Question 3 evidence tables

Question 3: For patients with ischaemic stroke with anterior circulation large vessel occlusion from 6-24 hours from last seen well, does mechanical thrombectomy plus best medical therapy improve functional outcome compared to best medical therapy alone?

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

EVT = endovascular therapy, sICH = symptomatic intracranial haemorrhage, LKW = last known well, GA = general anaesthesia, SAE = SERIOUS ADVERSE EVENT, NCCT = non-contrast computed tomography, CT = computed tomography, CTA = computed tomography angiography, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, MT = mechanical thrombectomy, CTP = computed tomography perfusion, LVO = large vessel occlusion, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery, IV = intravenous, TPA = tissue plasminogen activator, BMT = best medical therapy, 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
555	G. W. Albers et al (2021). Assessment of Optimal Patient Selection for Endovascular Thrombectomy beyond 6 Hours after Symptom Onset: A Pooled Analysis of the AURORA Database. JAMA Neurology. 78: 9. 1064-1071.	Meta-analysis of 6 RCTs for EVT >6 hours from onset, 504 patients – 266 EVT, 239 control Included studies with differing inclusion criteria predominantly DAWN (<24hours) and DEFUSE (<16 hours) – only 29/372 were from other studies.	EVT vs control.	Primary outcome – ordinal change in mRS. Secondary outcome – mRS 0-2 at 90 days. Stratification into clinical mismatch (based on age (>/<80), NIHSS (>/<10) and mismatch <21ml, 31ml or 51ml on imaging) or target perfusion mismatch (core, Tmax, penumbra vol).	372 patients with available clinical and imaging data OR increased for all 3 groups versus control: OR 3.14 overall with imaging data, OR 3.57 clinical mismatch, OR 3.13 target perfusion mismatch No SD between EVT and control groups in mortality.	+ Meta-analysis of existing RCTs heavily drawn from DAWN and DEFUSE added value to literature.
555	G. W. Albers et al (2021).	Analysis of Pooled Data from Randomized Studies of	Thrombectomy in those who met	Modified Rankin Scale at 90 days.	Patients for whom both imaging profiles could be determined	Moderate level of evidence.

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	Assessment of Optimal Patient Selection for Endovascular Thrombectomy beyond 6 Hours after Symptom Onset: A Pooled Analysis of the AURORA Database. JAMA Neurology. 78: 9. 1064-1071.	Thrombectomy More Than 6 Hours After Last Known well. 505 patients. 266 in the MT group and 239 in the control group. Data from DAWN. DEFUSE 3, RESILIENT, ESCAPE, REVASCAT, POSITIVE. Core estimated as <30% CBF/ADV<620. Penumbra estimated as TMAX>6. In those with clinico-radiological mismatch: >80 years: NIHSS>9 Core <21ml in those >80 <80 years: NIHSS>9 Core <31ml OR NIHSS>19 Core 32-51mls. Those with target mismatch: Ratio of >1.8 (TMAX>6)	imaging/clinic-radiological criteria.		(372) OR 3.14 (2.12-4.64) p<.001 Patients with clinical mismatch profile (295) OR 3.57 (2.29-5.57) p<.001 Patients with target perfusion mismatch profile (359) OR 3.13 (2.10-4.66) p<.001 Patients with undetermined imaging profile (132) OR 1.59 (0.82-3.06) p=.17.	

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		Core <70mls.				
556	G. W. Albers et al (2018). Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. New England Journal of Medicine. 378: 8. 708-718.	Multicentre PROBE trial (DEFUSE-3) in patients with M1 and ICA occlusion 6-16h after onset with CTP fulfilling criteria (core <70ml, mismatch >1.8). Stopped early after interim review at n=182.	EVT+ best medical care vs best medical care.	Primary: mRS distribution d90 Secondary: mRS 0-2 at d90 Safety: Death, SICH.	EVT associated with favourable shift in mRS day 90 distribution (odds ratio, 2.77; P<0.001) and a higher percentage of mRS 0 to 2 (45% vs. 17%, P<0.001). Mortality 14% EVT vs 26% medical-therapy (P = 0.05). SICH not significantly different between the two groups (7% and 4%, respectively; P = 0.75).	++
556	G. W. Albers et al (2018). Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. New England Journal of Medicine. 378: 8. 708-718.	DEFUSE 3 trial in 38 US centres. 6-16 hours after last known well (LKW). Rapid perfusion imaging mandatory: Core <70ml; 1.8 ratio core:penumbra; penumbra >15ml. Proven LVO. Randomised, open-label, blinded MT vs standard medical therapy. Randomised 1:1.	Any approved device +/- carotid stenting allowed. GA discouraged but not excluded.	Blinded assessment of MRS at 90 days. MRS 0-2 at 90 days. Safety endpoints: death, SICH. Imaging outcomes: Infarct volume; Infarct growth; recanalization and reperfusion. Clinical assessment: baseline; 24 hours; discharge; 30 and 90d.	May 2016-2017 182 randomised: 92 EVT; 90 control. Groups balanced for severity etc EVT associated with more favourable disability scores at 90d OR 2.77. Functional independence at 90d: 45% EVT vs 17% medical therapy arm. Mortality 14% and 26% respectively. 5 deaths with SICH in EVT group and 2 in control group. SAEs 43% and 53% respectively. 10% had failed recanalisation.	++ Randomised controlled study but very select population

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					Infarct growth 23ml EVT vs 33ml control.	
557	P. Bhuva et al (2020). Noncontrast Computed Tomography Alberta Stroke Program Early CT Score May Modify Intra-Arterial Treatment Effect in DAWN. Stroke. 2404-2412.	Subgroup analysis of trial patients.123 CT ASPECTS. 82 DWI ASPECTS.	Mechanical thrombectomy.	Multiple comparisons Main one mRS0-2 at 3 months.	Using NCT ASPECTs and choosing higher ASPECTS score may identify patients who do better. The lower ASPECTS were not significant.	Poor Hypothesis generating
557	P. Bhuva et al (2020). Noncontrast Computed Tomography Alberta Stroke Program Early CT Score May Modify Intra-Arterial Treatment Effect in DAWN. Stroke. 2404-2412.	To look at whether non contrast CT can identify patients who will benefit from IAT in the extended time window. Post Hoc analysis of DAWN results.	IAT.	Baseline NCCT ASPECTS appears to modify IAT effect in DAWN.Higher NCCT ASPECTS was associated with greater benefit from IAT. No treatment interaction from DWI Aspects.	N/A	**N/A**
558	J. M. Boulanger et al (2018). Canadian Stroke Best Practice Recommendations for Acute Stroke	Setting Comprehensive systematic review of research evidence on the identification and management of acute stroke or TIA. Guidelines developed using established methodology	Section 5: Acute ischaemic stroke treatment considers evidence for extended time window endovascular	Outcomes for recanalisation and functional independence at 90/7 were quoted for DAWN and DEFUSE3.	Recanalisation outcomes at 24 hours noted to be significantly higher in endovascular treatment groups for both DAWN and DEFUSE3 and independence noted to be	Strong methodology and detailed review of research evidence to May 2018

