Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Seventh Edition, Update 2022

Section 5: Acute Ischemic Stroke Treatment - Thrombolytic Therapy

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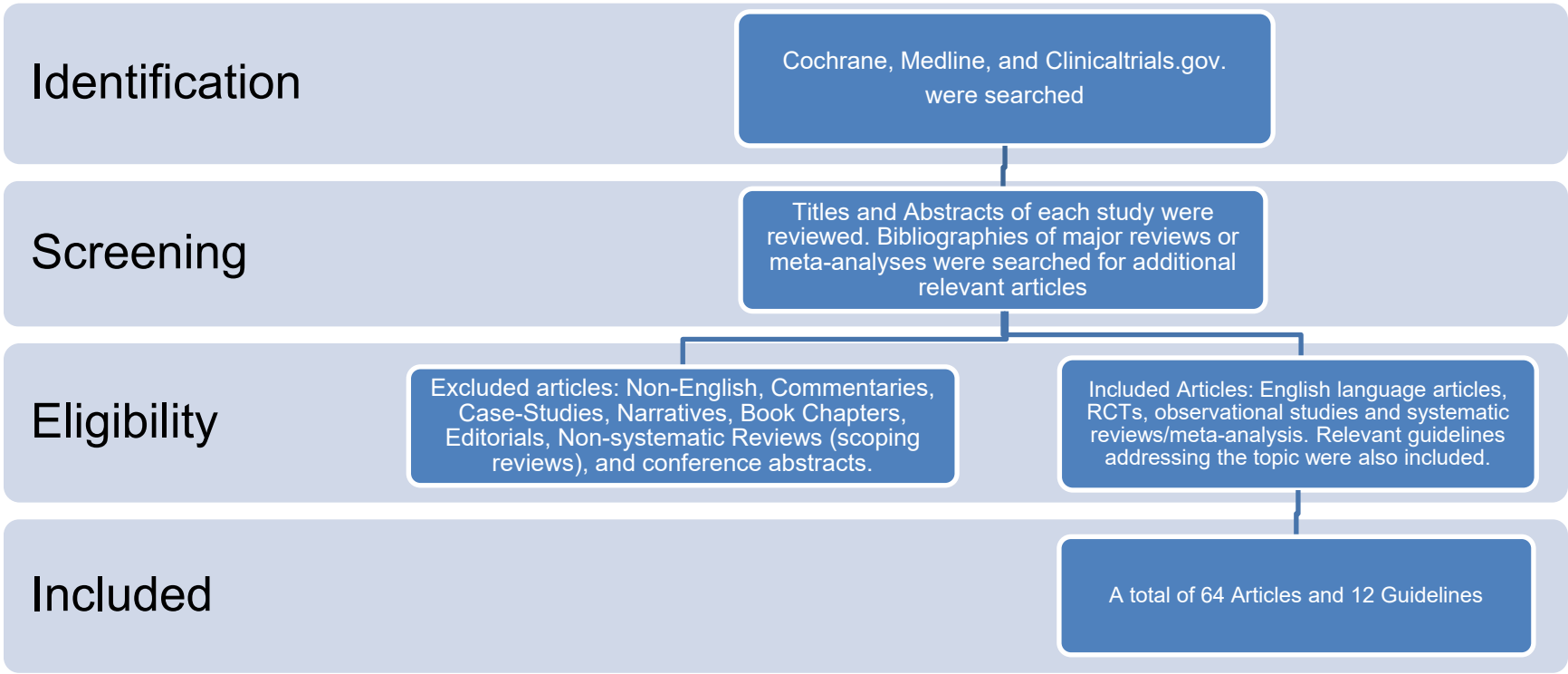
Table of Contents

Search Strategy



Cochrane, Medline, and Clinicaltrials.gov were search using the terms (“ischemic stroke” and “Tissue Plasminogen Activator” OR alteplase OR tenecteplase OR thrombolysis). 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 64 articles and 12 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Rodgers ML, Fox E, Abdelhak T et al. **American Heart Association Council on Cardiovascular and Stroke Nursing and the Stroke Council. Care of the Patient with Acute Ischemic Stroke (Endovascular/Intensive Care Unit-Postinterventional Therapy): Update to 2009 Comprehensive Nursing Care Scientific Statement: A Scientific Statement from the American Heart Association.** ***Stroke* 2021 May;52(5):e198-e210.** **(selected)**	*Eligibility Recommendations for IV Alteplase in Patients with Acute Ischemic Stroke* IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility. (COR I; LOE A). For otherwise medically eligible patients ≥18 y of age, IV alteplase administration within 3 h is equally recommended for patients ≤80 and >80 y of age. (COR I; LOE A) IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility. (COR I; LOE B-R) Age IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y 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. (COR I; LOE B-R) IV alteplase is recommended in patients with BP <185/110 and in those patients whose BP can be lowered safely to this level with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase. (COR I; LOE B-NR) IV alteplase is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH. (COR I; LOE B-NR) In AIS patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5- h window, IV alteplase may be as effective as treatment in the 0- to 3-h window and may be a reasonable option. (COR IIb; LOE B-NR)
Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, et al. **European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke.** ***Eur Stroke J* 2021;6(1): I–62.** **(selected)**	For patients with acute ischaemic stroke of <4.5 h duration, we recommend intravenous thrombolysis with alteplase. Quality of evidence: High, Strength of recommendation: Strong ↑↑ For patients with acute ischaemic stroke of 4.5–9 h duration (known onset time), and with no brain imaging other than plain CT, we recommend no intravenous thrombolysis. Quality of evidence: Moderate, Strength of recommendation: Strong ↓↓ For patients with ischaemic stroke of 4.5–9 h duration (known onset time) and with CT or MRI core/perfusion mismatch*, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Low, Strength of recommendation: Strong ↑↑ For patients with acute ischaemic stroke on awakening from sleep, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase. Quality of evidence: High, Strength of recommendation: Strong ↑↑ For patients with acute ischaemic stroke on awakening from sleep, who have CT or MRI core/perfusion mismatch* within 9 h from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Moderate, Strength of recommendation: Strong ↑↑

Guideline	Recommendations
	For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. Quality of evidence: Low, Strength of recommendation: Weak ↓? For patients with acute ischaemic stroke of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg. Quality of evidence: Low, Strength of recommendation: Weak ↑? For patients with acute ischaemic stroke of < 4.5 h duration who are eligible for intravenous thrombolysis, we recommend standard-dose alteplase (0.9 mg/kg) over low-dose alteplase. Quality of evidence: High, Strength of recommendation: Strong ↑↑ For patients with acute ischaemic stroke of < 4.5 h duration, we recommend no antithrombotic drugs within 24 h of intravenous thrombolysis over antithrombotic drugs as an adjunct therapy to intravenous thrombolysis with alteplase. Quality of evidence: Low, Strength of recommendation: Strong ↓↓ For patients with acute minor, disabling ischaemic stroke of < 4.5 h duration, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Moderate, Strength of recommendation: Strong ↑↑ For patients with acute minor non-disabling ischaemic stroke of < 4.5 h duration, and with proven large-vessel occlusion, there is insufficient evidence to make an evidence-based recommendation. Quality of evidence: Very low, Strength of recommendation: - For patients with acute ischaemic stroke of < 4.5 h duration, and with systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg, which has subsequently been lowered to < 185 and < 110 mm Hg, we recommend intravenous thrombolysis with alteplase. Quality of evidence: Low, Strength of recommendation: Strong ↑↑
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.** **(selected)**	**Reperfusion therapy for AIS** 1. Patients with elevated blood pressure and other aspects suitable for IV rt-PA therapy should be cautious in lowering blood pressure before thrombolysis. The recommended goal systolic blood pressure is <180mm Hg and diastolic blood pressure is <105mm Hg (class I, level of evidence B). 2. It is reasonable to maintain blood pressure (≤180/100mm Hg) before intra-arterial therapy in patients who do not receive IV thrombolysis (class II, level of evidence B). 3. Within 24hours after IV rt-PA therapy, blood pressure should be <180/105mm Hg (class I, level of evidence B). 4. Within 3hours of onset, rt-PA IV thrombolytic therapy is recommended for patients aged over 18 years and who meet other criteria (class I, level of evidence A). 5. For patients who are suitable for IV thrombolysis within 3 hours of onset, IV rt-PA thrombolysis is recommended (drug dose 0.9mg/kg, maximum dose 90mg, continuous infusion within 60min, of which 10% of the first dose is IV infusion within 1min) (class I, level of evidence A). 6. For patients with AIS with severe symptoms within 3hours of onset, IV rt-PA thrombolysis is recommended. Although the risk of bleeding events increases, it still benefits (class I, level of evidence A). 7. For patients with mild symptoms but with disabling stroke symptoms within 3 hours of onset, IV rt-PA thrombolytic therapy is recommended. Current studies have shown that IV rt-PA thrombolytic therapy is beneficial for these patients (class I, level of evidence B).

