Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Acute Ischemic Stroke Treatment: Thrombolytic Therapy

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

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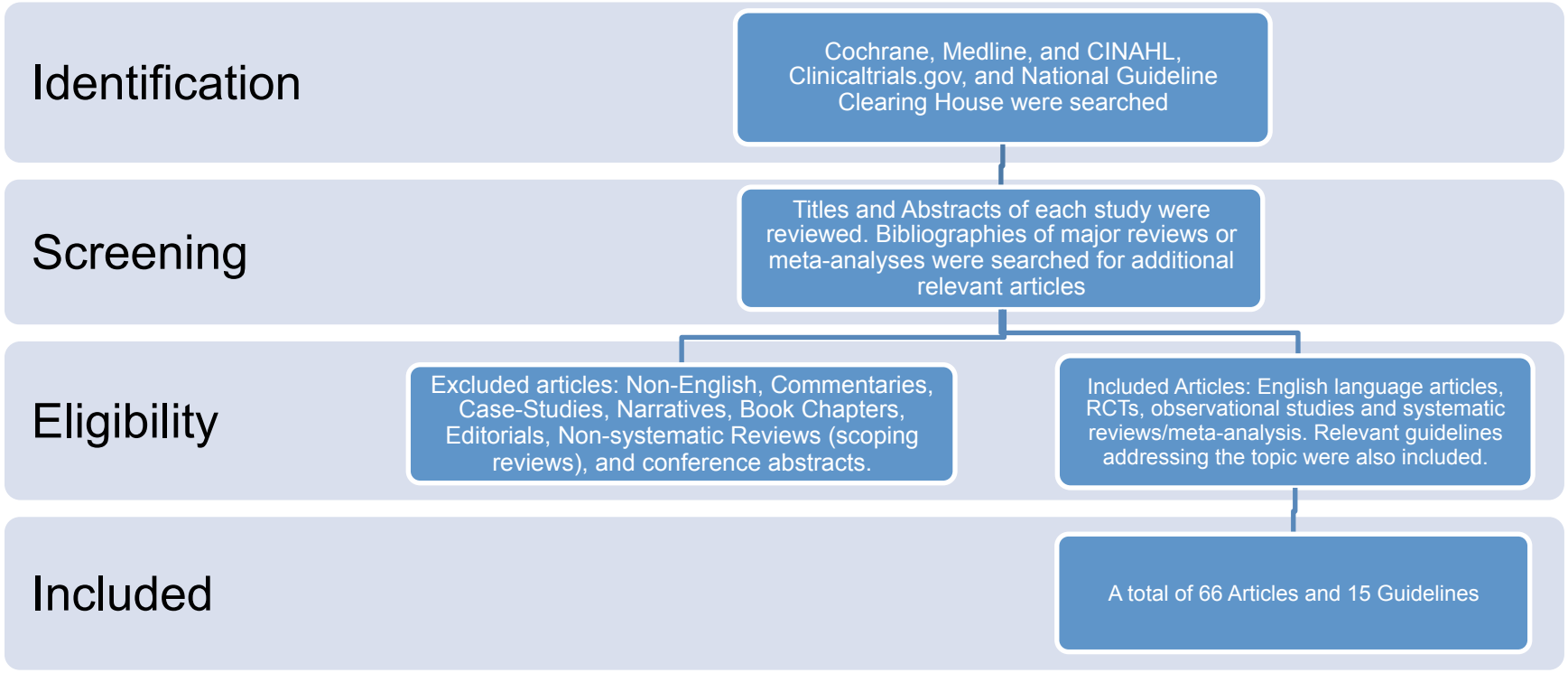
Search Strategy



Cochrane, Medline, and CINAHL, Clinicaltrials.gov, and National Guideline Clearing House were search using the medical subject headings (“ischemic stroke” and “Tissue Plasminogen Activator” and pregnancy and “pediatric” OR “neonate” OR child*”). 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 66 articles and 15 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)**	**3.5. IV Alteplase** 1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 6 to determine patient eligibility. Class I; LOE A. 2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in Table 6 determine patient eligibility. Class I; LOE B-R. 3. For otherwise eligible patients with mild stroke presenting in the 3- to 4.5-hour window, treatment with IV alteplase may be reasonable. Treatment risks should be weighed against possible benefits. Class IIb; LOE B-NR. 4. In otherwise eligible patients who have had a previously demonstrated small number (1–10) of CMBs on MRI, administration of IV alteplase is reasonable. Class IIa; LOE B-NR. 5. In otherwise eligible patients who have had a previously demonstrated high burden of CMBs (>10) on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit. Class IIb; LOE B-NR. 7. Abciximab should not be administered concurrently with IV alteplase. Class III: Harm; LOE B-R. 8. IV alteplase should not be administered to patients who have received a treatment dose of low-molecular-weight heparin (LMWH) within the previous 24 hours. Class III: Harm; LOE B-NR. 9. The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making. Class I; LOE C-EO. 14. BP should be maintained <180/105 mmHg for at least the first 24 hours after IV alteplase treatment. Class I; LOE B-NR. 16. In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. Class I; LOE A. **3.6. Other IV Thrombolytics and Sonothrombolysis** 1. The benefit of IV defibrinogenating agents and of IV fibrinolytic agents other than alteplase and tenecteplase is unproven; therefore, their administration is not recommended outside a clinical trial. Class III: No Benefit; LOE B-R. 2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion. Class IIb; LOE B-R.
Stroke Foundation. Clinical	Strong recommendation Updated For patients with potentially disabling ischaemic stroke who meet specific eligibility criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered.

Guideline	Recommendations
Guidelines for Stroke Management 2017. Melbourne Australia (Part 3)	Thrombolysis should commence as early as possible (within the first few hours) after stroke onset but may be used up to 4.5 hours after onset.
Dong Q, Dong Y, Liu L, et al. **The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischaemic stroke.** ***Stroke and Vascular Neurology* 2017;2: e000074. doi:10.1136/svn-2017-000074** **selected**	For AIS patients with onset time <3hours, intravenous thrombolysis should be offered if there are no contraindications (Class I, Level of Evidence A). Intravenous alteplase within the 3–4.5hour window is also recommended for those patients who are <80 years old, without a history of both diabetes and prior stroke, NIHSS <25, not taking any oral anticoagulants and without imaging evidence of ischaemic injury involving more than one-third of the MCA territory (Class I, Level of Evidence B) When considering intravenous tPA, the sooner the treatment, the greater the benefit and the less the risk (Class I, Level of evidence A). The dosage of intravenous tPA is 0.9mg/kg (maximum 90mg), of which 10% is given as an intravenous bolus in 1min, the remaining given as intravenous continuous infusion over 1hour (Class I, Level of Evidence A). Lower dose of tPA (0.6mg/kg, maximum 60mg, of which 15% is given as an intravenous bolus in 1min, the remaining given as intravenous continuous infusion over 1hour) could be considered in AIS patients with high risk of developing haemorrhage (Class IIB, Level of Evidence C). If there is no tPA available or it is unaffordable, AIS patients within 6hours of onset can be considered to receive IV UK. The dosage of UK is 100 million to 1.5 million IU, dissolved in 100–200mL of saline and given as a continuous intravenous infusion over 30min (Class IIb, Level of Evidence C).
Demaerschalk BM, Kleindorfer DO, Adeoye OM et al. **Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association.** ***Stroke 2016*;47(2):581-641.** **selected**	**Age Issues: Recommendations** 1. For otherwise medically eligible patients ≥18 years of age, intravenous alteplase administration within 3 hours is equally recommended for patients <80 and >80 years of age. Older age is an adverse prognostic factor in stroke but does not modify the treatment effect of thrombolysis. Although older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years of age, compared with control subjects, intravenous alteplase provides a better chance of being independent at 3 months across all age groups (*Class I;Level of Evidence A*). **Stroke Severity: Recommendations** 1. For severe stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms (*Class I; Level of Evidence A*). 2. For patients with mild but disabling stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms in the opinion of the treating physician from treatment with intravenous alteplase because there is proven clinical benefit for those patients (*Class I; Level of Evidence A*). 3. Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio (*Class IIb; Level of Evidence C*). **Rapidly Improving: Recommendations** 1. Intravenous alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner (*Class IIa;Level of Evidence A*). 2. Because time from onset of symptoms to treatment has such a powerful impact on outcome, delaying treatment with intravenous

Guideline	Recommendations
	alteplase to monitor for further improvement is not recommended (*Class III; Level of Evidence C*). **Time From Symptom Onset: Recommendations** 1. The time from last seen normal to treatment with intravenous alteplase should be <3 hours for eligible patients with the use of standard eligibility criteria (*Class I; Level of Evidence A*). 2. Intravenous alteplase treatment in the 3- to 4.5-hour time window is also recommended for those patients <80 years of age without a history of both diabetes mellitus and prior stroke, NIHSS score <25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory (*Class I; Level of Evidence B*). 3. Treatment should be initiated as quickly as possible within the above listed time frames because time to treatment is strongly associated with outcome (*Class I; Level of Evidence A*). 4. In patients in the 0- to 4.5-hour time window who meet criteria for treatment with intravenous alteplase, substantially delaying intravenous alteplase treatment to obtain penumbral imaging before treatment is not recommended (*Class III; Level of Evidence C*). **Major Surgery Within 14 Days: Recommendation** 1. Use of intravenous alteplase in carefully selected patients presenting with acute ischemic stroke who have undergone a major surgery in the preceding 14 days may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits (*Class IIb; Level of Evidence C*). **Major Trauma Within 14 days and Severe Head Trauma Within 3 Months: Recommendations** 1. In acute ischemic stroke patients with recent major trauma (within 14 days), intravenous alteplase may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke (*Class IIb; Level of Evidence C*). 2. In acute ischemic stroke patients with recent severe head trauma (within 3 months), intravenous alteplase is contraindicated (*Class III; Level of Evidence C*). 3. Given the possibility of bleeding complications from the underlying severe head trauma, intravenous alteplase is not recommended in posttraumatic infarction that occurs during the acute in-hospital phase (*Class III; Level of Evidence C*). **History of Ischemic Stroke Within 3 Months: Recommendations** 1. Use of intravenous alteplase in patients presenting with acute ischemic stroke who have had a prior ischemic stroke within 3 months may be harmful (*Class III; Level of Evidence B*). 2. The potential for increased risk of sICH and associated morbidity and mortality exists but is not well established (*Class IIb; Level of Evidence B*). 3. The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making (*Class I; Level of Evidence C*). **Uncontrolled Hypertension, Severe Hypertension, Repeated Blood Pressure, or Requiring Aggressive Treatment: Recommendations** 1. Intravenous alteplase is recommended in patients whose blood pressure can be lowered safely (to <185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous alteplase (*Class I; Level of Evidence B*). 2. If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous alteplase and maintained below 180/105 mm Hg for at least the first 24 hours after

Guideline	Recommendations
	intravenous alteplase treatment (*Class I; Level of Evidence B*). **Serious Medical Comorbid Illnesses: Recommendations** 1. In patients with end-stage renal disease on hemodialysis and normal aPTT, intravenous alteplase is recommended (*Class I; Level of Evidence* C). However, those with elevated aPTT may have elevated risk for hemorrhagic complications. 2. Patients with preexisting dementia may benefit from intravenous alteplase (*Class IIb; Level of Evidence B*). Individual considerations such as life expectancy and premorbid level of function are important to determine whether alteplase may offer a clinically meaningful benefit. 3. The safety and efficacy of alteplase in patients with current malignancy are not well established (*Class IIb; Level of Evidence C*). Patients with systemic malignancy and reasonable (>6 months) life expectancy may benefit from intravenous alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist. **Preexisting Disability: Recommendation** 1. Preexisting disability does not seem to independently increase the risk of sICH after intravenous alteplase, but it may be associated with less neurological improvement and higher mortality. Thrombolytic therapy with intravenous alteplase for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account relevant factors other than mRS (including quality of life, social support, place of residence, need for a caregiver after alteplase administration, patients' and families' preferences, and goals of care) (*Class IIb; Level of Evidence B*). **Blood Glucose: Recommendations** 1. Intravenous alteplase is recommended in otherwise eligible patients within initial glucose levels >50 mg/dL (*Class I; Level of Evidence A*). 2. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels before intravenous initiation. Intravenous alteplase is not indicated for nonvascular conditions (*Class III;Level of Evidence B*). 3. Treatment with intravenous alteplase in patients with acute ischemic stroke who present with initial glucose levels >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable (*Class IIb; Level of Evidence C*). **Early Ischemic Changes on CT: Recommendations** 1. Intravenous alteplase administration is recommended in the setting of EICs of mild to moderate extent (other than frank hypodensity) (*Class I; Level of Evidence A*). 2. There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering intravenous alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite intravenous alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury (*Class III; Level of Evidence* A). **Extended 3- to 4.5-Hour Window: Recommendations** 1. Intravenous alteplase is recommended for carefully selected patients who meet ECASS III criteria and are treated in the 3- to 4.5-hour window (*Class I; Level of Evidence B*). 2. For patients >80 years of age presenting in the 3- to 4.5-hour window, intravenous alteplase treatment is safe and can be as effective as in younger patients (*Class IIa; Level of Evidence B*). 3. For patients taking warfarin and with an INR <1.7 who present in the 3- to 4.5-hour window, intravenous alteplase treatment appears safe and may be beneficial (*Class IIb; Level of Evidence B*). 4. The benefit of intravenous alteplase administration for acute stroke patients with a baseline NIHSS score >25 and presenting in

Guideline	Recommendations
	the 3- to 4.5-hour window is uncertain (*Class IIb; Level of Evidence C*). 5. In acute ischemic stroke patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5-hour window, intravenous alteplase may be as effective as treatment in the 0- to 3-hour window and may be a reasonable option (*Class IIb; Level of Evidence B*). **Wake-up/Unclear Onset Time Stroke: Recommendations** 1. Intravenous alteplase is not recommended in ischemic stroke patients who awoke with stroke with time last known to be at baseline state >3 or 4.5 hours (*Class III; Level of Evidence B*). 2. Intravenous alteplase is not recommended in ischemic stroke patients who have an unclear time and/or unwitnessed symptom onset and in whom the time last known to be at baseline state is >3 or 4.5 hours (*Class III; Level of Evidence B*). 3. Use of imaging criteria to select ischemic stroke patients who awoke with stroke or have unclear time of symptom onset for treatment with intravenous alteplase is not recommended outside a clinical trial (*Class III; Level of Evidence B*).
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	A- Patients with acute ischaemic stroke, regardless of age or stroke severity, in whom treatment can be started within 3 hours of known onset should be considered for treatment with alteplase. B- Patients with acute ischaemic stroke under the age of 80 years in whom treatment can be started between 3 and 4.5 hours of known onset should be considered for treatment with alteplase. C- Patients with acute ischaemic stroke over 80 years in whom treatment can be started between 3 and 4.5 hours of known onset should be considered for treatment with alteplase on an individual basis. In doing so, treating clinicians should recognise that the benefits of treatment are smaller than if treated earlier, but that the risks of a worse outcome, including death, will on average not be increased. D-Patients with acute ischaemic stroke otherwise eligible for treatment with alteplase should have their blood pressure reduced to below 185/110 mmHg before treatment. E- Alteplase should only be administered within a well-organised stroke service with: − processes throughout the emergency pathway to minimise delays to treatment, to ensure that thrombolysis is administered as soon as possible after stroke onset; − staff trained in the delivery of thrombolysis and monitoring for post-thrombolysis complications; − nurse staffing levels equivalent to those required in level 1 or level 2 nursing care with training in acute stroke and thrombolysis; − immediate access to imaging and re-imaging, and staff appropriately trained to interpret the images; − protocols in place for the management of post-thrombolysis complications. F- Emergency medical staff, if appropriately trained and supported, should only administer alteplase for the treatment of acute ischaemic stroke provided that patients can be subsequently managed on a hyperacute stroke unit with appropriate neuroradiological and stroke physician support. G- Patients with acute ischaemic stroke should be considered for combination intravenous thrombolysis and intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.

