

Question 10 evidence tables

Question 10: For eligible patients with ischaemic stroke and large vessel occlusion, does proceeding direct to mechanical thrombectomy improve functional outcome compared to thrombectomy plus intravenous thrombolysis (IVT) before?

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

LAO = large artery occlusion, BT = best therapy, CSC = comprehensive stroke centre, LKW = last known well, DEVT = direct endovascular therapy, sICH = symptomatic ICH, EVT = endovascular therapy, TICl = thrombolysis in cerebral infarction, MT = mechanical thrombectomy, IVT = intravenous thrombolysis, LVO = large vessel occlusion, tPA = tissue plasminogen activator, mRS = modified Rankin scale, SOP = standard operating practice, DMT = direct mechanical thrombectomy, MI = myocardial infarction, MCA = middle cerebral artery, IV = intravenous, FPE = final prediction error, DSA = Digital Subtraction Angiography, DTN = door-to-needle, ICA = internal carotid artery, BA = basilar artery, TnK = tenecteplase, rTPA = recombinant tissue plasminogen activator, 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
310	Z.-J. Chen et al. (2021). Comparison of Prior Bridging Intravenous Thrombolysis With Direct Endovascular Thrombectomy for Anterior Circulation Large Vessel Occlusion: Systematic Review and Meta-Analysis. <i>Frontiers in Neurology</i> , 12: 602370	SR & MA in ant. Circulation LAO.	Whether BT superior to DEVT.	mRS 0-2 @ 90/7 Mortality & sICH safety endpoints.	Not superior No difference in key safety endpoints Any ICH increased by BT over DEVT.	+ (only 45% of data RCT derived and of those 3 all have biases of concern, 1 very substantial)
310	Z.-J. Chen et al. (2021). Comparison of Prior Bridging Intravenous Thrombolysis With Direct Endovascular Thrombectomy for	Systematic review and meta-analysis of 8 studies (3 RCTs - DIRECT-MT, DEVT, SKIP – 4 retrospective studies and 1 prospective observational study) 2145 patients.	Bridging (prior IVT + EVT) compared to direct EVT therapies.	Primary: mRS 0-2 at 3 months. Secondary: mortality, TICl 2b-3, sICH, asymptomatic ICH.	No differences in mRS 0-2 (OR = 1.008, 95% CI = 0.845–1.204, P = 0.926) mortality (OR = 1.060, 95% CI = 0.840–1.336, P = 0.624), recanalization rate (OR =	+ Inclusion of retrospective and prospective observational studies.

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	Anterior Circulation Large Vessel Occlusion: Systematic Review and Meta-Analysis. <i>Frontiers in Neurology</i> , 12: 602370				1.015, 95% CI = 0.793–1.300, P = 0.905), SICH (OR = 1.320, 95% CI = 0.931–1.870, P = 0.119) between bridging therapy and direct EVT. After adjusting for confounders, bridging therapy showed a lower recanalization rate (effect size or ES = -0.377, 95% CI = -0.684 to -0.070, P = 0.016), but no other outcomes compared with direct EVT.	
311	Y. Jian et al. (2021). Direct versus bridging mechanical thrombectomy in elderly patients with acute large vessel occlusion: A multicenter cohort study. <i>Clinical Interventions in Aging</i> , 16: 1265-1274	A Multicenter Cohort Study nested within a registry. Patients over 65 years.	This study compared the efficacy and safety between elderly patients treated with MT alone and those treated with both IVT and MT	Modified Rankin Scale at 90 days.	There was no significant difference in the 90- day modified Rankin Scale score between the two groups.	This was an average study. Two cohorts were identified within a registry.
311	Y. Jian et al. (2021). Direct versus bridging mechanical thrombectomy in elderly patients with acute large vessel occlusion: A multicenter cohort study. <i>Clinical Interventions in Aging</i> , 16: 1265-1274	Prospective. Multicentre. Registry-based. Non-randomised. Comparison of cohorts.	IVT plus MT (187) vs MT (295) within 4.5 hours in patient 65 years and over. 18.3%>80 years old.	Timings, Procedural factors (passes) Functional outcome (immediate – NIHSS) and at 90 days (mRs). Safety: symptomatic haemorrhage at 24 hours/parenchymal haematoma.	Direct MT group had a shorter onset-to-puncture time (225 vs 255 min, P<0.001). Lower number of passes in the direct group. Lower NIHSS at 24 hours in direct group. No sig difference in functional outcome. Trend to lower level of parenchymal haematoma type 2 in the direct group (2.80% vs 6.63%).	Moderate. Non-randomised. Not clear why patients were denied IVT in the direct group. All direct to MT centre.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
312	S. Jung et al. (2017). Direct mechanical intervention versus bridging therapy in stroke patients eligible for intravenous thrombolysis a pooled analysis of 2 registries. <i>Stroke</i> , 48:12 3282-3288	Two prospective registries comparing 249 bridging and 111 direct MT patients. Essen June 2012-aug 2013 and Bern Feb 2009-Aug 2014. Propensity matching utilised.	Comparison of direct MT to bridging with MT. All bridging patients received full or 2/3 dose IVT.	All 111 MT patients would have qualified for bridging therapy. Baseline characteristics; co-morbidity, mean NIHSS, vessel occlusion similar. Shorter time from onset to diagnosis in direct MT (1.47 vs 1.78) and onset to intervention 4.26 bridging; 3.23 direct ($p<0.001$).	ICH and 3/12 clinical outcomes no different; neither functional independence or excellent outcome. Mortality 27% in each group. Matched pair and multivariate matching also showed no difference in outcomes. Patients with ICA occlusion had higher mortality with bridging; 54% vs 28%.	Older study, possibly with older protocols, older SOPs, non-matched but with post hoc statistical matching.
312	S. Jung et al. (2017). Direct mechanical intervention versus bridging therapy in stroke patients eligible for intravenous thrombolysis a pooled analysis of 2 registries. <i>Stroke</i> , 48:12 3282-3288	2 centre registry study (Germany & Switzerland) undertaken 2009-2014 and 2012-13. 249 bridging and 111 direct MT patients.	Direct MT versus bridging therapy.	mRS 3 months (0-2, 0-1), mortality, SICH, asymptomatic ICH.	No difference in any outcomes either for full cohort or subgroup of matched pairs analysis (n=103).	Historical data from two centres. Interventionalist-determined treatment.
313	J. Kaesmacher et al. (2021). SWIFT DIRECT: SolitaireTM With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT SolitaireTM Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke: Methodology of a randomized,	A multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial utilizing an adaptive statistical design.	MT alone (direct MT) with stent retrievers compared to patients treated with combined intravenous thrombolysis (IVT) with alteplase plus MT (IVTflMT) with stent retrievers.	Non-inferior functional outcome at 90 days.	Not available.	Excellent trial.

