


European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke

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Abstract

Mechanical thrombectomy (MT) has become the cornerstone of acute ischaemic stroke management in patients with large vessel occlusion (LVO). The aim of this Guideline document is to assist physicians in their clinical decisions with regard to MT. These Guidelines were developed based on the European Stroke Organisation (ESO) standard operating procedure and followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. An interdisciplinary working group 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. We found high-quality evidence to recommend MT plus best medical management (BMM, including intravenous thrombolysis whenever indicated) to improve functional outcome in patients with LVO-related acute ischaemic stroke within 6 hours after symptom onset. We found moderate quality of evidence to recommend MT plus BMM in the 6–24 hour time window in patients meeting the eligibility criteria of published randomised trials. These Guidelines further detail aspects of pre-hospital management, patient selection based on clinical and imaging characteristics, and treatment modalities. MT is the standard of care in patients with LVO-related acute stroke. Appropriate patient selection and timely reperfusion are crucial. Further randomised trials are needed to inform clinical decision-making with regard to the mothership and drip-and-ship approaches, anaesthesia modalities during MT, and to determine whether MT is beneficial in patients with low stroke severity or large infarct volume.

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Introduction

Mechanical thrombectomy (MT) in addition to best medical management (BMM) has become the standard of care for acute ischaemic stroke patients with large vessel occlusion (LVO) since the publication in 2015 of five pivotal trials using modern endovascular devices.^{1–5} Those trials demonstrated major benefits for patients randomised to MT plus BMM versus BMM alone, with numbers needed to treat of 3 and 5 to achieve any better functional outcome and functional independence, respectively.⁶ Major scientific advances have been made since the publication of the 2014/2015 Consensus statement by the ESO-Karolinska Stroke Update and the 2016 European Recommendations on Organisation of Interventional Care in Acute Stroke (EROICAS),^{7,8} notably regarding treatment of patients in late time windows.^{9,10} The European Stroke Organisation (ESO) and the European Society for Minimally Invasive Neurological Therapy (ESMINT) decided to update those recommendations and provide Guidelines based on a systematic literature review and on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. The aim of this Guideline document is to assist physicians treating patients with acute ischaemic stroke in their clinical decisions with regard to MT.

Methods

These joint ESO–ESMINT Guidelines were initiated by the ESO. A module working group (MWG) was formed, composed of five ESO representatives (GT: co-chair, UF, MM, PDS, DT), five ESMINT representatives (JF: co-chair, PB, JdV, KL, PW) and one U.S. expert (PK). The MWG consisted of six neuro-interventionalists (5 radiologists and 1 neurologist) and five vascular neurologists. Based on the review of the intellectual and financial disclosures of all MWG members (Supplemental Table 1), the composition of the group was approved by the ESO Guidelines board, the ESMINT Guidelines committee, and the Executive Committees of ESO and ESMINT.

These guidelines were prepared following the GRADE methodology and the ESO standard operating procedure.^{11,12}

The steps undertaken by the working group are summarised below:

1. A list of topics of clinical interest for Guidelines' users was produced and agreed by all MWG members.
2. A list of relevant outcomes was produced and rated according to GRADE definitions as critical, important or of limited importance.^{11,12} Functional outcome and survival were the only outcomes rated as of critical importance. As a consequence, three-month modified Rankin Scale (mRS), which encompasses functional outcome and vital status, was considered to be the most important parameter to be extracted from studies of interest. Functional independence was defined as mRS 0–2, while any better functional outcome corresponded to ordinal shift analysis of the mRS. Time to reperfusion, symptomatic intracerebral haemorrhage (sICH) and final infarct volume were considered to be important outcomes.
3. The MWG formulated 15 Population, Intervention, Comparator, Outcome (PICO) questions, which were reviewed and subsequently approved by the ESO Guidelines board, the ESMINT Guidelines committee, and the Executive Committees of ESO and ESMINT.
4. For each PICO question, a systematic review of three major bibliographic databases (PubMed, EMBASE and the Cochrane Library) was conducted with the help of the ESO Guidelines methodologist, Avtar Lal (AL). AL, GT and JF agreed on the search terms for each PICO question (Supplementary Appendix). The literature search was conducted from the inception of each database to February 2018 and subsequently updated with the results of the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE-3) trials.
5. Two authors (GT and JF) independently screened the titles and abstracts of the publications identified by the electronic search and assessed the full text of potentially relevant studies. Only those studies in which modern thrombectomy devices were

- predominantly used (stent retrievers or contact aspiration devices) were considered to be eligible.
6. For each PICO question, a PICO group consisting of three MWG members was formed. The members of each PICO group confirmed that, to the best of their knowledge, no randomised trial or systematic review had been omitted in the systematic literature search. Whenever no randomised trial or systematic review was identified, the PICO group confirmed that no key observational study was omitted in the literature search.
 7. The risk of selection, performance, detection, attrition and reporting biases in each randomised trial was assessed using the Cochrane Collaboration's tool.¹³
 8. Random-effects meta-analyses of the impact of therapeutic interventions on functional independence, defined as three-month mRS score ≤ 2 , were conducted using Stata software version 11.0 (Statacorp). Results were summarised as odds ratios (ORs), risk ratios (RRs) and their 95% confidence intervals (CIs). Heterogeneity across studies was assessed using Cochran's Q (reported as a p value) and the I^2 statistics. Heterogeneity was classified as moderate ($I^2 \geq 30\%$), substantial ($I^2 \geq 50\%$), or considerable ($I^2 \geq 75\%$).¹⁴ Publication bias was assessed with the help of funnel plots.
 9. The results of data analysis were imported into the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.). For each PICO question and each outcome, the quality of evidence (QoE) was rated as high, moderate, low or very low based on the type of available evidence (randomised or observational studies) and considerations on inconsistency of results, indirectness of evidence, imprecision of results, and risk of bias.¹² GRADE evidence profiles/summary of findings tables were generated using GRADEPro.
 10. Each PICO group addressed their respective PICO question by writing up to three distinct paragraphs. Firstly, a paragraph named "Analysis of current evidence and evidence-based recommendation", in which the results of the dedicated randomised trials were summarised and briefly discussed. Whenever no randomised trial was available, this paragraph described the results of systematic reviews of non-randomised trials. At the end of the first paragraph, an evidence-based recommendation was provided, based on the GRADE methodology. The direction, the strength and the formulation of the recommendation were determined according to the GRADE evidence profiles and the ESO standard operating procedure. Secondly, an "Additional information" paragraph could be added to provide more details

on randomised trials mentioned in the first paragraph, to summarise results of observational studies, or to provide information on ongoing or future trials. Thirdly, according to the first addendum to the ESO standard operating procedure, an 'Expert opinion' paragraph was added whenever the PICO group considered that not enough evidence was available to provide evidence-based recommendations for situations in which practical guidance is needed for the everyday clinical practice. In that particular case, a pragmatic suggestion was provided, with the results of the votes of all 11 MWG members on this proposal. Importantly, the suggestions provided in this paragraph should not be mistaken as evidence-based recommendations. They only reflect the opinion of the MWG.

11. The Guidelines document was subsequently reviewed several times by all MWG and modified until a consensus was reached according to the Delphi method.
12. Finally, the Guideline document was reviewed and approved by six external reviewers, the ESO Guidelines board, the ESMINT Guidelines committee, and the ESO and ESMINT Executive committees.

PICO 1: For adults with LVO-related acute ischaemic stroke within 6 hours of symptom onset, does MT plus BMM compared with BMM alone improve functional outcome?

Analysis of current evidence and evidence-based recommendation

A total of nine randomised controlled trials (RCTs) of MT were included into the analysis: Multicenter Randomized CLinical trial of Endovascular treatment of Acute ischemic stroke in the Netherlands (MR CLEAN),¹ Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND-IA),² Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE),³ Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME),⁴ Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT),⁵ Mechanical Thrombectomy after Intravenous Alteplase versus Alteplase alone after Stroke (THRACE),¹⁵ The

Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY),¹⁶ Pragmatic Ischaemic Thrombectomy Evaluation (PISTE),¹⁷ and Endovascular Acute Stroke Intervention (EASI).¹⁸ All these trials recruited patients with acute stroke and proven LVO (internal carotid artery (ICA), M1, M2) with or without tandem stenosis/occlusion within a 6-h time window from stroke onset, and two of these up to 8⁵ and 12 h,³ respectively. Patients were randomised to MT plus BMM versus BMM alone including, whenever indicated, intravenous thrombolysis (IVT) in both arms. We intentionally excluded three previous trials which

used older thrombectomy devices.¹⁹⁻²¹ In all trials, there was no blinding of patient or staff for treatment arm. However, the primary endpoint (mRS at 90 days) was assessed in a blinded fashion in all trials except THRACE and EASI (Figure 1). Other risk of bias for the EASI trial included the enrolment of patients without proven occlusion, the fact that 10/40 patients randomised to MT did not get MT, and that 8% of patients from BMM crossed over to MT. A total of 1906 patients (951 MT+BMM vs. 955 BMM alone) were entered into the meta-analysis, which showed a statistically significant difference in rates of functional independence (mRS score ≤ 2) at day 90 in favour of

	Random sequence generation (selection b.)	Allocation concealment (selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (detection)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
MR CLEAN (2015)	+	+	-	+	+	+	+
EXTEND IA (2015)	+	+	-	+	+	+	+
ESCAPE (2015)	+	+	-	+	+	+	+
SWIFT PRIME (2015)	+	+	-	+	+	+	+
REVASCAT (2015)	+	+	-	+	+	+	+
THRACE (2016)	+	+	-	-	+	+	+
THERAPY (2016)	+	+	-	+	+	+	+
PISTE (2016)	+	+	-	+	+	+	+
EASI (2017)	+	+	-	-	+	+	-

Figure 1. Risk of bias in each trial.