Guideline	Recommendations
Toni D, Mangiafico S, Agostoni E, Bergui M, Cerrato P, Ciccone A, Vallone S, Zini A. and Inzitari D. **Intravenous thrombolysis and intra-arterial interventions in acute ischemic stroke: Italian Stroke Organisation (ISO)-SPREAD guidelines.** ***Int J Stroke 2015*;10(7):1119-1129.**	1. Treatment with i.v. rt-PA (0·9 mg/kg, maximum dose 90 mg, 10% of the dose as bolus, the remainder in 60 min infusion) is recommended within 4·5 hours of onset of ischemic stroke, without upper limits of age and severity. However, treatment must be carried out as early as possible. Grade A 2. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with mild deficits or rapidly improving symptoms which are however still detectable at the time of starting treatment. Grade B 3. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with a history of prior stroke and diabetes. Grade B. 4. Treatment with i.v. rt-PA is recommended in patients with unwitnessed stroke or stroke present on awakening, when advanced neuro-imaging (DW/PW MR or pCT) define an area of tissue mismatch and/or enable dating of the event within at least three-hours (compare DW with FLAIR MR). Grade D 5. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with focal neurological deficit onset with seizure, when there is clinical evidence, if necessary supported by neuro-imaging (DW/PW MR or PCT), that the residual neurological deficit is not a post-critical deficit but is attributable to a cerebral ischemia. GPP 6. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with blood glucose 400 mg/dl if, treated with s.c. or i.v. insulin, it drops below 200 mg/dl. GPP 7. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with a history of stroke over the last three-months taking into account: the extension of the previous lesion and time interval since the first stroke (higher risk of hemorrhage for larger and more recent lesions), patient age (potential increased risk of bleeding with older age and risk/benefit ratio as a function of life expectancy), potential severity of the new event (also definable by means of neuro-imaging techniques such as MR DW/PW or pCT). GPP 8. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients with severe arterial hypertension after reaching the pressure range SBP < 185 and DBP < 110, which must be maintained during treatment and for 24 h after thrombolysis. GPP 9. Treatment with i.v. rt-PA within 4·5 hours of symptom onset is recommended in patients on oral anticoagulant treatment with vitamin K antagonists and INR ≤ 1·7. GPP
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. (Selected)**	Patients with acute ischemic stroke whose neuroimaging excludes contraindications, and who can be treated within three hours of symptom onset, should be offered rt-PA with the goal of improving functional outcome (STRONG RECOMMENDATION, HIGH QUALITY EVIDENCE). Stroke patients meeting eligibility criteria for thrombolytic therapy should be treated as rapidly as possible, with a target door-to-needle time of less than 60 minutes (STRONG RECOMMENDATION, MODERATE QUALITY EVIDENCE). Thrombolytic therapy for acute ischemic stroke patients should not be routinely offered for the treatment of acute ischemic stroke for patients if administered beyond three hours of stroke symptom onset (WEAK RECOMMENDATION, MODERATE QUALITY EVIDENCE). The administration of thrombolytic therapy for acute ischemic stroke beyond 3 hours from stroke symptom onset should be restricted to specialized stroke centers with advanced imaging capabilities or as part of a research protocol (WEAK RECOMMENDATION, LOW QUALITY EVIDENCE).

Guideline	Recommendations
Anderson D, Larson D, Bluhm J, Charipar R, Fiscus L, Hanson M, Larson J, Rabinstein A, Wallace G, Zinkel A. **Diagnosis and initial treatment of ischemic stroke. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 Jul. 122 p.**	Consider IV Tissue Plasminogen Activator (tPA)/See Stroke Code Algorithm Qualified clinician (i.e., trained and experienced in acute stroke management or supported via telemedicine arrangement by such a clinician) should administer IV tPA to selected and qualifying patients with acute ischemic stroke within 4.5 hours of symptom onset or of time last known to be at their baselines in appropriate care circumstances (i.e., in a "stroke-ready" emergency department or hospital). ICSI or other guidelines for selection and management specifics should be followed (Strong Recommendation, High Quality Evidence). Qualified clinician (i.e., appropriately trained in neurocritical care, neurointerventional procedures, or neurosurgery) should consider treating selected and qualifying patients with acute ischemic stroke with intra-arterial thrombolysis under the following circumstances: 1. Arrival within the window for IV tPA <4.5 hours but contraindication for IV tPA 2. Arrival beyond window for IV tPA <4.5 hours and within accepted time windows for relevant vascular site and thrombolytic strategy 3. Continued major deficit after IV tPA and evidence for persisting occlusion of a relevant and accessible large artery (*Strong Recommendation, Moderate Quality Evidence*) Intra-arterial (IA) thrombolytic therapy may be a treatment option for selected patients presenting in an early time frame but beyond the time window for IV tPA (i.e., the 3 hours or 4.5 hours in selected patients; see Annotation #18, "Consider IV Tissue Plasminogen Activator [tPA]/See Stroke Code Algorithm," above). It is emphasized that there is no evidence that IA tPA has greater efficacy in any time frame in which IV tPA has been shown to be effective, i.e., within 4.5 hours of symptom onset. Trials are under way to determine whether sequential IV and IA tPA provides benefit compared with IV tPA alone in selected patients. The availability of IA option will be institution dependent, and patients must be highly selected. If considering this treatment option for a patient, a clinician must explain to the patient and family that IA therapy is beyond standard of usual care and has substantial risk. Despite the limitations of available study data, in cases of more severe presentation with middle cerebral or basilar artery occlusion, IA thrombolytic treatment may be appropriate because the prognosis without treatment is poor. If the patient is an appropriate candidate for this treatment, consideration should be given to immediate transfer to an institution offering this intervention. If an endovascular interventionist skilled in this technique is available elsewhere, the patient should be mobilized quickly. See also Appendix A, "Broader Issues," in the original guideline document.
Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA. **Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed:**	Acute Ischemic Stroke Treatment Intravenous Recombinant Tissue Plasminogen Activator (IV r-tPA) for Acute Ischemic Stroke In patients with acute ischemic stroke in whom treatment can be initiated within 3 h of symptom onset, the expert panel recommends IV r-tPA over no IV r-tPA (Grade 1A). In patients with acute ischemic stroke in whom treatment can be initiated within 4.5 but not within 3 hours of symptom onset, the expert panel suggests IV r-tPA over no IV r-tPA (Grade 2C). In patients with acute ischemic stroke in whom treatment cannot be initiated within 4.5 hours of symptom onset, the expert panel recommends against IV r-tPA (Grade 1B).

Guideline	Recommendations
American College of Chest Physicians evidence-based clinical practice guidelines. ***Chest 2012* Feb;141(2 Suppl):e601S-36S.**	

Evidence Tables

Major Trials & Studies of Intravenous Thrombolysis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
ISRCTN71616222 **RCT** ***European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits ECASS-4: ExTEND***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	264 patients (planned), aged ≥18 years, who had suffered an acute ischemic stroke (NIHSS score 4-26) 4.5- hours, previously with perfusion volume (PWI) to infarct core (DWI) ratio of ≥ 1.2, and a minimum perfusion lesion volume of 20 ml.	Patients were randomized 1:1 to receive 0.9 mg of alteplase/kg (with 10% administered as a bolus and the remainder by infusion during a 60-minute period) or matching placebo.	**Primary outcome:** Categorical shift in the mRS at 90 days **Secondary outcomes:** Disability at day 90, dichotomized as a favorable outcome (mRS) 0–1 vs. 2–6; change of ≥11 NIHSS points or reaching 0 or 1 at day 1 and day 90; reperfusion at 12–24 h after treatment; recanalization at 12–24 hours after treatment; infarct growth within 12–24 hours after treatment; NIHSS score at day 7; Barthel Index day 90 and MoCA at day 90. **Safety outcomes:** All-cause mortality, neurological death and symptomatic ICH	TBA
Thomalla et al. 2018 **Germany** **RCT** ***Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	503 patients (800 planned), aged 18-80 years, with ischemic stroke and disabling neurological deficit, with unknown time of symptom onset (i.e. upon wakening) and > 4.5 hrs. Patients were eligible if they had a pattern of "DWI-FLAIR-mismatch. Patients in whom thrombectomy was	Patients were randomized 1:1 to receive 0.9 mg of alteplase/kg (with 10% administered as a bolus and the remainder by infusion during a 60-minute period) or matching placebo.	**Primary efficacy outcome:** Favourable clinical outcome (mRS 0-1) at 90 days. **Secondary outcomes:** Median mRS score at 90 days, the proportion of patients who had a treatment response at 90 days, defined by baseline stroke severity, Beck Depression Inventory (BDI) and EQ-5D scores at 90	Median interval between last known well and treatment initiation was 10.3 hours. Median time from time from symptom recognition to treatment initiation was 3.1 hours. A significantly higher proportion of patients in the alteplase group had a favourable outcome (53.3% vs. 41.8%, adj OR=1.61, 95% CI 1.06-2.36, p=0.02). The median mRS score was significantly lower in the alteplase group (1 vs. 2, common OR=1.62,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		planned and those with severe stroke (NIHSS >25), were excluded. Mean age was 65 years, 65% were men. Median baseline NIHSS scores was 6.		days, infarct volume 22-36 hours after treatment **Safety outcomes:** Mortality, death or dependency (mRS 4-6) at 90 days, symptomatic ICH (sICH)	95% CI 1.17- 2.23, p=0.003). The proportion of treatment responders was significantly higher in the alteplase group (29.3% vs. 18.0%, adj OR=1.88, 95% CI 1.22- 2.89, p=0.004). There was no significant difference between groups in median BDI scores (6 vs. 7, p=0.69). Total mean EQ-5D score was significantly lower in alteplase group (1.9 vs. 2.4, p=0.004). There was no significant difference in median infarct volume following treatment (3 mL alteplase vs. 3.3 mL placebo, p=0.32). There were 10 deaths (4.1%) in the alteplase groups vs. 3 (1.2%) in the placebo group (adj OR=3.38, 95% CI 0.92–12.52, p=0.07). 33 patients (13.5%) in the alteplase group were dead or dependent at 90 days vs. 44 (18.3%) in the placebo group (adj OR=0.68, 95% CI 0.39–1.18, p=0.17). Depending on the criteria used, 2%-8% of patients in alteplase groups suffered a sICH vs. 0.4%-4.9% in the placebo group. The difference was not significant (p=0.13). The incidence of parenchymal hemorrhage type 2 was significantly higher in the alteplase group (4% vs. 0.4%, adj OR=10.46, 95% CI 1.32 to 82.77, p=0.03).
Anderson et al. 2016 **International** **Non-inferiority RCT** ***Enhanced***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	3,310 patients ≥18 years from 111 centres in 13 countries who were eligible for thrombolytic therapy. Mean age was 67.5 years, 38% were female. Median NIHSS score	Patients were randomized to a standard dose of alteplase (0.9 mg/kg, n=1,643, administered as: 10% bolus, 90% as infusion over 60 minutes) or a low dose (0.6 mg/kg, n=1,644, administered	**Primary outcome:** Death or disability (mRS 2-6) at 90 days **Secondary outcomes:** Symptomatic ICH, distribution of mRS scores at 90 days, major disability at 90 days, deaths at 7 and 90	The primary outcome occurred in 53.2% of low-dose patients and 51.1% in standard dose patients (OR=1.09, 95% CI 0.95-1.25, p for non-inferiority=0.51), which exceeded the upper boundary set for non-inferiority of 1.14. The risk of sICH was significantly higher in patients that received the standard dose of t-PA, using wither the SITS-MOST (<0.01) or NINDS (p<0.02)

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Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED)		was 8	as: 15% bolus, 85% as infusion over 60 minutes) within 4.5 hours of symptom onset	days	criteria. Low-dose t-PA was non-inferior in the ordinal analysis of mRS scores (common OR=1.00, 95% CI 0.89-1.13, p=0.04). 7-day mortality was significantly lower in the low-dose group (3.6% vs. 5.3%; OR=0.67, 95% CI 0.48-0.94, p=0.02) The risks of death within 90 days or serious adverse events did not differ significantly between groups (low dose vs. standard dose: 8.5% vs. 10.3%; OR=0.80, 95% CI 0.63-1.01, p=0.07 and 25.1% vs. 27.3%; OR=0.89, 95% CI 0.76-1.04, p=0.16, respectively). In sub group analysis, there were no interactions between sub groups and treatment in the primary outcome (age, sex, race, time from stroke to randomization, baseline SBP, baseline NIHSS score, final diagnosis of ischemic stroke, infarct on CT, use of antiplatelets or atrial fibrillation.
The IST-3 Collaborative Group, 2012, 2016 **International (UK)** **RCT** ***International Stroke Trial-III (IST-III)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	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	Patients who had been admitted to a stroke unit were randomized to receive: 0.9 mg/kg intravenous rt-PA (n=1,515) or control (avoid, n=1,520) within 6 hours of symptom onset. Patients from UK and Scandinavia were followed for up to 3 years using data from national registries.	**Primary outcome:** Percentage of patients alive and independent (Oxford Handicap Score-OHS of 0–2) at 6 months, mortality at 7 days. **3-year outcome:** Mortality	There was no significant difference in the percentage of patients who were treated with t-PA who were alive and independent at 6 months (37% vs. 35%, adjusted OR (95% CI) =1.13, (0.95 to 1.35), p=0.181. (Secondary ordinal analysis suggested a significant, favourable shift in the distribution of OHS scores at 6 months). Significantly improved odds of a good outcome at 6 months were associated with the sub groups of older patients (≥80 years), higher NIHSS scores, higher baseline probability of good outcome and treatment within 3 hours (favouring rt-PA group). More patients in the t-PA group died within 7 days: 11% vs. 7%, adjusted OR (95% CI) =1.60 (1.22 to 2.08), p<0.01, but there was no difference at 6 months (27% vs. 27%).