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. International Journal of Stroke. 13: 9. 949-984	and draft recommendations further reviewed by separate expert panel.	thrombectomy (DAWN and DEFUSE3 studies).		higher at 90/7 in endovascular groups in both DAWN (49% v 13%) and DEFUSE3 (44.6% v 16.7%). Section 5.1 Recommendations for consideration of endovascular treatment up to 24 hours in highly selected patients (highest evidence level) using advanced neuroimaging ((highest evidence level).	
558	J. M. Boulanger et al (2018). Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. International Journal of Stroke. 13: 9. 949-984	Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018.	Canadian stroke guidelines, recommendations based on results from Diffuse 3 and Dawn trials.	N/A	Recommendation of Canadian guideline: Highly selected patients with large vessel occlusion who can be treated with EVT within 24 h of symptom onset (i.e., arterial access within 24 h of onset) and those patients with stroke discovered on awakening should receive EVT [Evidence Level A]. Separately list Imaging Inclusion Criteria for EVT beyond 6 h from onset: All patients with suspected ischemic stroke who arrive at 6–24 h after stroke onset (late presentation and stroke on awakening with unknown	**N/A.** Canadian guidelines, recommendations are based on review of best available evidence.

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					onset time) and are potentially eligible for late window EVT treatment should undergo immediate brain imaging with NCCT with CTA and CTP, or MRI with MRA and MRP [Evidence Level B], and should meet Dawn and Diffuse 3 selection criteria.	
559	M. Bouslama et al (2021). Novel selection paradigms for endovascular stroke treatment in the extended time window. Journal of Neurology, Neurosurgery and Psychiatry. 92: 11. 1152-1157.	Retrospective study single centre examining imaging selection rates based on FIVE imaging paradigms in patients undergoing MT (Extended time window> 6 hours, wake up and late presenters, NIHSS > 10, anterior circulation) and their association with 90 day outcomes. Imaging paradigms were based following criteria 1) DEFUSE 2) DAWN criteria (CT perfusion only) and 3-5) Variety of CT imaging based on ASPECTS score (age, cortical involvement and standard). Total of 310 patients screened from 1211 patients (very selective and all based on complete CTP maps).	Five imaging paradigms based on CT and CTP in patients who underwent MT.	Selection rates in each imaging paradigm 90 day outcome (mRS 0-2) 90 day mortality sICH Recanalisation	Selection rates were highest for patients with DAWN criteria but all achieved rates of > 90%. All imaging paradigms ASPECTS and DAWN 3 were associated with good outcome at 90 days (but not DEFUSE 3) both in univariate and multivariate analyses.	Average. Retrospective (very selective). Non Randomised. No control group or arm with BMT.
559	M. Bouslama et al (2021). Novel selection paradigms for endovascular stroke	Retrospective analysis of prospective single centre registry. 310 patients undergoing EVT beyond 6h.	Categorised into 5 different triage approaches compared with each other for predictive value.	Proportion of EVT eligible. DISCRIMINATION FO R90/7 GOOD FUNCTIONAL OUTCOME.	ASPECTS based paradigms had comparable proportions of qualifying patients and similar 90/7 outcomes to the D-3 & DAWN paradigms.	**0**

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	treatment in the extended time window. Journal of Neurology, Neurosurgery and Psychiatry. 92: 11. 1152-1157.					
560	I. Casetta et al (2020). Endovascular Thrombectomy for Acute Ischemic Stroke beyond 6 Hours from Onset: A Real-World Experience. Stroke. 2051-2057.	Italian registry data on MT treated patients >6hr compared with MT patients <6hours. No control group.	MT >6 hours	Primary outcome – mRS 0-2 90 days.	mRS 0-2 at 90 days 41.3% in >6 hours group vs 46.6%.	- Registry data only Comparing <6 hours group to >6 hours group – no control.
560	I. Casetta et al (2020). Endovascular Thrombectomy for Acute Ischemic Stroke beyond 6 Hours from Onset: A Real-World Experience. Stroke. 2051-2057.	Italian Registry. Patients with EVT >6h with good ASPECTS (>5) & ps Rankin <3. N=327 of 3057 (~11%) but all had CTP mismatch and good CS so all selected in fact had very favourable advanced brain imaging.	None other than had had EVT for LVO stroke and comparing <6h with >6h outcomes.	90/7 mRS Mortality & sICH.	OTP time median 430 mins in late group (IQR 390-570) – this indicates most were treated within 7.5h. Early = 220mins. FI 41% (>6h) vs 46.6%, adOR 0.58 (0.43-0.77). 17% mortality vs 16%; adOR= 1.19 (0.8-1.7). 6.7% sICH vs 6.9% (but IVT used) – adOR = 0.97 (0.58-1.6).	+ Large prospective registry. Selection biases pronounced.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
561	L. Dekker et al (2021). Endovascular treatment in anterior circulation stroke beyond 6.5 hours after onset or time last seen well: Results from the MR CLEAN Registry. Stroke and Vascular Neurology. 6: 4. 572-580	MR CLEAN registry data from 106 patients treated >6.5h from onset (3.2% of all patients), almost all of unknown onset (n=93) compared to propensity score matched registry patients <6h from onset.	EVT + best medical care undertaken as standard care; no CTP selection.	mRS at 3m Secondary: mRS 0-2, eTICI 2b-3 reperfusion, clinical improvement by >3 NIHSS points at 24-28h.	Proportions of functional independence at 3 months (43.3% vs 40.5%, p=0.57), successful reperfusion (56.9% vs 61.7%, p=0.33) and mortality (24.0% vs 28.9%, p=0.28) were comparable between late and early window patients.	**+** Multicentre registry but highly selected cases and non-randomised.
561	L. Dekker et al (2021). Endovascular treatment in anterior circulation stroke beyond 6.5 hours after onset or time last seen well: Results from the MR CLEAN Registry. Stroke and Vascular Neurology. 6: 4. 572-580	Data from prospective MR CLEAN registry, Netherlands, 16 INR centres, March 2014 to November 2017. Included all patients with an anterior circulation LVO (intracranial ICA, MCA M1/M2 or ACA A1/A2) treated with EVT in late window, where treatment started at or beyond 6.5 hours from symptom onset or LKW. Compared with early group treated with EVT prior to 6.5 hours. Propensity score matching of late and early window pts, 1:2 ratio also undertaken to minimise risk of confounding by indication. Matched on age, prestroke mRS, baseline NIHSS, baseline ASPECTS, location of occlusion, collateral status and treatment	EVT for Ant circ LVO patients treated at or beyond 6.5 hours from symptom onset/LKW compared with early time window patients treated with EVT within 6.5 hours.	Primary Outcome: mRS at 3 months after stroke Secondary outcomes: functional independence, TICI 2b or greater, clinical improvement after intervention (decrease of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) between presentation and 24–48 hours postintervention or complete recovery (NIHSS 0). Safety outcomes: complications, sICH, mortality at 3 months.	Prior to matching, rates of mRS 0-2 at 3 months, successful reperfusion, and mortality were comparable between late and early window patients. Logistic regression analysis showed no difference in outcomes. Following matching, no significant difference in mRS distribution between late and matched early window patients, or proportions of functional independence at 3 months. No significant difference in rates of complications, sICH or mortality.	**++** Differences in baseline characteristics between early and late window patients however undertook propensity score matching to address this. Some missing data (4.0% of data points in the imputation model were missing, missing mRS scores in 6.5%) however from methods, seems to have been addressed appropriately.