Guideline	Recommendations
	8. IV rt-PA thrombolysis is still recommended for patients suitable for IV thrombolysis within 3–4.5 hours of onset (class I, level of evidence B). 9. The benefit of rt-PA thrombolytic therapy for patients with AIS aged over 80 years within 3–4.5 hours after onset is not clear (class IIb, level of evidence B). 10. Within 4.5hours of AIS onset, low-dose IV rt-PA can be given to patients with potential high risk of haemorrhagic events. Usage: rt-PA 0.6mg/kg (maximum dose is 60mg), of which 15% of the total amount was intravenously injected within the first 1min, and the remaining 85% was intravenously infused with infusion pump for 1 hour (class IIb, level of evidence B). 11. Considering the low incidence of platelet abnormalities and coagulation dysfunction in the general population, IV thrombolysis should not be delayed while waiting for the results of platelet counts when there is no reason to suspect that the results of the tests are abnormal (class IIa, level of evidence B). 12. The safety and efficacy of IV rt-PA therapy in patients with AIS with potential haemorrhagic risk or coagulation disorders have not been determined (class III, level of evidence C).
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* 2019;50:e344–e418.** **(selected)**	**3.5. IV Alteplase** **3.5.1 General Principles** 1. 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. 2. In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction. Class I; LOE B-NR. 3. The potential risks should be discussed during IV alteplase eligibility deliberation and weighed against the anticipated benefits during decision making. Class I; C-EO. 4. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and determine blood glucose levels before IV alteplase initiation. IV alteplase is not indicated for nonvascular conditions. Class III: No Benefit; B-NR 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-NR. **3.5.2. Time Windows** 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 can 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 8 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 or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility. Class I; LOE B-R.

Guideline	Recommendations
	3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. Class IIa; LOE B-R. **3.5.3. Mild Stroke** 1. For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Class I; LOE B-R. 2. For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Class IIb; B-NR. **3.5.5. Bleeding Risk** 1. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test. Class IIa; LOE B-NR. **3.6. Other IV Thrombolytics and Sonothrombolysis** 1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy. Class IIb; LOE B-R 3. The use of sonothrombolysis as adjuvant therapy with IV thrombolysis is not recommended. Class III LOE B-R.
Stroke Foundation. Clinical Guidelines for Stroke Management 2017. Melbourne Australia (Part 3)	**Strong recommendation** For patients with potentially disabling ischaemic stroke within 4.5 hours of onset who meet specific eligibility criteria, intravenous thrombolysis should be administered as early as possible after stroke onset. **Strong recommendation** For patients with potentially disabling ischaemic stroke due to large vessel occlusion who meet specific eligibility criteria, intravenous tenecteplase (0.25mg/kg, maximum of 25mg) or alteplase (0.9mg/kg, maximum of 90mg) should be administered up to 4.5 hours after the time the patient was last known to be well. **Weak Recommendation** For patients with potentially disabling ischaemic stroke without large vessel occlusion who meet specific clinical and brain imaging eligibility criteria, tenecteplase may be used as an alternative to alteplase within 4.5 hours of onset. **Strong Recommendation** When using intravenous alteplase, a dose of 0.9 mg/kg, maximum of 90 mg should be administered. **Strong Recommendation** For patients with potentially disabling ischaemic stroke who meet perfusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) should be administered up to 9 hours after the time the patient was

Guideline	Recommendations
	last known to be well, or from the midpoint of sleep for patients who wake with stroke symptoms, unless immediate endovascular thrombectomy is planned. **Weak Recommendation** For patients with potentially disabling ischaemic stroke of unknown onset time who meet MRI FLAIR-diffusion mismatch criteria in addition to standard clinical criteria, intravenous alteplase (dose of 0.9 mg/kg, maximum of 90 mg) may be administered. **Change (7/11/2019)** Time window for thrombolysis extended to 9 hours (including 9 hours from the mid-point of sleep for wake-up stroke) using CT or MR perfusion imaging selection; and thrombolysis with tenecteplase as an alternative to alteplase.
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. (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.**	**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*).

Guideline	Recommendations
(Selected)	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 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*).

Guideline	Recommendations
	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 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*).

Guideline	Recommendations
	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 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:

Guideline	Recommendations
	− 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.
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**	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). Due to limited resources and practical constraints, the administration of thrombolytic therapy within 3 hours in rural hospital and may not be feasible and hence not recommended in all of these settings but should fall to the discretion of the local decision-making team (WEAK RECOMMENDATION, LOW 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). Post thrombolysis recommendations Following intravenous thrombolysis, vital signs (including neurovitals) should be monitored q15- mins ×2hours, then q30 mins ×6 hours, then q1h ×24 hours (STRONG RECOMMENDATION, LOW QUALITY EVIDENCE). Avoidance of arterial or central venous puncture in the first 24 hours following intravenous thrombolysis is recommended (BEST PRACTICE STATEMENT). Antithrombotic drugs (antiplatelet and anticoagulant agents) should be avoided for 24 hours after intravenous thrombolysis administration (WEAK RECOMMENDATION, LOW QUALITY EVIDENCE).

Guideline	Recommendations
	Patients who have received intravenous thrombolysis should be monitored closely for signs of airway compromise, which may be an indication of hemilingual angioedema. This is especially true in the case of patients who have been taking angiotensin converting enzyme inhibitors (ACEI). Emergency Department staff should be trained in the management of hemilingual angioedema (BEST PRACTICE STATEMENT). Onsite neurosurgical support is not required for managing post-thrombolytic care (WEAK RECOMMENDATION, LOW QUALITY EVIDENCE)
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**	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).

Guideline	Recommendations
Stroke. ***CJEM* 2015; 17(02):217-226. (Selected)**	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).
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: American College of Chest Physicians evidence-based clinical practice guidelines.** ***Chest 2012* Feb;141(2 Suppl):e601S-36S.**	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).

Evidence Tables

Major Trials & Studies of Intravenous Thrombolysis with Alteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ma et al. 2019 **International** ***Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	225 patients (310 planned), enrolled from 16 centres in Australia, New Zealand, Finland and Taiwan, ≥18 years with an ischemic stroke (NIHSS score of 4-26) where symptom onset was estimated to be 4.5 to ≤9 hours previously with hypo perfused but salvageable regions of brain detected on automated perfusion imaging. Patients with with excellent functional status before stroke (mRS 0-2), were eligible. Mean age was 72 years, 55.6% men. Median NIHSS score was 11. 65% of patients awoke with stroke symptoms. In patients who woke with symptoms, onset time was estimated to be the midpoint of sleep (i.e., the time between going to sleep and waking up with symptoms).	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:** mRS score of 0-1 at 90 days **Secondary outcomes:** Ordinal analysis of mRS scores at 90 days, proportion of patients with mRS score of 0-2 at 90 days **Safety outcomes:** 90-day mortality, sICH at 36 hours	Recruitment was suspended after the results of the WAKE-UP trial were available. The primary outcome occurred in 35.4% of the patients in the alteplase group and 29.5% in the control group. In the unadjusted analysis, the risk of the primary outcome was not significantly increased in the alteplase group (RR=1.2, 95% CI 0.82–1.76, p=0.35). After adjustment for age and baseline severity, the risk of the primary outcome was significantly increased (RR=1.44, 95% CI 1.01–2.06, p=0.04). There was no significant between-group difference in functional improvement at 90 days (i.e. shift in mRS scores). RR=1.55; 95% CI,0.96 to 2.49. The proportion of patients who attained a mRS score of 0-2 at 90 days was significantly higher in the alteplase group (49.6% vs. 42.9%; adjusted RR=1.36, 95% CI, 1.06 to 1.76). 11.5% of patients in the alteplase group died at 90 days vs. 8.9% in the placebo group (adjusted RR=1.17, 95% CI 0.57–2.40), p=0.67). The risk of sICH was non-significantly higher in the alteplase group (6.2% vs. 0.9%, adjusted RR=7.22, 95% CI 0.97–53.54, p=0.053).
Thomalla et al. 2018, Barow et al. 2019	Concealed Allocation: ☑ Blinding:	503 patients (800 planned) aged 18-80 years, with ischemic stroke and disabling	Patients were randomized 1:1 to receive 0.9 mg of alteplase/kg (with 10%	**Primary efficacy outcome:** Favourable clinical outcome (mRS 0-1) at 90 days.	Median interval between last known well and treatment initiation was 10.3 hours. Median time from time from symptom recognition to