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	controlled, multicentre study. <i>International Journal of Stroke</i> , :					
313	J. Kaesmacher et al. (2021). SWIFT DIRECT: SolitaireTM With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT SolitaireTM Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke: Methodology of a randomized, controlled, multicentre study. <i>International Journal of Stroke</i> , :	Randomized controlled trial: Multicentre, prospective, randomized 1:1, blinded end-point design. 48 stroke centres in Europe and Canada. First patient enrolled October 2017. 408 patients enrolled (201 in direct MT group) Inclusion criteria: Patients with Anterior circulation LVO (intracranial ICA, M1), ASPECTS 4 or greater, eligible for IV thrombolysis (alteplase) and MT, randomization performed within 4 Hr 15 min from stroke onset, receive tPA within 4.5 Hr from onset, have MT within 75 min from CTA, within 90 min from door to arterial puncture. Analysis: primary efficacy assessed for non inferiority of direct MT compared to standard IVT + MT. Non inferiority margin 12%, absolute risk difference.	Direct MT with solitaire not preceded by alteplase, compared with control/standard of MT with solitaire after IV thrombolysis Rescue device use allowed after 3 passes with solitaire for both groups.	Primary outcome: Proportion of patients with good outcome (mRS 0-2) at 90 days Secondary outcomes: 90 day mortality, level of disability at 90 days (mRS shift analysis), change in NIHSS at 24 hours, door to reperfusion time, health related quality of life at 90 days. Secondary technical efficacy outcomes: successful reperfusion prior to MT, successful reperfusion by end of MT, total reperfusion (TICI 3). Safety outcomes: serious adverse events, symptomatic and asymptomatic haemorrhage.	Taken from reference U. Fischer et al. (2022). Results unavailable from abstract. Primary outcome: Failed to meet non-inferiority margin for experimental arm direct MT . 90 day good outcome 56.7% direct MT vs 65.2% IVT + MT, adjusted risk difference -7.3%, lower limit of one sided 95% CI -15.1%. Secondary outcomes: no significant differences between groups for reduced disability, mortality, sICH. Post MT reperfusion higher with IVT + MT (96% vs 91%, p=0.05).	++ Limited results but if conducted as per protocol. The results of this study are directly applicable to the patient group targeted by this guideline.
314	S. Kandregula et al. (2021). Direct thrombectomy versus bridging thrombolysis with mechanical thrombectomy in middle cerebral artery stroke: a real-world analysis through National Inpatient	Retrospective analysis of prospectively collected National Inpatient Sample data of patients receiving MT without and with prior TPA using ICD 10 codes.	2895 patients: 1669 MT alone; 1226 MT + TPA.	Baseline NIHSS, co-morbidities balanced. ICH, MRS.	23.8% in MT+ IVT vs 18.2% in MT alone groups had minimal disability (p<0.001). Ordinal regression analysis showed reduced odds ratio of progressing to severe disability of 0.762 for MT/IVT vs MT alone. No sig difference in ICH rates: 177% vs 21.5% MT vs MT/IVT.	+

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Sample data. <i>Neurosurgical focus</i> , 51:1 E4					
314	S. Kandregula et al. (2021). Direct thrombectomy versus bridging thrombolysis with mechanical thrombectomy in middle cerebral artery stroke: a real-world analysis through National Inpatient Sample data. <i>Neurosurgical focus</i> , 51:1 E4	Retrospective analysis of prospectively collected National Inpatient Sample data of patients receiving MT without and with prior TPA using ICD 10 codes.	2895 patients: 1669 MT alone; 1226 MT + TPA.	Baseline NIHSS, co-morbidities balanced. ICH, MRS.	23.8% in MT+ IVT vs 18.2% in MT alone groups had minimal disability (p<0.001). Ordinal regression analysis showed reduced odds ratio of progressing to severe disability of 0.762 for MT/IVT vs MT alone. No sig difference in ICH rates: 17.7% vs 21.5% MT vs MT/IVT.	+
315	N. E. LeCouffe et al. (2021). A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke. <i>N Engl J Med</i> , 385:201833-1844	Randomised trial. Europe. 539 patients.	IVT + EVT VS EVT alone, primary end point functional outcome at 90 days. Death and sICH main safety end points.	Primary end point functional outcome at 90 days. Death and sICH main safety end points.	Results showed neither superiority nor noninferiority of EVT alone. Incidence sICH similar. Mortality slightly lower in IVT plus EVT group.	++
316	R. R. Leker et al. (2018). Direct Thrombectomy versus Bridging for Patients with Emergent Large-Vessel Occlusions. <i>Interventional Neurology</i> , 7:6 403-412	Prospective multicentre national registry of patients presenting within 4 hours of stroke onset. Cohort. Non-randomised.	Direct MT v Bridging IVT plus MT. 159 patients underwent bridging and 111 underwent direct to MT.	Recanalisation (TICI 2b/3 and 3). Functional outcome (excellent outcome mRs 0-1). In-hospital mortality Home discharge.	Higher TICI 3 rate in the MT alone group (74% v 61%) No significant difference in the major outcome markers.	Non-randomised.

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317	H. Li et al. (2021). Mechanical Thrombectomy with or without Intravenous Thrombolysis in Acute Ischemic Stroke: A Meta-Analysis for Randomized Controlled Trials. <i>European Neurology</i> , :	Meta-analysis of seven RCT's involving 2,143 patients examining the efficacy and safety outcomes of MT versus IVT/MT in patients with anterior LVO at 90 days. Searches (Pub Med, Embase and Cochrane) up to June 2021.	MT vs MT/IVT Note differing doses of IVT (alteplase 0.9 mg/kg vs 0.6 mg /kg) MT delivered within 8 hours of onset.	90 day mRS (0-2) Primary outcome/good outcome. mRS 0-1 excellent outcome (secondary). Recanalisation TICI 2b/3. Mortality 90 days. sICH.	Primary efficacy outcome: No significant difference between both groups OR: 0.96 (0.79 to 1.17) P=0.39 (low heterogeneity) 7 trials. 44.3% vs 45.6% (no differing effects between Asian and non Asian group). For secondary outcome (ms RS 0-1). Higher rates seen in MT group versus IVT/MT with a risk difference of -10.1% (p=0.04) 4 trials. I think heterogeneity is high though (64%) No significant difference in recanalization rates No difference in mortality 16.6% vs 17.6% (DMT) sICH 5.6% (IVT/MT) vs 4.6% (MT): non significant Onset to puncture quicker in MT versus IVT/MT.	+ Inclusive of 7 RCT (note: REVESCAT study included in analysis and terminated early). Not convinced this should have been included in analysis as comparing medical therapy (IVT if eligible) and MT with medical therapy alone. Exclusions of trials documented. Studies low bias (Cochrane criteria). Studies are open label. However studies carried out were in large direct MT centres (generalisability). Non inferiority analysis not carried out.
317	H. Li et al. (2021). Mechanical Thrombectomy with or without Intravenous Thrombolysis in Acute Ischemic Stroke: A Meta-Analysis for Randomized Controlled Trials. <i>European Neurology</i> , :	Meta-analysis, search conducted June 15 2021. Selection method: study was an RCT, study investigated effects of MT with or without IVT in anterior circulation stroke patients presenting within 8 hours of onset, and patients were eligible for IVT. Included 7 RCTs for meta-analysis.	Comparison of outcomes following MT alone (intervention/experimental group) compared with standard of IVT + MT.	Primary outcome: good outcome (mRS 0-2) at 90 days. Secondary outcomes: excellent outcome (mRS 0-1 at 90 days), recanalization, sICH, mortality at 90 days.	Primary outcome: No significant difference in mRS 0-2 at 90 days between groups. Secondary outcomes: Higher proportion of excellent outcome at 90 days in MT only group (risk difference -10.1%, RR 0.82, OR 0.75, p=0.04). Higher rate of recanalization in IVT + MT group. No difference between groups in sICH and mortality.	0 Poor quality study with significant flaws. In design, one of search criteria is listed that patient be eligible for IV thrombolysis, however in 4 of the included studies patients in direct MT group were largely those ineligible for IVT or IVT contra-indicated (REVASCAT, STAR, SWIFT, MR CLEAN). There is therefore