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		with intravenous thrombolysis. Unmatched patients were excluded from further analysis. 96.4% of the late window patients could be matched to two early window patients. CT perfusion was not a standard imaging modality in the registry. Blinded evaluation by core lab. Selection mainly CT and CTA. Of 3264 included patients, 3158 (96.8%) had EVT within 6.5 hours from onset/LKW. 106 late window patients. Late window patients were slightly younger, received IVT less frequently and had lower baseline ASPECTS and better collaterals.				
562	P. S. Dhillon et al (2022). Association between time to treatment and clinical outcomes in endovascular thrombectomy beyond 6 hours without advanced imaging selection. Journal of NeuroInterventional Surgery.	Registry from the SSNAP database UK. 3278 patients. 2610 in the 0-6 hour window 668 in the 6-244 hour window.	Mechanical Thrombectomy.	Shift in mRS outcome at 3 months or simply outcome mRS 0-2 at 3 months.	There was a time effect in the early window group but not in the late window group. Therefore, this suggests that without using fancy imaging, it may be possible to select patients for treatment in the late window for treatment.	Hypothesis generating study with no medical treatment only group. It would have been interesting to compare the outcome of those with advanced imaging and those without in the late window.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	18564					
562	P. S. Dhillon et al (2022). Association between time to treatment and clinical outcomes in endovascular thrombectomy beyond 6 hours without advanced imaging selection. Journal of NeuroInterventional Surgery. 18564	Patients that underwent EVT selected with non contrast CT/CTA angio without CT perfusion or MR imaging frpm Oct 15 to March 20 were included from a national data base.	EVT.	Functional and safety outcomes were assessed in both early < 6hours and late windows with time analysed as a continuous variable.	In the late window, for every hour delay there was no significant association with shift to a poorer functional outcome or change in predicted functional independence. In contrast predicted functional independence was time sensitive in the early 1 to 6 hr window.5.2% reduction per hr delay.	+
563	P. S. Dhillon et al (2022). Perfusion Imaging for Endovascular Thrombectomy in Acute Ischemic Stroke Is Associated With Improved Functional Outcomes in the Early and Late Time Windows. Stroke.	Observational study using SSNAP across 25 MT centres across 123 hospitals in England, Wales and NI to examine the effects of NCCT/CTA versus CTP on a wide range of outcomes for patients undergoing MT in early time windows (<6 hours) and ate time windows 6-24 hours.[Oct 2015-March 2020].	Non contrast CT and CTA versus CTP across two time windows : early vs late adjusted for case mix variables wrt functional outcome.	mRS at discharge mRS at six months Futile recanalization (mRS 4-6 despite successful reperfusion) TICI 2b/3 scores Safety: in hospital mortality and sICH.	4249 patients analysed undergoing MT. Of note, 2.4% treated > 24 hours (excluded). < 6 hours 3203 (75.4%) CTP (593) 18.5% NCCT/CTA (2610) 81.5%. 6-24 hours (1046) 24.6% CTP (378) 36.1% NCCT/CTA (668) (63.9%).	Observational only but reflective of real world data across the England, Northern Ireland, Wales and examining a wider heterogenous group of patients compared to DAWN/DEFUSE 3 Highlights what is currently deliverable in the UK. Limitations exist with observational data with section bias, confounding by indication

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					66% had documented time of onset. Onset to treatment in CTP (671 minutes) cf non Perfusion in late time window (619 mns). Outcomes: LATE: CTP associated with higher odds of change in mRS by 1 point (OR: 1.45, 1.16 to 1.83). Lower odds of futile recanalization (OR: 0.70, 0.5 to 0.97). No difference in mRS< 2, sICH or in hospital mortality. Sensitivity analysis (confirmed similar direction of odds ratios when using documented time of onset. EARLY: CTP associated with improved odds for ordinal shift (OR 1.51, 1.28 to 1.78) and functional mRS < 2. Lower odds of sICH and futile recanalization compared with NCCT imaging.	and lack of detailed imaging data. Hypothesis generating to examine the merits of NCCT/CT vs CTP in later presenters in RCT.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					Patients who had access to either CTP/NCCT in early presenters had lower rates of sICH. Futile recanalization was observed in patients with higher baseline NIHSS scores with higher rates of sICH	
563	P. S. Dhillon et al (2022). Perfusion Imaging for Endovascular Thrombectomy in Acute Ischemic Stroke Is Associated With Improved Functional Outcomes in the Early and Late Time Windows. Stroke.	Retrospective cohort study. This is not a study directly comparing MT in late time window with best medial therapy; it is an outcome assessment with and without CTP. SSNAP data retrieved from 1/10/15 to 31/3/20; divided into early (<6h) and late (6-24h) and further dichotomised into with or without CTP. 4249 patients included: 22.9% with and 7.1% without CTP.	All patients receiving MT Best medical therapy not studied.	Primary: mRS at discharge. Secondary: mRS at 6/12, mRS<2, early neurological improvement, early neurological worsening, futile recanalization. Procedural: successful reperfusion. Safety: sICH, in-hospital mortality. Time metrics: onset to puncture; imaging to puncture; total procedure time	Lower IV TPA rate late window. NIHSS similar. Longer onset to MT in late group with CTP; 671 vs 619 min. Late CTP increased odds of improvement of mRS score by 1 point at discharge: OR 1.45. Lower futile recanalisation with CTP (53.7% vs 60.4%). No difference in safety outcomes. Early Improved odds of better functional outcome with CTP: OR 1.51 and functional independence: 41.6% vs 33.6%. Slightly reduced death rates and futile recan.	**+** Large number, and real-world experience of busy centres.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
564	M. Goyal et al (2015). Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke New England Journal of Medicine. 372: 11. 1019-1030.	Setting Multicentre international study. Design multicentre, prospective, randomized, open-label, controlled trial with blinded outcome evaluation (PROBE design).20 Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone. Subjects 311 subjects recruited (164 in endovascular group) 296 subjects recruited of whom 182 patients met all inclusion criteria (92 with endovascular treatment). Study terminated early at recommendation of Safety Committee following publication of MR CLEAN results showing efficacy of endovascular treatment.	Comparison of endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone.	The primary outcome was mRS at 90 days Secondary and safety outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death.	Functional independence (mRS 0 – 2) 53% in treatment group v 29% in control group. The primary outcome favoured the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; P = 0.04).	**++** Study terminated before full recruitment. Median time from stroke onset to reperfusion was 241 mins (IQR 176 – 359) for intervention. Although patients could be recruited to 12 hours small numbers post 6 hours and no data for late presenters provided in main study report.
564	M. Goyal et al (2015). Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke	Randomised control trial (multicentre). Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset.	Thrombectomy plus medical management versus medical management. Baseline criteria:	Modified Rankin scale at 90 days. Favourable: 0-2.	Modified Rankin 0-2 in 53% EVT group v 29.3% of controls. Common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001),	Good quality study but single RCT.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	New England Journal of Medicine. 372: 11. 1019-1030.		Occlusion: M1, 2 or TICA. (Including tandem cervical ICA) ASPECTS 6-10. Moderate to good collateral filling (filling of 50% or more of the middle-cerebral artery pial arterial circulation on CTA – preferably multiphase CTA).		Intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; P = 0.04). Symptomatic intracerebral haemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (P = 0.75).	
565	A. P. Jadhav et al (2019). Benefit of Endovascular Thrombectomy by Mode of Onset: Secondary Analysis of the DAWN Trial. Stroke. 50: 11. 3141-3146.	Secondary analysis of DAWN multicentre PROBE trial comparing wake-up (n=114) with known onset time (n=25 witnessed, n=67 unwitnessed) patients, fulfilling clinical and imaging criteria (ICA or M1 occlusion, DWI or CTP core < 21-51ml age-adjusted) 6-24h after last seen well.	EVT + best medical care vs best medical care	Utility-weighted mRS at 3m, mRS 0-2, SICH and radiographic ICH.	No heterogeneity of treatment effect by mode of presentation.	+ Subgroup analysis of RCT.
565	A. P. Jadhav et al (2019). Benefit of Endovascular Thrombectomy by	Subset analysis of DAWN trial data assessing type of onset and relationship to outcomes. 206 patients; 55% Wake-up. WU and UW onset had higher NIHSS.	No difference in treatment types between the groups.	As per DAWN trial results all groups had significantly better outcomes after MT than best medical therapy.	No significant difference in outcomes whether wake-up stroke, witnessed or unwitnessed onset in late time	+