MT + BMM (453/951; 47.6%) versus BMM alone (295/955; 30.9%): OR 2.03 (95% CI 1.68–2.46, $p < 0.0001$; $I^2 = 0\%$; Figure 2); RR 1.50 (95% CI 1.34–1.68, $p < 0.0001$; $I^2 = 0\%$; Figure 3).

The absolute effect was 154 additional independent patients for 1000 patients treated (95% CI 105–210). There was no sign of statistical heterogeneity across trials. The overall QoE was rated as high, with no

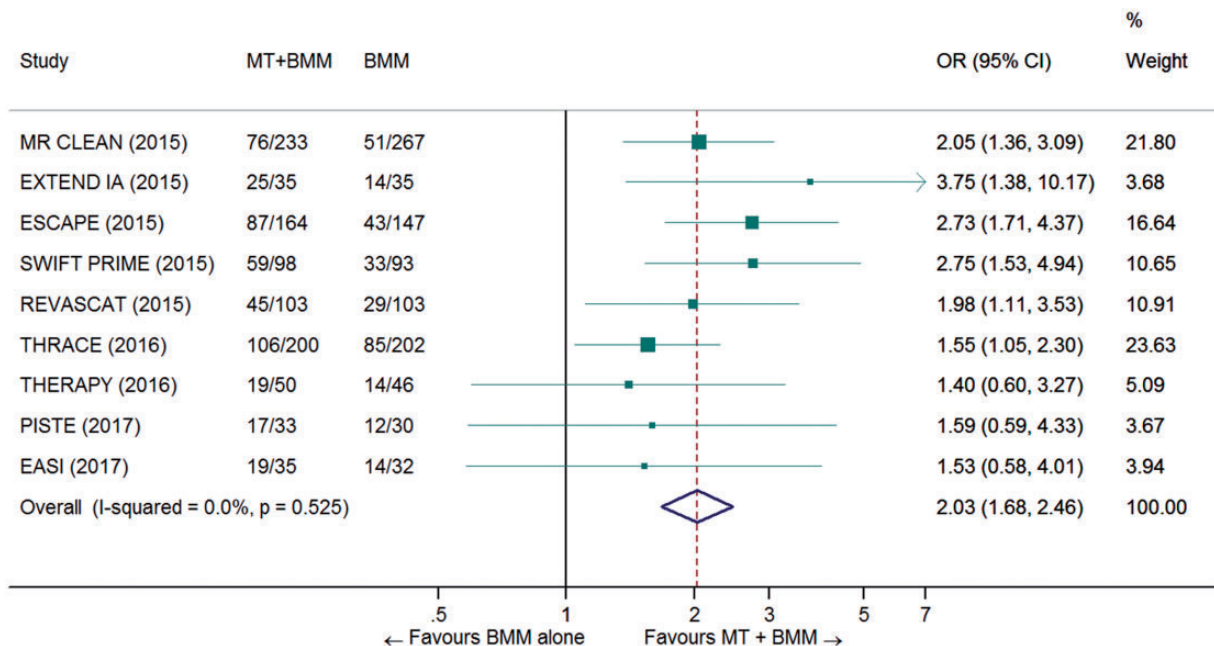


Figure 2. Pooled odds ratio for functional independence in patients treated with MT + BMM vs. BMM alone in the 0–6 h time window. Random-effects meta-analysis.

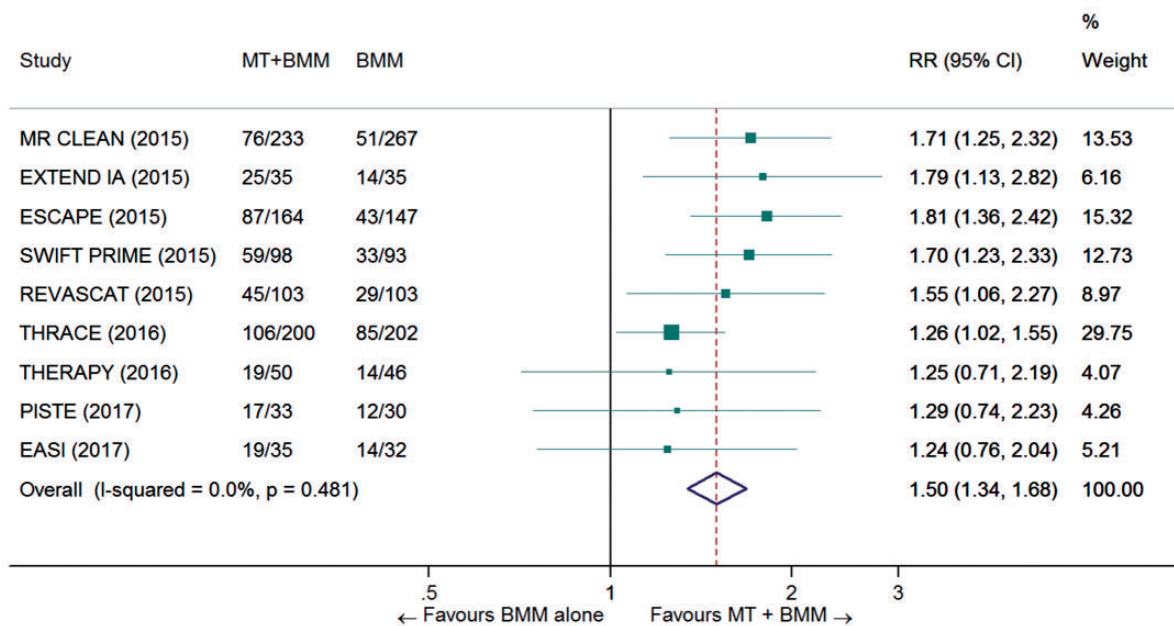


Figure 3. Pooled risk ratio for functional independence in patients treated with MT + BMM vs. BMM alone in the 0–6 h time window. Random-effects meta-analysis.

serious risk of bias, inconsistency, indirectness, or imprecision (Table 1).

Recommendation

In adults with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting within 6 h after symptom onset, we recommend mechanical thrombectomy plus best medical management – including intravenous thrombolysis whenever indicated – over best medical management alone to improve functional outcome.

Quality of evidence: **High** ⊕⊕⊕⊕

Strength of recommendation: **Strong** ↑↑

Additional information

From EASI, only the anterior circulation strokes were included in the analysis. For THRACE, the four patients with BA occlusion could not be extracted from the meta-analysis. For PISTE the denominator was changed from 32 to 30 patients in the BMM only group because of missing mRS scores at day 90.

The primary results of the randomised Basilar Artery Occlusion Chinese Endovascular Trial (BEST, NCT02737189) have been presented at the World Stroke Congress 2018, suggesting that patients treated with MT plus BMM achieved significantly better outcomes than patients treated with BMM alone. However, these results have not been published at the moment.

The present analysis does not differentiate patients pretreated with IVT (85% according to the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration individual patient data meta-analysis of the first 5 trials⁶) versus primary MT (8.4% of the whole population in the HERMES collaboration), and trials with additional imaging selection criteria and narrower versus broader imaging inclusion criteria. Those issues will be further addressed with PICO questions 3, 8 and 9.

It is worth mentioning that many of the included RCTs closed to recruitment early and in some instances before a pre-specified sample size was reached. Such premature trial termination will on average lead to overestimation of the treatment effect.²² Nonetheless, since RCTs showed consistent benefit of MT over BMM alone, and a dose-effect relation (reperfusion rates vs. clinical outcome), the benefit of MT is considered established.

Expert opinion

A major point of debate is the effect of MT in patients with M2 occlusions. Some trials did (MR CLEAN,¹ EXTEND-IA,² PISTE,¹⁷ EASI,¹⁸ THERAPY¹⁶),

Table 1. Summary of findings for PICO 1.

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Quality of evidence	Importance
							MT + BMM	BMM alone	Relative (95% CI)	Absolute (95% CI)		
3-month mRS 0–2												
9	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	453/951 (47.6%)	295/955 (30.9%)	RR 1.50 (1.34–1.68) OR 2.03 (1.68–2.46)	154 more per 1000 (from 105 more to 210 more)	⊕⊕⊕⊕ High	Critical

CI: confidence interval; RR: risk ratio.

while others did not (ESCAPE,³ SWIFT PRIME,⁴ REVASCAT,⁵ THRACE¹⁵) allow recruitment of these patients (Table 2). In the HERMES collaboration subgroup analysis, the number of patients with an M2 occlusion was 67/818 (8%) in the MT + BMM and 64/828 (8%) in the BMM arms, respectively.⁶ The common adjusted OR for better functional outcome was 1.68 (95% CI 0.90–3.14) in this subgroup. This result did not reach statistical significance, but there was no evidence for heterogeneity of treatment effect across occlusion sites ($p_{\text{interaction}} = 0.32$).²³ Of note, MT was significantly associated with functional independence in the subgroup of patients with M2 occlusion (adjusted OR = 2.35, 95% CI: 1.07–5.14). No patient with M2 occlusion experienced sICH after MT. Despite these results, we believe that data is insufficient to give a specific evidence-based recommendation for or against MT + BMM in patients with M2 occlusions, especially as some patients probably were misclassified as M1 occlusions and then adjudicated as proximal M2 occlusions.²⁴

Expert opinion on mechanical thrombectomy for M2 occlusion

There is a consensus among the Guideline group (11/11 votes) that patients with M2 occlusion fulfilled the inclusion criteria in most randomised trials and therefore mechanical thrombectomy is reasonable in this situation.

For basilar artery stroke there are currently no published randomised trial results. An international prospective registry of patients with basilar artery occlusion did not suggest the superiority of intra-arterial therapy over IVT.²⁵ However, this study was observational and the intra-arterial therapy group did

not only correspond to patients treated with MT, but also to patients treated with intra-arterial thrombolysis or stenting. Furthermore, older generation MT devices were used in most instances.

