Question 1 evidence tables

Question 1: Does thrombolysis improve functional outcomes in patients with ischaemic stroke with unknown (including wake up stroke) or late time of onset?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

AIS = acute ischaemic stroke, ICH = intracerebral haemorrhage, mRS = Modified Rankin Scale, sICH = symptomatic intracerebral haemorrhage, rtPA = recombinant tissue plasminogen activator, tPA = tissue plasminogen activator, IV = intravenous, IVT = intravenous thrombolysis, LVO = large vessel occlusion, DWI = diffusion-weighted imaging, PWI = perfusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery, LVO = large volume occlusion, EVT = endovascular thrombectomy, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
1	E. Berge et al. (2021). European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European Stroke Journal,* 6:1 I-LXII	ESO guidelines. Summary of the evidence expressed through a PICO question then a recommendation using GRADE methodology.	Alteplase v placebo in: (1) patients with AIS of 4.5–9 h duration (known onset time) selected with plain CT (2) patients with AIS of 4.5-9hrs duration using advanced imaging (known onset time) (3) AIS on waking	(1) mRS, death, sICH (2) mRS, death, sICH (3) mRS, death, sICH	(1) In a 9 RCT IPDMA, 6 trials included patients in this time-window. No benefit of alteplase in this time window (OR for excellent outcome at 3–6 months: 1.15, 95% CI: 0.95–1.40) with increased harm OR for PH2=6.89 (95% CI: 4.17–11.38) (2) Pooled IPDMA (Campbell et al IBID 40) of EPITHET (3-6hr DWI-PWI mismatch); ECASS4 & EXTEND (4.5-9hr, MRI mismatch), n=414: IVT led to a higher rate - mRS0-1 (36% vs 29%, OR 1.86, 95% CI: 1.15–2.99, P 0.01),	**++** The SR is high quality. Further comments below on the included studies. (1) (**++**) Evidence from high quality IPDMA (2) Reduced evidence quality due to bias: EPITHET – small n=101, included wake up ECASS4 – stopped early n=119, underpowered EXTEND – included wake-up, stopped early due to WAKE-UP results (3) No EVT performed in these trials

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					- higher rate of sICH (5% vs.<1%; OR 9.7, 95% CI: 1.23–76.55, P 0.03) - no *significant* difference in mortality (14% vs. 9%; OR 1.55, 95% CI: 0.81–2.96, P 0.19) In IPDMA, 51% were wake-up but no interaction between the time strata (p=0.87 for interaction); however, sensitivity analysis of those meeting EXTEND criteria and wake-up excluded, benefit was lost. (3) Pooled IPDMA from MRI/CTP selected participants (WAKE-UP, THAWS; EXTEND, ECASS-4). IVT was significantly associated with - mRS0-1 OR 1.49, 95% CI: 1.10–2.03, P=0.01 - higher sICH (3% vs. 0.5%, P 0.02) - increased mortality OR 2.06, 95% CI: 1.03–4.09, P 0.04). Recommendations considered WAKE-UP separately due to the differences between WAKE-UP (DWI-FLAIR selection), THAWS (alteplase dose 0.6mg/kg, stopped early). The other trials were not dedicated to WAKE-UP only	All used MRI selection, EXTEND also used CTP.

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1	E. Berge et al. (2021). European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European Stroke Journal,* 6:1 I-LXII	Guidelines, incorporating meta-analysis of extended time window and wake-up stroke.	1) Thrombolysis at 4.5-9h of onset using plain CTH (9 RCTs – 1229 with alteplase, 1166 placebo). 2) Thrombolysis at 4.5-9h of onset using "advanced" imaging (3 RCTs – based off Campbell meta-analysis, n=414). 3) Thrombolysis in wake-up stroke/unknown onset (based on EOS meta-analysis of 4 RCTs, n=843).	1) mRS 0-1 at 3-6 months, mRS 0-2 at 3-6 months. 2) mRS 0-1 at 3 months, mRS 0-2 at 3 months. 3) mRS 0-1 at 3 months, Rankin shift, sICH, mortality within 3 months.	1) OR for mRS 0-1: 1.15 (0.95-1.4), cOR mRS 0-2 1.03 (0.9-1.18). 2) For all 4.5-9h (including wake-ups), OR for mRS 0-1: 2.23 (1.1-4.5) and OR for mRS 0-2 2.14 (1.07-4.28). When using EXTEND mismatch criteria and excluding wake-ups: OR for mRS 0-1 was 2.46 (0.44-13.76) and mRS 0-2 was 2.4 (0.99-5.85). 3) aOR for mRS 0-1 1.49 (1.1-2.03), adjusted cOR for better functional outcome 1.39 (1.05-1.8), significantly higher sICH (3% with tPA, 0.5% with placebo, p=0.02), and aOR for mortality 2.06 (1.03-4.09).	1) **++** 2) **+** 3) **+**
2	M. Koga et al. (2020). Thrombolysis with Alteplase at 0.6 mg/kg for Stroke with Unknown Time of Onset: A Randomized Controlled Trial. *Stroke,* : 1530-1538	Japan; investigator-initiated, multicenter, randomized, open-label, blinded-end point trial; n=131	Alteplase at 0.6 mg/kg or standard medical treatment in ischemic stroke with unknown time of onset	Favourable outcome (90-day modified Rankin Scale score of 0–1)	Favorable outcome was comparable between the alteplase group (32/68, 47.1%) and the control group (28/58, 48.3%; RR, 0.97 [95% CI, 0.68–1.41]; P=0.892)	**+** Stopped early due to WAKE-UP results. No difference between alteplase and control Comparable safety.
2	M. Koga et al. (2020). Thrombolysis with Alteplase at 0.6 mg/kg for Stroke with Unknown Time of Onset: A Randomized Controlled Trial. *Stroke,* : 1530-1538	Stroke symptoms on awaking or with unknown time of onset >4.5 hours since last-known-well and within 4.5 hours after symptom recognition with no upper time limit, were 20 years or older and had a premorbid modified Rankin Scale (mRS)	Alteplase at 0.6 mg/kg vs no alteplase	mRS score of 0 to 1 at 90 days	131 enrolled, 70 to alteplase and 61 to control Wake-up stroke 53 patients (75.7%) and 40 patients (65.6%) in the control group. Median 10 hours symptom recognition to randomisation	Trial stopped early after WAKE-UP so smaller than anticipated. No placebo. Use of argatroban in control group.