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **RCT** ***Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP)***	Patient ☑ Assessor ☑ ITT: ☑	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 planned and those with severe stroke (NIHSS >25), were excluded. Mean age was 65 years, 65% were men. Median baseline NIHSS scores was 6.	administered as a bolus and the remainder by infusion during a 60-minute period) or matching placebo.	**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 days, infarct volume 22-36 hours after treatment **Safety outcomes:** Mortality, death or dependency (mRS 4-6) at 90 days, symptomatic ICH (sICH)	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, 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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					p=0.03). **Barrow et al. (2019)** Subgroup of 108 patients with lacunar infracts Treatment with alteplase was associated with higher odds of favorable outcome (59% vs. 46%, adj OR=1.67, 95% CI 95% CI 0.77-3.64). There was a nonsignificant shift in the distribution of mRS scores 90 days after stroke that favoured treatment with alteplase (adjusted common OR=1.94, 95% CI 0.95-3.93).
Sandercock et al. 2012, Berge et al. 2016 **The IST-3 Collaborative Group** **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 subgroups 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%). 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. There were 96 losses to follow-up. **Long-term follow-up (2016)**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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)					
Wahlgren 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-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	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. **Secondary outcomes:** Proportion of patients who were independent at 3 months (mRS scores of 0-2).	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 independent at 3 months compared with 49.0% of patients in the pooled RCT cohort.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		had received alteplase during routine clinical practice.			
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). 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%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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=4,056) 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: adj 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 lower, after adjusting for age and baseline NIHSS.
European Acute Stroke Study (ECASS I, II & III)					
Hacke et al. 1995 **Germany**	Concealed Allocation: ☑ Blinding:	620 patients with acute ischemic stroke with moderate-severe neurological deficit from	Patients were randomized to receive alteplase (1.1 mg/kg, max dose 100 mg,	**Primary outcome:** Barthel Index (BI) score, mRS score at 90 days	109 patients were excluded from the exploratory analysis (n=66 alteplase, n=43 placebo). There was no difference in the median BI score

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT **ECASS I**	Patient: ☑ Assessor: ☑ ITT: ☑	75 centres in 14 European countries who could be treated within 6 hours of stroke onset.	n=313) or placebo (n=307) within 6 hours of onset of symptoms.	(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	(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 (max dose 90 mg) of alteplase (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 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)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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, Bluhmki et al. 2009 **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. *Additional Secondary outcomes (Bluhmki et al. 2009)* 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 differences in the percentages of patients with mRS score of 0-2 (59% vs. 53%, p=0.097) or BI score≥85

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(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)					
Hill et al. 2005	NA	All patients (n=1,135)	Prospective data	**Primary outcome:**	Median (IQR) baseline NIHSS score: 14 (9-19)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **Observational monitoring**		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).	collection	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) 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:

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					higher in the t-PA group: 6.4% vs. 0.64% Losses to follow-up (combined): n=5

Systematic Reviews & Meta-Analyses

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Darvesh & Butcher 2022 **Canada** **Rapid review**	8 studies, including 3 systematic reviews (including the Cochrane review, authored by Wardlaw et al. 2014) and 3 RCTs (including IST-3, TESPI and ECASS III), published between January 1, 2014, and January 19, 2022.	Patients were randomized to receive intravenous alteplase (0.9 mg/kg) or placebo within 3 hours of symptom onset or 3.0-4.5 hours of symptom onset.	**Primary outcomes:** Effectiveness and safety	*Within 3 hours of symptoms* *Mortality* 7-day follow-up: no significant differences between groups reported in 1/1 publications. 3-month follow-up: no significant difference between groups in 2/2 publications) 6 months and 3-year follow-up: no significant differences between groups in 1/1 publications 18 months follow-up: Significantly greater survival in alteplase group in 1/1 publications Follow-up duration not reported: Among 4 publications reporting, in one there were significantly greater odds of survival. In the other 3, survival was not increased with alteplase. *Functional outcome* (defined differently in each publication) 3-month follow-up: Significantly better outcome associated with alteplase in 1/4 publications. 6-month follow-up: Significantly better outcome associated with alteplase in 1/1 publications Follow-up duration not reported: The odds of better functional outcome were significantly higher in 2/4 publications *Symptomatic ICH* Within 3 months, the odds of sICH were significantly increased in the alteplase group in 1/3 publications *Within 3-4.5 hours of symptoms*

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Mortality Within 3 months, survival was increased with alteplase treatment in 1/6 publications *Functional outcome* (defined differently in each publication) Within 3 months, functional outcome was improved significantly with alteplase in 1/3 publications. Within 6 months, alteplase was not associated with significantly improved outcome in 1/1 publications. *Symptomatic ICH* Within 7 days, the odds of sICH were significantly increased in the alteplase group in 3/3 publications
Roaldsen et al. 2021 **Norway** **Cochrane review**	5 RCTs including WAKE-UP, EXTEND, THAWS, and ECASS-4 (n=775). Participants had an ischemic stroke with unknown timing of symptom onset (i.e., wake-up stroke). 2 additional trials included patients who received treatment with EVT.	Patients were randomized to receive thrombolytic drugs (alteplase 0.9 mg/kg) or placebo	**Primary outcome:** Independent functional outcome (mRS 0-2) at 90 days **Secondary outcomes:** Symptomatic intracranial hemorrhage (sICH), mortality at 90 days	The likelihood of the primary outcome was significantly higher in the treatment group (RR=1.13, 95% CI 1.01 to 1.26). High certainty of evidence The risk of sICH was not significantly higher in the treatment group (RR=3.47, 95% CI 0.98 to 12.26). High certainty of evidence The risk of all-cause mortality was not reduced significantly in the treatment group (RR=0.68, 95% CI 0.43 to 1.07). High certainty of evidence
Thomalla et al. 2020 **Germany** **Systematic review & patient-level meta-analysis**	4 RCTs including WAKE-UP, EXTEND, THAWS, and ECASS-4 (n=843). Participants had ischemic stroke with unknown time of onset and had imaging using perfusion-diffusion MRI, perfusion CT, or MRI with diffusion weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR) mismatch. Mean age was 68·5 years, 38% were women. Median time from last seen well to symptom recognition was 7·0 hours. Median NIHSS on admission was 7.	Patients were randomized to receive alteplase or placebo. Analyses were adjusted for age and symptom severity at baseline.	**Primary outcome:** Favourable functional outcome (mRS 0-1) at 90 days **Secondary outcomes:** mRS shift towards a better functional outcome and independent outcome (mRS 0–2) at 90 days. **Safety outcomes:** Death, severe disability or death (mRS score 4–6), and sICH	The odds of a favourable outcome were significantly higher in the alteplase group (47% vs. 39%, adj OR=1·49, 95% CI 1·10–2·03, p=0·011). Alteplase was associated with a significant shift towards better functional outcome (adj common OR= 1·38, 95% CI 1·05–1·80; p=0·019), and higher odds of independent outcome (adjusted OR=1·50, 95% CI 1·06–2·12; p=0·022). The odds of death and sICH were significantly higher in the alteplase group (6% vs. 3%, adj OR=2·06, 95% CI 1·03–4·09; p=0·040 and 3% vs. <1%, adj OR=5·58, 95% CI 0·22–25·50, p=0·024, respectively).
Campbell et al.	3 trials EXTEND, ECASS4-EXTEND, and	Pooled patient-level	**Primary outcome:**	The median time from when the patient was last

