Blinding: Patient ☑	256 patients ≥18 yrs, recruited from 12 sites, with ischemic or hemorrhagic stroke, temp of ≥ 36.5° C, treated	Patients were randomized to receive high-dose paracetamol (6 grams, n=136) or placebo (n=118) for 3 days.	**Primary outcome:** Shift in distribution of mRS scores at day 90. **Secondary outcomes:**	Recruitment was stopped early due to lack of funding. Sample size of 1,500 patients was planned. There was no significant shift in mRS scores at 90

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT *Paracetamol (Acetaminophen) in Stroke 2 (PAIS 2)*	Assessor ☑ ITT: ☑	within 12 hours of symptom onset. Mean age was 69 years, 56% were male. Median NIHSS score was 5.5.		Favourable outcome (mRS 0-2), Barthel index, Telephone Interview for Cognitive Status score, and Euroqol 5D at 3 months, body temperature and markers of inflammation at 24 h after start of treatment	days associated with paracetamol (common adj OR=1.15, 95% CI 0.74-1.79) The odds of a favourable outcome or a BI score >100 at 90 days were not significantly increased with paracetamol (adj OR=1.01, 95% CI 0.55-1.78 and adj OR=1.02, 95% CI 0.58-1.80, respectively).
Saxena et al. 2015 **Australia** **Retrospective study**	NA	53,942 admissions to ICUs in Australia/NZ and 56,696 patients in the UK with a diagnosis of TBI, stroke or CNS infection from 2005 to 2013.	The relationship between peak temperature in the first 24 h of ICU admission and all-cause hospital mortality was assessed	**Primary outcome:** In hospital mortality	For the Australia/NZ stroke cohort, the odds of in-hospital morality were significantly increased among patients who were hypothermic (<37ºC) and for those with a peak temp >39ºC), relative to those with a peak emp of 37.0–37.4. The same pattern of results was observed for the UK stroke cohort. For patients with CNS infection, elevated peak temperature was not associated with an increased risk of death, relative to the risk at 37–37.4 C (normothermia).
den Hertog et al. 2011 **The Netherlands** **Further analysis from RCT**		1,332 patients admitted within 12 hours of stroke onset, included in the Paracetamol (Acetaminophen) In Stroke (PAIS) trial. Patients were treated with 6 g acetaminophen daily or placebo for the 3 days. Mean age was 70 years, 56% were men. Median admission NIHSS score was 6.	The relationship between admission body temperature and the change in body temperature from admission to 24 hours, was assessed.	**Primary outcome:** Poor outcome (death or mRS score >2) at 90 days **Secondary outcome:** Death at 3 months	The mean body temperature was 36.9ºC on admission, and 37.1ºC 24 hours later. Body temperature >37.5C was observed in 160 patients (12%) on admission and in 298 (22%) 24 hours later. Body temperature on admission was not related to poor outcome or death. In analyses adjusted for age, sex, NIHSS score, stroke type, ischemic stroke subtype, treatment with rtPA, admission body temperature and occurrence of infections, for each degree of temperature increase from 12-24 hours, the odds of poor outcome increased by 1.3 (95% CI, 1.05–1.63), and the odds for death increased by 1.51 (95% CI, 1.15–1.98). (The overall effect of acetaminophen on outcome was not statistically significant).
Supplemental Oxygen					
Roffe et al. 2017	CA: ☑	8,003 adults with acute	Participants were	**Primary outcome:**	Oxygen supplementation did not significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
UK **RCT** ***Stroke Oxygen Study (SO_2S)***	Blinding: Patient ☒ Assessor ☑ ITT: ☑	stroke recruited from 136 participating centers within 24 hours of hospital admission, with no clear indications for or contraindications to oxygen treatment. Mean age was 72 years, 55% were men. Median baseline NIHSS score was 5. 82% of qualifying events were ischemic stroke	randomized 1:1:1 to receive continuous oxygen for 72 hours, nocturnal oxygen (21:00 to 07:00 hours) for 3 nights, or control (oxygen only if clinically indicated). Oxygen was given via nasal tubes at 3 L/min if baseline oxygen saturation was 93% or less and at 2 L/min if oxygen saturation was greater than 93%.	Ordinal shift in mRS scores at 90 days **Secondary outcomes:** Neurological improvement (≥4-point decrease on NIHSS from randomization and day 7), the highest and lowest oxygen saturations within the first 72 hour, 1-week mortality, 90-day mortality, independence at 90 days (mRS 0-2)	improve functional outcome at 90 days. The unadjusted OR for a lower mRS were not increased significantly for the 2 combined oxygen groups vs. control (0.97, 95% CI, 0.89 to 1.05; P = .47), or for continuous vs. nocturnal oxygen (1.03, 95% CI, 0.93 to 1.13; P = .61). There were no significant differences between groups (2 oxygen groups combined vs. control and continuous oxygen vs. nocturnal oxygen) for any of the 7 or 90-day outcomes (neurological improvement, mortality, or disability). No interactions were identified based on subgroup analysis

Abbreviations

CA: concealed allocation	CI: confidence interval	HR: hazard ratio
ITT: intention-to-treat	NA: not assessed	OR: odds ratio
RR: relative risk		

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