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						selection bias in these studies, with potential significant baseline confounders in the MT alone groups. It is misleading to claim this is a meta-analysis of 7 RCTs. Four of the RCTs were not designed to directly compare MT alone with IVT + MT, and data is post hoc/subgroup analysis from those trials. The current meta-analysis did not undertake analysis of individual patient data from those trials, but conducted only study level analysis.
318	S. Li et al. (2021). Endovascular Treatment With and Without Intravenous Thrombolysis in Large Vessel Occlusions Stroke: A Systematic Review and Meta-Analysis. <i>Frontiers in Neurology</i> , 12: 697478	A systematic review with meta-analysis of all available studies comparing clinical outcomes between BT and EVT alone A total of 93 studies enrolling 45,190 patients.	Compared bridging therapy with endovascular therapy alone.	Odds ratio of a good outcome. modified Rankin Scale (mRS) at discharge and 90 days or the longest available follow-up time point.	BT was associated with a higher likelihood of a good outcome at 90 days in the meta-analysis of 58 studies (cOR 1.361) BT resulted in a lower rate of mortality within 90 days than EVT alone (cOR 0.619).	This was a good attempt to maximise data. However, the data is not clean. When confined to randomised data, there was similar rate of good outcome between BT and EVT.
318	S. Li et al. (2021). Endovascular Treatment With and Without Intravenous Thrombolysis in Large Vessel Occlusions Stroke: A Systematic Review and Meta-Analysis. <i>Frontiers in Neurology</i> , 12: 697478	Meta-analysis of 93 studies with 45,190 patients included. Comparison of bridging therapy with direct MT.	Patients proceeding direct to MT versus thos with bridging therapy who went on to receive any kind of clot retrieval.	90 day MRS, SICH, mortality, recanalisation, early recovery, number of passes. Time from symptom onset to groin puncture	1.36 increased odds of good outcome with BT cf MT, increased recanalisation OR1.271, lower 90-day mortality OR 0.619. SICH rates similar, early recovery and number of passes. No difference in time form onset to groin puncture	+ Huge number of patients. Complex statistical methodology to synthesised data to ensure minimal bias.

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319	C.-H. Lin et al. (2021). Endovascular thrombectomy without versus with intravenous thrombolysis in acute ischemic stroke: A non-inferiority meta-analysis of randomized clinical trials. <i>Journal of NeuroInterventional Surgery</i> , :	Systematic review & meta-analysis of 4 RCTs (DIRECT-MT, DEVT, SKIP, MR CLEAN No IV) 1633 participants.	EVT alone versus IVT before EVT.	Primary: mRS 0–2, at 90 days Secondary: mRS 0–1 at 90 days; successful reperfusion at final angiogram eTICI score ≥2 b; any ICH; SICH; all-cause mortality by 90 days	Primary: (mRS 0–2) at 90 days, crude cumulative rates 46.0% with direct EVT versus 45.5% with bridging IVT plus EVT. Pooled results from a random-effect model showed the risk difference of functional independence was 1% (95% CI –4% to 5%). The lower 95% CI bound of –4% fell within the non-inferiority margins of –15%, –10%, –6.5%, and –5%, but crossed the most stringent non-inferiority margin of –1.3%. Secondary endpoints: mRS 0–1 at 90 days, 25.6% with direct EVT versus 24.2% with bridging IVT plus EVT; eTICI 2b-3 76.5% with direct EVT versus 81.0% with bridging IVT plus EVT; SICH symptomatic intracranial hemorrhage were 4.9% with direct EVT versus 5.8% with bridging IVT plus EVT; mortality 17.4% with direct EVT group versus 16.4% with bridging IVT plus EVT.	++
319	C.-H. Lin et al. (2021). Endovascular thrombectomy without versus with intravenous thrombolysis in acute ischemic stroke: A non-inferiority meta-analysis of randomized	Meta-analysis of four randomised trials	Direct MT vs Bridging IVT and MT. 817 patients assigned to MT alone and 816 to IVT plus MT.	Functional outcome (mRs). Mortality. Recanalisation (TICI) Safety: any intracranial haemorrhage, SICH (Heidelberg/SITS MOST classification).	No significant difference in functional outcome or mortality. Slightly lower recanalization with MT alone (76.5% versus 81.0%). Risk difference for any intracranial haemorrhage was	Acceptable quality of study.

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	clinical trials. <i>Journal of NeuroInterventional Surgery</i> , :				9% (95% CI 3% to 15%), favouring MT alone. Risk difference for SICH was 1% (95% CI -1% to 3%) between MT alone and IVT plus MT.	
320	I. L. Maier et al. (2021). Inhouse Bridging Thrombolysis Is Associated With Improved Functional Outcome in Patients With Large Vessel Occlusion Stroke: Findings From the German Stroke Registry. <i>Frontiers in Neurology</i> , 12: 649108	Setting:German Stroke Registry. Design:Multicentric retrospective study' Subjects:881 patients.	Patients with acute LVOS. To assess whether bridging IVT prior to EVT has positive effect on reperfusion times ,successful reperfusion and functional outcome compared to EVT alone.	486 received IVT and EVT. 395 EVT Alone. Outcome measures: mRS and mortality at 90 days, change in NIHSS from admission to discharge, groin puncture to reperfusion times; rates of successful recanalization (TICI 2b or greater) Any ICH, groin haematoma, MI, recurrent stroke, MCA oedema.	No difference in groin to reperfusion time. Rates of successful reperfusion higher in patients with bridging IVT.Trend towards higher improvement in NIHSS during hospitalisation in EVT group.Non significant lower 90 day mortality in bridging IVT goup.No difference in ICH.	+ Retrospective study but shows IVT prior to EVT safe and no reason from this study to change to EVT alone.
321	P. J. Mitchell et al. (2022). DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval versus Standard Bridging Therapy. <i>J Stroke</i> , 24:157-64	To test the hypothesis that clinical outcome of ischemic stroke patients with in-tracranial internal carotid artery, middle cerebral artery or basilar artery occlusion treated with direct endovascular thrombectomy within 4.5 hours will be non-inferior compared with that of standard bridging IV thrombolysis followed by endovascular thrombectomy.	1:1 to direct thrombectomy or bridging IV thrombolysis with thrombectomy.	mRS 0-2 at 90 days or return to baseline.	No data.	Excellent trial.
321	P. J. Mitchell et al. (2022). DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular	Methods for a multicentre, international randomised trial.	Direct MT vs Bridging IVT plus MT.	Primary outcomes: Functional independence (mRS 0-2 at 90 days)		