We recommend enrolment of patients with basilar artery occlusion into RCTs whenever and wherever possible (Basilar Artery International Cooperation Study trial (BASICS): NCT01717755).²⁶ If inclusion in a dedicated RCT is not possible, the decision for or against MT + BMM versus BMM alone should be based on institutional guidelines, standard operating procedures and individual patient characteristics.

Expert opinion on mechanical thrombectomy for basilar artery occlusion

There is a consensus among the panel (11/11 votes) that in analogy to anterior circulation large vessel occlusion and with regard to the grim natural course of basilar artery occlusions, the therapeutic approach with intravenous thrombolysis plus mechanical thrombectomy should strongly be considered.

Finally, in addition to active trials, future registry data may shed more light on the effect of MT on top of BMM including IVT.

PICO 2: For adults with LVO-related acute ischaemic stroke 6 to 24 h from time last known well, does MT plus BMM compared with BMM alone improve functional outcome?

Analysis of current evidence and evidence-based recommendation

Two RCTs of endovascular therapy recruited highly selected patients from 6 up to 16 (DEFUSE-3¹⁰: $n = 182$) or 24 h (DAWN⁹: $n = 206$) after symptom onset or last known well. The inclusion of patients with stroke upon awakening, if otherwise fitting the inclusion criteria, was encouraged. A small number of patients were recruited beyond 6 h in REVASCAT (up to 8 h, $n = 21$)⁵ and ESCAPE (up to 12 h, $n = 49$).³ Inclusion criteria varied between the trials (Table 3). DAWN used a stratification by age and National Institutes of Health Stroke Scale (NIHSS) score leading to differing maximum infarct core cut-off volumes measured by imaging software in an automated fashion (>80 years, infarct core up to 20 mL; <80 years and NIHSS 10–19, infarct core up to 30 mL; <80 years and NIHSS 20 or more, infarct core up to 51 mL). DEFUSE-3 allowed a larger core volume (up to

Table 2. Number of patients with M2 occlusion in each randomised trial.

Trial	M2 occlusions MT arm	M2 occlusions BMM arm
MR CLEAN	18/233 (7.7%)	21/266 (7.9%)
EXTEND-IA	6/35 (17%)	4/35 (11%)
ESCAPE ^a	6/163 (3.7)	3/147 (2.0%)
SWIFT PRIME ^a	6/94 (6%)	13/93 (14%)
REVASCAT ^a	10/102 (9.8%)	8/101 (7.9%)
THRACE ^a	2/208 (1%)	0/204 (0%)
PISTE	5/32 (16%)	3/33 (10%)
THERAPY	6/55 (11%)	5/53 (9.4%)
EASI	12/40 (30%)	6/37 (16%)
Total	71/962 (7.4%)	63/969 (6.5%)

^aM2 inclusion not allowed.

70 mL) but required a perfusion mismatch measured by perfusion CT or MRI of more than 1.8 (ratio) and a penumbra volume ≥ 15 mL (Table 3), again measured by imaging software in an automated fashion. The median infarct core volume was 8 (75th percentile: 20 mL) and 10 mL (75th percentile: 25 mL) in DAWN and DEFUSE-3, respectively. A large majority of patients enrolled in DAWN or DEFUSE-3 had an unknown time of stroke onset (stroke on awakening or unwitnessed stroke): 88% in DAWN and 64% in DEFUSE-3. It is possible that many of those patients had an actual stroke-onset-to-treatment time within the 6-h time window. The total numbers of IVT patients and M2 occlusions were negligible.

There was no blinding of patient or staff for treatment arm in DAWN and DEFUSE-3. However, the primary endpoint (mRS at 90 days) was assessed in a blinded fashion. Each trial was considered to be at low risk of bias (Figure 4).

An individual patient data meta-analysis of DAWN, DEFUSE-3 and patients recruited beyond 6 h in ESCAPE and REVASCAT (AURORA Collaboration) was presented at the 2018 ESO Conference. A total of 459 patients were included in this meta-analysis. Compared with BMM alone, MT + BMM was strongly associated with better functional outcome (adjusted common OR 2.77, 95%CI: 1.95–3.94, $p < 0.001$) and functional independence at three months (mRS ≤ 2): 46.7% vs. 16.7%, adjusted OR 4.65 (95% CI: 2.02–10.72, $p < 0.001$). It should be borne in mind that the vast majority (84.5%) of patients included in the analysis of the AURORA collaboration were included in DAWN and DEFUSE-3. Therefore, the evidence-based recommendations presented for the 6–24 h time window are only based on the results of these two trials.

Despite a low risk of bias in each trial (Figure 4), the overall QoE to provide recommendations for the 6–24 h time window was rated as moderate (see Table 4 for details).

Recommendation

In adults with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting between 6 and 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3* or DAWN**, we recommend mechanical thrombectomy plus best medical management over best medical management alone to improve functional outcome.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: **Strong** ↑↑

(see below and Table 3 regarding patient selection)

*6–16 h since time last known well:

- Age ≤ 90 years and NIHSS ≥ 6 : infarct core volume < 70 mL and penumbra volume > 15 mL and penumbra volume/core volume > 1.8 .

**6–24 h since time last known well:

- Age < 80 years: infarct core ≤ 30 mL if NIHSS ≥ 10 ; infarct core ≤ 51 mL if NIHSS ≥ 20 .

- Age ≥ 80 years: infarct core ≤ 20 mL and NIHSS ≥ 10 .

See Table 3 for further details.

Additional information

The DAWN and DEFUSE-3 trials selected patients in the late time window of up to 24 h after unwitnessed (last known well) or witnessed stroke onset. Both trials have a very narrow set of inclusion criteria (Table 3), including volumetric quantification of the infarct core

Table 3. Main inclusion criteria in the DEFUSE-3 and DAWN trials.

	DEFUSE-3 ¹⁰	DAWN ⁹
Time window	6–16 h since time last known well	6–24 h since time last known well
Age	18–90 years	≥ 18 years
mRS before qualifying stroke	≤ 2 ; life expectancy ≥ 6 months	≤ 1 ; life expectancy ≥ 6 months
NIHSS score	≥ 6	≥ 10 (see below)
Arterial occlusion	ICA and/or MI ^a	ICA and/or MI
Mismatch definition	Target mismatch profile on CT or MR perfusion imaging, as determined by an automated image post-processing system: Infarct core volume < 70 mL ^b and mismatch volume > 15 mL ($T_{\max} > 6$ s ^c) and mismatch ratio (penumbra/core) > 1.8	Clinical-imaging mismatch Age < 80 y.o. and NIHSS ≥ 10 and infarct core 0–30 mL or age < 80 y.o. and NIHSS ≥ 20 and infarct core 31–51 mL or age ≥ 80 y.o. and NIHSS ≥ 10 and infarct core 0–20 mL

^aCarotid occlusions could be cervical or intracranial, with or without tandem middle cerebral artery (MCA) lesions in DEFUSE-3.

^bBased on CT-perfusion or MRI diffusion.

^cThe size of the penumbra was estimated from the volume of tissue for which there was delayed arrival of an injected tracer agent (time to maximum of the residue function (T_{\max}) exceeding 6 s.³¹

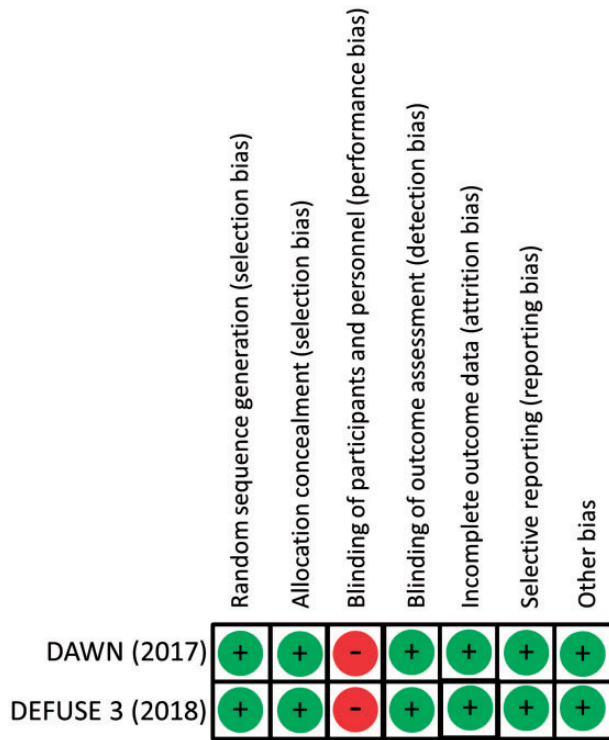


Figure 4. Risk of bias in each trial.

and penumbra using a specific imaging analysis software. In addition, the 2018 ASA/AHA guidelines do give a stepwise recommendation: I-A for selected patients within 6–16 h fulfilling DEFUSE-3 or DAWN eligibility criteria and IIa-BR within 16–24 h for patients fulfilling DAWN criteria.²⁷

Recently, the WAKE-UP trial of intravenous alteplase alone versus placebo in patients with unknown time of onset and for whom MT was not planned has been reported. Patients were selected based on mismatch between diffusion-weighted imaging and FLAIR on MRI, and showed a considerable therapy effect (adjusted OR for mRS ≤ 1 : 1.61, 95% CI: 1.09–2.36, $p=0.02$; adjusted common OR for better functional outcome: 1.62, 95% CI: 1.17–2.23, $p=0.003$).²⁸ A subgroup analysis for differential efficacy in different occlusion sites, among those enrolled, is under way and might further inform decision making.

According to a recent publication, about 2.7% of acute ischaemic stroke patients presenting to a comprehensive stroke centre (CSC) within 24 h after stroke onset meet the DEFUSE-3 and/or DAWN criteria.²⁹ According to the same study, about 9% of all acute ischaemic stroke patients presenting in the 6- to 24-h time window meet the DEFUSE-3 and/or DAWN inclusion criteria.