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		Mismatch defined by mismatch between the presence of an abnormal signal on DWI and no marked signal change on FLAIR (negative FLAIR pattern) in the corresponding region of the acute stroke. Patients with clinically acute ischemic stroke and a negative FLAIR pattern who did not display an abnormal signal on DWI were also enrolled. ASPECT <5 excluded			mRS 0–1 RR, 0.97 [95% CI, 0.68–1.41]; *P*=0.892 Common OR 0.88 (0.47–1.63)	
3	D. Luan et al. (2019). Efficacy and safety of intravenous thrombolysis in patients with unknown onset stroke: A meta-analysis. *Behavioural Neurology,* 2019: 5406923	Setting: USA, Germany, Switzerland, Korea, UK, and Canada Design: SR and MA Subjects: n=1271. Ischemic Stroke (median NIHSS 6-17 lysis group, 6-14 in conservative group). (542 had lysis vs 729 conservative)	Alteplase 0.9mg/kg (lysis) vs placebo (conservatives)	Primary outcome: Proportion of participants with: ● Good outcome at 90 days and on discharge(MRS 0-2) ● 90 Day Mortality ● ICH ● sICH	Higher proportion of mRS 0-2 at 90 days in the lysis group versus the conservative group (57.66% vs. 46.96%; P=0.0005) No difference between groups for discharge good outcome mRS 0-2. Non-significantly higher incidences of ICH in lysis group (16.81% vs. 6.62% in conservative group; P=0.42) Non-significantly higher incidence sICH (6.32% vs. 2.97%; P=0.06).	– Low Quality. Included only 2 RCTs with low numbers in each study, unclear what time frame was between symptom and onset in majority of studies and variability in radiology methods used to assess suitability for inclusion. Large degree of heterogeneity.
3	D. Luan et al. (2019). Efficacy and safety of intravenous thrombolysis in patients with unknown onset stroke: A meta-analysis. *Behavioural Neurology,* 2019: 5406923	Study-level MA of wake-up stroke	Thrombolysis vs control	mRS 0-2 at d/c & day 90 mortality day 90 ICH sICH Quality/RoB	8 trials, n=1271 (542v729) • 3 retrospective • 3 prospective observational • 2 RCTs (n=12, n=503) Day 90 mR S0-2 favoured rtPA 57.7% vs. 47%; P=0.0005	– Blend of various study designs including retrospective and observational data. Article poorly written in places. Selective reporting evident – no RoB results for the non-RCTs.

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					mortality 8.7 v 4.8% P=0.11 sICH (6.3 v 3% P=0.06)	
4	B. Mac Grory et al. (2021). Thrombolytic therapy for wake-up stroke: A systematic review and meta-analysis. *European Journal of Neurology,* 28:6 2006-2016	MA of 16 studies; 2 RCT and 14 observational studies (cohort studies (prospective or retrospective), and single arm studies; total 14,017 patients with ischaemic stroke >4.5h from time last seen well. Most studies conducted in Europe and North America	Patients receiving tPA =1757 Patients not receiving tPA=12,260	Primary outcome: Recovery at 90-days (mRS score 0-2); Secondary outcomes: sICH within 36h; mortality and other adverse outcomes	Proportion of patients receiving tPA who had functional recovery (12 studies reporting 90-day outcomes): 0.61 (95% CI 0.43-0.69), with RR 1.21 (95% CI: 1.01-1.46, 4 studies) compared with patients not receiving tPA; and stratified by use of imaging modality: • Non-contrast CT: 0.56 (0.41-0.71) • MRI: 0.56 (0.43-0.69) • CT perfusion: 0.56 (0.43-0.69). Proportion of patients treated with IV tPA who had sICH within 36h: 0.033 (0.025-0.041; I^2 (0%, 95% CI 0%-0%). Proportion of patients who received tPA and died at 90 days (10 studies) was 0.05 (0.03-0.07; I^2 49.86%, 0%-75.7%); RR 0.75 (0.30-1.84) compared to not treated patients. Other adverse events not reported with consistency to permit meta-analysis.	**+** Includes data from observational studies (14) and 2 RCT. Among the 2 RCTs; overall RoB rated low in one and some concerns for the other. Overall RoB for half of the 14 observational studies rated as serious and half as critical. Not all patients included had wake up stroke.