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	Clot Retrieval versus Standard Bridging Therapy. <i>J Stroke</i> , 24:1 57-64			Secondary outcomes: Excellent outcome (mRS 0-1) Ordinal shift mRS. sICH up to 72 hours post intervention Good angiographic reperfusion (mTICI 2b-3) at completion of procedure.		
322	M. Mokin et al. (2021). Intravenous alteplase has different effects on the efficacy of aspiration and stent retriever thrombectomy: analysis of the COMPASS trial. <i>Journal of neurointerventional surgery</i> , :	Post hoc analysis of COMPASS trial data (RCT between aspiration and stent retriever) looking at outcomes with and without prior 'bridging' TPA. 270 patients.	Subgroups presenting within 4 hours who would have been eligible for IV TPA 235 of 270.	Age, NIHSS, co-morbidity, pre MRS, occlusion site, onset to groin puncture all balanced. TIC score, FPE, SICH, MRS at 3/12. Higher proportion of patients receiving Alteplase were direct admissions.	Similar FPE between tpa and non-tpa groups (38.6% vs 35.9%) and number of passes (2.1 vs 1.9). Increased proportion MRS 0-2 in TPA group: 55.6% vs 40% in univariate analysis. Multivariate analysis showed only pre NIHSS and MRS and age were independent predictors of favourable outcomes @3/12. In aspiration only group higher recanalisation without TPA and SR groups were balanced.	+ Balanced groups clinically, blinded angiographic assessment. Interesting conclusions that TPA has no interaction with stent retrievers and aspiration alone is better than with TPA.
323	M. J. H. L. Mulder et al. (2019). Endovascular Treatment With or Without Prior Intravenous Alteplase for Acute Ischemic Stroke. <i>Journal of the American Heart</i>	Observational study, MR Clean data.	IVT +EVT and EVT alone compared. &8% IVT +EVT ,22% EVT alone 1161 vs 324 patients.	90 day functional outcome, mortality, reperfusion, first pass effect and symptomatic ICH .	IVT + EVT was associated with better functional outcome and lower mortality. Successful reperfusion , first pass effect and sICH did not differ.	+ Observational study

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	<i>Association</i> , 8:11 e011592					
324	J. C. Purrucker et al. (2021). Efficacy and safety of bridging thrombolysis initiated before transfer in a drip-and-ship stroke service. <i>Stroke and Vascular Neurology</i> , :	Germany. Patients from a prospective data base. Drip and ship stroke service. 442 bridging thrombolysis 370 no bridging thrombolysis.	BT group compared with non-BT group	Functional outcome before stroke and at 3 months. ICH and mortality at 3 months. LVO before and after transfer at DSA.	More patients in the BT group recanalized without EVT. 11.7% vs 1.3%. BT was strongest independent predictor of excellent outcome at 3 months. No difference in safety between BT and non-BT groups.	+ Non-randomised. BT better outcomes than non-BT in drip and ship patients.
325	J. Qiu et al. (2021). Outcomes of mechanical thrombectomy with pre-intravenous thrombolysis: a systematic review and meta-analysis. <i>Journal of Neurology</i> , 268:7 2420-2428	Meta analysis. 30 studies.	Compared Mt with IV plus MT.	Functional outcome at 3/12. successful reperfusion. Symptomatic ICH.	IVT plus MT benefited more in functional outcome without significantly increasing sICH comparing with MT in a metanalysis of 8970 patients with AIS of large vessel occlusion in the anterior circulation. Rate of successful reperfusion was higher and mortality lower.	++
326	A. Sarraj et al. (2021). Clinical and Neuroimaging Outcomes of Direct Thrombectomy vs Bridging Therapy in Large Vessel Occlusion: Analysis of the SELECT Cohort Study. <i>Neurology</i> , 96:23 e2839-e2853	USA. Prospective multicentre cohort study with 226 included. Anterior Circulation LAO strokes reaching CSC within 4.5h of onset.	Stratified but not randomised as Bridging therapy (BT) and direct to EVT (E=DEVT) 72% BT, 28% DEVT	90/7 mRS 0-2 primary Secondary: Shift analysis mRS Mortality sICH	57% FI for BT vs 44% for DEVT, adOR 2.02 (1.2-3.6) Lower mortality for BT (adOR 0.2, 0.07-0.58) No differences in other outcomes but trends for BT better in lower NIHSS (<15), Drip n ship and smaller cores (<50mls).	+ Many biases