In ESCAPE ($n=49$) and REVASCAT ($n=21$) patients were recruited beyond 6 h. These patients

Table 4. Summary of findings table for PICO 2.

Certainty assessment		No. of patients		Effect					
No. of studies	Risk of bias	Other considerations	MT + BMM	BMM alone	Relative (95% CI)	Absolute (95% CI)	Quality of evidence	Importance	
mRS 0–2									
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	Strong association	RR 3.12 (2.15–4.53) OR 5.01 (3.07–8.17)	314 more per 1000 (from 170 more to 523 more)	⊕⊕⊕ Moderate ⊕⊕⊕⊕ Critical

CI: confidence interval; RR: risk ratio.

The RR and OR presented in the table correspond to an aggregate data meta-analysis of DAWN and DEFUSE-3.

Explanation

The overall QoE to provide recommendations for the 6–24 h time window was rated as moderate for the following reasons:

- Starting with a high QoE due to the randomised trial design, the QoE was downgraded by one step due to indirectness because the DEFUSE-3 trial did not enrol patients beyond 16 h.
- The QoE was rated up by one step due to a strong association (pooled RR larger than 2.0).
- Although there was no evidence of heterogeneity in our meta-analysis, we still considered the risk of inconsistency due to other bias to be serious because of the varying inclusion and exclusion criteria across trials.

represent an unaccounted 17.8% of patients relevant for PICO question 2. ESCAPE used imaging inclusion criteria of ASPECTS score ≥ 6 plus good/intermediate collaterals on CTA collateral scoring (assessed on multiphase CTA) up to 12 h. In the REVASCAT trial, patients with CTA/MRA obtained within 4.5–8 h after stroke onset had to have a good ASPECTS (≥ 7) and eligibility confirmed by advanced brain imaging (CT-perfusion (CTP), diffusion weighted imaging (DWI) or CTA-source images analysis). Data from the HERMES collaboration suggest a therapy effect of MT up to 7 h 18 min.³⁰

Expert opinion. The stratified core volume approach as well as the necessity of perfusion imaging compatible hardware and software restrict the application of DAWN/DEFUSE-3 criteria for patient selection, making generalisability and implementation of late time window MT according to the published evidence difficult at best.²⁹

Because the DAWN and DEFUSE-3 inclusion criteria only correspond to a low proportion of patients seen within the 6–24 h time window, the Guidelines group suggest the two following expert-opinion based recommendations:

Expert opinion on mechanical thrombectomy in late time windows

Patients should be treated with mechanical thrombectomy plus best medical management up to approximately 7 h 18 min after stroke onset, without the need of perfusion imaging-based selection.³⁰

10/11 experts agree that patients can be treated in the 6–12 h time window if they fulfil the ESCAPE criteria, notably ASPECTS ≥ 6 and moderate-to-good collateral circulation. However, such patients should preferably be treated in the context of clinical studies. Also, concurrent software applications utilising similar perfusion algorithms and rendering equivalent volumetric results as those used in the DAWN and DEFUSE-3 trials may be options, as well as simple volumetry on a high-quality DWI scan for core volume when applying DAWN criteria. Therefore we advocate further research, inclusion of patients into late window trials, and implementation of institutional imaging standard operating procedures.

If patients are treated without strict DAWN/DEFUSE-3 criteria, centres are encouraged to collect their data and compare their outcomes with those treated with the more stringent DAWN/DEFUSE imaging criteria.

PICO 3: For adults with LVO-related acute ischaemic stroke, does IVT plus MT compared with MT alone improve functional outcome?

Analysis of current evidence and evidence-based recommendation

MT + IVT vs. MT alone. The literature search did not identify any RCT directly addressing this PICO question.

In the pivotal RCTs demonstrating the benefit of endovascular therapy, the experimental treatment arm comprised not only MT but also BMM, including IVT with alteplase in 83% of patients.⁶ Therefore, the current standard of care for adults with LVO-related acute ischaemic stroke is MT plus IVT (bridging therapy), if the patient has no contraindications for IVT. The HERMES collaboration individual patient data meta-analysis of the first five RCTs (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT) reported a common OR for a better functional outcome of 2.45 (95% CI: 1.68–3.57) in patients receiving IVT plus MT vs. 2.43 (95% CI: 1.30–4.55) in those receiving MT alone,⁶ apparently not suggesting a higher benefit of MT in patients treated with vs. without IVT. This result might be explained by a selection bias, as good responders to IVT might have been less likely to be enrolled in REVASCAT, in which the response to IVT had to be evaluated after 30 min,⁵ and in MR CLEAN, in which the median time between IVT and randomisation was 2 h.¹

A systematic review and meta-analysis of 13 studies allowing the non-randomised comparison of MT + IVT vs. MT alone in adults with anterior circulation LVO-related acute ischaemic stroke suggested a superiority of MT + IVT regarding functional independence (mRS ≤ 2 : OR = 1.27, 95% CI: 1.05–1.55; $I^2 = 17\%$).³² However, this analysis is limited by potential selection bias, confounding by indication and indirectness. Therefore, the QoE was downgraded as very low (Table 5). Another meta-analysis did not suggest the superiority of MT + IVT vs. MT alone in the subgroup of patients eligible for IVT (OR for mRS ≤ 2 : 0.93, 95% CI: 0.57–1.49; $I^2 = 41\%$).³³

MT alone in patients not eligible to IVT. The above-mentioned results of the HERMES collaboration individual patient data meta-analysis of the five first RCTs suggest that in the subgroup of patients not receiving IVT ($n = 180$), MT was effective as stand-alone therapy as compared to BMM without IVT (OR for functional independence 2.43, 95% CI: 1.30–4.55).⁶ However, this subgroup analysis suffers from very serious

indirectness, because the five above-mentioned RCTs were not designed to address the question of the effectiveness and safety of MT in patients with a contraindication to IVT. The reasons for non-eligibility to IVT were likely heterogeneous, including not only patients with a contraindication to IVT (e.g. oral anticoagulation) but mostly patients outside of the 4.5 h time window.

Recommendations

- In large vessel occlusion-related ischaemic stroke patients eligible for both treatments, we recommend intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone. Both treatments should be performed as early as possible after hospital arrival. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis and intravenous thrombolysis should not delay mechanical thrombectomy.

Quality of evidence: **Very low** ⊕, Strength of recommendation: **Strong** ↑↑

- In large vessel occlusion-related ischaemic stroke patients not eligible for intravenous thrombolysis, we recommend mechanical thrombectomy as stand-alone treatment.

Quality of evidence: **Low** ⊕⊕, Strength of recommendation: **Strong** ↑↑

Additional information

Ongoing trials comparing MT alone vs. MT + IVT. Several dedicated RCTs comparing MT alone vs. MT + IVT in mothership patients with LVO are currently ongoing (Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke (SWIFT DIRECT): NCT03192332; MR CLEAN No IV: NL58320.078.17; A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval (DIRECT-SAFE): NCT03494920).

IVT with alteplase or tenecteplase before MT. EXTEND-IA TNK is a recently published phase II RCT designed to assess the non-inferiority of IV tenecteplase (0.25 mg/kg) over IV alteplase (0.9 mg/kg) in patients with LVO-related acute ischaemic stroke eligible for IVT and for whom MT was planned.³⁴ CTP mismatch was originally required for patient enrolment in EXTEND-IA TNK, but that criterion was removed after the inclusion of the first 80 patients, leaving 122 patients enrolled based on non-contrast CT plus CTA. The primary outcome – successful reperfusion at the time of the initial angiographic assessment

Table 5. Summary of findings for PICO 3. (IVT+ MT compared with MT alone for LVO-related acute ischaemic stroke)

mRS 0–2	Certainty assessment			Effect		Quality of evidence	Importance				
	No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision			Other considerations	No. of patients	Relative (95% CI)	Absolute (95% CI)
I3	Observational studies	Very serious ^a	Not serious	Serious ^b	Not serious	None	861/1769 (48.7%)	OR 1.27 (1.05–1.55)	60 more per 1000 (from 12 more to 109 more)	⊕○○○ Very low	Critical

CI: confidence interval; OR: odds ratio.

^aSelection bias; confounding by indication.

^bPotential differences in populations.

(TICI score $\geq 2b$) – occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (absolute difference 12%, 95% CI: 2–21; $p=0.002$ for non-inferiority; $p=0.03$ for superiority). Tenecteplase notably resulted in a better 90-day functional outcome than alteplase (common OR 1.7, 95% CI: 1.0–2.8; $p=0.04$), but the trend in favour of a higher rate of functional independence ($mRS \leq 2$) failed to reach statistical significance (adjusted OR = 1.8, 95% CI: 1.0–3.4, $p=0.06$).

The median time from stroke onset to successful reperfusion (modified TICI (mTICI) 2b/3) or completion of the procedure was 203 (175–255) min in the tenecteplase group vs. 232 (185–268) min in the alteplase group ($p=0.07$).

The optimal tenecteplase dose for acute ischaemic stroke is currently uncertain.^{34,35} A clinical trial comparing two different doses of tenecteplase (0.25 vs. 0.4 mg/kg) in patients eligible for IVT and MT is currently ongoing (Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischaemic Stroke (EXTEND-IA TNK Part 2): NCT03340493).