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					Adverse events: Fatal or non-fatal symptomatic intracranial hemorrhage within 7 days occurred more frequently in patients in the t-PA group (7% vs. 1%, adjusted OR (95% CI) = 6.94 (4.07 to 11.8), p<0.0001. Losses to follow-up: n=96 **Long-term follow-up** Data from 1,946 patients were available The absolute risk difference (ARD) for mortality was non-significantly lower in the rt-PA group 6 months: 27% vs. 29%; ARD=1.4%, 95% CI -2.6 to 5.4 18 months: 37% vs. 40%; ARD=2.6%, 95% CI -1.7to 6.9 36 months: 47% vs. 47%, 95% CI 3.6%, 95% CI -0.8 to 8.1. Patients who received rt-PA had a significantly higher risk of death during the first 7 days (10% vs. 7%; HR=1.52, 95% CI 1·11–2·08; p=0·004). Patients who received rt-PA had a significantly lower risk of death between 8 days and 3 years (41% vs. 47%; HR= 0.78, 95% CI 0·68–0·90, p=0·007).
Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) & Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)					
Ahmed et al. 2007 **Sweden (SITS-MOST)** **Observational monitoring study**	NA	Participating sites were those located in the EU + Norway and Iceland who were practicing thrombolysis with alteplase within 3 hours of stroke onset and were treating patients who met eligibility criteria (stroke unit care with evidence-	Patient outcomes from study cohort were compared with those from pooled results from alteplase arms of NINDS, ECASS I-II and ATLANTIS trials.	**Primary outcome:** Symptomatic ICH (defined as evidence of local or remote parenchymal hemorrhage within 22-36 hours post treatment on scan combined with a deterioration in NIHSS score of ≥4) and death within 3 months.	7.3% of patients in the SITS-MOST cohort experienced a symptomatic ICH at 3 months compared with 8.6% of patients in the pooled RCT cohort. 11.3% of patients in the SITS-MOST cohort died within 3 months compared with 17.3% of patients in the pooled RCT cohort. 54.8% of patients in the SITS-MOST cohort were

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		based protocols for early management of stroke). The SITS-MOST cohort was embedded within SITS-ISTR. 6,483 patients from 285 centres were recruiting from 2002-2006. Patients were 18-80 years and had received alteplase during routine clinical practice.		**Secondary outcomes:** Proportion of patients who were independent at 3 months (mRS scores of 0-2).	independent at 3 months compared with 49.0% of patients in the pooled RCT cohort.
Ahmed et al. 2008 **Sweden** **Observational monitoring study (SITS-ISTR)**	NA	International registry of unselected patients who received thrombolysis in one of 700 sites in 35 countries from 2002-2007 according to accepted clinical guideline practices. Included subset of patients from SITS-MOST cohort.	Patients who had been treated with alteplase (0.9mg/kg, max dose 90mg) within 3 hour of symptom onset (n=11,865) were compared with those treated from 3-4.5 hours (n=644)	**Primary outcome:** Symptomatic ICH (defined as evidence of local or remote parenchymal hemorrhage within 22-36 hours post treatment on scan combined with a deterioration in NIHSS score of ≥4) and death within 3 months. **Secondary outcomes:** Proportion of patients who were independent at 3 months (mRS scores of 0-2).	There was a trend towards increased number of patients treated from 3-4.5 hours who experienced a symptomatic ICH: 14/649 (2.2%) vs. 183/11,681 (1.6%), adjusted OR=1.32, 95% CI 1.00-1.75, p=0.052. There was a trend towards increased number of patients treated from 3-4.5 hours who died: 70/551 (12.7%) vs. 1263/10,368 (12.2%), adjusted OR=1.15, 95% CI 1.00-1.33, p=0.053. There was no between-group difference in the number of patients who were independent at 3 months: 314/541 (58.0%) vs. 5,756/10,231 (56.3%), adjusted OR=0.93, 95% CI 0.84-1.03, p=0.18.
Diedler et al. 2011 **Germany** **(SITS-ISTR)**	NA	Patients included in SITS-ISTR Registry from 2002-2009.	Comparisons of patients who weighed ≤100 kg (n=26,720) vs. >100 kg (n=1,190) to determine whether these patients, who received <0.9 mg/kg alteplase (based on 90 mg maximum total dose) had poorer clinical outcomes	**Primary outcome:** Percentage of patients with major neurological improvement (NIHSS ≥8 points or score of 0 at 24 hours) **Secondary outcomes:** Symptomatic ICH within 24 hours, independence (mRS score 0-2) and mortality at 3 months	There were baseline imbalances between groups. Patients >100 kg had lower median NIHSS scores, were more likely to be male, younger (62 vs. 70 years), current smokers, with a history of HTN, diabetes and hyperlipidemia. Patients >100 kg received a lower median t-PA dose (0.82 vs.0.90 mg/kg) There was no between-group difference in the percentage of patients with major neurological improvement (27.7% vs. 27.7%, adjusted OR=1.12, 95% CI 0.97-1.30, p=0.13).

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					Patient who weighed> 100 kg were more likely to experience a symptomatic ICH (2.6% vs. 1.7%, adjusted OR=1.60, 95% CI 1.06-2.41, p=0.02) Although there was no difference in crude 3-month mortality between groups (14.4% vs. 15.1%), when adjusted for baseline imbalances the odds of death were increased for patients >100 kg: OR=1.37, 95% CI 1.08-1.74, p=0.01. There was no difference in the percentage of patients who were independent at 3 months (59.7% vs. 53.6% after adjusting for baseline imbalances (OR=0.99, 95% CI 0.87-1.18, p=0.87)
Ahmed et al. 2013 **Sweden** **Observational monitoring study (SITS-ISTR)**	NA	Patients who were registered in the SITS-ISTR database from 2002-2011 who had been treated with t-PA	The outcomes of patients treated between 4.5-6 hours (n=283) with t-PA were compared with patients who had received treatment within 3-4.5 hours (n=4056) and within 3 hours (n=25,279)	**Primary outcomes:** Functional independence, defined as mRS score of 0-2, no/minimal disability (mRS score 0-1) and mortality at 3 months, symptomatic ICH (STS-MOST criteria). **Secondary outcomes:** SICH defined using NINDS and ECASS II criteria	Median time from stroke onset to initiation of treatment was significantly longer in the 4.5-6 hrs group: 138 vs. 210 vs. 295 minutes (p<0.01). Baseline NIHSS scores among the groups were: 12 (<3 hrs) and 9 (3-4.5 hrs, 4.5-6 hrs), p<0.01. Comparison of <3 vs. 4.5-6 hr groups The risks of SICH, mortality or functional dependency at 3 months were not significantly elevated the later-treated group SICH (SITS-MOST): adj OR=1.16, 95% CI 0.89-1.49, p=0.27. Mortality: sdj OR=1.05, 95% CI 0.65-1.70, p=0.85 Functional independence: adj OR=1.08, 95% CI 0.76-1.54, p=0.65. Comparison of <3 vs. 3-4.5 hr groups The risks of SICH and mortality were not significantly elevated in the later-treated group. Patients treated within 3 hrs were more likely to have no/minimal disability at 3 months (adj OR=0.90, 95% CI 0.82-0.98, p=0.02). When time from stroke onset to treatment was treated as continuous variable, the odds of SICH and mortality were significantly higher while the odds of 3-month survival with no/minimal disability and functional independence were significantly

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					lower, after adjusting for age and baseline NIHSS.
European Acute Stroke Study (ECASS I, II & III)					
Hacke et al. 1995 **Germany** **RCT** **ECASS I**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor: ☑ ITT: ☑	620 patients with acute ischemic stroke with moderate-severe neurological deficit from 75 centres in 14 European countries who could be treated within 6 hours of stroke onset.	Patients were randomized to receive alteplase (1.1 mg/kg, max dose 100 mg, n=313) or placebo (n=307) within 6 hours of onset of symptoms.	**Primary outcome:** Barthel Index (BI) score, mRS score at 90 days (a 15-point BI and 1 mRS grade difference between groups were considered clinically significant) **Secondary outcomes:** Combined BI/mRS at 90 days, Scandinavian Stroke Scale (SSS) score at 90 days, 30-day mortality	109 patients were excluded from the exploratory analysis (n=66 alteplase, n=43 placebo). There was no difference in the median BI score (alteplase vs. placebo) on ITT analysis: 85 vs. 75, p=0.99, median mRS scores: 3 vs. 3, p=0.41, or median SSS scores: 39 vs.36, p=0.54, at 90 days. Patients in the alteplase group had significantly higher combined scores (BI/mRS): 97.5 vs. 90, p=0.003. There was no between-group difference in 30-day mortality (17.9% vs. 12.7%, p=0.08). A higher percentage of patients in the alteplase group experienced an ICH but the results was not significant (42.8% vs. 36.8%, p=0.14).
Hacke et al. 1998 **Germany** **RCT** **ECASS II**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor: ☑ ITT: ☑	800 patients aged 18-80 years, presenting with moderate-severe ischemic stroke who could be treated within 6 hours of symptom onset and who could be followed for 90 days	Patients were randomized to receive 0.9 mg/kg of alteplase (max dose 90 mg)(n=409) or placebo (n=391)	**Primary outcome:** Percentage of patients with favorable outcome (mRS <2) at 90 days **Secondary outcomes:** Change in NIHSS scores from baseline to 30 days, Barthel Index (BI) and mRS score at 90 days, BI scores at 90 days, Scandinavian Stroke Scale scores (SSS) at 90 days, LOS and SF-36 at 90 days.	The percentages of patients with mRS<2 at 90 days (alteplase vs. placebo) were 40.3% vs. 36.6%, absolute difference =3.7%, p=0.277. Median BI + mRS scores at 90 days were similar between groups (alteplase vs. placebo): 90 vs. 90, p=0.153 Median change in NIHSS (alteplase vs. placebo): -6 vs. -5, p=0.035. Median SSS scores at day 90 were similar (alteplase vs. placebo): 42 vs. 41, p=0.103. Median LOS (days) was similar (alteplase vs. placebo): 42 vs. 41, p=0.469. There were no differences in the mental or physical subscores of the SF-36 at 90 days (49.8 vs. 48.1, p=0.183, 38.4 vs. 36.7, p=0.284, respectively). In subgroup analysis of patients treated < 3 hours

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					and 3-6 hours, there were no between-group differences on any of the outcomes. 7 patients were randomized, but not treated (n=5, placebo, n=2, alteplase) Adverse events: There was no between group difference in 90-day mortality (43 vs. 42) During the first 7 days there were more deaths due to ICH in the alteplase group (11 vs. 2). There were more parenchymal hemorrhages in the alteplase group (11.8 vs. 3.1%).
Hacke et al. 2008 **Europe** **RCT** **ECASS III**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor: ☑ ITT: ☑	821 patients 18-80 years, with onset of clinically confirmed acute ischemic stroke symptoms 3–4.5 h before initiation of study drug and persistence of symptoms for at least 30 minutes without significant improvement. Those with severe stroke (eg, NIHSS score >25) were excluded.	Patients were randomized to receive 0.9 mg/kg of alteplase (max dose 90 mg)(n=418) or placebo (n=403)	**Primary outcome:** Percentage of patients with favorable outcome (mRS <2) at 90 days **Secondary outcomes:** Percentage of patients with Barthel Index (BI) scores≥95, NIHSS score of 0 or 1, or Glasgow Outcome Scale (GOS) score of 1, at 90 days	A higher percentage of patients in the alteplase group experienced a favourable outcome (52.4% vs. 45.2%, adjusted OR=1.34, 95% CI 1.02 to 1.76, p=0.04). A higher percentage of patients in the alteplase group had NIHSS scores of 0 or 1(50.2% vs. 43.2%, adjusted OR=1.33, 95% CI 1.01 to 1.75, p=0.04). There were no between-group differences in the percentages of patients with BI scores≥95 (63.4% vs. 58.6%, p=0.16) or GOS scores of 1 (51.0% vs. 45.4%, p=0.11) Drop-outs and losses to follow-up: n=43 alteplase group, n=48 control group Adverse events: More patients in the alteplase groups experienced any ICH (27% vs. 17.6%, p<0.001) and symptomatic ICH (1.9% to 7.9% vs. 0.2% to 3.5%), depending on definition used, p<0.05). There were no other differences in other serious adverse events between groups.
Bluhmki et al.2009 **Europe** **RCT**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor: ☑	As above	As above	**Additional secondary outcomes:** Percentage of patients with mRS 0-2, Barthel Index (BI) scores≥85, 8-point improvement in NIHSS	There were no between-group differences in the percentages of patients with mRS score of 0-2 (67% vs. 62%, p=0.138) or BI score≥85 (69% vs. 66%, p=0.337) at 30 days (based on ITT analysis) At 90 days, there were no between-group