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Mode of Onset: Secondary Analysis of the DAWN Trial. Stroke. 50: 11. 3141-3146.				window with CTP used to case selection for MT.	
566	A. P. Jadhav et al (2018). Eligibility for endovascular trial enrollment in the 6-to 24-hour time window analysis of a single comprehensive stroke center. Stroke. 49: 4. 1015-1017.	Retrospective single centre audit. Review of stroke admissions in time windows for extended MT. Not comparing MT with control.	Nil.	None stated.	Results related to number of patients potentially suitable for MT – no treatment data.	- No MT provided – all retrospective audit of MT suitability on timings/imaging data. No control.
566	A. P. Jadhav et al (2018). Eligibility for endovascular trial enrollment in the 6-to 24-hour time window analysis of a single comprehensive stroke center. Stroke. 49: 4. 1015-1017.	Retrospective analysis of all acute ischemic stroke presenting to a single comprehensive stroke centre during DAWN trial enrolment period (November 2014 to February 2017), using the Get With The Guidelines database. Patients filtered for analysis based on DAWN and DEFUSE-3 enrolment criteria. Aim: to understand incidence of patients who could benefit from EVT in the extended time window	Analyses of baseline characteristics, imaging findings, presence of LVO etc. to determine number and proportion of patients presenting to a comprehensive stroke centre who are eligible for late window EVT.	Absolute number and proportion of patients meeting DAWN and/or DEFUSE 3 trial inclusion criteria.	30% (n=792) presented within the 6- to 24-hour time window, and 47% (n=1242) had NIHSS ≥6. Further clinical trial-specific selection criteria were applied based on the presence of LOVO, baseline mRS, core infarct, and perfusion imaging (when available). 45 patients met all DAWN trial criteria and 47 to 58 patients met DEFUSE-3 trial criteria (perfusion imaging not available in all). 33% of	+ Data predict rate of increase in thrombectomy utilization in late window in patients meeting RCT criteria, has important implications for service planning.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
		2667 patients with acute ischemic stroke admitted within the study period.			DAWN-eligible patients are DEFUSE-3 ineligible. Of all AIS patients presenting to a single CSC, 1.7% of patients qualified for DAWN clinical trial enrolment with an additional 0.6% to 1% qualifying for the DEFUSE-3 trial.	
567	T. G. Jovin et al (2022). Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. The Lancet. 399. 249-258.	Systematic review and meta-analysis. 505 patients from 6 trials. AURORA (Thrombectomy for Anterior Circulation Stroke Beyond 6 hours From Last Known Well (Analysis of Pooled Data From Randomized StUdies of ThROmbectomy MoRe than 6 Hours After Last Known Well) Collaboration.	Mechanical thrombectomy v best medical treatment.	mRS at 90 days by ordinal logistic regression.	Thrombectomy resulted in better out comes 45.9% v 19.3% (mRS0-2). There was no heterogeneity in the subgroups. A few subgroups were non-significant including non DAWN-DEFUSE3 imaging.	This was very good.
567	T. G. Jovin et al (2022). Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. The Lancet.	Analysis Of Pooled Data From Randomized Studies Of Thrombectomy More Than 6 Hours After Last Known Well. 505 individuals (n=266 intervention, n=239 control).		Modified Rankin Scale (mRS) at 90 days.	Primary outcome: benefit of thrombectomy: unadjusted common OR of 2·42 (95% CI 1·76–3·33; p<0·0001) and an adjusted common OR (for age, gender, baseline stroke severity, extent of infarction on baseline head CT, and time from onset to random	Good level of evidence. Hindered by differing selection criteria.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	399. 249-258.	Data from DAWN. DEFUSE 3, RESILIENT, ESCAPE, REVASCAT, POSITIVE. . Minimum criteria: ASPECTS >5			assignment) of 2·54 (1·83–3·54; p<0·0001). Higher rates of independence with thrombectomy: 122 [45·9%] of 266 vs 46 [19·3%] of 238; p<0·0001. 90 day mortality and SICH similar: 44 [16·5%] of 266 vs 46 [19·3%] of 238) or symptomatic intracerebral haemorrhage (14 [5·3%] of 266 vs eight [3·3%] of 239).	
568	M. G. Lansberg et al (2019). Association of Thrombectomy with Stroke Outcomes among Patient Subgroups: Secondary Analyses of the DEFUSE 3 Randomized Clinical Trial. JAMA Neurology. 76: 4. 447-453.	Pre-specified secondary analysis of the prospective open-label randomised DEFUSE 3 study of endovascular therapy plus medical management vs medical management alone for patients presenting in the 6- to 16-hour time window Study terminated early due to efficacy. Setting Multicentre study performed in the US. Design Prespecified analyses assessing association of endovascular treatment in sub-groups based on patient, age, site	Endovascular thrombectomy treatment plus medical management versus medical management in eligible patients presenting in 6-16 time window since stroke onset.	The primary outcome for the DEFUSE 3 study analyses was 90-day functional outcome assessed using modified Rankin Scale (mRS). Adjusted common odds ratios were calculated for group effect on improved functional outcome of age, stroke severity, time from onset, imaging selection and site of occlusion.	Common OR for improved functional outcome with endovascular therapy, adjusted for age, NIHSS score, and serum glucose was 3.1 (95% CI, 1.8-5.4). No interaction seen between time to treatment, site of occlusion, age to 90 years, stroke severity, imaging selection modality or site of occlusion.	**++** Pre-specified secondary analysis. Main study terminated early for efficacy and numbers small in this analysis (particularly for time to treatment group). However, despite sample size, no trend to change in proportional benefit of endovascular treatment across each group studied.