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
2019 **Australia** **Systematic review & meta-analysis**	EPITHET (n=414) who were treated with alteplase (0.9 mg/kg) or placebo, ≥ 4·5 hours after stroke onset, or with wake-up stroke, who were imaged with perfusion-diffusion MRI or CT perfusion.	meta-analysis, with adjustment for age and baseline severity	Excellent (mRS 0-1) outcome at 3 months **Secondary outcome:** good (mRS 0-2) outcome at 3 months **Safety outcomes:** Death within 3 months and symptomatic ICH within 36 hours	known to be well to treatment in patients with wake-up stroke was 10 h 42 min. The median perfusion mismatch was 47 mL (IQR 17–85) with a median volume of critical hypoperfusion of 64 mL (30–109) and relatively small core of median volume 8 mL (0–22). A significantly higher proportion of patients in the alteplase group had excellent and good outcomes (35% vs. 29%; OR= 1·86, 95% CI 1·15–2·99, p=0·011). There were significantly more ICHs in the alteplase-treated group (5% vs. <1%; OR= 9·7, 95% CI 1·23–76·55, p=0·031 and 49% vs. 44%, OR= 1·74, 95% CI 1·08–2·81, p=0·0.2, respectively) 14% of patients in the alteplase group died vs. 9% in the placebo group (OR= 1·55, 0·81–2·96, p=0·66)
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. 2018 Stroke Thrombolysis	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,	Pooled analysis, were conducted, using patients who would and would not meet current European	**Primary outcome:** Excellent outcome (mRS 0-1) at 3 months, and symptomatic ICH defined in	**Patients who would have met current EU label criteria** 2449 (40%) patients would have met the current EU label criteria. Alteplase was associated with

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
Trialists' Collaborators Group **International** **Meta-analysis**	III, ATLANTIS a/b, EPITHET, IST-3). Data from ECASS I, was excluded (dose of 1.1 mg/kg).	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).	3 ways (type 2 parenchymal hemorrhage [PH-2] within 7 days, (SITS-MOST) hemorrhage within 24–36 hours and fatal ICH within 7 days)	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 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**

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				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 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

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				(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 review & 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)	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 within 24-36 hours and fatal ICH within 7 days.	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). 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	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

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
			up (mRS 3-5).	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). 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

Study/Type	Sample Description	Method	Outcomes	Key Findings and Recommendations
				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 mg total dose was most common (n=8). Subgroup analysis of time to treatment and age.	**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 3-5) Final follow-up: 1 months (n=2), 3 months (n=9), 6 months (n=1)	**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 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

Low Dose Alteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dong et al. 2020 **China** **Retrospective study**	NA	3,479 patients who received lower-dose (0.6 mg/kg) thrombolysis treatment, who were included in 2 registries. Median age was 65 years, 64% were men.	The outcomes of patients among 3 subgroups were compared. Baseline NIHSS ≤4 (mild), 5-14 (moderate) and ≥15 (severe).	**Primary outcomes:** Clinical improvement (NIHSS 0 or 1 or an improvement of ≥ 4 points within 7 days or at discharge from admission), sICH	Compared with those treated with a standard dose of t-PA, the odds of clinical improvement were not significantly lower or higher for patients with mild (OR=0.81, 95% CI 0.51 to 1.28), moderate (OR=1.23, 95% CI 0.71 to 2.13) or severe (OR=1.12, 95% CI 0.58 to 2.17) stroke, treated with lower dose t-PA. The odds of sICH were significantly lower in patients treated with lower doses of t-PA with moderate stroke (OR=0.13, 95% CI 0.02 to 0.68), but not among those with mild or severe stroke (OR=2.71, 95% CI 0.80 to 7.69 and OR=0.65, 95% CI 0.19 to 2.55, respectively).
Wang et al. 2020 **Australia** **Observational study**	NA	3,197 patients from the ENCHANTED trial (development cohort) 1,526 patients admitted to 15 stroke centres with acute ischemic stroke (validation cohort)	Clinical prediction models were developed to determine individual patient factors that contributed to the risk–benefit balance of low-dose compared with standard-dose alteplase treatment.	**Primary outcome:** Excellent outcome (mRS 0-1) at 90 days (benefit outcome), sICH (risk outcome)	In the development cohort, 1,530 patients (47.8%) had an excellent outcome (48.9% in the low-dose group and 46.8% in the standard dose group). Independent predictors of an excellent outcome were younger age, lower SBP, lower NIHSS score, lack of atrial fibrillation, diabetes mellitus, or premorbid comorbidities. Independent predictors of sICH were higher SBP, atrial fibrillation. Allocation to the low dose group was protective. In both cohorts, patient characteristics associated with net benefit were younger age, lower SBP, lower NIHSS score, lack of atrial fibrillation and diabetes mellitus, and low pre-stroke disability. In the validation cohort, those with a net advantage had the same combination of characteristics to the development cohort
Anderson et al. 2016, Robinson et al. 2017 **International**	Concealed Allocation: ☑ Blinding: Patient ☒	3,310 patients ≥18 years from 111 centres in 13 countries who were eligible for thrombolytic therapy.	Patients were randomized to a standard dose of alteplase (0.9 mg/kg, n=1,643, administered as: 10%	**Primary outcome:** Death or disability (mRS 2-6) at 90 days **Secondary outcomes:**	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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Non-inferiority RCT ***Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED)*** **Alteplase dose-assessment arm**	Assessor ☑ ITT: ☑	Mean age was 67.5 years, 38% were female. Median NIHSS score was 8	bolus, 90% as infusion over 60 minutes) or a low dose (0.6 mg/kg, n=1,644, administered as: 15% bolus, 85% as infusion over 60 minutes) within 4.5 hours of symptom onset	Symptomatic ICH, distribution of mRS scores at 90 days, major disability at 90 days, deaths at 7 and 90 days	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) 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 subgroup analysis, there were no interactions between subgroups 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. **Robinson et al. 2017 (prior antiplatelet therapy)** N=3,285 752 (22.9%) patients reporting the prior APT use at baseline. After adjustment for baseline characteristics and differences in early management, there were no significant differences in outcomes (percentage of patients with mRS 0-2, mRS 0-3, ordinal shift in mRS and mortality) between patients with and without prior APT. Prior APT was also associated with an increased risk of sICH. Low dose group: There was a trend towards more

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					favorable 90-day outcomes in patients on prior APT compared with those without prior APT. Standard dose group: There was a trend toward more favorable outcomes in patients without prior APT.