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4	B. Mac Grory et al. (2021). Thrombolytic therapy for wake-up stroke: A systematic review and meta-analysis. *European Journal of Neurology,* 28:6 2006-2016	Setting: Europe and North America Design: SR and MA Subjects: Adults with wake-up stroke who were administered IV tPA and who had MRI or CT imaging. Median NIHSS score ranged 5 to 11.9, moderate severity strokes (n= 14,017), 1757 got tPA, and 12,260 did not.	IV tPA (0.9mg/kg) vs normal saline, placebo or no treatment	Primary outcomes: • Recovery at 90 days • (mRS 0-2) • sICH within 36 hrs • Mortality	61% receiving IV tPA achieved mRS 0-2 at 90 days (95% CI: 51%– 70%, RR of 1.21) compared with patients not receiving IV tPA (95% CI: 1.01– 1.46). Participants were 20% more likely to achieve Functional Improvement in Lysis group. 3% IV tPA patients had sICH within 36 hrs (95% CI: 2.5%– 4.1%;, RR of 4.00) compared with patients not receiving IV tPA (95% CI: 2.85– 5.61). The pooled proportion of patients treated with tPA who died was 0.05 (95% CI: 0.03– 0.07; I2 = 49.86%, 95% CI: 0%– 75.7%). The RR of mortality among patients with wake-up stroke treated with IV tPA compared with patients not treated with IV tPA was 0.75 (95% CI: 0.30– 1.84).	**++** High quality
5	L.-K. Muntendorf et al. (2021). Cost-Effectiveness of Magnetic Resonance Imaging-Guided Thrombolysis for Patients With Stroke With Unknown Time of Onset. *Value in Health,* 24:11 1620-1627	Cost-effectiveness analysis of WAKE-UP data	WAKE-UP analysis aimed to assess the cost-effectiveness of the intervention compared to placebo		Treatment with IV-tPA resulted in cost savings of €51009 and 1.30 incremental gains in quality-adjusted life-years at a 5% discount rate.	

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6	M. W. Parsons et al. (2019). Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *The Lancet,* 394:10193 139-147	SR and IPDMA of studies investigating alteplase versus placebo in individuals >4.5h of onset or with wake-up stroke, who were imaged using perfusion-diffusion MRI or CT perfusion. 3 RCTs (EXTEND, ECASS4-EXTEND, EPITHET. n=414; 213 (51%) receiving alteplase, 201 (49%) receiving placebo. All studies used alteplase at 0.9mg/kg.	Alteplase versus placebo.	Primary outcome: • mRS 0-1 at 3 months. Secondary outcomes: (i) mRS improvement (by >1 point) (ii) mRS 0-2 at 3 months. (iii) sICH within 36h (iv) death at 3 months. (v) mRS 0-1 at 3 months.	Significant increase in those achieving independence with alteplase: mRS 0-1 achieved in 76/211 (36%) of alteplase group, 58/199 (29%) in placebo group. aOR 1.86 (1.15-2.99). (i) aOR 1.6 (1.12-2.99) [for mRS improvement by >1 point) (ii) Significant increase in those achieving mRS 0-2 with alteplase: 103/211 (49%) versus 87/199 (44%). aOR 1.74 (1.08-2.81). (iii) Significant increase in risk of sICH: 10/213 (5%) in alteplase group, 1/201 (<1%) in placebo. aOR 9.7 (1.23-76.55). (iv) No significant difference in death by 3 months: 29/213 (14%) in alteplase group, 18/201 (9%) in placebo group. aOR 1.55 (0.81-2.96). (v) Significantly increased with alteplase: 55/152 (36%) with alteplase versus 39/151 (26%) in	**++** NB: 51% woke with stroke. EXTEND and ECASS4-EXTEND used criteria of within 9 hours of mid-point of sleep.

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					placebo. aOR 2.06 (1.17-3.62).	
6	M. W. Parsons et al. (2019). Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *The Lancet,* 394:10193 139-147	Setting: Australia, New Zealand, Europe, Asia Design: SR and IPDMA Subjects: patients (aged ≥18 years) with ischaemic stroke treated more than 4·5 h after onset, or with wake-up stroke, who were imaged with perfusion-diffusion MRI or CT perfusion N=414 (213 alteplase group V 201 placebo group)	Alteplase vs placebo	Primary Outcome: Excellent functional outcome (modified Rankin Scale [mRS] score 0–1) at 3 months Secondary Outcomes: Functional improvement (≥1 point reduction in mRS score at 3 months, Functional independence (mRS score 0–2) at 3 months, Early neurological improvement (reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1) at 72 h Safety Outcomes: Symptomatic ICH Death from any cause	Significantly more patients in the alteplase group (76 (36%) of 211) achieved mRS score 0–1) at 3 months compared with (58 (29%) of 199) in placebo group (adjusted odds ratio [OR] 1·86, 95% CI 1·15–2·99, p=0·011. Significantly More patients in the alteplase group achieved functional improvement and independence at 3 months, and had early neurological improvement Higher rate of sICH in alteplase group v placebo ten [5%] of 213 patients vs one [<1%] of 201 patients, adjusted OR 9·7, 95% CI 1·23–76·55, p=0·031 No difference in mortality between two groups	**+** Small sample size, only included 3 trials
7	M. W. Parsons et al. (2021). Association of Reperfusion after Thrombolysis with Clinical Outcome across the 4.5- To 9-Hours and Wake-up Stroke Time Window: A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials. *JAMA*	IPDMA of RCTs performed from August 2001 to June 2018 with 3-month follow-up. Patients had acute ischemic stroke with 4.5- to 9-hours poststroke onset or with wake-up stroke were randomized to alteplase or placebo after perfusion mismatch imaging. Analysis began July 2019 and ended May 2020.	No: observed achieved reperfusion: Reperfusion was defined as more than 90% reduction in time to maximum of more than 6 seconds' lesion volume at 24- to 72-hour follow-up.	mRS with common odds ratio	Overall, reperfusion was associated with improved functional outcome (common odds ratio, 7.7; 95%CI, 4.6-12.8; *P* < .001)	- Low quality