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		of occlusion, imaging modality for selection. Subjects 296 subjects recruited of whom 182 patients met all inclusion criteria (92 with endovascular treatment).				
568	M. G. Lansberg et al (2019). Association of Thrombectomy with Stroke Outcomes among Patient Subgroups: Secondary Analyses of the DEFUSE 3 Randomized Clinical Trial. JAMA Neurology. 76: 4. 447-453.	Secondary analyses of major RCT 6-16h DEFUSE-3 TRIAL To assess if benefit universal or confined to prespecified subgroups: -ICA vs MCA -MRI vs CT -Age -bNIHSS -Onset to Random time N = 182 Last Obs carried forward for 3 with missing 90/7 data.	D-3 RCT: BMT vs EVT for 6-16h ant circ. LVO Proportional odds model to identify independent predictors of outcome	Usual efficacy (90/7 Rankin) & safety ones.	Predictors of 90/7 outcome were: EVT OR 3.12 (1.81-5.38) Age OR 0.95 (0.93-0.97) bNIHSS OR 0.88 (0.84-0.92) Glucose OR 0.94 (0.9-0.99) The proportional benefit of MT was uniform across age range, baseline NIHSS, time (OTR) and occlusion site Whilst proportionate benefit is uniform, differences do exist in absolute Rx benefit across patients.	++
569	T. M. Leslie-Mazwi et al (2019). DEFUSE 3 Non-DAWN patients: A closer look at late window thrombectomy selection. Stroke. 50: 3.	Application of the effects of MT in patients in the DEFUSE 3 study who were not eligible for the DAWN study criteria with the aim of assessing effects of MT in patients with low NIHSS scores (6-9), pre-stroke mRS>1 and in patients with large core volumes (as stipulated by DAWN criteria).	Application of MT on DEFUSE 3 study with patients not deemed to satisfy DAWN criteria (non- eligible DAWN criteria). Stratified comparing NIHSS 6-9 vs > 10 and	Process ad procedural variables (reperfusion rates) as well as outcomes (functional independence at 90 days s 0-2,mortality at 90 days and safety (sICH).	DEFUSE 3 study randomised 182 patients (of note study stopped prematurely due to DAWN study results). 71 patients enrolled DEFUSE 3 non DAWN eligible study.	+ Data from RCT but subgroup analyses and more hypothesis generating given the small subgroup size with comparisons and was not the premise of the original study

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	618-625.	These included the following: age >80 with core volumes > 20mls, age < 80, > NIHSS <20 and core volumes> 30 mls , any core volumes> 50 mls with either MRI or CTP (CTL). Comparison made between non eligible DAWN DEFUSE 3 patients and entire DEFUSE 3 cohort (with NIHSS > 10 and Core volumes not to large (CNTL).	core volumes (too large vs non too large).		Comparing CTL (non DAWN eligible) vs CNTL (whole DEFUSE): 33 vs 149. CTL: older, lower ASPECTS (7), lower collaterals, larger core volumes (45.2 mls vs 7.3 mls) and perfusion volumes as well as larger infarct volumes at 24 hours. Functional independence 90 days non sig difference and with non-significant differences in mortality and safety. Of note, after adjusting for case mix the odds for Functional independence at 90 days when comparing MT vs medical treatment in patients with CTL volumes was 20.9 (1.3 to 337.8). Note wide confidence intervals due to small numbers. Comparing NIHSS 6-9 CTL (non DAWN eligible) vs NIHSS > 10 (whole DEFUSE): 31 vs 151. NIHSS 6-9, higher ASPECTS.	Raises hypothesis that large core volumes (ie < 70 mls but larger than DAWN core volumes) have potential to benefit from MT but requires further refinement. Of note, only analysed patient up to 16 hours and not between 16-24 hours therefore generalisability.

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					Higher rate of functional independence at 90 days and lower infarct volumes and lower mortality rates. Similar reperfusion rates. After adjusting for case mix, odds for functional independence at 90 days 1.86 (0.36 to 9.529) when comparing MT to medical therapy.	
569	T. M. Leslie-Mazwi et al (2019). DEFUSE 3 Non-DAWN patients: A closer look at late window thrombectomy selection. Stroke. 50: 3. 618-625.	Looks at the effect of Thrombectomy in DEFUSE 3 patients excluded by DAWN.	Looks at intervention in DEFUSE 3 infarct core too large, NIHSS 6 to 9 and mRS of 2.		Patients with pretreatment core infarcts < 70mL but too large for inclusion by DAWN criteria benefit from thrombectomy. Only a trend toward benefit of patients with NIHSS 6 to 9 was found in this subgroup.	+
570	D. S. Liebeskind et al (2022). Collateral Circulation in Thrombectomy for Stroke after 6 to 24 Hours in the DAWN Trial. Stroke. 29: 2. 742-748.	Secondary analysis of DAWN trial exploring collateral grade as a modifier of outcome in 161/206 participants	EVT + best medical care vs best medical care	Baseline characteristics and outcomes by collateral grade	Poor collaterals associated with larger core, greater infarct growth, poorer d90 mRS, higher mortality	-

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
570	D. S. Liebeskind et al (2022). Collateral Circulation in Thrombectomy for Stroke after 6 to 24 Hours in the DAWN Trial. Stroke. 29: 2. 742-748.	Nature and impact of collaterals on outcomes in the late time window DAWN trial.	The relationship between collateral grade and day 90 outcomes were analysed separately for each treatment arm.	Collateral flow was a significant predictor of 90day mRS 0 to 2 in the endovascular arm.	Even in late time window better collaterals lead to better outcomes.	+
571	T. N. Nguyen et al (2022). Noncontrast Computed Tomography vs Computed Tomography Perfusion or Magnetic Resonance Imaging Selection in Late Presentation of Stroke with Large-Vessel Occlusion. JAMA Neurology. 79: 1. 22-31.	International comparison of CT/CTP vs MRI selection for MT in extended window <24 hours. No control population.	MT for LVO <24 hours – no control.	Primary outcome - ordinal shift analysis of mRS at 90 days. Secondary outcome – mRS at 90 days, workflow metrics.	Mutlivariate analysis – no difference in outcomes for CT vs CTP or CT vs MR.	- No control population Retrospective analysis based on initial imaging modality.
571	T. N. Nguyen et al (2022). Noncontrast Computed Tomography vs Computed	Multinational cohort study Of ant circ LVO 6-24H Jan 201-Dec 2020 (CLEAR study) & bNIHSS >5. N = 1604.	MT in AC LVO stroke in 6-24h window.	90/7 Rankin – shift & FI. Reperfusion. Usual safety measures.	No differences in 90/7 functional outcome on shift analysis by selection modality. Slightly lower 90/7 FI Rate with MRI than CT & lower reperfusion rate.	+ Should not include ASPECTS+CTA CS as being the “simple CT” paradigm often used in CLEAR – (this paradigm