Timing of Thrombolytic Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Man et al. 2020 **USA** **Retrospective study**	NA	61,426 Medicare patients aged ≥65 years, admitted to Get With The Guidelines (GWTG)–stroke participating hospitals between January 1, 2006, and December 31, 2016, with acute ischemic stroke and treated with IV t-PA within 4.5 hours from the time last known to be well. Median age was 80 years, 43.5% were men. Median NIHSS score was 10.	The outcomes of patients with door-to-needle times (DTNT) of >45 (n=48,666) vs. ≤45 minutes (n=12,760), and >60 (n=34,367vs. ≤60 (n=27,059) minutes, were compared.	**Primary outcomes:** 1-year all-cause mortality, 1-year all-cause readmission, and the composite of all-cause mortality or readmission at 1 year **Secondary outcomes:** 1-year cardiovascular readmission, admission for recurrent stroke Analyses were adjusted for age, sex, race/ethnicity; vascular risk factors, arrival by EMS and arrival during off hours, hospital region, urban or rural location, total number of hospital beds and other hospital factors	*≤45 vs. > 45 minutes* All-cause mortality was significantly higher in the >45 minutes group (35.0% vs. 30.8%, HR=1.13, 95% CI 1.09 to 1.18, p <.001) as were all-cause readmission and the composite outcome (40.8% vs. 38.4%, HR=1.08, 95% CI 1.05 to 1.12, p<.001 and 56.0% vs. 52.1%, HR=1.09, 95% CI 1.06 to 1.12, p <0.001, respectively). Cardiovascular readmission was significantly higher in the >45-minute group (19.8% vs 18.4%; HR=1.05, 95% CI, 1.00-1.10), but not recurrent stroke readmission (9.3% vs 8.8%; HR=1.05, 95% CI 0.98-1.12). *≤60 vs.> 60 minutes* All-cause mortality was significantly higher in the >60 minutes group (35.8% vs. 32.1%, HR=1.11, 95% CI 1.07 to 1.14, p <.001) as were all-cause readmission and the composite outcome (41.3% vs. 39.1%, HR=1.07, 95% CI 1.04 to 1.10, p<.001 and 56.8% vs. 53.1%, HR=1.08, 95% CI 1.05 to 1.10, p <0.001, respectively). Cardiovascular readmission was significantly higher in the >60-minute group (20.2% vs 18.6%; HR=1.01, 95% CI, 1.01-1.10), but not recurrent stroke readmission (9.3% vs 8.9%; HR=1.03, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					CI 0.97-1.09). Every 15-minute increase in DTN times was associated with significantly higher all-cause mortality (HR= 1.04, 95% CI, 1.02-1.05) within 90 minutes after hospital arrival, but not after 90 minutes (HR=1.01, 95% CI, 0.99-1.03), higher all-cause readmission (HR=1.02, 95% CI, 1.01-1.03), and higher all-cause mortality or readmission (HR=1.02, 95% CI, 1.01-1.03).
Goyal et al. 2019 (HEREMES Collaborators) **International** **Pooled analysis**	NA	601 patients, from the alteplase only arm of 7 trials of endovascular therapy (ESCAPE, EXTEND-IA, PISTE, REVEASCAT, SWIFT-PRIME and THRACE). Mean age was 66.0 years, 50% were women. Median NIHSS score was 17.	Individual patient-level data were analyzed to determine the effect of treatment delay on outcome. Patients were stratified according to onset to treatment time (OTT): early (0–90 minutes, n=158), intermediate (91–180 minutes, n=336), and late (181–270 minutes, n=99)	**Primary outcome:** mRS scores at 3 months	Median OTT time was 125 minutes and median DTT was 38 minutes. In adjusted ordinal analysis of the distribution of mRS scores, the common odds of a better outcome were decreased by each 60-minute delay in OTT (OR=0.80, 95% CI 0.68–0.95). The odds of an excellent outcome (mRS 0-1) were also decreased by each 60-minute delay in OTT (OR=0.76, 95% CI 0.58–0.99). The odds of a good outcome (mRS 0-2), death or sICH did not decrease significantly with each 60-minute delay in treatment. In adjusted ordinal analysis of the distribution of mRS scores, the common odds of a better outcome were decreased by each 60-minute delay in DTT (OR=0.55, 95% CI 0.37-0.81). The odds of an excellent outcome (mRS 0-1) and a good outcome (mRS 0-2) also decreased by each 60-minute delay in DTT (OR=0.47, 95% CI 0.28–0.80 and OR=0.51, 95% CI 0.29–0.92, respectively). The odds of death or sICH did not decrease significantly with each 60-minute delay in treatment. The absolute decline in the rate of excellent outcome at 90 days was 20.3 per 1,000 patients treated per 15-minute delay in door-to-needle time.
Emberson et al. 2014 **UK**	NA	Data from 6,756 patients from 9 major t-PA trials (NINDs a/b, ECASS I/II, III, ATLANTIS a/b,	Analysis to determine if age, treatment delays and baseline stroke severity modified the	**Primary outcome:** Good stroke outcome (mRS 0-1) at 3-6 months.	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Meta-analysis		EPITHET, IST-3)	outcome of patients treated with t-PA vs. placebo.	**Secondary outcomes:** Fatal ICH at 7 days, symptomatic hemorrhage, 90-day mortality	>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 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	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	**Primary outcomes:** 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		was 11.	acute stroke care. One of the components addressed strategies to decrease: door to needle (DTN) for t-PA administration.		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** **Observational study**	NA	58,353 ischemic stroke patients included in the Get With the Guidelines Stroke registry who were treated with tPA within 4.5 hours of symptom onset, from 2003-20012.	Clinical outcomes of patients with onset to treatment times of 0-90 (n=5404), 91-180 (n=45029) and 181-27) n=7920) min, were compared.	**Primary outcome:** Factors associated with onset to treatment (OTT) and association between OTT and outcome	The median OTT times of the groups were 80, 140 and 208 minutes. 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	Clinical outcomes of patients with door-to-needle times of ≤60 and >60 minutes were compared	**Primary outcomes:** 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=0.78, 95% CI 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		the registry.			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 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	**Primary outcomes**: 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 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
Bluhmki et al. 2020 **Germany** **Pooled analysis**	NA	Patient data from 7 RCTs (n= 6,035) including patients with acute ischemic stroke (onset <4.5 hours) 2,420 patients aged >80 years included in the European SITS-UTMOST registry who	The outcomes of patients who received alteplase (0.9 mg/kg) were compared with those who received placebo or open control, separately in the RCT group and the registry group.	**Primary outcome:** Good functional outcome (mRS 0-1 at day 90 or Oxford Handicap Score day 180), 90-day mortality, sICH	In the full RCT population, alteplase was associated with better outcomes. The effect was independent of age (P=0.738 for interaction). In the subgroup of patients >80 years (n=1,699), a significantly higher proportion who received alteplase had a good functional outcome compared with those who in the control group (19.1% vs. 13.1, p=0.0109), but had higher sICH (3.7% vs.0.4%, p=0.0002). 90-day mortality was similar

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		met existing European regulatory criteria (excluding upper age restriction)			between groups (29.5% vs. 30.2%, p=0.8382). In the SITS-UTMOST registry, a significantly higher percentage of patients who receive alteplase had a good outcome (19.1% vs. 13.1%, p=0.0109) compared with those in the control group. There was no significant difference between treatment groups in the percentage of patients with 90-day mortality (29.5% vs. 30.2%, p=0.84). Both sICH and fatal ICH within 7 days were significantly higher in the alteplase group (19% vs. 2%, p=0.0002 and 18% vs. 2%, p=0.0004, respectively).
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 at 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 Analyses 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 years.
Reuter et al. 2015 **Germany**	NA	101,349 patients included in the Baden-Wuettemberg stroke registry from 2008-2012, which included the data	The outcomes of patents across different age groups (increments of 10 years) who received thrombolysis were	**Primary outcome:** mRS ≤1 at discharge **Secondary outcomes:** mRS ≤2 at discharge, in-	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		from 142 hospitals. All stroke patients ≥18 years and admitted within 7 days of stroke are registered.	compared with those who did not, are reported.	hospital mortality Analysis were adjusted for pre-stroke and admission mRS, NIHSS score, prior stroke, diabetes, AF, admitting facility and LOS	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).
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)	**Primary outcomes:** 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= 1.56, 95% CI 1.35 to 1.82 and 5.73% vs. 4.40%; OR=1.31, 95% CI 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, 95% CI 0.93-1.89, p=0.13), but was a predictor of ICH (OR=9.69, 95% CI 6.25-15.02, p<0.0001)
Ford et al. 2010	NA	21,242 patients from the SITS-ISTR database.	Comparisons of patients >80 years (n=1,831) and	**Primary outcomes:** 90-day mortality,	The median ages of the 2 groups were 82 and 68. The initial median NIHSS score of patients >80

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
UK **Observational study**			≤80 years (n=19,411).	independence at 90 days (mRS 0-2), complete recovery at 90 days (mRS 0-1), ICH	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).
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)