Expert opinion

Several important limitations need to be taken into account regarding the use of tenecteplase vs. alteplase:

- The superiority of tenecteplase over alteplase in patients eligible for MT has only been shown in a single phase II RCT (EXTEND-IA TNK³⁴), in which functional outcome was a pre-specified secondary outcome. The superiority of tenecteplase was shown for better functional outcome (ordinal analysis over the whole range of the mRS), but failed to reach statistical significance for functional independence ($mRS \leq 2$) and excellent outcome ($mRS \leq 1$).
- The non-inferiority of tenecteplase over alteplase has not been established in other situations.^{35–39}
- Neither vascular imaging nor advanced imaging is needed to make a therapeutic decision regarding IVT.²⁷ IVT should be initiated without delay.⁴⁰
- Whether the results of EXTEND-IA TNK may be generalised to all patients with LVO-related acute ischaemic stroke or only to those patients with both LVO and CTP mismatch is uncertain.
- Several randomised trials evaluating tenecteplase for acute ischaemic stroke are ongoing (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST2): NCT02814409; A RCT of TNK-tPA Versus Standard of Care for Minor

Ischemic Stroke With Proven Occlusion (TEMPO-2): NCT02398656; Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST): NCT03181360; Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE): NCT01472926; Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischaemic Stroke (EXTEND-IA TNK Part 2): NCT03340493).

Expert opinion on tenecteplase in patients eligible for mechanical thrombectomy

In large vessel occlusion-related ischaemic stroke patients eligible for intravenous thrombolysis before mechanical thrombectomy, 7/11 experts suggest the use of tenecteplase (0.25 mg/kg) over alteplase (0.9 mg/kg) if the decision on intravenous thrombolysis is made after vessel occlusion status is known.

PICO 4: For adults with suspected acute stroke, does the use of a pre-hospital scale compared with no pre-hospital scale: Improve identification of patients eligible for MT? Reduce time to reperfusion?

Analysis of current evidence and evidence-based recommendation

The literature search did not identify RCTs or observational studies directly comparing the use of a pre-hospital scale vs. no pre-hospital scale to identify patients with LVO. However, two before-and-after studies allowed such a comparison.

In the study by Zaidi et al.,⁴¹ emergency medical services personnel underwent training in the RACE score, a clinical scale designed for pre-hospital identification of patients with LVO.⁴² All patients with a RACE score ≥ 5 (range 0–9) were taken to a facility with interventional capability. The authors used a historical control group to compare patients triaged before or after the implementation of the RACE scale. Patients assessed by the RACE score were more likely to have a discharge diagnosis of acute ischaemic stroke compared to those without RACE assessment (52.3% vs. 31%). There was an increase in the rate of MT (20.1% vs. 7.7%, $p=0.03$) and improvement in the treatment times (median arrival-to-recanalisation times: 101 vs. 205 min, $p=0.001$). No statistically significant difference was found in the rate of functional independence (90-day mRS ≤ 2 : 50% vs. 36.4%, $p=0.3$). A similar study conducted by Mohamad et al.⁴³ following the implementation of

four-item screening showed the median system delay for MT fell from 234 min (IQR: 184–282) to 185 min (IQR: 141–226), corresponding to an adjusted relative delay of 0.79 (95% CI: 0.67–0.93). The reduction in the delay occurred in both the pre-hospital phase (adjusted relative delay 0.86, 95% CI: 0.71–1.04) and in the in-hospital phase (adjusted relative delay 0.76, 95% CI: 0.62–0.94) but did not reach statistical significance in the pre-hospital phase. There was significantly higher chance of functional independence at 90 days among the patients treated with MT in the post-interventional period than among the pre-interventional patients with a total of 62% (40/65) vs. 43% (15/35) achieving functional independence (OR = 3.08, 95% CI: 1.08–8.78).

The results of these studies suggest that the use of a pre-hospital scale may reduce the time to reperfusion. However, both studies had serious limitations, notably the use of a historical cohort as control group, the important risk of residual confounding and the lack of assessment of the impact of misclassification. As such, we believe that the associated level of evidence is too low to provide evidence-based recommendation on the use of such scales.

Recommendation

In patients with suspected stroke, we cannot make a recommendation on the use of a pre-hospital scale for improving identification of patients eligible for mechanical thrombectomy. We suggest enrolling patients in a dedicated randomised controlled trial, whenever possible.

Quality of evidence: **Very low** ⊕, Strength of recommendation: -

Additional information

A consensus statement and practical guidance for pre-hospital management of stroke has been published by the European Academy of Neurology (EAN) and the ESO in 2018.⁴⁴

A RCT comparing the mothership vs. the drip-and-ship approach (see PICO question 5) in patients with suspected LVO based on the RACE score is currently ongoing (Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT): NCT02795962). Another randomised trial using the Pre-hospital Acute Stroke Severity (PASS) score⁴⁵ is also currently ongoing (Treatment Strategy In Acute Ischemic Large Vessel STROKE: Prioritise Thrombolysis or Endovascular Treatment (TRIAGE): NCT03542188).

Numerous clinical scales have been proposed for the identification of patients with LVO-related acute ischaemic stroke.^{42,45–49} However, the vast majority of them have been derived in a population of confirmed acute ischaemic strokes and very few scales have been validated in patients suspected to have a stroke in the pre-hospital field.⁵⁰ Furthermore, there is heterogeneity across studies regarding who conducted the clinical assessment. Most of the studies did not use paramedics as the primary assessor with only the RACE score assessed by trained emergency medical technicians.⁴² A further study assessed the utility of the Cincinnati Stroke Triage Assessment tool, performed by personnel of the Cincinnati fire department, in comparison to FAST with comparable results between the two scoring systems despite no formal training for the assessors.⁵¹ More recently, the Los Angeles Motor Scale (LAMS) has been validated in field by paramedics,⁵² as has the Ambulance clinical triage for acute stroke treatment (ACT-FAST) system.⁵³

In a recent systematic review, Vidale and Agostoni compared the predictive values of 19 pre-hospital scales to identify LVO.⁴⁶ Most of the considered scales was assessed by neurologists, while only four scales were applied by paramedics. The authors observed a substantial and considerable heterogeneity of sensitivity and specificity between studies, which they mainly attributed to methodology and cut-off levels for detecting LVO. They conclude that the scales with the highest predictive power to detect LVO were the Stroke vision, aphasia, neglect assessment (VAN),⁵⁴ LAMS⁵⁵ and the NIHSS.⁵⁶ By contrast, scales with a lower predictive power were the Large Vessel Occlusion Scale (LVOS),⁵⁷ the Cincinnati Prehospital Stroke Scale (CPSS)⁵⁸ and The 3-item Stroke Scale (3I-SS).⁵⁹ However, it is important to keep in mind that these scales were compared across different populations. The authors did not observe a significant difference of the overall accuracy between scoring systems that contained a gaze assessment or not. However, the presence of hemi-neglect did increase precision.

Several of the studies have included patients with basilar artery and/or M2^{42,47,48,59,60} occlusions and although these are amenable to MT, there is very limited or no RCT data as of yet to confirm MT in such situations (see PICO question 1).⁶ The recent publication of the DAWN⁹ and DEFUSE-3¹⁰ trials has resulted in the extension of the time window in which to perform MT. Importantly, the sensitivity of clinical scales to identify LVO markedly decreases with time.⁶¹

Expert opinion

There is no convincing evidence that a particular scoring system is superior to any of the others. Although several clinical scales show a good accuracy to predict LVO, at least 20% of patients with LVO would be missed when applying published cut-offs.^{60,62} Therefore, systems that use LVO prediction instruments for triage will miss milder stroke with LVO, who may benefit from MT, even though there is very limited evidence of the potential benefits of MT in patients with low NIHSS scores (see PICO question 7).^{63–66}

The question of how well the scoring systems work when administered by paramedics has been poorly addressed. Many scales were derived or evaluated in patients with a diagnosis of ischaemic stroke. Their diagnostic performances are likely to be lower in an unselected pre-hospital population of patients with suspected stroke.⁶⁰ Prospective studies are needed to assess the accuracy of LVO prediction instruments in the pre-hospital setting in all patients with suspected stroke, including those with haemorrhagic stroke and stroke mimics.

Expert opinion on using pre-hospital scales to identify patients with large-vessel occlusion

- 11/11 experts concluded that there is currently not enough evidence to use a clinical scale in routine care to help triage of potential thrombectomy candidates in the pre-hospital field.
- All patients suspected of having an acute stroke, irrespective of the time of onset, should undergo emergency imaging of the brain, including vascular imaging.

PICO 5: For adults identified as potential candidates for MT in the pre-hospital field, does the mothership model, compared with the drip-and-ship model, improve functional outcome?

Different organisational models are used for patients with acute ischaemic stroke that are potential candidates for MT. The most widely used are the mothership and the drip-and-ship models.⁶⁷ Briefly, the mothership model transports patients directly to a CSC to minimise time to MT. In the drip-and-ship model patients are transported to the nearest primary stroke centre (PSC) to have rapid diagnostic imaging and administration of IVT followed by transport to the CSC in case additional MT is indicated.⁶⁸

Analysis of current evidence and evidence-based recommendation

The literature search did not identify any completed RCTs comparing the different models.

In one large-scale observational study, including 1000 patients with severe stroke and treated with MT within 8 h, clinical outcomes were better in the mothership model with 60.0% (299/498) achieving functional independence compared with 52.2% (213/408) in the drip-and-ship model (OR = 1.38, 95% CI: 1.06–1.79; $p = 0.02$).⁶⁹ Hypothetical bypass modelling for all transferred patients suggested that IVT would be delayed by 12 min, but MT would be performed 91 min sooner if patients were routed directly to endovascular-capable centres.

In six further observational studies^{70–76} and one RCT of MT,⁴ functional outcomes in the mothership and in the drip-and-ship model were not significantly different.

In five of the above-mentioned studies, onset-to-groin puncture times in the mothership model were significantly shorter than in the drip-and-ship model (range 23–120 min faster; $p < 0.001$ in all studies).^{70–74} One observational study documented a significantly shorter onset-to-revascularisation time in the mothership model (277 vs. 420 min, $p < 0.001$).⁷⁶

In an HERMES collaboration meta-analysis, onset-to-reperfusion times were significantly shorter in the mothership group as compared with the drip-and-ship group (median 251 vs. 345 min, $p < 0.001$).³⁰ Rates of functional independence at three months declined with delay in onset-to-reperfusion time.