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	Neurology, 78:2 236-240					
7	M. W. Parsons et al. (2021). Association of Reperfusion after Thrombolysis with Clinical Outcome across the 4.5- To 9-Hours and Wake-up Stroke Time Window: A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials. *JAMA Neurology,* 78:2 236-240	IPDMA of 2 RCT (EXTEND and EPITHET) The studies were performed from August 2001 to June 2018 with 3 months follow up, in patients with ischemic stroke with 4.5 to 9-hours post-stroke onset EXTEND: RCT of alteplase vs placebo in 225 patients with CT perfusion or magnetic resonance perfusion-diffusion mismatch. EPITHET: RCT of altepalse vs placebo in 100 patients treated 3 to 6 hours after stroke onset. For this MA only patients treated between 4.5 to 6h after stroke onset were included	Alteplase versus placebo after perfusion mismatch imaging, in EXTEND; in EPITHET all patients had MR perfusion-diffusion but mismatch not required for study eligibility.	Reperfusion defined as more than 90% Reduction in time to maximum of more than 6 seconds lesion volume between baseline and 24-hour perfusion imaging in EXTEND, and between baseline and day 3 imaging in EPITHET. Functional outcome at 90-day by reperfusion status assessed by clinicians blinded to treatment allocation Early neurological improvement defined as reduction of 8 points or more on the NIHSS between baseline and 3 days or reaching 0 or 1.	Reperfusion assessable in 270 of 295 patients (215 of 225 from EXTEND and 55 of 70 from EPITHET). Median (interquartile range) age was 76 (66-81) years in the reperfusion group vs 74 (64.5-81.0) years in the group with no reperfusion. The median (interquartile range) baseline NIHSS score was 10 (7-15) in the reperfusion group vs 12 (8.0-17.5) in the no reperfusion group. Alteplase was associated with increased reperfusion vs placebo (alteplase: 68 of 133 (51%) vs placebo: 38 of 137 (28%) (p<0.001). RR: 1:84; 95% CI 1.34-2.53, p<0.001) In ordinal logistic regression analysis reperfusion was associated with improved functional outcome (common OR, 7.7; 95% CI, 4.6-12.8; p<0.01, for improvement by at least 1 mRS category) In each of the 4.5- to 6-hours, 6-to 9-hours, and wake up time strata, reperfusion was associated with significant	**++** This is a MA of 2 RCT, however, majority of patients included were from one trial (EXTEND). Baseline median age and NIHSS score not significantly different in both groups. Patients with reperfusion had smaller core and hypoperfusion lesion and volumes and were less likely to have LVO. Comments: the 95% CI crossed unity for mRS 0 to 1 in the 6-to 9hours group.

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					improvement in ordinary analysis of mRS score, mRS score 0 to 2, and early neurological improvement but the 95% CI crossed unity for mRS 0 to 1 in the 6-to 9hours. Symptomatic haemorrhage in alteplase group occurred in 3 of 5 (5.9%) in the 4.5- to 6-hours group, 2 of 28 (7.1%) in the 6- to 9-hours group and 4 of 73 (5.5%) in the wake-up stroke (Fisher p=0.91)	
7	M. W. Parsons et al. (2021). Association of Reperfusion after Thrombolysis with Clinical Outcome across the 4.5- To 9-Hours and Wake-up Stroke Time Window: A Meta-Analysis of the EXTEND and EPITHET Randomized Clinical Trials. *JAMA Neurology,* 78:2 236-240	SR and MA	This MA looked at 3 pieces of research that met their criteria The EXTEND, ECASS4-EXTEND, and EPITHET. These studies identified patients that had an onset of symptoms between 4.5 and 9 hours or were wake-up stroke with salvageable tissue when scanned using CT perfusion.	There was a better outcome for patients that received alteplase than received placebo There was an increase in the amount of ICH documented within this group of patients but those completing the analysis believed that this did not override the overall benefit. There was an increase of 5% (9% top 14%) in the number of deaths recorded in the intervention groups	Over the analysis the patients who received alteplase in the cohort had a better outcome against the control group. There was an increased death and ICH rate but the investigators believed that the use of alteplase was of greater benefit.	**++** High quality
8	M. B. Roaldsen et al. (2021). Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke. *Cochrane*	Cochrane review looking at RCTs for patients with wake-up stroke who received thrombolysis or intra-arterial treatments. All trials used advanced imaging Analysis by:	All types of thrombolytic drugs, given in any dose by IV route: urokinase, recombinant pro-urokinase, streptokinase, and tPA (including	• Good functional outcome at end of follow-up. • Death from all causes at end of follow-up. • Symptomatic intracranial haemorrhage at end of follow-up.	Based on mRS at 90 days Better outcomes seen in endovascular intervention in all studies although a slightly higher death rate (0.69%) Better out comes in all intravascular studies except	**++** High quality

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	Database of Systematic Reviews, 2021:12 CD010995	• Age (under and over 60 years). • Sex. • National Institutes of Health Stroke Scale (NIHSS) score (under and over 10). • Participants characterised by specific imaging criteria (e.g. LVO absent or present). • Participants treated at different time intervals (e.g. within 3 hours after first observation of stroke symptom after awakening from sleep or > 3 hours). 2064 references were discovered with the following being the research projects with the most patients (DAWN; DEFUSE 3; ECASS-4; EXTEND; Michel 2012; THAWS; WAKE-UP). All of these trials had some element of bias within them classed as: Random Sequence reporting bias; allocation concealment; and selective reporting bias being present in all of the mentioned trials.	alteplase, Duteplase, Lumbrokinase, Tenecteplase, and Desmoteplase). All types of intra-arterial treatments: administration of thrombolytic drugs through intra-arterial catheters, mechanical thrombus disruption using a microcatheter or guidewires or both, angioplasty, and the use of endovascular devices.		for ECCAS study which demonstrated a slightly poor outcome when compared to standard treatment The death rate was more evident in the standard arm but there was an outlier with the THAWS trail showing more deaths in the intervention arm. Increased ICH in all studies. All age groups showed a slightly better outcome.	
8	M. B. Roaldsen et al. (2021). Intravenous thrombolytic treatment and	Cochrane systematic review assessing the effects of IVT and thrombectomy versus control in patients with ischaemic stroke	IVT (0.9 mg/kg) vs standard medical care.	Functional outcome: mRS (0-2) at 90 days sICH at 90 days	775 patients randomised. Good functional outcome:	**++** Treatment effects were consistent across trials. Low