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ECASS III	ITT: ☑			scores (or NIHSS score of 0 or 1) at 30 and 90 days	differences in the percentages of patients with mRS score of 0-2 (59% vs. 53%, p=0.097) or BI score≥85 (60% vs. 56%, p=0.249, but a significantly greater percentage of patients had improved NIHSS scores (58% vs. 51%, p=0.031)(based on ITT analysis) In subgroup analysis of symptomatic ICH, time from initiation to alteplase treatment and chronic use of antiplatelet medications did not increase bleeding risk, but age ≥65 years did (p=0.04)
Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)					
Davis et al. 2008 **Australia** **RCT**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor: ☑ ITT: ☑	101 patients with ischemic stroke presenting 3-6 hours after symptom onset, >18 years with NIHSS score>4 and a premorbid mRS score of ≤2. (25 patients were>80 years)	Patients were randomized to receive 0.9 mg/kg alteplase (max dose 90 mg, n=52) or placebo (n=49) following baseline diffusion-weighted MRI (DWI) and perfusion-weighted MRIs (PWI) to establish the extent of the ischemic penumbra. Scans were repeated 3-5 days following therapy and T-2 weighted MRI conducted day 90.	**Primary outcome:** Infarct growth at 90 days in mismatch patients (PWI/DWI volume >1.2, and PWI-DWI volume ≥10 mL), using geometric mean relative growth, Symptomatic ICH **Secondary outcomes:** Good neurological outcome (NIHSS 0-1 or ≥ 8-point improvement from baseline at 90 days), good functional outcome (mRS 0-2) at 90 days)	Data from 37 alteplase patients and 43 placebo patients were included in 90-day analysis. 86% of patients had mismatch between PWI and DWI. Overall, there was no between-group difference in the geometric mean infarct growth (1.24 alteplase vs. 1.78 placebo, p=0.39). Median relative infarct growth was 1.18 (alteplase) vs. 1.79 (placebo), p=0.054. More patients in the alteplase group achieved ≥90% reperfusion (56% vs. 26%, p=0.01). The incidence of symptomatic ICH was higher among patients in the alteplase group (7.7% vs. 0%). The percentage of patients who achieved a good neurological outcome did not differ between groups (alteplase vs. placebo): 50% vs. 37%, p=0.278. Among the subset of 77 patients with mismatch, there was less infarct growth (geometric mean=0.79 vs. 2.25, p=0.001) and better neurological and functional recovery in patients in the alteplase group (73% vs. 27%, p<0.0001 and 63% vs. 32%, p=0.007, respectively).
Canadian Activase for Stroke Effectiveness Study (CASES)					

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Hill et al. 2005 **Canada** **Observational monitoring**	NA	All patients (n=1,135) who received treatment with alteplase from 1999 to 2001were included. (Participating centres (n=60) were required to perform a baseline CT scan and another scan within 24–48 hours after thrombolytic therapy to look for intracranial hemorrhage).	Prospective data collection	**Primary outcome:** Percentage of patients with excellent functional outcome (mRS 0-1) at 90 days **Secondary outcomes:** Percentage of patients who were independent (mRS score 0–2) and complete neurologic recovery (NIHSS score 0–1) at 90 days.	Median (IQR) baseline NIHSS score: 14 (9-19) Median (IQR) door-to-needle time was 155 minutes (130-175) 36.8% of patients experienced an excellent outcome (adjusted analysis) at day 90. 24.5% of patients were independent at day 90. 25.3% of patients had NIHSS scores of 0 or 1 at 90 days. Symptomatic ICH was observed in 52 patients (4.6%). Orolinguinal angioedema was observed in 15 patients (1.3%). Losses to follow-up: n=148
Alteplase Thrombolysis in Ischemic Stroke (ATLANTIS)					
Clark et al. 1999 **USA** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	613 patients 18-79 years with measurable deficit associated with ischemic stroke and onset of symptoms within 3-5 hours of initiation of treatment	Patients were randomized to receive 0.9 mg/kg alteplase (max dose 90 mg, n=307) or placebo (n=306).	**Primary outcome:** Percentage of patients experiencing excellent neurological recovery (NIHSS of 0-1) at 90 days. **Secondary outcomes:** Percentage of patients experiencing excellent functional recovery at 30 and 90 days, defined as Barthel Index (BI) scores ≥95, mRS score<2 and Glasgow Coma Score (GCS) of 1.	547 patients were treated within 3-5 hours of symptom onset of which 275 received placebo and 272 were treated with alteplase. There were no significant between group differences on any of the outcomes (alteplase vs. placebo) NIHSS score of 0-1 at: 30 days: 32.1% vs. 24.6%, p=0.06 90 days: 33.8% vs. 32.0%, p=0.65 BI score ≥95 at 30 days: 46.6% vs. 46.8%, p=0.96 90 days: 53.7% vs. 53.5%, p=0.96 mRS<2 at 30 days: 36.5% vs. 31.2%, p=0.20 90 days: 42.3% vs. 38.9%, p=0.42 GCS 0-1 at 30 days: 41.1% vs. 36.9%, p=0.32 90 days: 46.3% vs. 44.0%, p=0.59 Adverse events:

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					A higher percentage of patients who received alteplase experienced symptomatic ICH (7.0% vs. 1.1%, p<0.001, and fatal ICH (3.0% vs. 0.3%, p=0.09). There was no significant increase in 30 or 90-day mortality (7.0% vs. 4.4%, p=0.18 and 11% vs. 6.9%, p=0.09, respectively)
The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study					
Marler et al. 1995 **USA** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☒	Patients with ischemic stroke with known time of onset of symptoms, marked clinical deficit and a base-line CT scan with no evidence of intracranial hemorrhage.	Patients were randomized to receive 0.9 mg/kg alteplase (max dose 90 mg) or placebo within 3 hours of symptom onset. Study was carried out in 2 parts-part 1 included 291 patients and assessed neurological improvement within 24 hours; part 2 included 333 patients and examined clinical outcomes at 3 months.	**Primary outcomes:** Part 1: Percentage of patients with improvement of 4 points over base-line values in NIHSS scores or the resolution of the neurologic deficit within 24 hours of onset of stroke. Part 2: Patients with good outcome at 90 days defined using 4 measures- NIHSS or mRS scores of ≤1, Barthel Index (BI) scores ≥95 and Glasgow Coma Score (GCS) of 1.	**Study 1** At 24 hours there was no between-group difference in the percentage of patients who achieved neurological improvement: 47% (t-PA) vs. 39% (placebo), RR=1.2, 95% CI 0.9 to 1.6, p=0.21. (In combined analysis of patients in both groups there was a trend towards improvement in t-PA treated patients 47% vs. 39%, RR=1.2, 95% CI 1.00-1.4, p=0.06.) **Study 2** At 3 months, significantly more patients in the t-PA group had experienced a good outcome (using any of the 4 metrics) compared with patients in the placebo group BI scores: 54% vs. 39%, OR=1.6, 95%CI 1.1-2.5, p=0.026 mRS scores: 39% vs. 26%, OR=1.7, 95% CI 1.1-2.6, p=0.019. GCS: 44% vs. 32%, OR=1.6, 95% CI 1.1-2.5, p=0.025 NIHSS scores: 31% vs. 20%, OR=1.7, 95% CI 1.0-2.8, p=0.033 (same pattern when results from all patient combined) 90-day mortality (combined):no significant differences between groups (17% t-PA vs. 21% control, p=0.30) Symptomatic ICH (combined) at 36 hours was higher in the t-PA group: 6.4% vs. 0.64%

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					Losses to follow-up (combined): n=5

Systematic Reviews & Meta-Analyses

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cheng et al. 2018 **China** **Systematic review & meta-analysis**	12 studies (7,686 patients) comparing standard dose and low-dose t-PA for treatment of acute ischemic stroke. Studies included 11 prospective/retrospective and 1 RCT (ENCHANTED)	Pooled analysis of standard-dose t-PA (0.9 mg/kg) vs. low dose (0.6-0.79 mg/kg; mean dose 0.75 mg/kg)	**Primary outcomes:** Excellent (mRS 0-1) and good (mRS 0-2) outcome at 3 months **Secondary outcomes:** sICH (using ECASS, SITS-MOST and NINDS definitions), 90-day mortality	Standard-dose t-PA was not associated with a significantly reduced risk of good or excellent outcomes were OR=0.92, 95% CI 0.8-1.02 and OR=0.97, 95% CI 0.88-1.08, respectively). Using the ECASS criteria, standard dose t-PA was not associated with in an increase in sICH (OR=1.08, 95% CI 0.81-1.43). Using the SITS-MOST and NINDS criteria, low-dose t-PA was associated with a decreased risk of sICH (OR=0.71, 95% CI 0.57-0.89 and OR=0.64, 95% CI 0.42-0.99, respectively). Low-dose t-PA was not associated with a decreased risk of 90-day mortality (OR=0.87, 95% CI 0.74-1.02).
Hacke et al. 2017 Stroke Thrombolysis Trialists' Collaborators Group **International** **Meta-analysis**	Patient level data from 8 RCTs (6,136 patients), comparing i.v. alteplase (0.9 mk/kg) vs. control, for treatment of acute ischemic stroke. (NINDs a/b, ECASS II, III, ATLANTIS a/b, EPITHET, IST-3). Data from ECASS I, was excluded (dose of 1.1 mg/kg).	Pooled analysis, were conducted, using patients who would and would not meet current European Union (EU) and US manufacturer's recommendations. Hypothetical cohorts were assembled, eliminating the upper age limit of 80 years (European restriction), and extending the treatment window to 4.5 hours (compared with 3.0 hours for US).	**Primary outcome:** Excellent outcome (mRS 0-1) at 3 months, and symptomatic ICH defined in 3 ways (type 2 parenchymal hemorrhage [PH-2] within 7 days, (SITS-MOST) hemorrhage within 24–36 hours and fatal ICH within 7 days)	**Patients who would have met current EU label criteria** 2449 (40%) patients would have met the current EU label criteria. Alteplase was associated with increased odds of an excellent outcome (OR=1.42, 1.21-1.68). The odds of sICH for patients treated with alteplase were increased significantly, using all 3 criteria, but there was no increased risk of 90-day mortality (HR=0.98, 95% CI 0.76–1.25). **Patients who would have met an age-revised EU label criterion** 3491 (57%) patients who would not have met new criteria. Alteplase was associated with increased odds of an excellent outcome (OR=1.43, 1.23-1.65). The odds of sICH for patients treated with alteplase

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				were increased significantly, using all 3 criteria, but there was no increased risk of 90-day mortality (HR=1.01, 95% CI 0.86–1.19). **Patients who would not have met an age-revised EU label criterion** 3645 (41%) patients who would not have met new criteria. Alteplase was not associated with increased odds of an excellent outcome (OR=1.06, 95% CI 0.90-1.26). The odds of sICH for patients treated with alteplase were increased significantly, using all 3 criteria. The risk of early (7-day) mortality associated with alteplase was increased significantly (HR=1.42, 95% CI 1.08–1.87). The risk of 90-day mortality associated with alteplase was HR=1.19, 95% CI 0.99–1.42. **Patients who would have met the current US label criteria** 1174 (19%) patients would have met the current US label criteria. Alteplase was associated with increased odds of an excellent outcome (OR=1.55, 95% CI 1.19-2.10). The odds of sICH for patients treated with alteplase were increased significantly, using all 3 criteria. but there was no increased risk of 90-day mortality (HR=0.99, 95% CI 0.77–1.26). **Patients who would have met a 4.5-h-revised US label criterion** 3326 (54%) patients would have met a 4.5-h-revised US label criterion. Alteplase was associated with increased odds of an excellent outcome (OR=1.37, 95% CI 1.17-1.59). The odds of sICH for patients treated with alteplase were increased significantly, using all 3 criteria. but there was no increased risk of 90-day mortality (HR=1.02, 95% CI 0.87–1.20). **Patients who would not have met a 4.5-h-revised US label criterion** 2810 (46%) patients would not have met a 4.5-h-revised US label criterion. Alteplase was not associated with increased odds of an excellent outcome (OR=1.14, 95% CI 0.90-1.18). The odds of

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				sICH for patients treated with alteplase were increased significantly, using all 3 criteria. The risk of early (7-day) mortality associated with alteplase was increased significantly (HR=1.40, 95% CI 1.05–1.86). The risk of 90-day mortality associated with alteplase was HR=1.17, 95% CI 0.98–1.41.
Lees et al. 2016 Stroke Thrombolysis Trialists' Collaborators Group **International** **Meta-analysis**	Patient-level data from 9 RCTs (6,756 patients) that compared alteplase vs. placebo for acute ischemic stroke. (NINDs a/b, ECASS I/II, III, ATLANTIS a/b, EPITHET, IST-3)	Pooled analysis comparing treatment with alteplase vs. control condition using ordinal regression analysis, adjusted for treatment delay, age, and stroke severity	**Primary outcome:** Good outcome at 3 months (using dichotomized mRS scores).	After a mean delay in treatment of 4 hours, the odds of a good outcome associated with alteplase use decreased as the cut points shifted from no disability to greatest disability: mRS 0 vs. 1-6, OR=1.40, 95% CI 1.22-1.62 mRS 0-1 vs. 2-6, OR=1.28, 95% CI 1.15-1.42 mRS 0-2 vs. 3-6, OR=1.16, 95% CI 1.05-1.28 mRS 0-3 vs. 4-6, OR=1.17, 95% CI 1.06-1.29 mRS 0-4 vs. 5-6, OR=0.99, 95% CI 0.89-1.10 mRS 0-5 vs.6, OR=0.82, 95% CI 0.82-1.06 For each level of dichotomization, earlier treatment was associated with odds of a better outcome. After accounting for treatment delay, neither patient age, nor baseline severity altered the proportional benefit of the odds of a good outcome. For each patient treated with alteplase within 4.5 hours of stroke onset, significantly more patients would benefit from treatment with alteplase (55/1,000, 95% CI 13-91, p=0.004) For each patient treated within 3 hours, significantly more patients would have a better outcome (122/1,000, 95% CI 16-171). For each patient treated >4.5 hours, only 20 patients/1,000 (95% CI -31-75, p=0.45) would have a better outcome
Whiteley et al. 2016 **UK** **Systematic**	Patient-level data from 9 RCTs (6,756 patients) that compared alteplase vs. placebo for acute ischemic stroke. (NINDs a/b, ECASS I/II, III, ATLANTIS a/b, EPITHET, IST-3)	Analysis to determine the risk of intracerebral hemorrhage (ICH) associated with thrombolysis with alteplase	**Primary outcome:** Type 2 parenchymal hemorrhage within 7 days, based on CT findings; type 2 parenchymal hemorrhage using SITS-MOST criteria	275 (4.1%) patients had a type 2 parenchymal hemorrhage within 7 days, of which 104 were fatal. Treatment with alteplase was associated with a significantly increased risk of ICH CT findings: OR=5.5, 95% CI 4.01-7.0).