Recommendation

We cannot make recommendations on whether for adults identified as potential candidates for mechanical thrombectomy in the pre-hospital field, the mothership or the drip-and-ship model should be applied to improve functional outcome.

Quality of evidence: **Very low** ⊕, Strength of recommendation: -

Additional information

A consensus statement and practical guidance for pre-hospital management of stroke has been published by the EAN and the ESO in 2018.⁴⁴

We identified two other less widely used organisational models: the drip-and-drive (also called: trip-and-treat, or mobile interventional stroke team) and mobile stroke unit (MSU) model. In the drip-and-

drive model, an interventional stroke team travels from the central CSC to the PSC with MT-capacity to perform MT.⁷⁷ In the MSU model, patients are managed in an MSU ambulance, in which the patient can be given IVT, and then can be transported to the CSC in case of LVO diagnosed with on-board CT angiography.^{78,79}

In one study, short-term clinical outcome in the drip-and-drive and drip-and-ship models was compared.⁸⁰ There was a trend in favour of improved admission-to-discharge change in NIHSS score for drip-and-drive compared with drip-and-ship ($p = 0.07$).

Controlled trials assessing the interest of MSUs in the era of MT are ongoing (Berlin PRehospital Or Usual Delivery of Acute Stroke Care (B_PROUD): NCT02869386; BENefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU): NCT02190500; 'Mobile Stroke Unit'-concept for delivery of specialised acute stroke care to patients in remote areas: NCT02465346).⁸¹

Expert opinion

As treatment delays lower the chance of functional independence, time-lag to clinical and imaging assessment and intervention should be minimised.^{30,40,82}

Expert opinion on pre-hospital organisational models:

- As there is lack of strong evidence for superiority of one organisational model, the choice of model should depend on local and regional service organisation and patient characteristics (vote: 11/11 experts agree).
- The mothership model might be favoured in metropolitan areas, with transportation time to a comprehensive stroke centre of less than 30–45 min and the use of the drip-and-ship model when transportation times are longer (vote: 11/11 experts agree).
- As there is limited experience with the other two models (drip-and-drive and mobile stroke unit) no expert opinion can be provided when to use these models (vote: 11/11 experts agree).

RCTs are needed to prospectively compare different models. Two RCTs to address the dilemma whether to use the mothership or the drip-and-ship model are ongoing (RACECAT: NCT02795962 and TRIAGE: NCT03542188).

PICO 6: For patients aged 80 years or more with LVO-related acute ischaemic stroke, does MT plus BMM compared with BMM alone improve functional outcome?

Analysis of current evidence and evidence-based recommendation

0–6-h time window. Patients aged 80 years or older were allowed to be enrolled in seven RCTs of MT plus BMM vs. BMM alone,^{1–3,5,16–18} but with an upper age limit of 85 years in both REVASCAT and THERAPY.^{5,16} In an individual patient meta-analysis of five RCTs (HERMES Collaboration⁶), 198/1278 (15.5%) patients were aged 80 or more. A clear benefit of MT was observed for those patients, with an adjusted common OR for a better functional outcome of 3.68 (95% CI: 1.95–6.92) and a RR for functional independence (mRS ≤ 2) of 2.09 (95% CI: 1.03–4.25). There was no evidence of a lower benefit of MT in patients aged 80 years or older compared with younger patients. On the basis of improved functional outcome, we rated the QoE as high. However, the QoE was downgraded to moderate for the outcome of functional independence, due to imprecision.

Later time windows. One out of four patients enrolled in DAWN (6–24 h from time last known well) and DEFUSE-3 (6–16 h from time last known well) were 80 years or older.^{9,10} In DAWN, there was no evidence of a lower benefit of MT in patients aged 80 years or older ($n = 54$) compared with younger patients. However, the inclusion criteria for patients aged 80 years or older were more stringent (infarct volume of less than 21 mL and no pre-stroke disability (mRS ≤ 1)). In that group, the unadjusted OR for functional independence with MT was 13.2 (95% CI: 1.51–114.8).⁹ In DEFUSE-3, the upper age limit for inclusion was set at 90 years (with no pre-stroke dependence (mRS ≤ 2)). There was no evidence of a lower benefit of MT in patients aged 70 years or older compared with younger patients, but no interaction analysis was reported using 80 years as a threshold. Patients aged 80 or older ($n = 46$) treated with MT had an unadjusted OR of 2.86 (95% CI: 0.72–11.37) for functional independence.¹⁰ We conducted a meta-analysis of DAWN and DEFUSE-3, in which MT was significantly associated with functional independence in patients aged 80 or older (OR = 4.87; 95% CI: 1.15–20.71; $I^2 = 29\%$; Figure 5), but this association failed to reach statistical significance when RR was used as

summary measure instead of OR (Figure 6; Table 6). The QoE was downgraded to low due to very serious imprecision, for the following reasons: (a) clinical recommendation (MT or no MT) would differ if the upper versus the lower boundary of the 95% CI of the RR

represents the truth; (b) the absolute number of patients over 80 years in DAWN and DEFUSE-3 was small ($n=100$) and the number of qualifying events (moved from dependence to independence) was much lower still.

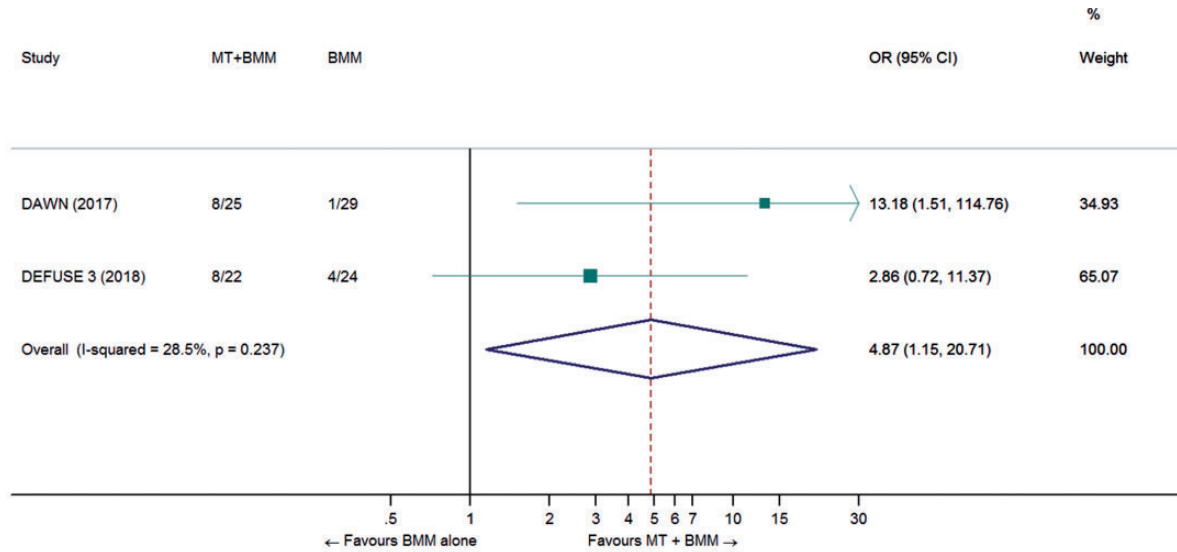


Figure 5. Pooled odds ratio for functional independence in elderly patients treated with MT + BMM vs. BMM alone in the 6–24 h time window. Random-effects meta-analysis.

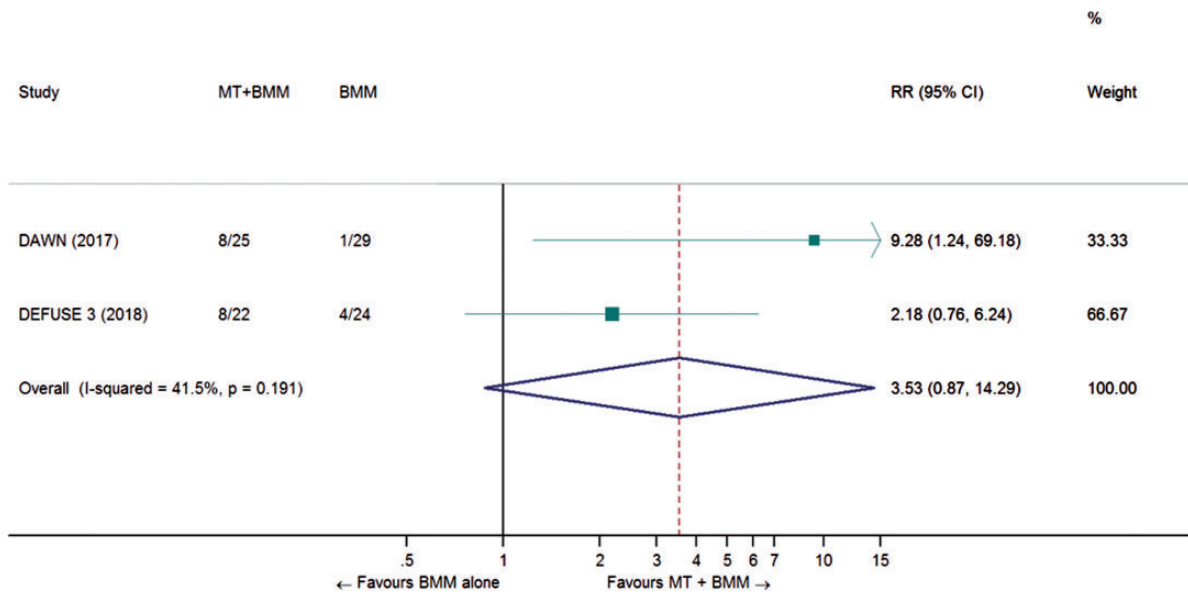


Figure 6. Pooled risk ratio for functional independence in elderly patients treated with MT + BMM vs. BMM alone in the 6–24 h time window. Random-effects meta-analysis.