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	endovascular thrombectomy for ischaemic wake-up stroke. *Cochrane Database of Systematic Reviews,* 2021:12 CD010995	presenting from wakening from sleep. Of a total of seven RCT, 5 studies evaluated the effects solely of IVT (775 participants). All trials used advanced imaging: WAKE UP, EXTEND, ECASS 4, THAWS and Michel 2012 study (12 participants: 9 wake-up).	Advanced imaging (DWI/FLAIR) and CT and MRI perfusion to identify penumbra).	Death at 90 days	66% (IVT) vs 58% (control): P=0.03 Death: 7% (IVT) vs 10% (control) P=0.09 sICH: 3% (IVT) vs 1% (control) P=0.05 Effects were consistent across stroke severity, LVO and time from observation of symptoms to treatment	loss to follow up rate. Double blinded. Generally low risk of bias. Note that 4 studies stopped prematurely and that different imaging modalities used
8	M. B. Roaldsen et al. (2021). Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke. *Cochrane Database of Systematic Reviews,* 2021:12 CD010995	Study level MA of trials of thrombolysis and thrombectomy after wake up stoke. 7 trials, 5 of thrombolysis, all using mismatch-based imaging selection • THAWS WAKEUP • ECASS4 • EXTEND • Michel, 2012			mRS score 0-2 at 90 days follow-up. 66% of participants randomised to thrombolytic treatment and 58% of participants randomised to control, RR 1.13, CI 1.01-1.26; P=0.03. Symptomatic intracranial haemorrhage occurred in 3% of participants randomised to IVT and 1% of participants randomised to control (RR 3.47, 95% CI 0.98-12.26; P=0.05; 754 participants, 4 RCTs; high-certainty evidence).	**++** High quality – a SR of high quality randomised trials
8	M. B. Roaldsen et al. (2021). Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke. *Cochrane Database of*	Cochrane systematic review assessing IVT and endovascular thrombectomy (EVT) for ischaemic wake-up stroke	IVT or EVT vs control I have considered the IVT aspect only here for this particular question.	• Day 90 mRS 0-2 • Day 90 mortality • sICH	IVT: 7 trials n=775 EVT 2 trials n=205 All used advanced imaging IVT v Control: • mRS0-2: 66% v 58% risk ratio 1.13 (95%CI 1.01 - 1.26; P=0.03)	**++** 4 of the IVT trials had an unclear RoB as they terminated early: WAKE-UP lack of funding; ECASS4 slow recruitment; EXTEND & THAWS lack of equipoise. Risk felt to be minimal.

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	Systematic Reviews, 2021:12 CD010995				• Death: 7% v 10% RR 0.68, p=0.09 • sICH: 3% v 1% RR 3.47, • 95%CI 0.98 - 12.26; P = 0.05 • Subgroup analysis, positive effect on mRS present also when no LVO RR 1.12	
9	G. Thomalla et al. (2020). Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *The Lancet,* 396:10262 1574-1584	IPDMA (EOS Investigators) assessing RCTs of thrombolysis in participants of unknown onset time. Eligible trials: • unknown onset time • selected with advanced imaging Excluded those from ECASS4 and EXTEND with known onset time. All imaging data re-analysed. Mismatch defined as • core vol <70mls • mismatch vol>10ml • ratio hypoperfused tissue[tmax>6s]:core >1.2 mRS 5&6 pooled	Alteplase vs placebo	Primary: mRS0-1 Secondary: mRS shift, mRS 0-2, death, mRS4-6, sICH.	N=843 from 4 RCTs (WAKE-UP, THAWS, ECASS4, EXTEND). 60% data from WAKE-UP. Median NIHSS 7 mRS0-1 in 47%(ALT) v 39%(control); aOR 1.49 [95% CI 1.10–2.03]; p=0.011). Similar ORs in mRS shift and mRS0-2. mRS4-6 21% v 25% aOR 0.76 [0.52–1.11]; p=0.15 death 6 v 3% (p=0.04) sICH 3 v <1% (p=0.024)	**++** PROSPERO Registered MA May not be generalisable to more severe stroke and large infarct core. A net benefit was observed for all functional outcomes despite an increased risk of symptomatic intracranial haemorrhage. Although there were more deaths with alteplase than placebo, there were fewer cases of severe disability or death.
9	G. Thomalla et al. (2020). Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review	IPDMA involving 4 RCTs (WAKE UP, EXTEND, THAWS and ECASS-4), included 843 patients. Hypothesis tested that IVT (alteplase) improves functional outcome compared with placebo in patients with	IVT alteplase (0.9mg/kg) vs placebo (WAKE UP, EXTEND, ECASS 4) and 0.6 mg/kg alteplase for THAWS.	Modified Rankin Score (0-1): Primary Outcome 90 days Secondary Outcomes: Ordinal Shift on mRS, 90 days	Median NIHSS 7 25% Large vesse occlusion Primary outcome data 98% Favourable outcome (mRS 0-1): 47% (IVT) versus 39% (placebo). P=0.011	**+** High to acceptable quality 4 randomised controlled trials