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
review & meta-analysis			within 24-36 hours and fatal ICH within 7 days.	SITS-MOST criteria: OR=6.67, 95% CI 4.11-10.84. Fatal ICH: OR=7.14, 95% CI 3.98-12.79 The odds were not altered significantly after adjusting for age, sex, treatment delay, stroke severity, previous stroke/TIA, diabetes, antiplatelet use, weight or SBP. Using the SITS-Most criteria, the absolute risk of ICH increased significantly from 1.5% (95% CI 0.8-2.6) for those with mild strokes (NIHSS 0-4) to 3.7% (95% CI 2.1-3.7%) in those with severed strokes (NIHSS≥22). The benefit of an excellent outcome (mRS 0-1) exceeded the absolute increase in risk of fatal ICH
Wardlaw et al. 2014 **UK** **Cochrane review**	27 trials (10,187 subjects) The majority of the trials (n=23) assessed intravenous administration of thrombolytic drugs (rt-PA, urokinase, streptokinase, r pro-urokinase or desmoteplase). In 4 trials, the intra-arterial route was used. The majority of trials recruited subjects within 6 hours of symptom onset.	Comparisons of patients who had received treatment with any thrombolytic agent following ischemic stroke vs. control (usually placebo)	**Primary outcome:** Death or dependency (mRS 3-6) at follow-up. **Secondary outcomes:** All-cause mortality 7-10 days following treatment, symptomatic and fatal ICH, all-cause mortality during follow-up, poor functional outcome at the end of follow up (mRS 3-5).	The risk of death or dependency was reduced for patients in the treatment group. OR= 0.85, 95% CI 0.78-0.93, p<0.0001. Results form 22 trials (9,318 subjects) were included. The risk of dependency was reduced for patients in the treatment group. OR=0.75, 0.69- 0.82, p<0.0001. Results form 22 trials (9,318 subjects) were included. The risk of death within 7-10 days of treatment was increased for patients in the thrombolysis group: OR= 1.69, 95% CI 1.44-1.98, p<0.0001. Results from 13 trials (7,458 subjects) were included. The risk of fatal ICH was increased for patients in the treatment group: OR= 4.53, 95% CI 3.47-5.91, p<0.0001. Results from 17 trials (9,066 subjects) were included. The risk of any symptomatic ICH was increased for patients in the treatment group: OR= 3.75, 95% CI 3.11-4.51, p < 0.0001. Results from 27 trials (10,187 subjects) were included. The risk of all-cause mortality during the follow-up period was increased for patients in the treatment group: OR= 1.18, 95% CI 1.06- 1.30, p < 0.0001).

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Results form 27 trials (10,187 subjects) were included.
Wardlaw et al. 2013 **UK** **Cochrane review**	20 trials (2,527 subjects) including trials comparing: a lower dose of a thrombolytic agent with a higher dose of the same agent, 2 different thrombolytic agents or different routes of administration.	13 trials compared higher vs. lower dose of the same agent, 5 compared one agent with another and 5 compared different routes of administration. There was overlap among studies in the treatment contrasts examined. No RCTs in this review included a placebo group. These studies are included in the 2009 Cochrane review (Wardlaw et al. 2009) included below.	**Primary outcome:** Death or dependency (mRS 3-6) at follow-up (minimum of 1 month). **Secondary outcomes:** Death from any causes, ICH, Major extracranial haemorrhage, other major extracranial events	**High vs. low dose:** High-dose t-PA was not associated with an increased risk of death/dependency or death. Death or dependency: OR= 0.86, 95% CI 0.62-1.19, p=0.35 Results from 7 studies included. Death from all causes at the end of follow-up: OR= 1.22, 95% CI 0.82-1.80, p=0.33. Results from 5 studies included. Higher doses of thrombolytic agents were associated with a significant increase in the risk of fatal ICH during follow-up. OR=2.71, 95% CI 1.22 to 6.04, p=0.015. Results from 10 studies included. There was no significant increase in the risk of major extracranial hemorrhage associated with high-dose t-PA during follow-up: OR= 1.72, 95% CI 0.93- 3.21, p=0.086. Results from 9 studies included. **Different routes of administration of the same drug:** IA t-PA was not associated with a significantly increased risk of: Death or dependency (OR= 1.08, 95% CI 0.75 to 1.55, p=0.68. Results from 4 trials included), Death at the end of follow-up (OR= 0.81, 95% CI 0.47 to 1.39, p=0.44. Results from 4 trials included), Significant intracranial haemorrhage during follow-up (OR= 1.28, 95% CI 0.61 to 2.68, p=0.51. Results from 4 trials included) Fatal ICH during follow-up (OR= 0.67, 95% CI 0.21to 2.11, p=0.69. Results from 5 trials included)
Wardlaw et al. 2012 **UK** **Systematic review & meta-analysis**	7,012 patients from 12 trials of t-PA, published from 1992-2012. Upper age limit was 80 years in all trials with upper age limit criteria, except IST-3.	Pooled comparison of patients who had received alteplase or placebo (open control in 1 trial and midway in a second trial) within 6 hours after symptom onset. Doses on t-PA ranged from 0.6 -1.1 mg/kg. 0.9 mg/kg with 90	**Early outcomes (7 days):** mortality, ICH **Outcomes at final follow-up:** Mortality, favourable outcome (mRS or Oxford Handicap Score of 0-1), alive and independent (mRS or OHS of 0-2), and dependency (mRS or OHS	**Early outcomes:** The risks of death, ICH (fatal and symptomatic) were all significantly increased among patients who received t-PA Mortality: OR (95% CI) =1.44 (1.18-1.76),p=0.003 Fatal ICH: OR (95% CI)=4.18 (2.99-5.84), p<0.001 Symptomatic ICH: OR (95% CI)=3.72 (2.98-4.64), p<0.0001 **Final outcomes:** The number of patients with favourable outcomes at final follow-up was

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		mg total dose was most common (n=8). Subgroup analysis of time to treatment and age.	3-5) Final follow-up: 1 months (n=2), 3 months (n=9), 6 months (n=1)	significantly increased among patients who received t-PA mRS 0-1: OR (95% CI)=1.29 (1.16-1.43), p<0.001 Alive and independent: OR (95% CI)=1.17 (1.06-1.29), p=0.01 Mortality: OR (95% CI)=1.06 (0.94-1.20), p=0.33. The odds of being alive and independent were higher among patients treated with t-PA within 3 hours: OR (95% CI)=1.53 (1.26-1.86), p<0.0001, compared with patients treated from 3-6 hours OR (95% CI)=1.07 (0.96-1.2), p=0.24 If treated within 3 hours, patients >80 were also more likely to be alive and independent OR (95% CI)=1.68 (1.20-2.35) compared with patients ≤80 years OR (95% CI)=1.51 (1.18-1.93)
Lansberg et al. 2009a) **USA**	Data from 1,622 patients from ECASS-1, ECASS-II, ECAS-III and ATLANTIS trials	Pooled comparison of patients who had received alteplase or placebo within 3-4.5 hours after symptom onset	Favourable outcome at 90 days, using a global outcome measure (mRS and NIHSS scores of 0-1 and Barthel Index scores ≥95), 90-day mortality	Patients who had received alteplase had a significantly greater likelihood of a favourable outcome: OR (95% CI)=1.31 (1.1-1.56), p=0.002, and were no more likely to be dead at 90 days. OR (95% CI)=1.01, (0.75-1.43), p=0.83

Timing of Thrombolytic Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Emberson et al. 2014 **UK** **Meta-analysis**	NA	Data from 6,756 patients from 9 major t-PA trials (NINDs a/b, ECASS I/II, III, ATLANTIS a/b, EPITHET, IST-3)	Analysis to determine if age, treatment delays and baseline stroke severity modified the outcome of patients treated with t-PA vs. placebo.	**Primary outcome:** Good stroke outcome (mRS 0-1) at 3-6 months. **Secondary outcomes:** Fatal ICH at 7 days, symptomatic hemorrhage, 90-day mortality	Earlier treatment was associated with a better stroke outcome (mRS 0-1) ≤3.0 h: OR=1.75, 95% CI 1.35-2.27 >3 to ≤4.5 h: OR=1.26, 95% CI 1.05-1.51 >4.5 h: OR=1.15, 95% CI 0.95-1.40 There was no effect of age on the odds of a good recovery (p for interaction =0.53) ≤80 years; OR=1.25, 95% CI 1.10-1.42 >80 years: OR=1.56, 95% CI 1.17-2.08 There was no effect of baseline stroke severity on

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					the odds of a good outcome (p for interaction =0.06): Baseline NIHSS score 0-4: OR=1.48, 95% CI 1.07-2.06 5-10: OR=1.22, 95% CI 1.04-1.44 11-15: OR=1.24, 95% CI 0.98-1.58 16-21: OR=1.50, 95% CI 1.03-2.17 ≥22: OR=3.25, 95% CI 1.42-7.47 Treatment with t-PA increased the risk of any ICH and fatal ICH at 7 days, irrespective of age, timing of treatment or stroke severity. Time to treatment with t-PA was not associated with an increased risk of mortality at 90 days ≤3.0 h: OR=1.00, 95% CI 0.81-1.24 >3.0-≤4.5 h: OR=1.14, 95% CI 0.95-1.36 >4.5 h: OR=1.22, 95% CI 0.99-1.50 Overall: OR=1.11, 95% CI 0.99-1.25, p=0.07
Fanarow et al. 2014 **USA** **Observational study**	NA	71,169 patients included in patients included in the Get with the Guidelines database, admitted to 103 hospitals from 2003-2013 who had received t-PA within 3 hours following acute ischemic stroke. Median age was 72 yrs, 50.1% were female. Median onset to arrival time was 51 minutes. Median NIHSS score was 11.	The outcomes of patients admitted prior to the implementation of the Target: Stroke program in 2010 (n=27319) were compared with those who were admitted afterwards (n=43850). The Target: Stroke initiative was a quality improvement project organized by the AHA/ASA, designed to improve timely access to acute stroke care. One of the components addressed strategies to decrease: door to needle (DTN) for t-PA administration.	In-hospital mortality, discharge home, ambulatory status at discharge, symptomatic ICH within 36 hours of t-PA, any t-PA complication within 36 hours of t-PA administration.	The percentage of patients who received t-PA within 60 minutes of arrival increased significantly from 29.6% to 41.3%, (p<0.001). The median DTN time decreased significantly 77 vs. 67 minutes, p<0.001). The odds of in-hospital all-cause mortality, symptomatic ICH and t-PA complications were all were significantly (p<0.001) decreased during the post-intervention period (adj ORs: 0.89, 95% CI 0.83-0.94; 0.83, 95% CI 0.76-0.91 & 0.83, 95% CI 0.77-0.90). The odds of discharge home were significantly increased (adj OR=1.14, 95% CI 1.09-1.19, p<0.001).
Saver et al. 2013 **USA**	NA	58,353 ischemic stroke patients included in the Get With the Guidelines	Clinical outcomes of patients with onset to treatment times of 0-90	Factors associated with onset to treatment (OTT) and association between OTT and	The median OTT times of the groups were 80, 140 and 208 minutes.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Observational study		Stroke registry who were treated with tPA within 4.5 hours of symptom onset, from 2003-20012.	(n=5404), 91-180 (n=45029) and 181-27) n=7920) min, were compared.	outcome	Mean baseline NIHSS scores were highest among patients in the 0-90 min group (13.2 vs. 12.5 vs. 7.3, p<0.001). The following patient characteristics were independently associated with earlier OTT: higher NIHSS scores, arrival to hospital by EMS, arrival during regular hours to hospital, a history of carotid stenosis. A prior history of stroke, diabetes, PVD and female sex were significant, independent predictors of increased OTT. Each 15-minute decrease in OTT was independently associated with: decreased mortality (OR=0.96, 95% CI 0.95-0.98, p<0.001), a decrease in t-PA complications (OR=0.97, 95% CI 0.96-0.98, p<0.001), decreased ICH (OR=0.96, 95% CI 0.95-0.98, p<0.001), increased odds of independent ambulation status at discharge (OR=1.04, 95% CI 1.03-1.05, p<0.001) and discharge home (OR=1.03, 95% CI 1.02-1.04, p<0.001).
Fanarow et al. 2011 **USA** **Observational study**	NA	25,504 ischemic stroke patients included in the Get with the Guidelines Stroke registry who were treated with tPA within 3 hours of symptom onset from 2003-2009. The sample represented 19.7% of all patients in the registry.	Clinical outcomes of patients with door-to-needle times of ≤60 and >60 minutes were compared	In-hospital mortality, discharge home, ambulatory status at discharge, symptomatic ICH, any t-PA complication	Patients treated within 60 minutes were less likely die during hospitalization: Adjusted OR (95% CI) =0.78 (0.69-0.90), p=0.0003. After adjusting for many demographic and prognostic factors, the odds of discharge home or being ambulatory at discharge were not significantly increased for patients treated ≤60 minutes, nor were they significantly reduced for the outcomes of any t-PA complication including symptomatic ICH.
Lansberg et al. 2009 b) **USA** **Pooled analysis**	NA	Data from NINDS (parts 1 &2), ECASS I & II and ATLANTIS trials (A & B trials)	The final 3-month mRS scores were compiled according to time to treatment with t-PA: 0-90 minutes, 91-180 minutes, 181-270 minutes and 271-360 minutes. Number needed to treat	NNTB & NNTH	The NNTB estimates for treatment within 0-90 minutes ranged from: 2.0-6.0; NNTH ranged from 65-82 The NNTB estimates for treatment within 91-180 minutes ranged from: 2.9-7.0; NNTH ranged from 37-49

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			to benefit (NNTB) and NNT to harm (NNTH) were estimated for each of the 4 time periods based on estimates using algorithms derived from individual patient outcomes per 100 patients, based on expert panel, computer simulation and minimum and maximum possible benefit		The NNTB estimates for treatment within 181-270 minutes ranged from: 3.9-9.7; NNTH ranged from 30-36 The NNTB estimates for treatment within 271-360 minutes ranged from: 12.1-30; NNTH ranged from 13-16.1.