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326	A. Sarraj et al. (2021). Clinical and Neuroimaging Outcomes of Direct Thrombectomy vs Bridging Therapy in Large Vessel Occlusion: Analysis of the SELECT Cohort Study. <i>Neurology</i> , 96:23 e2839-e2853	Multi-centre prospective observational cohort study in US. Comparing processes, outcomes and safety between patients undergoing MT and IVT/MT in centres (both in transferred and direct capability MT centres) with LVO. Assessed baseline patient and process characteristics in relation effects on outcome (subgroup analysis with tests of heterogeneity). Enrollment up to 24 hours using CTP (initially 8hrs). ICA, M1 and M2, NIHSS > 6, pre-morbid mRS 0-1. ASPECTS >6.	IVT (alteplase 0.9mg/kg) plus MT vs MT.	Primary outcome: mRS 0-2 (functional independence) Secondary outcome: mRS 0-1 (ordinal scale) 90 day mortality sICH TICI 3 reperfusion Subgroup analysis based on NIHSS <15, ischaemic core 50 cm3 and mode of transfer	226 Patents with LVO. MT: 64 pts IVT/MT 162 pts 34% of patients incurred transfer to MT centre No significant differences in key process times such as arrival to groin puncture between both groups. Also no differences in time from LKW to MT centre arrival time (suggesting IVT doesn't contribute to any further additional delay). No sig difference in primary outcome MT (44%) vs IVT/MT (57%) For excellent outcome on ordinal scale benefits seen with IVT/MT OR 2.02 95% 1.01 to 4.03, p=0.046. Lower mortality with IVT/MT 10.5% vs MT 21.9% p=0.025 No difference in TICI 3 scores 57% IVT/MT vs 56% MT No significant differences in other safety outcomes (sICH) Subgroup analysis demonstrated patients benefitted with IVT/MT in patients < NIHSS 15 and trends suggestive with lower infarct volume and transfer to MT centre rather than direct however the interaction terms (tests for heterogeneity were not significant) and so caution needs to applied.	Quality acceptable however: 1 Non randomised 2 Confounders 3 Small study 4 Unclear what percentage of patients from each centre contributed to study (generalisability). Subgroup analysis tempered with caution with small numbers.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
327	K. Suzuki et al. (2021). Effect of Mechanical Thrombectomy without vs with Intravenous Thrombolysis on Functional Outcome among Patients with Acute Ischemic Stroke: The SKIP Randomized Clinical Trial. <i>JAMA - Journal of the American Medical Association</i> , 325:3 244-253	Japan. RCT of 204 Non-inferiority design in anterior circ stroke presenting to CSC within 4.5h of onset.	BT with lower dose alteplase versus DEVT.	mRS 0-2 @ 90/7 With non-inferiority margin an OR of 0.74. Usual safety outcomes.	Non-inferiority of DEVT could not be demonstrated despite generous non-inferiority margin FI: 59% BT vs 57% DEVT No safety differences Long DTN times but very short needle to puncture times is a confounder.	+ Modest bias Small size Not generalisable as low dose IVT
327	K. Suzuki et al. (2021). Effect of Mechanical Thrombectomy without vs with Intravenous Thrombolysis on Functional Outcome among Patients with Acute Ischemic Stroke: The SKIP Randomized Clinical Trial. <i>JAMA - Journal of the American Medical Association</i> , 325:3 244-253	Multi centre randomised open label-controlled trial (Japan) involving 23 centres. Assessing whether MT alone is non inferior to combination of IVT/MT in patients with LVO (2017-2019). Participants: ICA or M1 occlusion, NIHSS > 6 with ASPECTS 6-10. mRS 0-2. No large core lesion. OR set for non-inferior margin at 0.74 (based on previous meta-analysis).	Ratio 1:1 MT vs IVT (alteplase 0.6 mg/kg) MT rtPA delivered < 4.5 hours.	Primary outcome mRS 0-2 at 90 days Secondary outcome ordinal shift analysis mRS sICH at 36. hours TICI ≥ 2b	04 patients randomised 101 (MT) 103 (IVT/MT) NIHSS 18 Median ASPECTS 8 Patients equally matched Note: randomisation to puncture time 20 minutes (MT) and 22 minutes (IVT/MT) Primary outcome: 59.4% (MT) v 57.3% (IVT/MT). No significant difference and odds ratio was 1.09 (0.63 to infinity). i.e. 9% increase in odds of favourable outcome with MT alone. The outer margins cross 0.74 non inferior margin. Demonstrating non inferiority not proven. No significant differences in secondary outcomes in ordinal shift or sICH	+ Randomised control trial (but perhaps numbers too small to verify non inferiority). Solely Japanese population with differing stroke subtype and degree of ICA disease compared to UK. No missing follow-up data All centres had capability to deliver both IVT and MT so may not be applicable to other modes of delivery. Open label. Fast process times. Non inferior margin set from meta-analyses based on 0.9

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					90 day mortality 7.9% vs 8.7% (NS) Effects were similar across multiple subgroups ie no heterogeneity.	mg/kg alteplase and CI intervals for OR very wide so effects may be underestimated.
328	X. Tong et al. (2021). Thrombectomy Versus Combined Thrombolysis and Thrombectomy in Patients with Acute Stroke: A Matched-Control Study. <i>Stroke</i> , : 1589-1600	Prospective registry from 111 Chinese hospitals. 788 patients after propensity score matching (of 1026 eligible, 600 MT and 426 IVT+MT).	MT patients retrospectively determined to have received IVT or not.	90-day mRS, successful recanalization, door-to-puncture time, SICH, and intraprocedural embolization.	No significant differences in the 90-day median mRS (median, 3 versus 3 points; P=0.82) and successful recanalization (86.6% versus 89.3%; P=0.23); MT group had shorter door-to-puncture time (median, 112 versus 136 minutes; β =-45.02 [95% CI, -68.31 to -21.74]), lower SICH (5.5% versus 10.1%; odds ratio, 0.52 [95% CI, 0.30-0.91]), and embolization (4.6% versus 8.1%; odds ratio, 0.54 [95% CI, 0.30-0.98]) than those of the combined group.	- Single country registry-based study. Non-use of IVT at physician discretion (reasons given – financial, side effects, non-consent). No data on interval from IVT to MT. Widespread use of intra-arterial thrombolytic and eptifibatide.
328	X. Tong et al. (2021). Thrombectomy Versus Combined Thrombolysis and Thrombectomy in Patients with Acute Stroke: A Matched-Control Study. <i>Stroke</i> , : 1589-1600	Data derived from ANGEL-ACT prospective nation-wide registry in China, 1793 consecutive patients with acute LVO of anterior or posterior circulation undergoing EVT at 111 hospitals from 26 provinces between Nov 2017 and March 2019. EVT: any type of endovascular treatment, including MT, IA thrombolysis, angioplasty, stenting, other mechanical fragmentation.	Thrombolysis eligible LVO patients treated with MT only, compared with MT + IVT.	Primary: 90 day mRS score Secondary: Proportions of mRS 0-1, 0-2, 0-3. Change in NIHSS score at baseline and day 7, successful recanalization TIC1 2b-3, door to puncture, puncture to recanalization, pass number of thrombectomy. Safety outcomes: mortality within 90 days, any ICH, symptomatic ICH, procedure related	Primary: No significant difference in 90 day mRS score between groups Secondary: Shorter door to puncture in MT only patients (median 112 vs 136 min; β =-45.02 [95% CI, -68.31 to -21.74]; P=0.05). No significant differences between both groups in the remaining secondary outcomes.	++ Real-world data, however confined to Chinese population. Large number of patients required rescue treatment including angioplasty, stenting, after failure of MT. Less SICH in MT only group but no difference in groups in functional outcome.