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Tomography Perfusion or Magnetic Resonance Imaging Selection in Late Presentation of Stroke with Large-Vessel Occlusion. JAMA Neurology. 79: 1. 22-31.	Median age = 70. CTP in 752 MRI in 318 CT in 534 (nearly all with ASPECTS 6+). Some of these patients were in DAWN or D3!			No differences in sICH or mortality. Trends to better outcomes with CTP.	has been largely proven by ESCAPE RCT already) – 4/15 sites used CTA CS but all could have done. Site adjudicated ASPECTS
572	R. G. Nogueira et al (2018). Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. New England Journal of Medicine. 378: 1. Nov-21.	Randomised controlled trial 206 patients. 107 in thrombectomy. 99 in control. 6-24 hours.	Mechanical thrombectomy v best medical treatment	Complicated outcomes. Utility weighted mRS and Bayesian analysis.	48% mRS 0-2 treated. 13% mRS 0-2 control.	++
572	R. G. Nogueira et al (2018). Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. New England Journal of Medicine. 378: 1. Nov-21.	26 US centres, Canada, Europe, Australia. DAWN trial; randomisation of LVO 6-24 h post onset with 2 groups: >80 NIHSS >9; core <21ml <80 NIHSS >9; core <31ml <80; NIHSS >19; core 21-51ml.	1:1 randomisation MT versus BMT. Trevo device mandated. No ICA stenting.	Primary 90-day mRS, functional independence. Secondary Reduction in NIHSS >10, NIHSS 0 or 1 by day 7 Death at 90d, recanalization, change in infarct volume.	Mean NIHSS 17 both groups; baseline characteristics balanced 49% vs 13% independent 79% and 36% recanalisation No sign difference in death rates at 90d.	++

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
573	A. C. Peultier et al (2019). Exploring the Cost-Effectiveness of Mechanical Thrombectomy Beyond 6 Hours Following Advanced Imaging in the United Kingdom. Stroke. 50: 11. 3220-3227.	Using a hypothetical UK cohort of stroke patients undergoing MT, cost effectiveness analysis per QALY gained was measured in two scenarios 1 Advanced imaging using CTP in < 6 hours and 6-24 hours. 2 NCTT/CTA < 6 hours.	A decision analytic model to ascertain cost effectiveness of 2 care pathways as described previously in methods.	Cost effectiveness ratios for 2 pathways/scenarios	Model predicted that advanced imaging > 6 hours (late window), improves health outcomes but increases costs per patient. 0.09 to 0.45 QALY (range) with £790 to £4460) per patient. Incremental cost-effectiveness ratios (ICERs) varied widely across scenarios, ranging from £6164 to £37 229 per QALY gained.	Exploratory results based on hypothetical modelling.
573	A. C. Peultier et al (2019). Exploring the Cost-Effectiveness of Mechanical Thrombectomy Beyond 6 Hours Following Advanced Imaging in the United Kingdom. Stroke. 50: 11. 3220-3227.	Decision tree and a Markov trace were developed using hypothetical United Kingdom cohort of suspected stroke patients aged 71 years. Costs, health outcomes, and probabilities were obtained from the literature.		Costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost effectiveness Ratios.	Advanced imaging, by extending the time window beyond 6 hours (up to 24 hours) for MT, improves health outcomes but increases costs when compared with conventional imaging (CT+CTA) coupled to MT up to only 6 hours from symptom onset. Incremental cost-effectiveness ratios resulting from deterministic analyses varied from $8199 (£6164) to $49 515 (£37 229) per QALY gained.	Based on a model that cannot account for all scenarios including more aged patients with co-morbidity. Recognises the limitations of trying to institute more advanced imaging in referring sites.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
574	L. C. Polding et al (2021). Quality of Life in Physical, Social, and Cognitive Domains Improves with Endovascular Therapy in the DEFUSE 3 Trial. Stroke. 1185-1191.	Secondary analysis of the prospective open label randomised DEFUSE 3 study of endovascular therapy plus medical management vs medical management alone for patients presenting in the 6- to 16-hour time window Study terminated early due to efficacy Setting Multicentre study performed in the US. Design Assessment of the impact of late-window endovascular treatment on self-reported QoL outcomes using a validated tool (Neuro-QoL). Subjects 296 subjects recruited of whom 182 patients met all inclusion criteria (92 with endovascular treatment) and 136 were alive at 90 day follow up.	Endovascular thrombectomy treatment plus medical management versus medical management in eligible patients presenting in 6-16 time window since stroke onset.	The primary outcome for the DEFUSE 3 study analyses was 90-day functional outcome assessed using modified Rankin Scale (mRS). At 90 days, functional outcome was assessed on the mRS and QoL on the QoL in Neurological Disorders (Neuro-QoL) measurement tool (v2.0), Differences in scores between treatment groups were compared using 2-sample t tests.	Endovascular therapy compared with medical therapy alone resulted in superior QoL outcomes in all 4 domains of QoL (social, mobility, depression and cognition).	**++** High capture rate for QoL assessment in living patients at 90 days.
574	L. C. Polding et al (2021). Quality of Life in Physical, Social, and Cognitive Domains Improves with Endovascular Therapy in the DEFUSE 3 Trial. Stroke.	Secondary analysis from DEFUSE 3 RCT (randomized pts to EVT + BMT versus BMT alone in late window (6 – 16 hour) patients fulfilling stringent inclusion criteria including use of advanced imaging for selection). The current analysis aimed to assess impact of late-window EVT on	DEFUSE 3 RCT, secondary QOL analysis in EVT + BMT compared to BMT only group.	Four Neuro-QoL short forms administered to assess QoL in the following domains commonly affected by stroke: lower-extremity function (mobility), ability to participate in social roles and activities,	EVT compared with BMT alone resulted in superior QoL outcomes in all 4 assessed domains. QoL scores in EVT arm were more similar to those of the general population than scores in BMT only arm. Benefit of EVT remained significant after	**++** Secondary analysis of RCT Defuse 3, a trial which directly addressed the PICO question.

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	1185-1191.	self-reported QoL outcomes and examine association between QoL outcomes and functional outcome. 182 patients in DEFUSE 3 RCT, 92 randomized to EVT group, and 90 to BMT alone. QoL outcomes data were collected and analysed for 136 (95%) of the patients living at day 90 (96% in the endovascular arm and 94% in the medical arm).		cognitive function, and depression. Reference population was the US general adult population for all domains except for mobility, which was calibrated using a sample of neurological patients	correction for multiplicity and adjusting for independent predictors of QoL. In each domain, worse QoL was correlated with higher mRS scores. mRS accounted for a high degree in the variability in mobility (Rs2=0.82) and a moderate degree in social participation (Rs2=0.62) but explained only a low degree of the variability in cognition (Rs2=0.31) and depression (Rs2=0.19; Figure 3).	
575	A. Sarraj et al (2019). Outcomes of thrombectomy in transferred patients with ischemic stroke in the late window: A subanalysis from the defuse 3 trial. JAMA Neurology. 76: 6. 682-689.	Subgroup analysis of DEFUSE 3 comparing transferred patients (n=121) with those presenting to direct presentation (n=61).	EVT+best medical care vs best medical care.	mRS distribution; mRS 0-2 at d90.	No differences in outcomes by mode of presentation; no heterogeneity of treatment effect.	+ Subgroup analysis of RCT; small numbers in subgroups.
575	A. Sarraj et al (2019). Outcomes of thrombectomy in transferred patients with ischemic stroke in	To evaluate whether the image based selection criteria in DEFUSE 3 would lead to comparable outcome rates and	IAT vs IAT and BMT.	90 modified ranking.	The overall functional independence rate in the thrombectomy group did not differ nor the treatment effect. Thrombectomy	+