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	and meta-analysis of individual patient data. *The Lancet,* 396:10262 1574-1584	ischaemic stroke with an unknown time of onset using MRI (DWI/FLAIR mismatch) or CT/MRI perfusion penumbra imaging.		mRS 0-2 90 days Safety Outcomes: Death at 90 days Death and dependency (mRS 3-6) Symptomatic ICH	NNT 12 Significant shift on the ordinal scale mRS (OR: 1.38 [1.05 to 1.80] mRS 0-2 (OR: 1.5 CI: 1.06 to 2.12) Deaths 6% (IVT vs 3% (placebo): P=0.04 Death and Dependency (mRS3-6): 35% (IVT) vs 42% (placebo) P=0.022 sICH 3% (IVT0 vs 1% (placebo). P=0.068 Effects were consistent through a number of secondary outcome measures (thereby highlighting consistency) as well as number of subgroup analyses with no heterogeneity observed (different doses of alteplase, LVO, imaging modality)	Treatment effects are consistent using advanced imaging modalities Trial population is relevant, although acknowledge that mild to moderate stroke were only studied Note that 4 trials stopped prematurely and therefore safety effects may be underestimated 60% of trial data provided by WAKE-UP
10	G. Thomalla et al. (2018). MRI-Guided thrombolysis for stroke with unknown time of onset. *New England Journal of Medicine,* 379:7 611-622	European; Multicenter; RCT; investigator-initiated, double-blind, placebo-controlled; n= 503	Randomisation to IV 0.9 mg/kg alteplase (n=254) or placebo (n=249)	Primary outcome - mRS 0-1 at day 90	Primary outcome - alteplase 53.3%, placebo 41.8%; (adjusted OR 1.61; 95% CI, 1.09 to 2.36; P=0.02) Safety end points: death at day 90: alteplase 4.1%, placebo 1.2% (OR, 3.38; 95% CI, 0.92 to 12.52; P=0.07	**++** 94% were wake-up strokes and 21% had anterior LVO Stopped early

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10	G. Thomalla et al. (2018). MRI-Guided thrombolysis for stroke with unknown time of onset. *New England Journal of Medicine,* 379:7 611-622	Multicentre, double blind RCT involving 503 patients with a clearly defined population of patients with ischaemic stroke on awakening (89%) with DWI/FLAIR mismatch on MRI. Subjects were equally matched apart from higher rate of ICA occlusion in treatment arm. Mild to moderate ischaemic stroke (NIHSS < 25). Median NIHSS 6. Patients excluded if planned thrombectomy, severe stroke (NIHSS> 25 or lesion > 1/3 of MCA territory). Note 1362 patients screened (therefore approximately one third of patients recruited). Also note, trial was effectively stopped prematurely due to funding and therefore pre-planned target of 800 was not reached. It is not clear from the paper what circulatory region was affected in patients in the study (anterior or posterior circulatory) but assumed anterior.	Assigned 1:1 ratio of IV alteplase (0.9mg/kg) versus placebo	Primary outcome: modified Rankin 0-1 (excellent) 90 days Secondary outcome: ordinal shift on modified Rankin. Median Rankin scale. Treatment response at 90 days. Global outcome score at 90 days. EQ5D at 90 days (QOL) Safety outcome: death, death or dependency (90 days). Symptomatic intracranial haemorrhage.	Excellent outcome achieved in 53.3% (alteplase) vs 41.8% (placebo). P=0.02. Alteplase treatment effect was consistent across a number of secondary outcome measures, including median modified Rankin, treatment response, Global outcome score and EQ5D at 90 days. Death 4.1% (Alteplase) vs 1.2% (placebo). P=0.07 (non significant) Symptomatic intracranial haemorrhage (2%: alteplase) vs (0.4% placebo). P=0.15)	**++** Defined population with MRI criteria. Large sample size> 500. Treatment effects were observed in secondary outcomes too indicating consistency and precision. Results of this study would be applicable to patient group with specific criteria used in this trial. Note study was stopped prematurely due to funding, therefore safety effects may be underestimated.
11	G. Thomalla et al. (2017). Stroke with Unknown Time of Symptom Onset: Baseline Clinical and Magnetic Resonance Imaging Data of the First Thousand Patients in WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in	Setting: European, multicentre Design: randomized, double-blind, placebo-controlled clinical trial Subjects: Acute stroke with unknown time of onset, Median NIHSS 6.	Alteplase vs Placebo Description of clinical and magnetic resonance imaging (MRI) characteristics of stroke patients with unknown time of symptom onset potentially eligible for thrombolysis	Primary Outcome: MRS 0-1 at day 90. Primary safety outcome measures = mortality and death or dependency (mRS 4–6 at 90 days)	Diffusion-weighted imaging and FLAIR mismatch was present in 479 patients (48.0%) of patients identified with unknown time of onset Only first 1000 patients in trial in this paper, describes clinical and MRI characteristics of participants	**+**