Table 6. Summary of findings table for PICO 6.

Certainty assessment		No. of patients		Effect		Quality of evidence	Importance		
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute (95% CI)
0–6 h time window: mRS 0–2									
4	Randomised trials	Not serious	Not serious	Not serious	None	RR 2.09 (1.03–4.25)	239 more per 1000 (from 12 fewer to 1000 more)	⊕⊕⊕○ Moderate	Critical
6–24 h time window: mRS 0–2									
2	Randomised trials	Not serious	Not serious	Very serious ^{a,b}	None	RR 3.53 (0.87–14.29) OR 4.87 (1.15–20.71)	239 more per 1000 (from 12 fewer to 1000 more)	⊕⊕○○ Low	Critical

CI: confidence interval; RR: risk ratio.

Recommendations

- We recommend that patients aged 80 years or more with large vessel occlusion-related acute ischaemic stroke within 6 h of symptom onset should be treated with mechanical thrombectomy plus best medical management, including intravenous thrombolysis whenever indicated. Application of an upper age limit for mechanical thrombectomy is not justified.
Quality of evidence: **Moderate** ⊕⊕⊕, Strength of recommendation: **Strong** ↑↑
- We suggest that patients aged 80 years or more with large vessel occlusion-related acute ischaemic stroke between 6 and 24 h from time last known well should be treated with mechanical thrombectomy plus best medical management if they meet the eligibility criteria of the DEFUSE-3* or DAWN** trials.
Quality of evidence: **Low** ⊕⊕, Strength of recommendation: **Weak** ↑?

*6–16 h since time last known well:

- Age ≤ 90 years and NIHSS ≥ 6: infarct core volume < 70 mL and penumbra volume > 15 mL and penumbra volume/core volume > 1.8.

**6–24 h since time last known well:

- Age ≥ 80 years: infarct core ≤ 20 mL and NIHSS ≥ 10.

See Table 3 for details.

Additional information

- Elderly patients enrolled in RCTs of MT were functionally independent before the qualifying stroke. Whether patients over 80 years with significant pre-stroke disability may benefit from MT is currently uncertain.
- Excessive vessel tortuosity, which is more frequent in the elderly, was an exclusion criterion in SWIFT PRIME and REVASCAT.^{4,5} In ESCAPE, the enrolment of patients with vessel tortuosity was not recommended if the investigator considered that this anatomical singularity would prevent meeting recommended time targets.³ In PISTE, vascular access contraindications included proximal vascular anatomy likely to render endovascular catheterisation difficult (but this was left to operator judgement).¹⁷ It was also one of many exclusion criteria in DAWN.⁹
- Elderly patients were eligible for enrolment beyond the 6 h time window in REVASCAT (up to 8 h; upper age limit 85 years⁵) and ESCAPE (up to 12 h³), but data for this age subgroup were not available for inclusion in our meta-analysis.

Regardless of age, only 20 patients were enrolled in the 6–8 h time window in REVASCAT, and 49 patients were enrolled in the 6–12 h time window in ESCAPE. The fact that no effect modification by age was demonstrated in the whole ESCAPE cohort is too indirect evidence to make recommendations based on that study regarding elderly patients in the 6–12 h time window.

PICO 7: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on a particular NIHSS threshold compared with no specific threshold improve functional outcome?

Analysis of current evidence and evidence-based recommendation

High NIHSS (>20). Patients with high stroke severity (NIHSS score >20) were enrolled in all nine RCTs testing MT within 6 h,^{1–5,15–18} although upper limits were required in SWIFT PRIME (≤ 30) and THRACE (≤ 25).^{4,15} A patient level pooled analysis ($n=1278$) of the five RCTs conducted by the HERMES collaboration showed no evidence of heterogeneity of treatment effect among severe strokes, as compared to other subgroups that were enrolled (NIHSS >20 ($n=321$): adjusted common OR for better functional outcome: 2.52, 95% CI: 1.40–4.54; $p_{\text{interaction}}=0.45$).⁶ The adjusted RR for functional independence (mRS ≤ 2) in patients with NIHSS >20 was 1.80 (95% CI: 1.09–2.96). There is limited data on patients with a NIHSS score >25 ($n=66$ in the first 5 RCTs). In two trials testing MT beyond 6 h (DAWN, and DEFUSE-3), there was also no evidence of modification of treatment effect by higher stroke severity.^{9,10}

Low NIHSS (0–5). Patients with low stroke severity (NIHSS score 0–5) could be enrolled in two RCTs of MT plus BMM vs. BMM alone within 6 h of symptom onset. MR CLEAN allowed NIHSS as low as 2 if there was sufficient uncertainty of MT benefit.¹ EXTEND-IA allowed enrolment of patients regardless of NIHSS score if the clinical decision was made to administer IVT.² The remaining seven RCTs had lower NIHSS limits ranging from 6 to 10.^{3–5,15–18} Of the 1916 randomised patients, only 14 (0.7%) had an NIHSS of 0 to 5, a number too small to draw any conclusion regarding this subgroup. Furthermore, there were no patients enrolled with NIHSS 0 to 5 in any RCT testing MT beyond 6 h (DAWN, DEFUSE-3, ESCAPE, REVASCAT).^{3,5,9,10}

Recommendations

- We do not recommend an upper NIHSS score limit for decision-making on mechanical thrombectomy. We recommend that patients with high stroke severity and large vessel occlusion-related acute ischaemic stroke be treated with mechanical thrombectomy plus best medical management, including intravenous thrombolysis whenever indicated. These recommendations also apply for patients in the 6–24 h time window, provided that they meet the inclusion criteria for the DAWN or DEFUSE-3 studies (see Table 3).

Quality of evidence: **High** ⊕⊕⊕⊕, Strength of recommendation: **Strong** ↑↑.

- We recommend that patients with low stroke severity (NIHSS 0–5) and large vessel occlusion-related acute ischaemic stroke within 24 h from time last known well be included in randomised controlled trials comparing mechanical thrombectomy plus best medical management versus best medical management alone.

Quality of evidence: **Very low** ⊕, Strength of recommendation: -.

Additional information

RCTs that include patients with low NIHSS scores are in preparation or under way (ENDO-LOW, MinOr Stroke Therapy Evaluation (In Extremis/MOSTE)).

Several observational studies have focused on the effect of MT in patients with low NIHSS scores. Haussen et al. reported 32 patients with a baseline NIHSS score ≤ 5 and confirmed LVO who were either treated with IVT alone (69% of patients at admission) or MT (31% at admission).⁸³ Of those treated with IVT, 41% deteriorated and required MT despite the fact that the median NIHSS score for patients in the medical treatment group was only 2. The median time to deterioration was 5.2 h (range 2–25 h). This group also demonstrated a mRS shift of –2.5 points in favour of MT. Dargazanli et al. published the results of prospectively collected consecutive patient data from four French registries.⁶⁶ The inclusion criteria included confirmed acute ischaemic stroke with proximal LVO and NIHSS score <8 at admission. Patients were sub-divided into two groups: those who went directly to MT in addition to BMM and those who were treated with BMM and only proceeded to MT in the event of clinical deterioration. Three hundred and one patients met the inclusion criteria, 170 in the MT group and 131 in

the group corresponding to BMM as first-line treatment. Overall 64.5% of patients achieved an excellent outcome (mRS ≤ 1) at 90 days with no significant difference between the two groups. Of those with a NIHSS score < 6 at admission, 80% achieved functional independence (mRS ≤ 2). A larger number of patients in the MT group achieved a perfect outcome (mRS = 0) than those in the BMM group (47.2% vs. 34.7%). Of note 18.3% of patients in the BMM group had clinical deterioration and therefore went to MT. This study, alongside others,^{63,64,84,85} suggest that MT could be of benefit to patients presenting with mild symptoms.⁸⁶ However, due to a high risk of confounding by indication in those observational studies, we recommend enrolling patients in dedicated RCTs.

Expert opinion

Expert opinion on mechanical thrombectomy in patients with low NIHSS scores

In patients with a low NIHSS score (≤ 5) who are not eligible for a dedicated randomised controlled trial, we suggest that treatment with mechanical thrombectomy in addition to intravenous thrombolysis (or alone in case of contraindication to intravenous thrombolysis) may be reasonable:

- In patients with deficits that appear disabling (e.g. significant motor deficit or aphasia or hemianopia) at presentation (vote: 9/11 experts)
- In the case of clinical worsening despite intravenous thrombolysis (vote: 9/11 experts)
- We did not reach majority vote to suggest mechanical thrombectomy in patients with deficits that appear non-disabling (e.g. mild hypoaesthesia⁸⁷) at presentation (vote: 5/11 experts)

PICO 8: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on a particular ASPECTS or infarct core volume threshold compared with no specific threshold: Improve identification of patients with a therapy effect of MT on functional outcome? Decrease the risk of sICH?

Analysis of current evidence and evidence-based recommendation

Of the nine RCTs evaluating MT+BMM vs. BMM within 6 h of anterior circulation stroke onset, only two large trials (MR CLEAN¹ and THRACE¹⁵)

allowed the enrolment of patients without restrictions regarding infarct volume or ASPECTS (Table 7). CT/CTA was the pre-therapeutic imaging of choice in the vast majority of patients, except in the THRACE trial, where MRI was first-line imaging in 73% of patients.