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		Inclusion criteria – patients having MT and eligible for thrombolysis Propensity score matching to improve comparability between groups (significant differences between MT vs IVT +MT groups at baseline before PSM, however, groups comparable post PSM) Total of 1026 patients included in study (600 MT, 426 MT+IVT), 788 patients/394 matched pairs post PSM.		complications including intraprocedural embolization.	Safety outcomes: Less sICH in MT only group (5.5% vs 10.1%; OR, 0.52 [95% CI, 0.30–0.91]; P=0.02). Less intraprocedural embolization in MT only group (4.6% vs 8.1%; OR, 0.54 [95% CI, 0.30–0.98]; P=0.04). No significant difference between groups in other safety outcomes. Also undertook adjusted analysis of whole 1026 patient group with adjusted analysis, yielded similar results.	
329	G. Turc et al. (2019). European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic Stroke Endorsed by Stroke Alliance for Europe (SAFE). <i>European Stroke Journal</i> , 4:1 06-Dec	Comprehensive methodologically rigorous appraisal and synthesis of available literature addressing above PICO. Considered two scenarios separately: 1. MT alone vs MT + IVT in patients eligible for both treatments presenting directly to mothership 2. Ship + MT alone vs IVT drip & ship + MT in patients presenting initially to non-MT-capable stroke centre. Methodology: Literature review, meta-analysis of best available evidence, evidence-based recommendation, expert consensus statement. For scenario 1. RCT evidence available from 6 separate RCTs directly addressing PICO question for mothership patients, 4 published (DIRECT_MT, DEVT, SKIP, MR CLEAN-NO IV), 2 conference presentations (SWIFT_DIRECT, DIRECT SAFE).	Scenario 1. Mothership patients, 5 of 6 RCTs non inferiority analysis for interventional arm MT alone compared to standard of MT + IVT (generous non-inferiority margins of 10-20%), one trial (MR CLEAN NO IV) superiority analysis. For meta-analysis blind polling decided on non-inferiority margin 1.3% Scenario 2. Meta-analysis of outcomes in 3 observational studies comparing intervention group MT alone vs standard bridging IV + MT in drip and ship patients	Primary outcome: Good functional outcome mRS 0-2 Secondary outcomes and safety outcomes: Reduced disability, excellent outcome, sICH, Mortality, successful reperfusion, time metrics to puncture and reperfusion.	Scenario 1: Mothership Primary outcome: IN 4 of 6 RCTs primary outcome was mRS 0-2, mRS (cOR) primary outcome in 2 of 6 RCTs. Individual trial data: Two RCTs (DIRECT-MT and DEVT) met prespecified non-inferiority margin (20% and 10% respectively) for MT only compared with standard MT + IVT group. MR CLEAN-NO IV did not show superiority and failed to meet prespecified non inferiority margin of 20%. SKIP, SWIFT-DIRECT and DIRECT-SAFE failed to meet prespecified non inferiority margin. Meta-analysis: OR good outcome in MT alone 0.93 (95% CI 0.79-1.10, p=0.38) failed to meet prespecified non inferiority margin of 1.3%	Quality Mothership scenario: ++ Drip and ship scenario: - The results of this study are directly applicable to the patient group targeted by this guideline. The highest level of evidence is for patients directly presenting to MT capable centre. There are however concerns re deviations from intended intervention in DIRECT-MT, overly long door to IV times in DIRECT-MT, DEVT and SKIP, low dose tPA in SKIP and tPA given only after puncture in 20% patients in SKIP. There is also inconsistency as two trials met their predefined criteria for non-inferiority while four others did not.

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		Trials in China (2), Japan(1), Europe (2), Asia & Oceania (1). Undertook meta-analysis of above 6 RCTs, total of 2332 patients. Majority Anterior circulation, 1 RCT allowed posterior circulation. For scenario 2. No RCT evidence available. Data from observational studies and registries. Undertook meta-analysis of observational studies comparing direct MT with bridging therapy in drip and ship patients.	(included subgroup analysis of SELECT study, data from prospective ETIS registry).		Secondary outcomes: Meta-analysis: no statistically significant difference in mortality rate and sICH. Occurrence of any haemorrhage less frequent in MT alone group. Successful reperfusion less frequent in MT alone group. Scenario 2: Drip and ship Primary outcome: Pooled OR for good outcome mRS 0-2 (2 studies) 0.63 (95%CI 0.48-0.83, p=0.001) Secondary outcomes: no significant difference between groups for excellent outcome, no difference in mortality.	Quality of evidence for drip and ship scenario is poor, mainly from observational and registry studies, no RCT, therefore selection bias as majority of patients in direct MT groups in these studies were ineligible for tPA, with potential significant baseline confounders. There is also reference in the article through review of RCT data on delivery of IV thrombolysis in wake up stroke. Limited evidence for this in patients undergoing thrombectomy.
330	H. Wang et al. (2017). Direct endovascular treatment: an alternative for bridging therapy in anterior circulation large-vessel occlusion stroke. <i>Eur J Neurol</i> , 24:7 935-943	Patients enrolled onto ACTUAL Chinese registry contributed to by 21 centres. Excluded shipped patients to avoid bias in timeframes. 632 TOTAL: 428 direct and 204 bridging screened with 203 direct and 160 bridging assessed. 276 wholly matched 1:1.	Direct MT versus patients having bridging TPA therapy.	NIHSS, co-morbidity, ASPECTS, ASITN collateral DSA score, 90-day good outcomes, mortality, door to puncture and recan, number of passes, TICl.	Direct had higher pre MRS, shorter time from door to recan (106 vs 147 min), higher proportion of GA. Balanced vessel occlusions. No difference in number of passes and recan scores. Similar MRS 0-1 and 0-2 outcomes at 90 days. Similar early NIHSS improvement. Asymptomatic ICH 28.3% vs 44.9% direct vs bridging but no difference in SICH (13%).	+ Differences may relate to logistical issues rather than pharmacological ones.
331	Y. Wang et al. (2020). Bridging Thrombolysis Achieved Better Outcomes Than Direct Thrombectomy after Large Vessel Occlusion:	Compared the outcomes of bridging thrombolysis (BT, IVT+MT) with direct MT (d-MT) after large vessel ischemic stroke based on meta-analysis. Thirty studies involving 7191 patients in	bridging thrombolysis (BT, IVT+MT) with direct MT (d-MT).	Combined estimates of odds ratios (ORs) of BT versus d-MT were derived.	Compared with patients in the d-MT group, patients in the BT group showed significantly better functional independence (modified Rankin Scale score 0–2) at 90	This was well conducted but suffers from bias accruing from using non randomised data.