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	Wake-Up Stroke: A Randomized, Doubleblind, Placebo-Controlled Tria. *Stroke,* 48:3 770-773	If MRI DWI/FLAIR mismatch present randomised to either alteplase or placebo N=1005	from a large prospective cohort.		793 patients (81.3%) had a visible DWI lesion, whereas 72 (7.2%) had findings of intracranial hemorrhage. DWI–FLAIR mismatch was present in 479 patients (48.0%) Daytime-unwitnessed stroke had a shorter delay between symptom recognition and arrival at the hospital (1.5 versus 1.8 hours; P=0.002), a higher NIHSS on admission (8 versus 6; P<0.001), and more frequently aphasia (72.5% versus 34.0%; P<0.001).	
12	K. Toyoda et al. (2021). Magnetic Resonance Imaging-Guided Thrombolysis (0.6 mg/kg) Was Beneficial for Unknown Onset Stroke above a Certain Core Size: THAWS RCT Substudy. *Stroke,* : Dec-19	Sub-study of THAWS Trial THAWS was an investigator-initiated, multicentre, randomized open-label, blinded endpoint evaluation, controlled trial. Inclusion criteria: Patients with stroke symptoms on awakening or with unknown time of onset if they presented > 4.5 hours since last-known-well and within 4.5 hours after symptoms recognition; patients ≥ 20 years old and had a premorbid mRS score available. Patients were excluded if NIHSS score < 5 (revised to < 2 in August 2015 to match this eligibility criterion with that of the WAKE-UP trial)	IV alteplase 0.6 mg/Kg (n=68 patients) or standard medical treatment (n=58). Patients were dichotomized by ischaemic score size or NIHSS score and the effect of assigned treatment were compared in each group.	The primary efficacy outcome was favourable outcome, defined as mRS score 0 to 1 at 90 days after stroke onset. Secondary efficacy outcomes were category shift in mRS score at 90 days and changes in NIHSS score at 7 days. Safety outcomes were any ICH, parenchymal haematoma type II ICH, and symptomatic ICH at 22 and 36 hours and major extra-cranial bleeding.	Total patients included in THAWS (n=131) from 2014 to 2018; 126 patients with 90-day follow up assessment. The median DWI-ASPECTS was 9 and the median ischemic core volume was 2.5 mL. Favourable outcome was comparable in both groups: Alteplase 32/68, 47.1% vs 28/58, 48.3%, p=0.892 in control group Mortality was comparable in both groups: alteplase 2/68, 2.9% versus 2/58, 3.4%, p=0.871 in control group.	This study used a smaller dosage of alteplase (0.6 mg/Kg). The number of patients enrolled were small

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		or severity stroke with NIHSS core >25. MRI examination with DWI, FLAIR, T2* and time-of-flight MRA of the circle of Willis. Patients were randomized if they showed mismatch between the presence of an abnormal signal on DWI and no marker signal change on FLAIR in corresponding region of acute stroke. Patients with large infarct with ASPECTS on DWI ≤4 in the territory of the MCA, with visual lesion volume ≥50% of the anterior cerebral artery or posterior cerebral artery , or with more than half of the brainstem or more than half of the unilateral cerebellar hemisphere involved were excluded.			Any ICH at 22 and 36 hours were 26% in alteplase group versus 14% in control group Favourable outcome was more common in the alteplase group than in controls in patients with DWI-ASPECTS 5 to 8 (RR, 4.75, 1.22-18.5, p=0.026) although not in patients with DWI-ASPECTS 9 to 10. Favourable outcome tended to be more common in the alteplase group than in control group in patients with core volume >6.4 mL (RR, 6.15, 0.87-43.64, p=0.069) but not statistically significant, although not in patients with volume ≤ 6.4 mL.	
12	K. Toyoda et al. (2021). Magnetic Resonance Imaging-Guided Thrombolysis (0.6 mg/kg) Was Beneficial for Unknown Onset Stroke above a Certain Core Size: THAWS RCT Substudy. *Stroke,* : Dec-19	Setting: Japan Design: multicenter, randomized, open-label, blinded–end point trial (this is a substudy) Subjects: Patients with stroke with a time last-known-well >4.5 hours who showed a mismatch between DWI and FLAIR. NIHSS 5-25 included	alteplase at 0.6 mg/kg intravenously or standard medical treatment	Primary Outcome: ● Favourable outcome: MRS 0 to 1 at 90 days Secondary Outcome: ● Category shift in mRS score at 90 days ● Change in NIHSS score at 7 days Safety Outcome:	No difference in achieving favourable outcome between lysis and std groups 47.1% vs 48.3% (p=0.892) NIH score changed from 7-3 in lysis group V 7-1 in control group (p=0.432), not a significant change. Non significant higher rate of any ICH in lysis group 26% (18) v 14%(8) P=0.08	**+** Acceptable

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		N= 131 randomised, 126 included, 68 alteplase group, 58 control group		• Any ICH • Parenchymal hematoma type II ICH • Asymptomatic ICH at 22 to 36 hours Major extracranial bleeding	sICH (1/68, 1% versus 0/58, P=0.354) No significant difference between lysis and std group in rates of sICH	
13	G. Tsivgoulis et al. (2020). Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. *Neurology,* 94:12 e1241-e1248	This MA used 4 studies • ECAS EXTEND MICHEL • And WAKE UP	Use of advanced imaging post 4.5hrs These patients were then stratified into control and intervention	Study showed that there was better in outcomes at 3 months following procedure in the intervention group although an increased in ICH There was a discussion point raised as to the use of DWI mismatch in one of the studies. In that this mode is usually reserved for patient below the normal 4.5hrs from onset They do state that there is evidence that suggests the use of DWI mismatch is comparable to CT prefusion	The study showed that IVT in patients with AIS with un-known symptom onset time or elapsed time from symptom onset >4.5 hours (but with substantial viable tissue in advanced baseline neuroimaging) was associated with improved functional outcomes at 3 months despite the higher risk of sICH.	**++** High quality
13	G. Tsivgoulis et al. (2020). Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. *Neurology,* 94:12 e1241-e1248	SR and MA to assess the safety and efficacy of IVT (alteplase 0.9mg/Kg) in patients with AIS and unclear symptoms onset time or with symptoms onset outside the conventional 4.5-hour time window but with evidence of substantial viable hypoperfused tissue documented by advanced baseline neuroimaging. Used CT	Alteplase vs placebo Patients taking tPA/placebo, n: ECASS IV 61/58; EXTEND 113/112; Michel et al. 6/6; WAKE-UP 254/249	Outcomes: • 3-month favourable functional outcome (mRS score 0-1) • 3-month functional independence (mRS 0-2)	4 RCT (859 total patients) Unadjusted analysis: IVT was associated with a higher likelihood of 3-month favourable functional outcome, FFO (mRs score 0-1, OR 1.48, 1.12-1.96), 3 months functional independence (mRS score 0-2, OR 1.42-1.07-1.90); sICH	**++** In this MA, IVT was decided on the basis of DWI-FLAIR mismatch, which aims to identify patients with unknown onset who are likely to be within the 0- to 4.5-hour time window in 251 (58%) of the patients included.