The Effect of Advanced Age on Outcome

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Arora et al. 2016 **USA** **Retrospective study**	NA	35,708 patients included in the Get with the Guidelines Registry, from 2009-2013 who had arrived to hospital within 120 minutes of symptom onset and received t-PA	Safety and outcome data from 4 age groups were compared: 18-64 years, 65-79 years, 80-89 years and ≥90 years.	**Primary outcomes:** Discharge disposition, independent ambulation at discharge, in-hospital mortality, symptomatic intracerebral hemorrhage (sICH), and systemic bleeding complications related to thrombolysis within 36 hours Analysis were adjusted for patient and hospital characteristics	2,585 patients (7.2%) were ≥90 years. The use of t-PA declined with advancing age. 18-64 years (7.1%) vs. ≥90 years (5.6%). Among eligible patients without contraindications, the number of patients treated with t-PA decreased significantly ($p<0.0001$) with age: 18-64 years 86.6%, 65-79 years, 84.6%, 80-89 years 80.6% and ≥90 years 67.4%. Compared with patients aged 18-64 years, fewer patients aged ≥90 years were discharged home (13.5% vs. 59.2%), or were independent in ambulation (13.4% vs. 58.7%). In-hospital mortality was higher (16.2% vs. 4.4%), as were s ICH (6.1% vs. 3.0%). Age ≥90 years was an independent predictor of not being discharged home, dependent in ambulation, in-hospital mortality, and in-hospital mortality or hospice care, compared with patients aged 18-89

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					years.
Reuter et al. 2015 **Germany** **Retrospective study**	NA	101,349 patients included in the Baden-Wuettemberg stroke registry from 2008-2012, which included the data from 142 hospitals. All stroke patients ≥18 years and admitted within 7 days of stroke are registered.	The outcomes of patents across different age groups (increments of 10 years) who received thrombolysis were compared with those who did not, are reported.	**Primary outcome:** mRS ≤1 at discharge **Secondary outcomes:** mRS ≤2 at discharge, in-hospital mortality Analysis were adjusted for pre-stroke and admission mRS, NIHSS score, prior stroke, diabetes, AF, admitting facility and LOS	Of the total sample, 32,576 patients were aged 80-89 years and 5,999 were ≥90 years. **80-89 yrs:** The odds of the primary outcome were significantly increased for patients (25%) who received thrombolysis (adj OR=2.20, 95% CI 1.95-2.47, p<0.0001). The odds of mRS ≤2 were significantly increased for patients (32%) who received thrombolysis (adj OR=1.90, 95% CI 1.69-2.14, p<0.0001). The odds of in-hospital mortality were significantly increased for patients (14%) who received thrombolysis (adj OR=1.14, 95% CI 1.00-1.30, p=0.05). **≥90 yrs**: The odds of the primary outcome were not increased significantly for patients (15%) who received thrombolysis (adj OR=1.25, 95% CI 0.88-1.78, p=0.21). The odds of mRS ≤2 were significantly increased for patients (17%) who received thrombolysis (adj OR=1.61, 95% CI 1.13-2.31, p=0.009). The odds of in-hospital mortality were not significantly increased for patients (20%) who received thrombolysis (adj OR=1.21, 95% CI 0.91-1.61, p=0.18).
Manawadu et al. 2013 **UK** **Observational study**	NA	68 thrombolyzed and 54 nonthrombolyzed patients included in a prospective database admitted to hospital from 2009-2010 with wakeup stroke (i.e last seen normal <12 hrs, but >4.5 hrs previously). Of the patients who were thrombolyzed, 48.5%	The outcomes of patients who were >80 years and thrombolyzed were compared with those who were not thrombolyzed.	**Primary outcome:** The percentage of patients who had an excellent (mRS score 0-1) or favourable (mRS score 0-2) outcome at 3 months **Secondary outcome:** ICH, mortality at 3 months	Patients who were thrombolyzed had significantly lower mortality (24% vs. 47%, p=0.034, OR=0.30, 95% CI 0.09-0.97), and were more likely to have achieved a favourable outcome (30% vs. 5%, p=0.023, OR=4.69, 95% CI 1.22-18.0). There were no significant differences between groups in the percentages of patients who had experienced an excellent outcome (15% vs. 5%, p=0.24), or those who had experienced any ICH (18% vs. 5%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		were >80 yrs. Of the patients who were not thrombolyzed, 38.9% were >80 yrs.			
Alshekhlee et al 2010 **USA** **Observational study**	NA	Cohort of 7,950 acute ischemic stroke patients from the National Inpatient Sample database who received thrombolysis, from 2000-2006.	Comparison of patients ≤80 years (n=6,291) and >80 Years (n=1,659)	In hospital Mortality and ICH	Patients >80 years were treated less frequently with thrombolytic therapy (1.05% vs. 1.72%). Mortality and risk of ICH were higher among patients >80 years: 16.9% vs. 11.5%; OR (95% CI)= 1.56 (1.35 to 1.82) and 5.73% vs. 4.40%; OR=1.31 (1.03 to 1.67), respectively. In multivariable analyses, use of thrombolytics in patients >80 years was not an independent predictor of mortality (OR=1.22, 0.93-1.89, p=0.13), but was a predictor of ICH (OR=9.69, 6.25-15.02, p<0.0001)
Ford et al. 2010 **UK** **Observational study**	NA	21,242 patients from the SITS-ISTR database.	Comparisons of patients >80 years (n=1,831) and ≤80 years (n=19,411).	**Primary outcomes:** 90-day mortality, independence at 90 days (mRS 0-2), complete recovery at 90 days (mRS 0-1), ICH	The median ages of the 2 groups were 82 and 68. The initial median NIHSS score of patients >80 years was higher (14 vs. 12, p<0.005) Patients >80 years had a higher 90-day mortality rate (30% vs. 12%, p<0.005; adjusted OR= 1.53; 95% CI, 1.43 to 1.65, p<0.005), were less likely to be independent at 90 days (35% vs. 57%; p<0.005; adjusted OR= 0.73; 95% CI, 0.68 to 0.78; p<0.005), or to have recovered completely (24.7% vs. 40.6%, p<0.005, adjusted OR=0.81, 95% CI 0.75-0.87, p=0.005. ICH risk was not significantly increased for patients >80 years after adjustment for other risk factors (>80 vs. ≤80 years). Using SITS-MOST definition 1.8% vs. 1.7%, p=0.70, adjusted OR= 0.90, 95% CI, 0.73 to 1.09; p=0.28. Using NINDS definition: 9.5% vs. 7.8%, p=0.005, adjusted OR= 0.96, 95% CI, 0.87 to 1.06, p=0.42).
Mateen et al. 2010	NA	Subset of patients ≥80 years from CASES	The outcomes of patients aged 80-89 years	**Primary outcomes:** Percentage of patients with	There were no significant between-group differences on any of the outcomes (80-89 vs. ≥90).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **Observational study**		study.	(n=242) and ≥90 years (n=28) were compared.	good clinical outcome at 30 days (mRS score of 0-1), 90-day mortality and symptomatic ICH	Good 30-day outcome: 26% vs. 30%, RR=1.2, 95% CI 0.6-2.2, p=0.647 Symptomatic ICH: 4% vs. 7%, RR=1.7, 95% CI 0.4-7.5, p=0.359 90-day mortality: 33% vs. 52%, RR=1.5, 95% CI 1.0-2.3, p=0.87.
Mishra et al. 2010 **UK** **Controlled study**	NA	23,334 patients from the SITS-ISTR and 6,166 patients who were not thrombolyzed from the VISTA registry	Comparison of patients who were thrombolyzed with those who were not, plus comparisons of outcomes of patients who were ≤80 years (n=15,527) and >80 years (n=3,472).	**Primary outcome:** Distribution of mRS scores at 3 months **Secondary outcomes:** Excellent outcome at 3 months (mRS 0-1), good outcome at 3 months (mRS 0-2), and mortality at 3 months	Treatment with thrombolysis was associated with significantly more favourable distribution of mRS scores. Adjusted OR=1.6, 95 CI 1.5-1.7, p<0.01. Patients who were>80 years were just as likely to benefit (unadjusted OR=1.4, 95% CI 1.3-1.6, p<0.0001) Excellent outcome: Overall adjusted OR=1.6, 95% CI 1.5-1.7, p<0.01, for patients >80 years unadjusted OR=1.9, 95% CI 1.5-2.3 (favours thrombolysis) Good outcome: Overall adjusted OR=1.9, 95% CI 1.8-2.1, p<0.01. For patients >80 years OR=2.1, 95% CI 1.7-2.5. (favours thrombolysis) 3-month mortality: Overall adjusted OR=0.85, 95% CI 0.78-0.92, p<0.01. For patients >80 years OR=0.89, 95% CI 0.76-1.0. (favours thrombolysis)

Intra-arterial Thrombolysis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Nam et al. 2013 **Canada** **Systematic review & meta-analysis**	NA	6 RCTs examining intraarterial thrombolysis with compared with either standard treatment or intravenous thrombolysis following acute ischemic stroke	4 trials compared IA t-PA (IAT) with standard care excluding I.V. t-PA, 2 trials compared IA t-PA with I.V. t-PA. Treatment contrasts: 1) IA vs. I.V alteplase	Poor functional outcome (mRS score 3-6), good functional outcome (mRS score 0-2), mortality, assessed at 60 or 90 days ICH within 24 hours	**IAT vs. standard care** Poor functional outcome (mRS 3-6): RR=0.80, 95% CI 0.67 to 0.95, p=0.01 (favours IAT) Results from 3 trials included (n=310). Poor functional outcome (mRS 2-6): RR=0.83, 95% CI 0.73 to 0.94, p=0.004 (favours

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		Samples sizes of included studies ranged from 16 to 180, median NIHSS scores of subjects were 17 (3 trials), 14 (1 trial) and 23 (1 trial)	(n=1) 2) IA prourokinase vs. I.V. urokinase (n=1) 3) IA prourokinase + heparin vs. I.V. heparin, (n=2) 4) IA urokinase + heparin vs. heparin (n=1) 5) IA prourokinase vs. standard medical treatment (n=1) Mechanical clot retrieval was permitted in a single study		IAT) Results from 4 trials included (n=350). Mortality: RR=0.82, 95% CI 0.56 to 1.21, p = 0.32 (trend favours IAT). Results from 4 trials (n=350) Symptomatic ICH: RR = 3·90, 95% CI 1.41 to 10.76, p = 0.009 (favours IAT). Results from 2 trials included (n=316) **IAT vs. IV t-PA** Poor functional outcome (mRS 3-6): RR = 0.68, 95% CI 0.46 to 1.00, p=0.05 (favours IAT). Results from 2 trials included (n=81). Mortality: (RR = 1.12, 95% CI 0·47 to 2.68; p = 0.79. Results from 2 trials included (n=81) Symptomatic ICH: RR = 1.13, 95%CI 0.32 to 3.99, p = 0·85. Results from 2 trials included (n=81).
Ogawa et al. 2007 **Japan** **RCT** ***The Middle cerebral artery Embolism Local fibrinolytic intervention Trial (MELT)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor: ☑ ITT: ☑	115 patients aged 20-75 years with ischemic stroke in the MCA distribution with symptom onset of <6 hours and a minimum NIHSS score of 5 with no premorbid disability	Patients were randomized to conventional treatment including medical and rehabilitation therapies (n=57) or intraarterial Urokinase (UK 120,000 IU over 5 minutes, and repeated up to a maximum dose of 600,000 IU)(n=57)	**Primary outcome:** Proportion of patients with good outcome (mRS of ≤2) at 90 days **Secondary outcomes:** Proportion of patients with NIHSS score of 0-1 and Barthel Index (BI) scores of ≥95, all-cause mortality at 90 days, incidence of ICH	Trial was terminated prematurely when I.V. t-PA was approved for ischemic stroke in Japan. The percentage of patients who experienced a good clinical outcome at 90 days did not differ between groups: 49.1% (UK) vs. 38.6% (standard care), p=0.345. A greater percentage of patients in the UK group had NIHSS scores of 0-1 at 90 days (35.1% vs. 14.0%, p=0.017). The percentage of patients with BI scores of ≥95 at 90 days did not differ between groups: 49.1% (UK) vs. 38.6% (standard care), p=0.345. There was no difference in all-cause mortality between groups at 90 days: 5.3% (UK) vs. 3.5% (standard care), p=0.647. Adverse events: No significant differences in frequency or severity between groups. ICH within 24 hours: 9% (UK) vs. 2% (standard care)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Brain edema: 5% (UK) vs. 4% (standard care) Recurrence: 7% (UK) vs. 2% (standard care) 2 patients, one in each group did not receive allocated treatment
Furlan et al. 1999 **USA** **RCT** ***Prolyse in Acute Cerebral Thromboembolism (PROACT II)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor: ☑ ITT: ☑	180 patients aged 18-85 years with ischemic stroke in the MCA distribution with symptom onset of <6 hours and NIHSS score of 4-30.	Eligible patients underwent diagnostic cerebral angiography and if still eligible were randomized within 6 hours of symptom onset to receive 9 mg of IA r-proUK over 2 hours +I.V. heparin (n=121) or I.V. heparin only (control) (n=59)	**Primary outcome:** Percentage of patients with mRS of ≤2 at 90 days. **Secondary outcomes:** Percentage of patients with NIHSS score of 0-1, percentage of patients with ≥ 50% reduction in NIHSS scores and Barthel Index (BI) scores of ≥90, mortality All secondary outcomes assessed at 90 days	A significantly higher percentage of patients in the IA r-proUK group had mRS scores of 0-2 at 90 days: 40% vs. 25% p=0.04, absolute difference 15%, OR=2.13, 95% CI 1.02 to 4.42, NNT=7. There were no significant differences between groups on any other outcomes (r-proUK vs. control) % of patients with mRS score≤1: 26% vs. 17%, p=0.16 % of patients with BI score ≥90: 41% vs. 32%, p=0.24 % of patients with ≥ 50% reduction in NIHSS scores: 50% vs. 44%, p=0.46 Mortality: 25% vs. 27%, p=0.80 Losses to follow-up: n=10 (r-proUK group), n=8 (control group) Adverse events: ICH with neurological worsening within 24 hours- 10% (r-proUK group), 2% (control group)

Tenecteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Logallo et al. 2017 **Norway** **RCT** ***Norwegian Tenecteplase Stroke Trial (NOR-TEST)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor: ☑ ITT: ☑	1,100 patients ≥18 years, recruited from 13 stroke units, with acute onset (within 4.5 hours) of ischemic stroke, or within 4.5 hours of awakening with symptoms, living independently pre-stroke. Patients eligible for bridging therapy before	Patients were randomly assigned (1:1) to receive intravenous tenecteplase 0.4 mg/kg (to a maximum of 40 mg) or alteplase 0.9 mg/kg (to a maximum of 90 mg)	**Primary outcome:** Excellent outcome (mRS ≤1) at 90 days **Secondary outcomes:** ICH and symptomatic ICH occurring within 24–48 hours, major neurological improvement at 24 hours (NIHSS score of 0 or	A final diagnosis other than ischaemic stroke or TIA was found in 18% of patients in the tenecteplase group and 17% of patients in the alteplase group. There were no significant differences between groups on the primary or any of the secondary outcomes in either the intention-to-treat or per-protocol analyses. **ITT analysis**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		endovascular treatment were also included. Mean and median ages were 71 and 77 years, respectively, 40% were women. Mean NIHSS score at baseline was 5.7.		improvement of ≥ 4 points compared with baseline), ordinal shift analysis of mRS at 3 months, and 90 day-mortality	64% of the patients in the tenecteplase group and 63% of those in the alteplase group had an excellent outcome at 90 days (OR=1.08, 95% CI 0.84-1.38, p=0.52). 9% of patients in each group experienced an ICH within 24-48 hours, 5% of patients in each group had died by 90 days. At 24 hours, there was major neurological improvement in 42% of tenecteplase patients vs. 39% in alteplase patients. The frequency of serious adverse events was similar between groups.
Huang et al. 2015 **UK** **RCT (Phase II)** ***Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor: ☑ ITT: ☑	104 patients≥18 years, living independently prior to stroke, admitted to a single centre over 20 months (2012-2013), who were eligible for thrombolytic therapy following an acute ischemic stroke. Mean age was 71 years, 64% were male. Median baseline NIHSS score was 12	Patients were randomized to receive tenecteplase (0.25 mg/kig, 25 mg max, n=52) or alteplase (0.9 mg/kg, 90 mg max, n=52) within 4.5 hours of stroke.	**Primary outcome:** Percentage of penumbra salvaged 24-48 hours post stroke (volume measured at baseline CT – volume measured at follow-up) **Secondary outcomes:** Infract volume at 24-48 hours, number of patients with recanalization, early clinical improvement (improvement in NIHSS score of ≥8 points, or score of zero at 24-48 hours, distribution of mRS scores at 30 and 90 days, number of patients with excellent functional recovery (mRS 0-1) at 30 and 90 days, 90-day mortality, **Safety outcomes:** Any and symptomatic ICH	8 patients had final non-stroke diagnoses and were excluded from primary and secondary outcome analyses Mean onset to treatment times were 184 minutes (tenecteplase) and 192 minutes (alteplase). There were no significant differences between groups for any of the primary or secondary outcomes. The primary outcome was achieved in 68% of patients in both groups (MD=1.3%, 95% CI -9.6-12.1%). Mean total infarct volume at 24-48 hours was 75 mL (tenecteplase) vs. 66 mL (alteplase) MD=5.0, 95% CI -25.6-35.4 mL) 40% of patients in the tenecteplase group had early neurological improvement vs. 24% in alteplase group (OR=2.1, 95% CI 0.9-5.2). 28% of patients in the tenecteplase group had excellent recovery at 90 days vs. 20% in alteplase group (OR=1.8, 95% CI 0.6-5.5). 90-day mortality was 17% (tenecteplase) vs. 12%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(alteplase) The incidences of symptomatic and any ICH were similar between groups The total numbers of serious adverse events (SAE) at 90 days were 32 (62%) for tenecteplase vs. 16 (31%) for alteplase. 6% of SAE were probably or definitely related to the study drug (tenecteplase) vs. 5 (10%) for alteplase

Combination of Thrombolysis and Statins

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Montaner et al. 2016 **Spain** **RCT** ***Stroke Treatment with Acute Reperfusion and Simvastatin (STARS)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor: ☑ ITT: ☑	104 patients admitted to one of 18 hospitals following acute ischemic stroke (within 12 hours of symptom onset) with a NIHSS score of 4-22. Median age was 74 years, 48% male, Median baseline NIHSS score was 7.53% of patients were treated with thrombolytic agents.	Patients were randomized to receive 40 mg simvastatin (n=50) or placebo (n=54) for 90 days.	**Primary outcome:** Excellent functional outcome at 3 months (mRS 0-1) **Secondary outcomes:** Improvement in NIHSS scores of ≥4 at 7 days **Safety outcomes:** Symptomatic hemorrhagic transformation	There was no significant difference between groups in the risk of the primary outcome (68.8% vs. 70%, adj OR=0.99, 95% CI 0.35-2.78, p=0.98). There was no significant difference between groups in the risk of the secondary outcome (64% vs. 68.8%, adj OR=0.85, 95% CI 0.36-2.02, p=0.71). There was no significant difference between groups in the risk of hemorrhagic transformation (0% vs. 3.7%, p=0.49).

Thrombolysis Delivered in Mobile Stroke Units

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	The outcomes of patients who received thrombolysis therapy using the mobile stroke unit, STEMO from 2011-2015 (n=505) were compared with patients	**Primary outcome:** Excellent functional outcome at 3 months (mRS 0-1) **Secondary outcomes:** Proportion of patients living without severe disability, or	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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		NIHSS score was 8.	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)	able to ambulate independently (mRS 0-3) at 3 months, 3-month mortality **Safety outcomes:** Intracranial hemorrhage, 7-day mortality	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**	Concealed Allocation: ☒ 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 alternating weeks.	**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). 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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					There were no significant differences among groups in hospital mortality, sICH or LOS.
Walter et al. 2012 Germany RCT	Concealed Allocation: ☑ 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.

Reversal of Anticoagulation

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pollack et al. 2017 **RE-VERSE AD** **International** **Prospective study**	NA	503 participants ≥18 years who were taking dabigatran. Group A (n=301) were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent. Group B (n=202) were those who required surgery or other invasive procedures that could not be delayed for at least 8 hours. Median age was 78 years, 54.5% were men. 31% had sustained a previous stroke or TIA.	Patients received 5 g of intravenous idarucizumab, administered as two 50-ml bolus infusions, (2.5 g each), no more than 15 minutes apart.	**Primary endpoint:** Maximum percentage reversal of the anticoagulant effect of dabigatran achieved within 4 hours **Secondary outcome:** Restoration of homeostasis, clinical outcomes	>95% of patients were receiving dabigatran for stroke prevention (treatment of atrial fibrillation). Intracranial bleeding accounted for 32.6% of patients in Group A. Abdominal conditions and fractures accounted for 44.6% of patients in group B. The median maximum percentage reversal within 4 hours after the administration of idarucizumab was 100% Among patients in group A, 67.7% had confirmed bleeding cessation within 24 hours. Median time to hemostasis after the administration of idarucizumab was 2.5 hours. Among patients in group B, hemostasis was assessed as normal in 93.4% patients, mildly abnormal in 5.1% of patients and moderately abnormal in 1.5%. 30-day mortality rate was 13.5% in group A and 12.6% in group B. 90-day mortality rate was 18.8% in Group A and 18.9% in group B. Thrombotic events occurred in 4.8% of patients within 90 days.
Pollack et al. 2015 **RE-VERSE AD** **International** **Prospective study (interim results)**	NA	90 participants ≥18 years who were taking dabigatran. Group A (n=51) were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent. Group B (n=39) were those who	Patients received 5 g of intravenous idarucizumab, administered as two 50-ml bolus infusions, (2.5 g each), no more than 15 minutes apart.	**Primary endpoint:** Maximum percentage reversal of the anticoagulant effect of dabigatran achieved within 4 hours **Secondary outcome:** Restoration of homeostasis	At study entry the results of 22 patients were excluded as their diluted thrombin time were within normal limits. The median maximum reversal in patients in both groups A and B was 100%, assessed by dilute thrombin time and ecarin clotting time. Among those whose data could be analyzed, the dilute thrombin time was normalized in 98% of the patients in group A and in 93% of those in group B.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		required surgery or other invasive procedures that could not be delayed for at least 8 hours. Mean age was 76.5 years, 56% were male.			The ecarin clotting time was normalized in 89% of Group A patients and in 88% of the Group B patients. At 12 hours and 24 hours, the dilute thrombin time was below the upper limit of the normal range in 90% of the patients in group A and in 81% of those in group B. The ecarin clotting time was below the upper limit of the normal range in 72% and 54% of the patients who could be evaluated, respectively. The concentration of unbound dabigatran was < 20 ng per milliliter in 93%and 79% of patients at 12 and 24 hours, respectively. There were 18 deaths (9 in each group) and 5 thrombotic events. 21 patients (13 patients in group A and 8 in group B) had serious adverse events. Among patients in group A who could be assessed, homeostasis was restored within a median of 11.4 hours.

Pediatric Thrombolytic Therapy

Published Guidelines

Guideline	Recommendations
Demaerschalk BM, Kleindorfer DO, Adeoye OM et al. **Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association.** ***Stroke* 201;47(2):581-641**	The efficacy and risk of intravenous alteplase administration in the pediatric population (neonates, children, and adolescents <18 years of age) are not well established (*Class IIb; Level of Evidence B*).
Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, Vesely SK. **Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines.** ***Chest* 2012 Feb;141(2 Suppl):e737S-801S.**	**Neonates** No recommendations made for the use of thrombolysis as a treatment following ischemic stroke. 2.18. For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented, ongoing cardioembolic source, we suggest supportive care over anticoagulation or aspirin therapy (Grade 2C). 2.19. For neonates with a first AIS and a documented cardioembolic source, we suggest anticoagulation with UFH or LMWH (Grade 2C). 2.20. For neonates with recurrent AIS, we suggest anticoagulant or aspirin therapy (Grade 2C). **Children** 2.52 For children with AIS, we recommend against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols (Grade 1C).
Roach ES, Golomb MR, Adams R et al. **Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young.** ***Stroke* 2008;39:2644-2691.**	**Recommendations for Perinatal Stroke** ***Class III Recommendation*** Thrombolytic agents are not recommended in neonates until more information about the safety and effectiveness of these agents is known (Class III, Level of Evidence C). **Recommendations for Thrombolytic Therapy for Childhood Stroke** ***Class II Recommendation*** Thrombolytic therapy with tPA may be considered in selected children with CVST (Class IIb, Level of Evidence C). ***Class III Recommendation*** Until there are additional published safety and efficacy data, tPA generally is not recommended for children with AIS outside a clinical trial (Class III, Level of Evidence C). However, there was no consensus about the use of tPA in older adolescents who

Guideline	Recommendations
	otherwise meet standard adult tPA eligibility criteria.
Royal College of Physicians, London. Paediatric Stroke Working Group. Paediatric Stroke Working Group. Stroke in childhood: clinical guidelines for diagnosis, management and rehabilitation, 2004. **www.rcplondon.ac.uk/pubs/books/childstroke/childstroke_guidelines.pdf**	No recommendation made "There is currently no evidence to support use of thrombolytic agents such as tissue plasminogen activator (tPA) in the acute treatment of arterial ischaemic stroke in children"

Evidence Table

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Alsheklee et al. 2013 **USA** **Retrospective study**	NA	9,257 children included in the Kid's Inpatient database who were admitted to hospital from 1998-2009 following acute ischemic stroke	The characteristics and outcomes of patients who had received t-PA (n=67) were compared with those who had not (n=9190).	**Primary outcome:** Mortality **Secondary outcomes:** ICH, Feeding tube and tracheostomy placement	Children who received t-PA were older (13.1 vs. 8.2 yrs, p<0.0001), had a history of diabetes (5.9% vs. 1.3%, p<0.01), congenital heart disease (4.5% vs. 0.14%, p=0.005) and cervical vessel dissection (4.4% vs. 1.1%, p<0.01). There were no differences race, sex distribution, income or vascular comorbidities between the groups. Children treated with t-PA had longer lengths of hospital stay (17 vs. 11 days, p<0.0001), and were less likely to be discharged home (48.5% vs. 82.9%) and more likely to be discharged to a rehabilitation facility or die (p<0.0001). In multivariable analyses independent predictors of mortality were hypertension, heart failure and ICH. Thrombolysis was not an independent predictor of death in bivariate or multivariable analysis (adj OR=1.78, 95% CI 0.86-3.64). A history of diabetes was the only independent predictor of ICH (adj OR=3.87, 95% CI 1.36-11.0).
Amlie-Lefond et	NA	Of 687 children included	Children treated with	Outcome at hospital	**Outcomes of 9 patients treated with intravenous**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
al. 2009 **Canada** **Observational study**		in the International Pediatric Stroke Study (IPSS) from 1999-2007, 18 children (2%), aged 2 months to 18 years, were treated with alteplase. The results of 15 cases are presented (3 cases had been described in previous reports). Of the 15 children included in the analysis, 6 were male. In all but one case, infarcts affected anterior (carotid) circulation.	alteplase in the IPSS study were compared with those from published case reports.	discharge: Good outcome (no, or mild neurological deficit), poor outcome (death or moderate-to-severe outcome), and time from stroke onset to treatment	**alteplase** At hospital discharge, (5-27 days) 7 patients had no or mild neurological deficits, 5 had moderate-severe deficits, 2 patients had died and the neurological status of 1 patient was unknown. Median time to treatment was 3.3 hours (range: 2-52 hours). Treatment was initiated within 3 hours in 4 cases. Total dose ranged from 0.02-0.9 mg/kg. ICH occurred in 2 cases and were both asymptomatic. **Outcomes of 6 patients treated with intra-arterial (IA) alteplase** At hospital discharge, 2 patients had no or mild neurological deficits, 3 had moderate-severe deficits, and 1patient had died. Median time to treatment was 4.5 hours (range: 3.8-24 hours). Treatment was initiated within 6 hours in 4 cases. Total dose ranged from 0.02-0.9 mg/kg. ICH occurred in 2 cases and were both asymptomatic. 14 case reports of children who had received alteplase for ischemic stroke were also identified. Of these, 10 received i.v. alteplase and 4, IA alteplase. 7/15 patients in the IPSS study experienced a good outcome at hospital discharge compared with 7/10 published case reports (p=0.41) 4/9 IPSS i.v. alteplase patients received treatment within 3 hours compared with 9/10 of case reports, p=0.057.
Arnold et al. 2009 **Switzerland** **Case reports and review**	NA	Case 1: 12-year-old boy with no significant medical history, presented with global aphasia and right hemiplegia 14 days after a streptococcal pharyngeal infection. Baseline NINSS score of	NA	NA	Description of 6 case studies, all treated with 0.9 mg/kg intravenous rt-PA, within 3 hours of symptom onset. Initial baseline NIHSS scores ranged from 7-22. 3 patients had returned to normal baseline function. For remaining 3 patients, mRS score was 1 for 2 patients (1, at discharge, the other at 5 months), and mRS was 3 at hospital discharge. Description of 3 case studies of patients, aged 7, 12