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	An Updated Meta-Analysis. <i>Stroke</i> , : 356-365	the BT group and 4891 patients in the d-MT group were included.			days (OR=1.43 [95% CI, 1.28–1.61]), had lower mortality at 90 days (OR=0.67 [95% CI, 0.60–0.75]), and achieved higher successful recanalization (modified Thrombolysis in Cerebral Ischemia score 2b-3) rate (OR=1.23 [95% CI, 1.07–1.42]). No significant difference was detected in the occurrence of symptomatic intracranial hemorrhage between 2 groups (OR=1.01 [95% CI, 0.86–1.19]).	
331	Y. Wang et al. (2020). Bridging Thrombolysis Achieved Better Outcomes Than Direct Thrombectomy after Large Vessel Occlusion: An Updated Meta-Analysis. <i>Stroke</i> , : 356-365	Meta-analysis, inclusion of 30 studies between January 2017 to June 2020 that directly compared outcomes of bridging thrombolysis (BT, IVT + MT) with direct MT (dMT). Total of 7191 patients in BT group, and 4891 patients in dMT group. DIRECT MT one of included studies.	Comparison of outcomes following bridging thrombolysis + MT (BT group) with MT alone (dMT group).	Functional independence mRS 0-2 at 90 days, excellent clinical outcome (mRS 0-1), mortality, haemorrhagic complications, recanalization, subgroup analyses of IVT eligible patients only.	BT group achieved significantly better functional independence (OR 1.43, CI 1.28-1.61) and excellent clinical outcome (OR 1.42, CI 1.21-1.67) at 90 days. Finding held for propensity score matched data. Subgroup analysis showed functional independence remained significantly higher in BT group regardless of IVT eligibility or study design (retrospective vs prospective). Difference in excellent clinical outcome however no longer significant in IVT eligible patients. Mortality at 90 days significantly lower in BT group. Difference became borderline in IVT eligible patients. No significant difference in sIHC	++ Main reason for not giving IVT in included studies was contraindication or ineligible. This introduces selection bias. Subgroup analysis of IVT-eligible patients only was however undertaken, functional independence remained higher in BT group. Data not included in studies on patients who reperfused or clinically improved after receiving IVT and did not proceed to MT. Since this publication data from a number of RCTS and subsequent meta-analysis available, therefore now have higher level evidence available.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					between groups. Higher rates of successful recanalization in BT group, however difference no longer significant in IVT eligible patients or in prospectively designed studies. Rate of complete recanalization (TICI 3) not different between groups.	
332	P. Yang et al. (2020). Endovascular thrombectomy with or without intravenous alteplase in acute stroke. <i>New England Journal of Medicine</i> , 382:21 1981-1993	RCT in 41 Chinese hospitals (DIRECT-MT). 656 patients (327 MT alone, 329 IVT+MT).	Iv alteplase 0.9mg/kg + MT versus MT alone	Primary: Non-inferiority of mRS at day 90 Secondary: mortality, eTICI pre-thrombectomy; eTICI 2b-3 after MT; CTA recanalization at 24-72h; 24h NIHSS; 24h infarct volume; EuroQOL; Barthel.	ET alone noninferior to IVT+ET + Median mRS (adjusted common odds ratio, 1.07; 95% confidence interval, 0.81 to 1.40; P = 0.04 for noninferiority) but was associated with lower successful reperfusion before thrombectomy (2.4% vs. 7.0%) and overall successful reperfusion (79.4% vs. 84.5%). Mortality at 90 days was 17.7% in the thrombectomy-alone group and 18.8% in the combination-therapy group.	Single country. Very short interval from IVT start to g.roin puncture (29 mins)
332	P. Yang et al. (2020). Endovascular thrombectomy with or without intravenous alteplase in acute stroke. <i>New England Journal of Medicine</i> , 382:21 1981-1993	Multicentre randomised clinical trial. Non-inferiority.	Direct MT (329 patients) vs Bridging IVT plus MT (327 patients).	Primary outcome: mRS at 90 days (functional independence). Secondary: ? superiority. Reperfusion (TICI score) Infarct extent on CT NIHSS score at 1 and 5-7 days.	No significant difference in primary outcome. Secondary outcome – mild improvement in recanalisation rate but not significant and no other significant findings.	Direct to MT noninferior in those presenting direct to tertiary (MT) centre.

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				Safety: All and symptomatic haemorrhage.		
333	J. Zhang et al. (2021). Direct endovascular treatment versus bridging therapy in patients with acute ischemic stroke eligible for intravenous thrombolysis: Systematic review and meta-analysis. <i>Journal of NeuroInterventional Surgery</i> , : neurintsurg-2021-017928	Systematic review and meta-analysis. Three RCTs and six observational studies (4 of which were propensity score-adjusted studies)	Direct MT v Bridging IVT plus MT. >3000 patients.	Recanalisation. Clot migration. Functional outcome at 90 days. Mortality. Symptomatic haemorrhage. Any haemorrhage.	No significant difference in recanalization, functional outcome or mortality. No sign diff in SICH in adjusted analysis. Direct MT had a lower risk ratio for any type of ICH	Acceptable quality of study. Based mostly on data from Chinese populations.
334	Y. Zhou et al. (2022). Effect of Occlusion Site on the Safety and Efficacy of Intravenous Alteplase before Endovascular Thrombectomy: A Prespecified Subgroup Analysis of DIRECT-MT. <i>Stroke</i> , 53:1 Jul-16	Prespecified subgroup analysis of a randomized trial evaluating risk and benefit of intravenous alteplase before thrombectomy (DIRECT-MT [Direct Intra-Arterial Thrombectomy in Order to Revascularize AIS Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals	To examine whether occlusion site modifies the effect of intravenous alteplase before thrombectomy	modified Rankin Scale at 90 days	There was no significant treatment-by-occlusion site interaction	This article was not fully relevant to PICO.
334	Y. Zhou et al. (2022). Effect of Occlusion Site on the Safety and Efficacy of Intravenous Alteplase before Endovascular Thrombectomy: A Prespecified Subgroup	Pre-specified subgroup analysis of the DIRECT-MT RCT evaluating effect of occlusion site on safety and efficacy of IVT before MT. DIRECT MT – RCT in Chinese population assessing non inferiority of MT only compared with standard care of IVT and MT	Assess if association of treatment allocation (MT vs IVT + MT) and outcome is modified by occlusion site.	Primary: mRS at 90 days Secondary: mortality a 90 days, rate of successful reperfusion before MT and after MT, recanalization at 24 hours on CTA, NIHSS score at 24 hrs and 5-7 days, final	35.3% ICA occlusion, 53% M1, 11.7% M2, Primary: No difference in mRS at 90 days between MT only vs IVT + MT group. No significant treatment by occlusion site interaction for ordinal mRS outcome in either	+ Missing data on occlusion site in 16 patients, limitations within DIRECT MT study itself including overly long door to needle time in IVT + MT group, short time from IVT to arterial

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	Analysis of DIRECT-MT. <i>Stroke</i> , 53:1 Jul-16	in anterior circulation LVO patients (intracranial ICA, M1, M2) between Feb 2018 and July 2019 presenting directly to an EVT capable centre. 640 of 656 trial patients had baseline occlusion site recorded, (315/49.2% MT only group). Undertook multivariable ordinal logistic regression, assessed association of functional outcome with different occlusion sites, analysis undertaken both unadjusted and adjusted for age, baseline NIHSS, time from onset to randomization, mRS before onset, collateral blood flow status. Linear or binary logistic regression analysis with same adjustments undertaken for secondary outcomes.		lesion volume on CT, comparisons of dichotomised mRS score at 90 days, all haemorrhage, sICH, puncture site complications, infarct in new territory at 5-7 days.	unadjusted or adjusted analyses. Secondary: No significant treatment by occlusion site interaction for secondary outcomes.	puncture, 30 patients in IVT group did not get IVT, 30 more patients did not get full dose IVT. No evidence from this study that occlusion location can inform IVT decision making in anterior circulation MT patients
335	W. Zi et al. (2021). Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke: The DEVT Randomized Clinical Trial. <i>Jama</i> , 325:3 234-243	China. 33 CSCs. 234 subjects. NI RCT with 10% absolute diff NI margin. Ant circ stroke presenting to CSC within 4.5h of onset.	BT vs DEVT Issues with receiving allocated Rx especially in BT arm.	mRS 0-2 @ 90/7 With non-inferiority margin of 10% Usual safety outcomes	Stopped after first planned review as NI for DEVT met (234/970 planned) 54% mRS 0-2 for DEVT vs 47% for BT. No safety differences. Long DTN times.	+ Important biases. Small size. Non-inferiority margin too generous.
335	W. Zi et al. (2021). Effect of Endovascular Treatment Alone vs	Multi centre open label randomised controlled trial in China (33 centres) testing non	MT vs IVT/MT with 0.9mg/kg of alteplase.	Primary outcome: mRS 0-2 at 90 days	24% (234 patients) of 970 patients were recruited before trial stopped	+ Randomised controlled trial