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		or MRI to identify substantial ischaemic core-ischemic penumbra mismatch or FLAIR-DWI mismatch. Exclusions: non-randomized trials, subgroup analysis of RCT, and studies reporting the use of endovascular treatments or thrombolytic agents other than alteplase. Studies included: • ECASS IV: 4.5-9h NIHSS score 4-26; premorbid mRS score ≤1 • EXTEND: 4.5-9h; Age > 18 y; NIHSS score 4-26; premorbid mRS score ≤1 • Michel et al: Stroke symptoms ≤24h ; age 18-80 y; NIHSS score 6-22; premorbid mRS score ≤1 • WAKE-UP: >4.5 h; Age 18-80 y; NIHSS ≤ 25; pre-morbid mRS score ≤1		• 3-month mortality • 3-month functional improvement (assessed with ordinary analysis on the mRS score) • sICH • Complete recanalization	(OR 5.28, 1.35-20.68) and complete recanalization (OR 3.29, 1.90-5.69) with no significant difference in the odds of all causes of mortality at 3-months (OR 1.75,0.93-3.29). Analyses adjusted for age and baseline stroke severity, IVT was also associated with higher probability of 3-month FFO (OR 1.62, 1.20-2.20); 3 months functional improvement (OR 1.42, 1.11-1.81), and sICH (OR 6.22, 1.37-28.26). There was no association of IVT with 3-month functional independence (OR 1.61, 0.94-2.75) or all-cause mortality (OR 1.75, 0.93-3.29) in the adjusted analysis. No evidence of heterogeneity was found in the unadjusted or adjusted analysis (I^2 =0).	
14	X. Jia et al. (2021). Intravenous thrombolysis for acute ischemic stroke with extended time window. *Chinese Medical Journal,* 134:22	MA of four RCT evaluating effect of IVT (alteplase) with unclear time of onset or with stroke onset > 4.5 hours. Total of 848 patients analysed from studies published between 2012-2019. (3 RCT, ECASS 4, EXTEND and WAKE UP with pilot study published in 2012.) Note THAWS study published in 2020 not	IV alteplase versus placebo in patients with disease onset > 4.5hours and unclear time of onset.	Modified Rankin Score 0-1, 0-2 and sICH, death at 90 days.	Patients in IVT group achieved favourable functional outcome 45.8% vs 36.7% (control). P=0.006 sICH occurred 3% (IVT) vs 0.5% (control). P=0.02 Death at 90 days 7% (IVT) vs 4.1% (control) P=0.08	- Low quality data presented No description of imaging studies in trials (DWI/FLAIR) or CT perfusion.

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		included therefore meta-analysis not up to date as analysis incomplete and other analyses (Campbell 2021 and Thomalla 2020) provide more comprehensive and up-to-date analysis.				No analysis conducted using CT perfusion criteria on EXTEND or ECASS 4 Incomplete data analysed with THAWS (published 2020 not included in meta-analysis. Therefore, imprecise effects and bias introduced and challenging to reflect on target population.
14	X. Jia et al. (2021). Intravenous thrombolysis for acute ischemic stroke with extended time window. *Chinese Medical Journal,* 134:22	Study-level MA of RCTs comparing alteplase versus placebo/usual care in individuals presenting >4.5h since stroke onset or unknown time of onset. 4 RCTs, n=848 (430 receiving alteplase, 418 placebo). All used alteplase 0.9mg/kg. Included EXTEND, ECASS4-EXTEND, WAKE-UP, AND Michel et al.	Alteplase vs placebo/usual care.	(i) mRS 0-1 at 90 days. (ii) mRS 0-2 at 90 days. (iii) Proportion with sICH. (iv) Death at 90 days.	(i) Significant increase in proportion with mRS 0-1 at 90 days: 192/419 (45.8%) with alteplase versus 151/412 (36.7%) with placebo (OR 1.48, 1.12-1.96). (ii) Significant increase in proportion with mRS 0-2 at 90 days: 271/425 (63.8%) with alteplase versus 233/418 (55.7%) (OR 1.43, 1.08-1.90). (iii) Significant increase in risk of sICH with alteplase: 13/430 (3%) with alteplase versus 2/418 (0.5%) with placebo (OR 5.28, 1.35-20.68). (iv) No significant difference in risk of death: 30/430 (7%) with alteplase versus 17/418 (4.1%) with placebo (OR 1.80, 0.97-3.34).	**+** Consistent with earlier MAs, most likely because of small number of studies and overlap in the studies. This MA done at a study level with heterogeneous eligibility and imaging criteria.