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		22. CT revealed L MCA infarct. Patient was treated with 750 000 IU intra-arterial urokinase, 5 hours after symptom onset. He continued to deteriorate over the next 48 hours and died. Case 2: 9-year-old boy with no significant medical history, who became suddenly ataxic and somnolent. Baseline NIHSS was 22. MRI revealed multiple acute infarcts in the left cerebellum, right posterolateral pons, left paramedian anterior pons, and bilateral deep and superficial PCA territories. Patient was treated with 750,000 IU intra-arterial urokinase, 12 hours after symptom onset. Patient was able to walk without assistance at day 10. 3-month mRS was 2.			and 15 years, treated with intra-arterial urokinase (n=2) and intra-arterial 2.5 mg t-PA (n=1) for MCA infarcts. Baseline NIHSS scores were 9, 22 and 28. Outcomes were no deficit at hospital discharge, mRS 3 at 2.5 months and death 2 days post stroke. Description of 7 cases of BA occlusion, treated with intra-arterial urokinase (median dose 750,000 IU) and intra-arterial t-PA (0.1 mg/kg, n=1 and dose not stated, n=1). Clinical outcome included complete resolution of the neurological deficits in 4 patients after 1 to 12 months, minimal symptoms (mRS score 1) after 6 months in one child, a moderate deficit (mRS score 2) after 3 months in one patient, and a severe deficit (mRS score 4) assessed after 4 months in another patient.
Janjua et al. 2007 **USA** **Retrospective study**	NA	2,904 patients entered into the National Inpatient Sample database who were between 1-17 years and admitted between 2000-2003 with ischemic stroke. (baseline stroke severity was not recorded in this database)	Children who received with thrombolytic therapy were compared with those who did not.	Medical comorbidities/ complications, LOS, status at discharge, mortality, and cost of hospitalization	46/2,904 patients (1.6%) were treated with thrombolytic therapy. These children were all male, and were more likely to have suffered from Moyamoya and sickle cell diseases (p=0.01). Medical complication rates were similar between groups (pneumonia, sepsis, pulmonary embolus and DVT) except children who did not received thrombolysis were more likely to have experienced a UTI (3.1% vs. 0%, p=0.01). 24 (52%) of those receiving thrombolysis also underwent cerebral angiography, compared with

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					793 (28%) of those managed conventionally. Patients who received thrombolysis had longer lengths of stay (median 15.3 vs. 7.4 days, p<0.05), were more likely to die during hospital stay (19.6% vs. 3.1%, p=0.22), be dead or dependent at discharge (37% vs. 9.7%, p=0.16) and were less likely to return home (43.5% vs. 80.4%, p=0.07). Their total hospital costs were also higher ($81,800 vs. $38,700, p=0.03).

Thrombolytic Therapy in Pregnancy

Published Guidelines

Guideline	Recommendations
Demaerschalk BM, Kleindorfer DO, Adeoye OM et al. **Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2016;47(2): 581-641. selected**	1. Intravenous alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding (Class IIb; Level of Evidence C). 2. The safety and efficacy of intravenous alteplase in the early postpartum period (<14 days after delivery) have not been well established (Class IIb; Level of Evidence C). 3. Urgent consultation with an obstetrician-gynecologist and potentially a perinatologist to assist with management of the mother and fetus is recommended (Class I; Level of Evidence C).
Jauch EC, Saver JL, Adams HP, Jr. et al. 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* 2013;44:870-	Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present: Only minor or rapidly improving stroke symptoms (clearing spontaneously), **Pregnancy,** Seizure at onset with postictal residual neurological impairments, Major surgery or serious trauma within previous 14 days Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days) Recent acute myocardial infarction (within previous 3 months) (Table 10)

Guideline	Recommendations
947.	

All other CPGs mention pregnancy as exclusion characteristic for tPA

Thrombolytic Therapy

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Landais et al. 2017 **France** **Case study**	32-year-old, right-handed woman, 13 weeks pregnant, with no significant history, presenting to the ER with brutal onset aphasia (blurred understanding, speaking disorders) and numbness of the right hand. Baseline NIHSS score was 3. MRI showed L MCA infarct, of presumed cardioembolic origin. She was treated with intravenous rt-PA (dose unspecified) 240 minutes after symptom onset.	NA	NA	Aphasia was improved significantly. She was transferred to a rehabilitation day center for speech therapy. Aspirin was later switched to subcutaneous low molecular weight heparin 2 weeks before delivery. Six months after her stroke she gave birth to a healthy term baby without complications.
Leffert et al. 2016 **USA** **Retrospective study**	24,641 women, aged 18-44 years admitted to one of 1,991 hospital following acute ischemic stroke from 2008-2013, who were included in the Get with the Guidelines Stroke Registry. Among them, 338 women were pregnant or <6 weeks postpartum at the time of stroke and 24,303 were nonpregnant.	The characteristics and outcomes of women: i) who were pregnant/postpartum vs. nonpregnant were compared and ii) who received any form of reperfusion therapy (n=40) were compared with those who did not (n=2,545)	Medical history, LOS, discharge destination	**Pregnant vs. nonpregnant women:** Women who were pregnant/postpartum were significantly younger (median 31 vs. 39 years, p<0.0001). A significantly higher proportion of nonpregnant women had a previous history of stroke or TIA (20.5% vs. 7.4%, p<0.001), coronary heart disease or previous MI (5.6% vs. 1.2%, p<0.0004), a history of diabetes (21.5% vs. 6.5%, p<0.001), HTN (42.5% vs. 17.5%, p<0.0001), smoker (32.9% vs. 22.9%, p<0.0001), dyslipidemia (16.4% vs. 3.3%, p<0.0001), heart failure (3.1% vs. 1.2%, p=0.041). Median admission SBP/DBP were significantly higher among nonpregnant women (139 vs. 127 mm Hg, p<0.0001 and 84 vs. 78 mm Hg, p<0.0001, respectively). A significantly higher proportion of nonpregnant women were taking antiplatelet/anticoagulant and antihypertensive medications. There were no significant differences between groups

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				for discharge outcomes. Overall, 3.7% of all women died in hospital, 72.9% were discharged home and 70.9% were independent in ambulation at D/C. A higher proportion of pregnant/postpartum women had hospital LOS>4 days (45% vs. 395, p=0.046). **Women who did/did not received reperfusion therapy by pregnancy status:** The percentage of pregnant/postpartum vs. nonpregnant women who received reperfusion therapy was similar (11.4% vs. 10.5%, p=0.42). Significantly fewer pregnant women received i.v t-PA monotherapy (4.4% vs. 7.95, p=0.03). Women who were pregnant/postpartum were significantly younger (median 31 vs. 39 years, p<0.0001). Medical histories were similar between groups, except a significantly higher proportion of nonpregnant women had a previous history HTN (35.4% vs. 17.5%, p=0.02). Median NIHSS score at admission was significantly lower among nonpregnant women (9 vs. 13, p=0.01). A significantly higher proportion of nonpregnant women were taking cholesterol-lowering medication (10.6% vs. 0%, p=0.03). Complications, including symptomatic ICH, serious hemorrhages and other complications were similar between groups. Discharge outcomes were similar between groups.
Tversky 2016 **USA** **Case report and review**	31-year- old woman, 5 months pregnant. presenting to the local ER with a chief complaint of sudden onset slurred speech, mild right hemiparesis, and hemisensory loss. NIHSS was 5. She had a medical history of ischemic stroke, associated with a prior pregnancy, with documented protein C and S deficiencies. She had decided to discontinue daily LMWH therapy and had not followed up with her primary physician. MRI revealed	NA	NA	By hospital day 2, her neurological symptoms completely resolved. Obstetrical evaluation did not reveal any complications with the placenta or fetus. The patient was discharged home on daily LMWH therapy for the remainder of the pregnancy.

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
	a left thalamic and internal capsular infarct. She was diagnosed with a PFO. She was treated with intravenous rt-PA (dose unspecified)			
Ritchie et al. 2015 **UK** **Case report**	28-year-old woman with a previous normal vaginal delivery presenting in her third trimester with a sudden onset of dense left hemiparesis. Baseline NIHSS score was 11. Patient was treated with intravenous rt-PA within 2 hours of stroke onset.	NA	NA	A post-thrombolysis MRI revealed a lacunar-type stroke (LACS) involving the right MCA. 24 hours post-thrombolysis, NIHSS score had improved to 6. Labour was induced at 48 hours post thrombolysis. Patient made a full recovery after normal delivery of a healthy infant. Post delivery, she was initiated on clopidogrel and prophylactic tinzaparin, and LMWH
Mantoan Ritter et al. 2014 **UK** **Case report**	32-year old women at 36 weeks' gestation during her first pregnancy presented to the ER within 40 minutes of symptom onset of L MCA stroke. There were no (other) stroke risk factors. NIHSS score was 22 on admission. She received 0.9 mg/kg intra-arterial rt-PA within 2 hours of stroke onset.	NA	NA	2 hours post thrombolysis, NIHSS score was 13. Investigations were normal with 2 slightly abnormal blood levels (total chol 5.4 mmol/l, Hgb 10.6 g/dl) A healthy baby was delivered by caesarean section, at term. The mother was discharged from rehabilitation 4 month after stroke onset. Final mRS was 2.
Tassi et al. 2013 **Italy** **Case report**	28-year old woman, who was 16 weeks pregnant, presenting to the ER within 1 hour of onset of stroke symptoms. Initial NIHSS score of 20. She was treated with intravenous rt-PA (0.9 mg/kg)	NA	NA	Within 1 hour of treatment her NIHSS score was 1, with slight aphasia. No evidence of ICH at 24 hours. Following discharge, a healthy infant was delivered without complication following an uneventful pregnancy.
Li et al. 2012 **USA** **Case report and review**	24-year-old woman at 11 weeks' gestation with ischemic stroke (NIHSS score of 13) was treated with 25 mg dose total of intra-arterial rtPA. The authors review 10 additional cases where t-PA was used in the first (n=5), second (n=2) and third (n=3) trimesters of pregnancy for ischemic stroke. In 7 of these cases intravenous t-PA was used (doses not specified), and in 3, the IA route.	NA	Narrative descriptive of status of mother and infant following treatment and incidence of ICH	The mother's status in the present case was described as complete recovery. The infant was healthy and there was no evidence of ICH. In the 10 remaining cases, the mother's outcome was described as complete recovery (n=1), recovered well (n=3), marked improvement (n=4), good (n=1), and death (n=1). ICH was reported in 4 cases. 7 infants were born healthy, 2 pregnancies were terminated and the fetus died in 1 case.
Ronning et al. 2010	29-year old woman whose delivery was induced at 38 weeks due to pre-	NA	NA	Neurological status improved rapidly over the next few hours. By the following day she had only a mild right

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Norway **Case report**	eclampsia. During the next 3 days she developed chest pain, tachycardia and orthopnea and was diagnosed with peripartum cardiomyopathy. She was treated with an ACE inhibitor and a diuretic and received unfractionated heparin. She then developed right-sided hemiplegia and global aphasia and was diagnosed with a L MCA stroke. NIHSS score was 14. She received 20 mg of intra-arterial rt-PA.			facial paralysis, reduced tempo of the right hand, a partial non-fluent aphasia, but normal comprehension. There was no evidence of carotid atherosclerosis, coagulopathy or immunological disease. 4 months after stroke NIHSS was 1 and a mRS was 1.
DeKoninck et al. 2008 **Netherlands** **Case report**	33-year old woman was admitted to hospital after resuscitation for cardiac arrest, 19 days after the birth of her second child. Emergency CT demonstrated extensive ischemic damage throughout the brain. A thrombus in left internal carotid artery and right vertebral artery and a complete occlusion of the basilar artery was found on cerebral angiography. She was treated with intra-arterial thrombolysis (dosage not reported).	NA	NA	The patient deteriorated neurologically. Clinical brain death was confirmed by isoelectric electroencephalography the following day.
Mendez et al. 2008 **Spain** **Case report**	37-year-old woman developed sudden onset of left arm/leg weakness with facial droop, homonymous hemianopsia, and slight dysarthria. Symptoms occurred 15 hours after delivery of a healthy baby at 36 weeks by cesarean delivery. She was diagnosed with a R MCA infarction. NIHSS score was 16. She received 100,000 U of urokinase over 15 minutes.	NA	NA	Patient's neurological status improved rapidly. Final angiogram demonstrated complete recanalization of entire R MCA. Day 2 after treatment, NIHSS score was 1. Patient was discharge home 9 days post stroke, with only minimal facial weakness. At 3 months, there were no residual deficits.
Wiese et al. 2006 **USA** **Case report**	33-year-old woman, 13 weeks gestation, admitted to a community hospital within 30 min of left MCA stroke, who received intravenous t-PA (0.9 mg/kg). She was then transferred to a tertiary-care facility. NIHSS score at the time of arrival to tertiary care facility was 13.	NA	NA	Patient was transferred to a rehabilitation facility. Final NIHSS score was 4. There was no mention of complications associated with the treatment. Delivered healthy baby at 37 weeks.
Johnson et al. 2005	39-year-old woman, 37 weeks' gestation admitted within 40 minutes of MCA	NA	NA	NIHSS score was 7 at 9 hours following treatment. There was no mention of complications associated with

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **Case report**	stroke. NIHSS score at baseline was 20. 15 mg of intra-arterial t-PA was administered			the treatment. Healthy baby was delivered 3 days following treatment.
Elford et al. 2002 **Canada** **Case report**	28-year-old woman with a 7-year history of infertility underwent in vitro fertilization. 7 days after embryo transfer she was admitted to hospital with severe ovarian hyperstimulation syndrome. 7 hours after acute treatments, she developed a R MCA stroke. NIHSS score was 11. She received 15.5 mg of intra-arterial rt-PA	NA	NA	After treatment her neurological status improved (NIHSS score 3). She developed a hematoma in the right basal ganglia which grew to 3.0 cm. Symptoms resolved over 3 weeks following treatment with fluids and drainage of pleural effusions. By 3 months she had only a mild incomplete left inferior quadrantanopia, normal strength, slight subjective sensory alteration in the left leg, and mild circumduction when ambulating. She was maintained on low-dose dalteparin for until the last 2 months of her pregnancy and delivered a healthy baby at term by spontaneous vaginal delivery.

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