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	Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke: The DEVT Randomized Clinical Trial. <i>Jama</i> , 325:3 234-243	inferiority of MT vs IVT/MT in patients with LVO with intervention randomisation within 4 hours 15 minutes. LVO: ICA, M1 and M2 mRS<2. Randomisation ratio 1:1. 970 patients planned to be randomised with risk difference between both group being -10% (as non-inferiority margin).		Secondary outcome: mRS as ordinal scale sICH 90 day mortality TICI ≥ 2b	MT (116 patients) IVT/MT (118 patients) Baseline characteristics similar Note: door to IVT (slow: 61 minutes) Functional independence 54.3% (MT) vs 46.6% (IVT/MT) with a difference of 7.7%. This does not cross this the line of inferiority thereby proving non inferiority. OR: 1.48 (0.81 to 2.74). No significant differences in mRS on an ordinal scale No sig differences in reperfusion. sICH and 90 day mortality NS.	Small numbers however All centres are MT centres (generalisability). Inferior margins set arbitrarily (not scientifically based in previous data). Chinese data solely so not necessarily generalisable.
699	U. Fischer et al. (2022). Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded outcome, randomised non-inferiority trial. <i>The Lancet</i> 400:10346 104-115	SWIFT DIRECT: Solitaire™ With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke: Methodology of a randomized, controlled, multicentre study.	Randomized controlled trial: Multicentre, prospective, randomized 1:1, blinded end-point design. 48 stroke centres in Europe and Canada. First patient enrolled October 2017.	Non-inferior functional outcome at 90 days.	201 (MT) vs 207 (bridging). Non inferiority not proven as risk difference crossed non inferiority margin. Successful reperfusion more likely in bridging.	Proceeding direct to mechanical thrombectomy does not improve functional outcome compared to thrombectomy plus intravenous thrombolysis (IVT).
699	U. Fischer et al. (2022). Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-	Randomized controlled trial: Multicentre, prospective, randomized 1:1, blinded end-point design. 48 stroke centres in Europe and Canada. First patient enrolled October 2017. 408	Direct MT with solitaire not preceded by alteplase, compared with control/standard of MT with solitaire after IV thrombolysis	Primary outcome: Proportion of patients with good outcome (mRS 0-2) at 90 days Secondary outcomes: 90 day mortality, level of disability at 90 days (mRS	Primary outcome: Failed to meet non-inferiority margin for experimental arm direct MT . 90 day good outcome 56.7% direct MT vs 65.2% IVT + MT, adjusted risk difference	++ The results of this study are directly applicable to the patient group targeted by this guideline.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	outcome, randomised non-inferiority trial. <i>The Lancet</i> 400:10346 104-115	patients enrolled (201 in direct MT group) Inclusion criteria: Patients with Anterior circulation LVO (intracranial ICA, M1), ASPECTS 4 or greater, eligible for IV thrombolysis (alteplase) and MT, randomization performed within 4 Hr 15 min from stroke onset, receive tPA within 4.5 Hr from onset, have MT within 75 min from CTA, within 90 min from door to arterial puncture. Analysis: primary efficacy assessed for non inferiority of direct MT compared to standard IVT + MT. Non inferiority margin 12%, absolute risk difference.	Rescue device use allowed after 3 passes with solitaire for both groups.	shift analysis), change in NIHSS at 24 hours, door to reperfusion time, health related quality of life at 90 days. Secondary technical efficacy outcomes: successful reperfusion prior to MT, successful reperfusion by end of MT, total reperfusion (TICI 3). Safety outcomes: serious adverse events, asymptomatic haemorrhage.	-7.3%, lower limit of one sided 95% CI -15.1%. Secondary outcomes: no significant differences between groups for reduced disability, mortality, sICH. Post MT reperfusion higher with IVT + MT (96% vs 91%, p=0.05)	
698	P. J. Mitchell et al. (2022). Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4.5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. <i>The Lancet</i> 400:10346 116-125	This is the DIRECT SAFE trial (abstract reviewed by Anthony P but no results but results summarised in meta-analysis by Turc 2022. Muti-centre open label RCT involving ICA, MCA, BA occlusive ischaemic stroke comparing direct MT with MT plus IVT (rTPA or TNK < 4.5 hours) China/Vietnam and NZ and Australia. Non inferiority trial. All comprehensive centres.	MT vs IVT/MT (standard care). 17% MT/IVT (TnK)	mRS 0-2 at 90 days. Inferiority margin -0.1. SICH. Death at 90 days.	148 (MT vs 147 (bridging) Risk difference (-0.51) [-0.16 to 0.59} Crosses non inferior margin. 55% vs 61% (MT/IVT) mRS at 90 days. No sig difference in sich or death at 90 days.	Non inferiority not proven and therefore supports bridging therapy as standard,

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
698	P. J. Mitchell et al. (2022). Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4.5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. <i>The Lancet</i> 400:10346-116-125	Muti-centre open label PROBE RCT involving ICA, MCA, BA occlusive ischaemic stroke comparing direct MT with MT plus IVT (rTPA or TNK < 4.5 hours). Non inferiority trial. All comprehensive centres.	Direct to MT omitting IVT vs usual care for LVO of IVT+MT (bridging IVT) Stopped early due to publication of meta-analysis of 4 earlier RCTs indicating non-inferiority in populations enrolled in them but this used an OR margin of 0.8 (20%) not 0.9 used in SAFE-DIRECT!	mRS 0-2 at 90 days Inferiority margin -0.1 (10% is overly generous based on expert opinion which was 1.2-5% range) SICH. Death at 90 days.	295 enrolled, 2 withdrew consent—both in direct arm. 5 crossovers, 1 to bridging & 4 to direct. Acceptably low. Risk difference (-0.51) [-0.16 to 0.59] – so crosses 0.1 non inferiority margin. P =0.19. PP mRS 0-2 or return to baseline 62% with bridging vs 54% DIRECT, aOR 0.69 (0.41-1.15) so trends to better outcome with combined (bridging IVT). No safety differences.	++ Generally good with low risk of bias. Limited value in isolation but important contributor to 6 trial meta-analysis published by TURC et al 2022 in <i>Journal of Neurointerventional Surgery</i> / <i>European Stroke Journal</i> – IVT+MT should be standard of care if eligible for both