Sonothrombolysis + Alteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Tsivgoulis et al. 2021 **Greece** **Systematic review & patient-level meta-analysis**	Using the Cochrane Risk of Bias assessment tool, most trials were found to be at low risk of bias (some issues with lack of concealed allocation and blinding of participants)	7 RCTs that included patients with large vessel occlusion, treated with standard dose t-PA within 4.5 hours of symptom onset. Median age was 68 years, 58% were men. Median baseline NIHSS score was 16. Approximately 8% of patients were treated with endovascular therapy.	Trials compared sonothrombolysis with or without addition of microspheres (treatment group, n=138) with intravenous thrombolysis alone (control group, n=134)	**Primary outcome:** Complete recanalization at 1 to 36 hours **Secondary outcomes:** Complete or partial recanalization, early clinical recovery (defined by improvement in NIHSS score at 2 and 24 hours, after t-PA), favourable outcome at 3 months (mRS 0-1), functional independence at 3 months (mRS 0-2) **Safety outcomes:** Symptomatic and asymptomatic ICH, mortality at 3 months	Patients in the treatment group had a significantly higher likelihood of both complete recanalization (40.3% vs. 22.4%; adjusted OR= 2.33, 95% CI, 1.02–5.34) and any (complete or partial) recanalization (66.4% vs. 53.0%; adjusted common OR= 2.01, 95% CI, 1.03–3.92). There were no significant differences between groups for any of the secondary or safety outcomes). Age and baseline systolic blood pressure were found to be significant effect modifiers on the primary outcome, with patients aged <67 years and those with SBP < 158 mm Hg) having significantly better outcomes.
Li et al. 2020 **China** **Systematic review & meta-analysis**	Using the Cochrane Risk of Bias assessment tool, most trials were found to be at low risk of bias	5 RCTs including 879 adult patients with acute MCA-M1 occlusions, with NIHSS score ≥10, treated with t-PA within 4.5 hours of symptom onset. Mean age ranged from 58 to 70 years, 24% to 78.4% were women. Mean NIHSS scores ranged from 14 to 18.	Trials compared sonothrombolysis without microbubbles (treatment group, n=436) with intravenous thrombolysis alone (control group, n=443)	**Primary outcomes:** Recanalization (TIBI 4-5), good clinical outcome at day 90 (mRS 0-1) **Safety outcomes:** Symptomatic ICH, asymptomatic ICH, 90-day all-cause mortality	Treatment was not associated with an increase in symptomatic ICH (OR=1.47, 95% CI 0.69–3.31) but did increase the risk of asymptomatic ICH (OR=1.94, 95% CI 1.14–3.29). The risk of all-cause mortality was not increased significantly with treatment (OR=1.13, 95% CI 0.77–1.65). Treatment was associated with improved odds of recanalization (OR=2.93, 95% CI 1.57–5.46), but not with improved odds of a good outcome (OR=1.48, 95% CI 0.77–2.87).
Alexandrov et al. 2019 **USA** **RCT** ***Combined Lysis of Thrombus***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	676 patients recruited from 76 medical centres in 14 countries, with acute ischemic stroke, NIHSS score ≥10 and who received standard dose t-PA within 3 (North America) or 4.5 (all other	Patients were randomized to receive either active ultrasound (2 MHz pulsed-wave ultrasound for 120 min [sonothrombolysis]; intervention group) or sham ultrasound (control	**Primary outcome:** mRS scores at 90 days (distribution of scores, using shift analysis) in persons treated within 3 hours **Secondary outcomes:** Primary outcome (persons	The trial was stopped early because of futility. The distribution of mRS scores at 90 days did not differ between groups, enrolled within 3 hours of symptom onset (adjusted common OR= 1·05, 95% CI 0·77–1·45; p=0·74), nor did mRS scores differ among patients enrolled within 4.5 hours (adjusted common OR 1·06, 95% CI 0·80–1·42;

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
using Ultrasound and Systemic Tissue Plasminogen Activator for Emergent Revascularization (CLOTBUST-ER) trial		countries) hours of symptom onset. Median age was 71 years, 58% were men. Median NIHSS score was 58%.	group).	treated within 4.5 hours), mRS scores of 0-1 and 0-2 (persons treated within 3 hours and 4.5 hours), mRS scores at 7 days, independence at 90 days, clinical recovery at 24 hours, NIHSS score at 7 and 90 days. Analyses were conducted among persons treated within 3 hours and 4.5 hours. **Safety outcomes:** Death within 90 days, symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment, adverse events	p=0·67). There were no significant differences between groups for any of the secondary or safety outcomes. 16% of patients in the intervention group died vs. 13% in the control group (unadjusted OR=1·24, 95% CI 0·80–1·92; p=0·37).
Nacu et al. 2017 **RCT** ***Norwegian Sonothrombolysis in Acute Stroke Study (NOR-SASS)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	183 patients treated with standard-dose t-PA or tenecteplase within 4.5 hours of symptom onset following acute ischemic stroke. Mean age was 68.8 years, 50% were men. Median baseline NIHSS score was 4.	Patients were randomized 1:1 to receive either contrast-enhanced sonothrombolysis (CEST), using wave 2 MHz pulse-wave transcranial Doppler (TCD) + microbubbles for one hour or sham CEST.	**Primary outcomes:** Neurological improvement at 24 hours (NIHSS score 0 or reduction of ⩾4 points compared with baseline), favorable functional outcome at 90 days (mRS score 0 to 1) **Safety outcomes:** Hemorrhagic transformation, symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment and death	The mean time from symptoms onset and CEST treatment was 170 minutes. At 24 hours following treatment, 51% of patients in the CEST group and 46% of patients in the control group demonstrated neurological improvement (p=0.50). At 90 days, 48% of patients in the CEST group had achieved a favourable functional outcome compared with 51% in the control group (p=0.71). There were no significant differences between groups on any of the safety outcomes.

Tenecteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Trials					
NCT02398656 **Canada** **RCT** ***A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke with Proven Occlusion (TEMPO-2)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,274 patients recruited from 61 sites worldwide, with an acute stroke, sustained within 12 hours, with a NIHSS score of <6 and an ASPECTS >7.	Patients were randomized to receive intravenous tenecteplase (0.25mg/kg, maximum 25mg) or best medical management.	**Primary outcome:** mRS score at 3 months **Secondary outcomes:** Major bleeding within 90 days, Complete or partial recanalization (4-24 hours), Lawton Instrumental Activities of Daily Living Scale (IADL) at 90 days, EuroQol 38 at 90 days	Estimated study completion date is December 2023
NCT03785678 **USA** **RCT** ***Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	456 patients (planned) with acute ischemic stroke with symptom onset within 4.5 to 24 hours, baseline NIHSS ≥5 and ICA or M1, M2 occlusion and target mismatch profile on CT perfusion or MR perfusion (ischemic core volume <70 mL, mismatch ratio ≥1.8 and mismatch volume ≥ 15 mL)	Patients were randomized to receive intravenous tenecteplase (0.25mg/kg, maximum 25mg) or placebo.	**Primary outcome:** Ordinal shift analysis of mRS scores at 90 days **Secondary outcomes:** Functional independence (mRS 0-2) at 90 days, reperfusion at 24 hours, median NIHSS score at 90 days, symptomatic intracranial hemorrhage within 48 hours, all-cause mortality at 30 and 90 days, parenchymal hematoma type 2 (PH2) at the 72–96-hour visit	Estimated study completion date is September 2022.
NCT03181360 **Norway** **RCT** ***Tenecteplase in Wake-Up Ischaemic Stroke Trial (TWIST)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	578 patients (600 planned), recruited from 83 centres, with stroke symptoms on awakening that were not present before sleep, with limb weakness and NIHSS score ≥3, or dysphasia, treatment	Patients were randomized to receive intravenous tenecteplase (0.25mg/kg, maximum 25mg) or best medical management.	**Primary outcome:** mRS score at 3 months **Secondary outcomes:** Symptomatic and asymptomatic intracranial hemorrhage during the first 7 days, recurrent ischemic stroke within 7 days, all-	Estimated study completion date is December 2022. Preliminary results, as presented at the ESC May 2022. In ordinal shift analysis of mRS sores at 3 months, there was no significant differences between groups (adj OR=1.18, 95% CI 0.88-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		with tenecteplase is possible within 4.5 hours of awakening. Patients who were eligible for thrombectomy were also eligible. Mean age was 73 years, 57% were men. Median NIHSS score was 6.		cause mortality at 7 days and 3 months	1.58). There was no significant difference between groups in the percentage of patients with an excellent functional outcome (mRS 0-1) at 3 months (adj OR=45.1% [tenecteplase] vs. 38.3% [control]; adj OR=1.33, 95% CI 0.94-1.87). There were no significant differences between groups on any of the safety outcomes. Symptomatic ICH defined using SITS-MOST criteria occurred in 3.1% of tenecteplase patients and 1.0% in the control group (adj OR=3.12, 95% CI 0.83-11.7). Any intracranial hemorrhage occurred in 11.5% of tenecteplase patients and 10.3% in the control group (adj OR=1.14, 95% CI 0.67-1.94). 9.7% of patients in the tenecteplase had died by 90 days vs. 7.9% in the control group (adj OR=1.29, 95% CI 0.74-2.26). 60 patients were treated with thrombectomy (42 in the control group and 18 in the tenecteplase group).
NCT02814409 **UK** **RCT** ***Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST2)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1870 patients (planned) with acute ischemic stroke (<4.5 hours), eligible for treatment with alteplase. Persons with acute endovascular treatments planned are excluded	Patients were randomized to receive intravenous tenecteplase (0.25mg/kg, maximum 25mg) or 0.9 mg/kg alteplase.	**Primary outcome:** Ordinal shift analysis of mRS scores at 90 days **Secondary outcomes:** Full neurological recovery (mRS 0-1) at 90 days, independent recovery (mRS 0-2) at 90 days, early neurological improvement (≥ 8 points drop on NIHSS), or score of 0-1) at 24 hours, 90-day mortality, symptomatic ICH	Estimated study completion date was August 2019
Menon et al. 2022	Concealed Allocation: ☑	1,600 patients, recruited from 22 centres with	Patients were randomized to receive	**Primary outcome:** Freedom from disability	Median stroke onset-to-needle time was 128 minutes in the tenecteplase group vs. 131