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	the late window: A subanalysis from the defuse 3 trial. JAMA Neurology. 76: 6. 682-689.	treatment benefits in transfer vs direct admission patients.			reperfusion rates, mortality and symptomatic IC did not differ.Both direct and transfer patients who received IAT +BMThad better outcomes that BMT alone.	
576	G. Turc et al (2019). European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic StrokeEndorsed by Stroke Alliance for Europe (SAFE). European Stroke Journal. 4(1). 06-Dec.	Guideline	N/A	N/A	Quote: In adults with anterior circulation LVO-related acute ischaemic stroke presenting between 6 and 24 hours from time last known well and fulfilling the selection criteria of DEFUSE-3* or DAWN**, we recommend MT plus BMM over BMM alone to improve functional outcome.	**N/A**
576	G. Turc et al (2019). European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in	Guidelines document based on the standard operating procedure of the European Stroke Organisation and followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.				**N/A**

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	Acute Ischaemic StrokeEndorsed by Stroke Alliance for Europe (SAFE). European Stroke Journal. 4(1). 06-Dec.	Identified 15 relevant questions, performed systematic reviews and meta-analyses of the literature, assessed the quality of the available evidence, and wrote evidence based recommendations. Expert opinion was provided if not enough evidence was available to provide recommendations based on the GRADE approach.				
577	T. Ullberg et al (2022). Endovascular thrombectomy for anterior circulation stroke beyond 6 hours of onset in Sweden 2015 to 2020: Rates and outcomes in a nationwide register-based study. Journal of NeuroInterventional Surgery. 18760.	National registry of MT <24 hours No control group	MT for AIS >6 hours	Comparison of treatment groups stratified by time (<6hours, 6-24 hours or unknown).	No significant difference in mRS outcomes between 3 groups. No control group.	**0**
577	T. Ullberg et al (2022). Endovascular thrombectomy for anterior circulation stroke beyond 6 hours	Retrospective review of prospective Swedish registry data, from two nationwide quality registers for stroke in 2015–2020. All cases of anterior	EVT for anterior circulation LVO, in early versus late time windows.	Favourable outcome (mRS 0–2) and all-cause mortality at 90 days were the main outcomes, also looked at successful	A favourable clinical outcome was seen in 42.4% in the early time window, compared with 38.9% in late window known onset patients, and 37.3% of	**+** Retrospective single cohort

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	of onset in Sweden 2015 to 2020: Rates and outcomes in a nationwide register-based study. Journal of NeuroInterventional Surgery. 18760.	circulation AIS (occlusion of the intracranial ICA, M1 or M2 MCA) , registered in two nationwide quality registers for stroke in 2015–2020. Three groups were defined based on onset-groin-puncture (OTG) time: early window (< 6 hours), late window (6-24 hours) known onset, late window LKW. No medical only group for comparison.		recanalization (mTICI 2b–3), sICH was safety outcome.	late time window LKW patients (p=0.737). The total rate of functional independence in the late time window was 37.8%. Compared with early time window the OR of achieving a favourable outcome in late time window was similar (known onset 0.863, 95%CI 0.598 to 1.247; LKW 0.809, 95%CI 0.630 to 1.040). When adjusted for variables that were unevenly distributed between groups, not directly associated with the time aspect but possibly with prognosis (occlusion location, NIHSS pre-treatment and type of anaesthesia), the OR of achieving a favourable outcome remained similar between the early and late time windows (known onset 0.681, 95%CI 0.463 to 1.003; LKW 0.781, 95%CI 0.602 to 1.013).	
578	K. S. Zachrison et al (2021). Frequency, characteristics, and outcomes of endovascular	US Registry				

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	thrombectomy in patients with stroke beyond 6 hours of onset in US clinical practice. Stroke. 52: 12. 3805-3814.					
578	K. S. Zachrison et al (2021). Frequency, characteristics, and outcomes of endovascular thrombectomy in patients with stroke beyond 6 hours of onset in US clinical practice. Stroke. 52: 12. 3805-3814.	US Registry 2009-1st October 2018 inclusive with a recorded onset to Tx or LKW time. 33% (17,720) treated beyond 6h.	MT in acute stroke.	Usual US care efficacy & STANDARD safety ones.	Worse adjusted functional outcomes in those treated beyond 6h than 2/3 treated within 6h (median of all cases was 4.7h). AdOR mortality = 1.2 (1.1-1.3) Independent ambulation at discharge AD or = 0.7 (0.67-0.74).	- Large volumes but major imbalances & potential biases.
579	Z. Zhao et al (2020). Efficacy and safety of endovascular treatment vs medical treatment in anterior circulation stroke beyond 6 hours: A systematic review and metaanalysis. Neurology Asia.	Meta analysis of studies comparing EVT with medical care >6h after onset; included 4 studies (DAWN and DEFUSE-3 RCTs; one matched case-control study; one subgroup of HERMES trials involving >6h presenting patients). Total n=642	EVT+ best medical care vs best medical care.	mRS d90 0-1, 0-2, 0-3 Recanalisation Mortality SICH PH2	EVT associated with higher odds of all mRS dichotomies, recanalization. No difference in mortality, SICH, PH2.	+ Inclusion of a case-control study reduces the quality of the data that otherwise derive from RCTs, although the HERMES data come from subgroups of two of the component trials that included

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	25(4). 439-446.					patients >6h (REVASCAT and ESCAPE).
579	Z. Zhao et al (2020). Efficacy and safety of endovascular treatment vs medical treatment in anterior circulation stroke beyond 6 hours: A systematic review and metaanalysis. Neurology Asia. 25(4). 439-446.	Meta-analysis of 4 studies with 642 patients.	MT versus BMT.	mRS 0-1 at 90d, functional independence, recanalization, mortality, sICH	EVT ass with higher odds of excellent outcome: OR 2.55; functional independence OR 3.64; recanalisation OR 8.81. No difference in mortality, sICH. CTP use improved numbers with moderate outcome.	-
580	Y. Zhongxing et al (2021). Efficacy and Safety of Endovascular Treatment for Acute Large-Vessel Ischemic Stroke Beyond 6 h After Symptom Onset: A Meta-Analysis. Frontiers in Neurology. 12. 654816	Meta-analysis of largely retrospective observational studies comparing efficacy and safety of MT comparing <6hr vs > 6 hours in patients with acute ischaemic stroke. Studies either registry studies or single centres. Eight studies included which varied between 2010-2019. Cut off points varied between 6 hours to 8 hours.	MT < 6hr vs > 6 hours with advanced imaging with a variety of imaging modalities.	90 days mRS 0-2 Recanalisation Mortality sICH All at 90 days.	No significant differences between both groups for 1 Functional independence 2 Mortality 3 Recanalisation 4 sICH However heterogeneity high for functional independence. (+) and recanalisation (++)	Quality average. All studies retrospective and observational. No RCT Heterogeneous in terms of types of devices, imaging modality, IVT and stroke type (anterior/posterior). Publication bias. Studies included from 2010 (old studies).
580	Y. Zhongxing et al (2021).	Metaanalysis.	EVT.	Functional independence,successful	Compable outcomes of delayed EVT cf early EVT.	+