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Canada **RCT** ***Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke (AcT)***	Blinding: Patient ☒ Assessor ☑ ITT: ☑	acute ischemic stroke, eligible for treatment with alteplase (+/- thrombectomy) within 4.5 hours of symptom onset. Median age was 74 years, 48% were women. Median NIHSS score was 9. Median symptom-to-randomization time was 2 hours. There were no exclusions based on baseline mRS scores.	intravenous tenecteplase (0.25mg/kg, maximum 25mg, n=816) or 0.9 mg/kg alteplase (n=784). 23 patients withdrew consent after randomization, leaving 806 in the tenecteplase group and 771 in the alteplase group.	(mRS 0-1) at 90 (up to 120) days **Secondary outcomes:** mRS score of 0-2 at 90 (up to 120) days, mRS score at 90 days, return to baseline function at 90 days, EQ-VAS at 90 (up to 120 days), successful recanalization (eTICI score of ≥2b on initial angiography) for patients who underwent EVT, process times, 90-day mortality, symptomatic ICH at 24 hours.	minutes in the alteplase group. 36.9% of patients in the tenecteplase group achieved the primary outcome vs.34.8% in the alteplase group (unadjusted difference=2.1%, 95% CI -2.6% to 6.9%; adjusted RR=1·1, 95% CI 1·0 to 1·2), meeting the non-inferiority threshold, (the lower bound 95% CI of which was set at greater than -5%). Median duration of follow-up was 97 days. 56.4% of patients in the tenecteplase group achieved had a mRS score of 0-2 at 90 days vs. 55.6% in the alteplase group (unadjusted difference=0·8, 95% CI –4·1 to 5·7; adjusted RR=1·0, 95% CI 1·0 to 1·1). Median 90-day mRS scores in both groups was 2 (common adjusted OR=0·9, 95% CI 0·8 to 1·1). 29.6% of patients in the tenecteplase group had returned to normal function at 90 days vs.27·9% in the alteplase group (unadjusted difference=1·7, 95% CI –2·9 to 6·4). Mean EQ-VAS scores at 90 days were 70.5 in the tenecteplase group vs. 68.1 in the alteplase group (mean unadjusted difference=2·4, 95% CI –0·1 to 4·8). There was no significant difference between groups in the proportion of patients treated with EVT (32.0% vs. 32.2%), or in those with successful perfusion (10.2% vs.10.5%). There were no group x treatment interactions found in subgroup (ITT or per protocol) analysis of the primary outcome (age, sex, baseline NIHSS, LVO, onset-to-needle time, registry or hospital type) At 90 days, 15.3% of patients in the tenecteplase

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					group had died vs.15.4% in the alteplase group. 3.4% of patients in the tenecteplase group suffered a symptomatic ICH by 24 hours vs. 3.2% in the alteplase group.
Kvistad et al. 2022 **Norway** **RCT** ***The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST 2)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑ (modified) Patients who did not receive thrombolysis or who withdrew their informed consent, were excluded	204 patients, recruited from 11 centres with an acute ischemic stroke, NIHSS >5, and who could begin treatment within 4.5 hours of symptom onset. Patients undergoing a thrombectomy were included if they received thrombolysis as a bridging therapy. Median age was 73 years, 48% were men. Median NIHSS score was 11.	Patients were randomized 1:1 to receive 0.4 mg/kg tenecteplase or 0.9 mg/kg alteplase.	**Primary outcome:** Favourable outcome (mRS 0-1) at 90 days **Secondary outcomes:** Any intracranial hemorrhage at 24-48 hours, symptomatic ICH, neurological improvement within 24 hours (NIHSS of 0 or decrease of >3 points), mortality at 90 days	The trial was halted prematurely due to safety concerns. There were more stroke mimics in the alteplase group (11.5% vs. 3.0%). Significantly fewer patients in the tenecteplase group achieved a favourable outcome (32% vs. 51%; unadjusted OR=0·45, 95% CI 0·25–0·80, adjusted OR=0·61, 95% CI 0·32 to 1·14) The risk of any intracranial haemorrhage was significantly higher in the tenecteplase group (21% vs. 7%; unadjusted OR= 3·68, 95% CI 1·49–9·11, adjusted OR=3·54, 95% CI ·40 to 8·99). Significantly more patients in the alteplase group experienced early neurological improvement (74% vs. 58%; unadjusted OR=0·48, 95% CI 0·26 to 0·88, adjusted OR=0·53, 95% CI 0·28 to 1·01). The risk of mortality at 3 months was significantly higher in the tenecteplase group (16% vs. 5%; unadjusted OR= 3·56, 95% CI 1·24–10·21, adjusted OR=2·94, 95% CI 0·97 to 8·89). Data at 3 months were missing for 4/100 patients in the tenecteplase group and 3/104 patients in the alteplase group. Significantly more patients in the tenecteplase group experienced at least one serious adverse events (45% vs. 21%, p=0.0003).
Campbell et al. 2020	Concealed	300 adult patients,	Patients were	**Primary outcome:**	The percentage of participants with ≥50%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Australia/NZ **RCT** ***EXTEND-IA TNK-2***	Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	recruited from 27 centres, with ischemic stroke due to occlusion of the intracranial internal carotid, basilar, or middle cerebral artery who were eligible to receive intravenous thrombolysis. Pre-morbid mRS score ≤3. Mean age was 72.7 years, 53% were men. Median NIHSS score was 17.	randomized 1:1 to receive 2.5 or 4.0 mg/kg intravenous tenecteplase given as a bolus prior to endovascular thrombectomy	Substantial reperfusion (the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus). **Secondary outcomes:** mRS scores at 90 days, early neurological improvement (a reduction of ≥ 8 points or a score of 0 or 1 on the NIHSS at 72 hours) **Safety outcomes:** Death, symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment	reperfusion of the previously occluded vascular territory was the same in each group (19.3% vs. 19.3%, unadjusted risk difference, 0.0% [95% CI, −8.9% to −8.9%]; adjusted risk ratio, 1.03 [95% CI, 0.66-1.61]; P = .89). Median mRS score was 2 in both groups at day 90 (p=0.73). The percentage of patients who were functionally independent at 90 days did not differ between groups (59% [0.40] vs. 56% [0.25], p=0.40). The percentage of patients who achieved substantial early neurological deficit improvement did not differ significantly between groups (68% [0.40] vs. 62% [0.25], p=0.39). Mortality was 17% in 0.40 group and 19% in the 0.25 group, p=0.35. sICH incidence was 4.7% in 0.40 group vs.1.3% in the 0.25 group, p=0.12.
Campbell et al. 2018 **Australia/NZ** **RCT** ***EXTEND-IA TNK***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	202 patients, ≥18 years, recruited from 13 centres, who were eligible to receive intravenous thrombolysis within 4.5 hours after the onset of ischemic stroke and had cerebral lesions that could be treated with intraarterial clot removal, which could commence within 6 hours of stroke onset. Pre-morbid mRS score ≤3. The original entry criteria requiring CT-perfusion mismatch for anterior circulation	Patients were randomized 1:1 to receive intravenous tenecteplase (0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (0.9 mg per kilogram; maximum dose, 90 mg).	**Primary outcome:** Substantial reperfusion (the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus). **Secondary outcomes:** mRS scores at 90 days, early neurological improvement (a reduction of ≥ 8 points or a score of 0 or 1 on the NIHSS at 72 hours) **Safety outcomes:** Death, symptomatic ICH (sICH) within 36 hours of	At initial angiographic assessment, a significantly higher number of patients in the tenecteplase group achieved substantial reperfusion (22% vs. 10%, incidence difference=12%, 95% CI 2- 21, p=0.002 for noninferiority, adjusted incidence ratio=2.2, 95% CI 1.1-4.4; p=0.03 for superiority and adjusted OR=2.6, 95% CI 1.1-5.9; p=0.02 for superiority). Thrombectomy was not performed in patients who met the primary outcome of reperfusion except for one patient in the tenecteplase group. The median mRS score at 90 days was significantly lower in the tenecteplase group (2 vs. 3, common OR=1.4, 95% CI 1.0-2.8, p=0.04). The percentage of patients who were functionally independent or who had achieved an excellent