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Efficacy and Safety of Endovascular Treatment for Acute Large-Vessel Ischemic Stroke Beyond 6 h After Symptom Onset: A Meta-Analysis. Frontiers in Neurology. 12. 654816	PubMed, Embase , Chinese Biomedical through 2019. To assess safety and efficacy of EVT with AIS > 6hours.		recanalization,mortality and SICH were assessed.		
702	J. M. Sequeiros et al. (2022). Stroke imaging modality for endovascular therapy in the extended window: Systematic review and meta-analysis. *Journal of NeuroInterventional Surgery* : neurintsurg-2022-018896	Systematic review and meta-analysis comparing advanced imaging and NCCT /CTA in patients with IS treated with MT in extended time window (anterior circulation). Combination of RCT and cohort studies.	MT in patients with advanced imaging vs NCCT/CTA in extended time windows (6-24 hours).	mRS 90 days ≤ 2 mortality 90 days sICH	4317 patients 3176 (Advanced imaging) 1141 (NCTT/CTA) 4 RCT in total / 32 studies Functional independence ADVI: 44% NCTT/CTA: 48% NS 13% mortality (ADVI) 16% NCTT/CTA NS 4% ADVI 6% NCTT NS.	Major limitation is that no study directly compared advanced imaging vs NCCT/CTA so results inferred from indirect comparisons. May support use of NCTT/CTA in centres where uptake of CTP is low but in the UK, CTP availability is increasing. This reference may be used a source for the recommendation that CTA/NCTT with favourable ASPECTS may be useful in extended time window (particularly 6-12 hours).

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
702	J. M. Sequeiros et al. (2022). Stroke imaging modality for endovascular therapy in the extended window: Systematic review and meta-analysis. *Journal of NeuroInterventional Surgery* : neurintsurg-2022-018896	Systematic review and meta-analysis comparing advanced imaging and NCCT /CTA in patients with IS treated with MT in extended time window (anterior circulation). Combination of RCT and cohort studies. However only 49 patients of 1141 CT/CTA selected were from a RCT(4%). Non RCT data very heterogenous. For AVI 15% were from RCT. Reliability of CT/CTA data.	MT in patients with advanced imaging vs NCCT/CTA in extended time windows (6-24 hours).	mRS 90 days ≤ 2 mortality 90 days sICH Did not analyse 6-12 separate form 12-24h, which is the standard approach. So no idea on utility of CT/CTA in 12-24h.	As above.	Borderline. 88% of data from non RCTs. Suspect more bias in non randomised data than suggested in paper, which downplays it – but 57% assessed at moderate risk of bias & 7% high risk! So ~2/3 of NON RCT data from studies at high-moderate risk of bias.
948	Huo, X. et al. (2023). Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct. *New England Journal of Medicine.*	Multi-centre open label randomised controlled trial across USA, Europe, Australia, Canada and New Zealand. Patients with ischaemic stroke enrolled within 24 hours of onset, pre-stroke Rankin 0-1, LVO (ICA or proximal M1 occlusion), ASPECT score between 3-5 on plain CT imaging or core volume infarct > 50 mls (CT or MR perfusion: > 97% underwent CTP). 18-85 year olds. Enrolled between 2019 -2022.	Mechanical thrombectomy (MT) versus best medical therapy. Note IVT was delivered if patients could be treated < 4.5 hours	Primary outcome: ordinal score of mRS. Secondary outcome: mRS 0-2. Safety: sICH at 24 hours and death at 90 days	178 patients assigned to MT and 174 to BMT. Trial stopped early due to efficacy. Age: 66.5, median ASPECTS 4 and NIHSS 19. Median mRS (MT: 4) vs (BMT:5) with an odds of favourable outcome 1.51 [1.2 to 1.98]. Secondary outcome 20.3% vs 7 % favouring MT. sICH (0.6%) and no significant differences in death at 90 days but higher vascular complications in MT group. Results of benefit were similar across pre-specified subgroups (ie ASPECTS 3-5 and	++ RCT, multi-centre, stopped early so possibility of overestimation of treatment effects. It is not clear of the effects of MT comparing 6-12 hours versus 12-24 hours.

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					CTP mismatch volumes > 15 mls).	
948	Huo, X. et al. (2023). Trial of Endovascular Therapy for Acute Ischemic Stroke with Large Infarct *New England Journal of Medicine*.	RCT.	Mechanical thrombectomy (MT) versus best medical therapy.	As above.	As above.	++ Patients with a pre-stroke mRS <2 & prox M1/ICA LVO should be considered for MT selection within 24 hours onset if they have an ASPECTS score of 3 or better. Between 6-24h CTP/MRI should confirm penumbral volume >15mls.
948	Sarraj, A., et al. (2023). Trial of Endovascular Thrombectomy for Large Ischemic Strokes *New England Journal of Medicine*.	Multi-centre open label randomised controlled trial across China. Patients with ischaemic stroke enrolled within 24 hours of onset, pre-stroke Rankin 0-1, LVO (ICA or proximal M1 occlusion), ASPECT score between < 24 hrs, 3-5 on plain CT imaging with unlimited core volume, ASPECTS 0-2 < 24 hrs, with core volumes 70-100 and ASPECTS > 5 6-24 hours with core volumes 70-100 mls. (CT or MR perfusion: majority CTP). 18-80 year olds. Enrolled between 2020 -2022.	Mechanical thrombectomy (MT) versus best medical therapy. Note IVT was delivered if patients could be treated < 4.5 hours	Primary outcome: ordinal score of mRS. Secondary outcome: mRS 0-2. Safety: sICH at 48 hours and death at 90 days	One third screened enrolled. 456 enrolled. 231 patients assigned to MT and 225 to BMT. Trial stopped early due to efficacy. 24% enrolled > 12 hours. Age: 68, median ASPECTS 3 and NIHSS 16. Median mRS (MT: 4) vs (BMT:4) with an odds of favourable outcome 1.37 [1.11 to 1.69]. Secondary outcome 30% vs 11.6 % favouring MT. sICH (6.1% vs 2.7%) and no significant differences in death at 90 days. Results of benefit were similar across pre-specified subgroups (ie ASPECTS 3-5 and CTP volumes > 70 mls).	+ RCT, multi-centre, stopped early so possibility of overestimation of treatment effects. Low IVT (28%), Chinese population (generalisability) and excluded 80 years. It is not clear of the effects of MT comparing 6-12 hours versus 12-24 hours.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
948	Sarraj, A., et al. (2023). Trial of Endovascular Thrombectomy for Large Ischemic Strokes *New England Journal of Medicine*.	RCT.	As above.	As above.	As above.	+ Patients with a pre-stroke mRS <2 should be considered for MT selection within 24 hours onset if they have an ASPECTS score of 3.