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		strokes, was removed after 80 patients. Mean age was 71 years, 55% were men. Median NIHSS score was 17.		treatment	outcome, did not differ between groups. The percentage of patients who experienced early neurological improvement did not differ between groups (71% vs. 68%, p=0.70). There were 10 deaths in the tenecteplase group vs. 18 in the alteplase group (adj OR=0.4, 95% CI 0.2-1.1, p=0.08). There was 1 sICH in each group.
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 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.	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 improvement of ≥ 4 points compared with baseline), ordinal shift analysis of mRS at 3 months, and 90 day-mortality	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** 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**	Concealed Allocation: ☑ Blinding:	104 patients≥18 years, living independently prior to stroke, admitted to a single centre over	Patients were randomized to receive tenecteplase (0.25 mg/kg, 25 mg max,	**Primary outcome:** Percentage of penumbra salvaged 24-48 hours post stroke (volume measured at	8 patients had final non-stroke diagnoses and were excluded from primary and secondary outcome analyses

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT (Phase II) ***Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST)***	Patient ☒ Assessor: ☑ ITT: ☑	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	n=52) or alteplase (0.9 mg/kg, 90 mg max, n=52) within 4.5 hours of stroke.	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	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% (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
Systematic reviews					
Katsanos et al. 2021 **Greece** **Systematic review & meta-analysis**	Risk of "other" bias high in 2 trials. The risk for performance	4 RCTs (n=433) patients with acute ischemic stroke and large vessel occlusion who received thrombolytic intravenous agents within 4.5 hours	Trials compared tenecteplase vs. alteplase. Doses of tenecteplase were 0.1, 0.25 and 0.4 mg/kg. Doses of alteplase were	**Primary outcome:** mRS 0-2 at 3 months **Secondary outcomes:** Excellent outcome (mRS scores of ≤ 1) at 3 months,	The odds of having a mRS score of 0-2 at 3 months were significantly higher in the tenecteplase group (OR= 2.06, 95% CI, 1.15–3.69), as were the odds of successful recanalization (OR=3.05, 95% CI, 1.73–5.40), and functional improvement (common OR=1.84,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
	bias was considered unclear in all RCTs.	of symptom onset. Trials included EXTEND-IA TNK, ATTEST, (n=2) and NOR-TEST.	the same in all studies (0.9 mg/kg)	3-month all-cause mortality, 3-month functional improvement (ordinal logistic regression analysis on the per 1-point decline in the ordinal mRS score) at 3 months, any ICH, symptomatic ICH, successful recanalization and early neurological improvement	95% CI, 1.18–2.87). The results of 2 or 3 RCTS included. There were no differences between groups for the outcomes of early neurological improvement, symptomatic ICH, any ICH, mRS score of 0 to 1, or all-cause mortality.
Burgos & Saver 2019 **USA** **Systematic review & meta-analysis**	Risk of bias was assessed as intermediate to low in all trials.	5 trials (n=1,585). including EXTEND-IA TNK, NOR-TEST, ATTEST (all described below) and Study of Tenecteplase (TNK) in Acute Ischemic Stroke (TNK-S2B) and The Australian TNK trial. Mean age 70.8 years, 58.5% men, baseline Mean NIHSS score mean was 7.0. Mean time since known well to treatment start was 148 minutes. Thrombectomy was not permitted in 3 trials, planned in one trial and 3-4% of patients received the procedure in the final trial.	Trials compared tenecteplase (TNK) vs. alteplase (ALT). Doses of TNK were 0.1 mg/kg in 6.8% of patients, 0.25 mg/ kg in 24.6%, and 0.4 mg/kg in 68.6%. Prespecified noninferiority margin was set at -6.5%.	**Primary outcomes:** Percentage of persons who were disability free (mRS score of 0-1) at 90 days, independence (mRS 0-2) at 3 months **Safety outcomes:** symptomatic intracranial hemorrhage (sICH) and mortality	The percentages of persons who were disability-free were TNK 57.9% vs. ALT 55.4% (risk difference=4%, 95% CI −1% to 8%), which fell inside the margin for non-inferiority. The percentages of persons who were disability-free were TNK 71.9% vs. ALT 70.5% (risk difference=8%, 95% CI −4% to 20%). The percentage of persons with sICH was 3% in each group. The percentages of persons who had died at 3 months were TNK 7.6% vs. ALT 8.1% (risk difference=0%, 95% CI −3% to 2%).

Strategies to Reduce Door-to-Needle Times

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Kamal et al. 2020 **Canada** **Retrospective study**	NA	Patients admitted to 17 designated stroke centers with acute ischemic stroke who received thrombolysis. Mean age was 71 years, 46% were women.	The outcomes and process times of guideline-treated patients (i.e. those treated within 4.5 hours of stroke onset), treated with thrombolysis before (July 1, 2007 to March 31, 2015, n=1,858) and after (October 1, 2016 to December 31, 2017, n=630) the initiation of the Improvement Collaborative intervention, were examined. The initiative involved the recruitment of interdisciplinary teams from all the stroke centers, 3 face-to-face workshops, site visits to all stroke centers, 10 webinars, data audit, data feedback, and a closing celebration.	**Primary outcome:** Change in door-to-needle (DTN) time, percentage of patients discharged home, mortality at discharge, 90-day home time	The number of patients receiving thrombolysis increased from 9.35% in the pre period to 15.73% in the post period. The median DTN time was reduced significantly from pre to post intervention (70.0 to 39.0 minutes (p<0.0001). A significantly higher number of patients were discharged home in the post period (46.5% to 59.5%, p<0.0001). The adjusted odds for being discharged home from acute care was 1.62 (95% CI 1.34–2.044). Mortality decreased non significantly from 14.5% to 10.5% (p=0.0990). The median 90-day home time increased from 43.3 to 53.6 days, p=0.0015).
Fonarow et al. 2014 **USA** **Retrospective study**	NA	71,169 patients admitted to 1,030 Get with The Guidelines—Stroke participating hospitals with acute ischemic stroke treated with tPA (27,319 during the preintervention period from April 2003-December 2009 and 43,850 during the postintervention period from January 2010-September 2013). Median age was 72	The outcomes and process times of patients admitted before and after the initiation of a quality improvement initiative (Target:Stroke) were examined. Main strategies of the initiative included promoting prenotification of hospitals by EMS personnel, activating the entire stroke team with a single call or page, rapid	**Primary outcome:** Door to needle (DTN) time, mortality, home discharge, sICH	The median DTN times were reduced significantly from pre- to post- intervention (77 vs. 67 minutes, p<0.001). The percentage of patients treated within 60 minutes of stroke onset increased significantly from 26.5% to 41.3% (p<0.001). In hospital mortality decreased significantly from pre to post-intervention from 9.93% to 8.25% (adj OR=0.89, 95% CI 0.83-0.94, p<0.001). The percentage of patients discharged home increased significantly from 37.6% to 42.7% (adj OR=1.14, 95% CI 1.09-1.19, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		years, 50.1% were women.	acquisition and interpretation of brain imaging, use of specific protocols and tools, premixing tPA for high likelihood candidates, a stroke team–based approach, and rapid feedback to the stroke team on performance.		The percentage of patients with sICH within 36 hours decreased significantly from 5.68% to 4.68% (adj OR=0.83, 95% CI 76-0.91, p<0.001).

Reversal of Anticoagulation

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pollack et al. 2017 **International** **Prospective study** **RE-VERSE AD**	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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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 **International** **Prospective study (interim results)** **RE-VERSE AD**	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 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.	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. 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.

Abbreviations

CA: concealed allocation	CI: confidence interval	HR: hazard ratio
ITT: intention-to-treat	NA: not assessed	NIHSS: National Institutes of Health Stroke Scale
NNTB: number needed to benefit	NNTH: number needed to harm	OR: odds ratio
RR: relative risk	TIBI: Thrombolysis in Brain Ischemia	

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9Sept2022