ASPECTS. In the HERMES collaboration individual patient data meta-analysis of seven RCTs (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT, THRACE and PISTE),²³ the median ASPECTS was 8 (IQR 7–9) in the patients treated with MT. MT was significantly associated with better functional outcome in patients with ASPECTS 8–10 ($n=975$; adjusted common OR (cOR) 2.36, 95% CI: 1.88–2.98), with ASPECTS 5–7 ($n=617$; adjusted cOR 1.58, 95% CI: 1.19–2.11), and also in those with ASPECTS 0–4 ($n=126$; adjusted cOR 2.15, 95% CI: 1.06–4.37; $p_{\text{interaction}}=0.054$). However, the numbers of patients with ASPECTS 0–4 were relatively small, namely 57/856 (7%) in the MT+BMM arm and 69/862 (8%) in the BMM arm. In this subgroup, MT was not significantly associated with functional independence (adjusted OR = 2.72, 95% CI: 0.89–8.33). Out of 11 patients with ASPECTS 0–2 in the MT+BMM arm, none achieved functional independence.

There was evidence for heterogeneity across ASPECTS subgroups in the risk of sICH associated with MT ($p_{\text{interaction}}=0.025$). In the ASPECTS 0–4 subgroup, the rate of sICH was 10/52 (19%) in the MT+BMM arm, compared with 3/66 (5%) in BMM arm (unadjusted $p=0.016$; adjusted OR = 3.94, 95% CI: 0.94–16.49).

All those results are based on a central reading of ASPECTS by a core lab. The applicability of using a specific ASPECTS threshold for treatment decision-making in clinical practice may be challenging because interobserver agreement for non-contrast CT ASPECTS is only moderate in the hyperacute stroke setting.⁸⁸ Furthermore, ASPECTS, which was designed for non-contrast CT, and its MRI counterpart (DWI-ASPECTS) are not equivalent, due to the higher sensitivity of diffusion MRI to diagnose acute ischaemia. It has been reported that for a given patient, the DWI-ASPECTS is generally one point lower than (CT-)ASPECTS.⁸⁹ Accordingly, the ASPECTS threshold for eligibility to participate in the REVASCAT trial was ≥ 7 and ≥ 6 in patients imaged by CT and MRI, respectively.⁵

Infarct volume. The HERMES collaboration recently led to a patient-level pooled analysis of CTP or MRI DWI-based infarct core volume in seven RCTs.⁹⁰ Pre-treatment CTP was available in a total

Table 7. Exclusion criteria based on ASPECTS or infarct volume in RCTs of MT + BMM vs. MT.

Trial	Exclusion criteria	Median (IQR) ASPECTS or infarct volume (mL) of enrolled patients
MR CLEAN	None	MT + BMM: ASPECTS 9 (7–10) BMM: ASPECTS 9 (8–10)
EXTEND-IA	Infarct core ≥ 70 mL	MT + BMM: 12 mL (4–32) BMM: 18 mL (4–29)
ESCAPE	ASPECTS ≤ 5	MT + BMM: ASPECTS 9 (8–10) BMM: ASPECTS 9 (8–10)
SWIFT PRIME	ASPECTS ≤ 5	MT + BMM: ASPECTS 9 (7–10) BMM: ASPECTS 9 (8–10)
REVASCAT	ASPECTS ≤ 6 (CT) ASPECTS ≤ 5 (MRI)	MT + BMM: ASPECTS 7 (6–9) BMM: ASPECTS 8 (6–9)
THRACE	None	DWI lesion volume: 17 mL (9.2–51.8) ^a
PISTE	Hypodensity $> 1/3$ of the MCA territory	MT + BMM: ASPECTS 9 (4–10) BMM: ASPECTS 9 (2–10)
THERAPY	Hypodensity $> 1/3$ of the MCA territory	MT + BMM: ASPECTS 7.5 (6–9) BMM: ASPECTS 8 (7–9)
EASI	None	MT + BMM: ASPECTS 8 (7–9) BMM: ASPECTS 9 (8–9)
DAWN	Infarct core ≥ 51 mL	MT + BMM: 7.6 mL (2.0–18.0) BMM: 8.9 mL (3.0–18.1)
DEFUSE-3	Infarct core ≥ 70 mL	MT + BMM: 9.4 mL (2.3–25.6) ASPECTS 8 (7–9) ^b BMM: 10.1 mL (2.1–24.3) ASPECTS 8 (7–9) ^b

^aPatients in whom the qualifying imaging study was MRI.

^bPatients in whom the qualifying imaging study was CT.

of 591 (34%) patients and the volume of infarct core, defined as relative cerebral blood flow $< 30\%$ of normal brain, was estimated with an automated software. DWI-MRI was available for 309 (18%) patients and the volume of infarct core was defined as an apparent diffusion coefficient less than $620 \mu\text{m}^2/\text{s}$. Median CTP-estimated infarct core volume was 10 mL (IQR 3–28 mL) and median DWI-estimated infarct core volume was 21 mL (IQR 10–52 mL). Increasing infarct core volume was associated with reduced likelihood of functional independence (mRS 0–2): CTP OR = 0.77 (95% CI: 0.69–0.86) per 10 mL increase; DWI-MRI OR = 0.87 (95% CI: 0.81–0.94) per 10 mL increase.

However, there was no significant modification of treatment effect by infarct volume. In the small subgroup of patients with > 70 mL infarct core volume on CTP ($n = 50$, median 100 mL, IQR 82–144 mL), two (8%) of 25 patients treated with MT and none of 25 control patients achieved functional independence. The unadjusted common OR for better functional outcome associated with MT was

3.1 (95% CI: 1.0–9.4) in this subgroup, but the sample size did not allow meaningful adjustment on potential confounders. The number needed to treat (NNT) remained stable across the spectrum of core volumes (NNT < 10 for functional independence).

The two RCTs randomising patients exclusively beyond 6 h had stringent inclusion criteria regarding infarct volume (Table 3). DAWN used a stratification by age and NIHSS score leading to differing maximum infarct core cut-off volumes measured by imaging software in an automated fashion (> 80 years core up to 20 mL, < 80 years and NIHSS 10–19 core up to 30 mL, < 80 years and NIHSS 20 or more core up to 50 mL).⁹ DEFUSE-3 allowed a core volume up to 70 mL, but required the presence of a perfusion mismatch.¹⁰ The median infarct core volumes were 8 (75th percentile: 20 mL) and 10 mL (75th percentile: 25 mL) in DAWN and DEFUSE-3, respectively. There was no evidence of a modification of treatment effect by infarct core volume in DEFUSE-3 ($p_{\text{interaction}} = 0.47$).

Recommendations

- In the 0–6 h time window, we recommend mechanical thrombectomy plus best medical management (including intravenous thrombolysis whenever indicated) over best medical management alone in large vessel occlusion-related anterior circulation stroke patients without evidence of extensive infarct core (e.g. ASPECTS ≥ 6 on non-contrast CT scan or infarct core volume ≤ 70 mL).

Quality of evidence: **High** $\oplus\oplus\oplus\oplus$, Strength of recommendation: **Strong** $\uparrow\uparrow$.

- In the 6–24 h time window, we recommend mechanical thrombectomy plus best medical management (including intravenous thrombolysis whenever indicated) over best medical management alone in large vessel occlusion-related anterior circulation stroke patients fulfilling the selection criteria of DEFUSE-3* or DAWN**, including estimated volume of infarct core.

Quality of evidence: **Moderate** $\oplus\oplus\oplus$, Strength of recommendation: **Strong** $\uparrow\uparrow$.

- We recommend that anterior circulation stroke patients with extensive infarct core (e.g. ASPECTS < 6 on non-contrast CT scan or core volume > 70 mL or > 100 mL) be included in randomised controlled trials comparing mechanical thrombectomy plus best medical management versus best medical management alone.

Quality of evidence: **Very low** \oplus , Strength of recommendation: -.

*6–16 h since time last known well:

- Age ≤ 90 years and NIHSS ≥ 6 : infarct core volume < 70 mL and penumbra volume > 15 mL and penumbra volume/core volume > 1.8 .

**6–24 h since time last known well:

- Age < 80 years: infarct core ≤ 30 mL if NIHSS ≥ 10 ; infarct core ≤ 51 mL if NIHSS ≥ 20 .
- Age ≥ 80 years: infarct core ≤ 20 mL and NIHSS ≥ 10 .

See Table 3 for details.

Additional information

Increased pre-treatment infarct volume has been consistently shown to be an independent predictor of functional dependency (mRS 3–6), worse functional outcome and mortality in patients undergoing MT.^{91–93} RCTs enrolling patients with low CT-ASPECTS or large infarct core volume are under way (Efficacy and Safety of Thrombectomy

in Stroke With Extended Lesion and Extended Time Window (TENSION): NCT03094715; In Extremis/LASTE).

Expert opinion

Expert opinion on mechanical thrombectomy in patients with low ASPECTS or large infarct volume

If inclusion of the patient in a dedicated randomised controlled trial is not possible, we suggest that treatment with mechanical thrombectomy may be reasonable on an individual basis in selected cases with ASPECTS < 6 or core volume > 70 mL (11/11 experts agree). Patient selection criteria might include age, severity and type of neurological impairment, time since symptom onset, location of the ischaemic lesion on plain CT scanner or MRI and results of advanced imaging, notably perfusion-core mismatch.

PICO 9: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on advanced perfusion, core or collateral imaging compared with no advanced imaging: Improve identification of patients with a therapy effect of thrombectomy on functional outcome? Decrease the risk of sICH?

Analysis of current evidence and evidence-based recommendation

The literature search did not identify any RCT of modern devices that compared the effect of the selection of MT candidates with and without advanced imaging selection (i.e. perfusion or core assessment on CTP or MRI, or collateral imaging on multiphase CTA). A higher therapeutic effect was observed in the RCTs randomising patients in the 0–6 h time window with more extensive use of advanced imaging analysis (EXTEND-IA², ESCAPE³ and SWIFT PRIME⁴) compared with other trials:^{1,5,15–18} the pooled unadjusted ORs for functional independence were 2.84 (95% CI: 2.02–4.01) and 1.75 (95% CI: 1.39–2.20) in trials with and without advanced imaging patient selection, respectively ($p = 0.02$ for heterogeneity between the two groups; Figures 7 and 8).

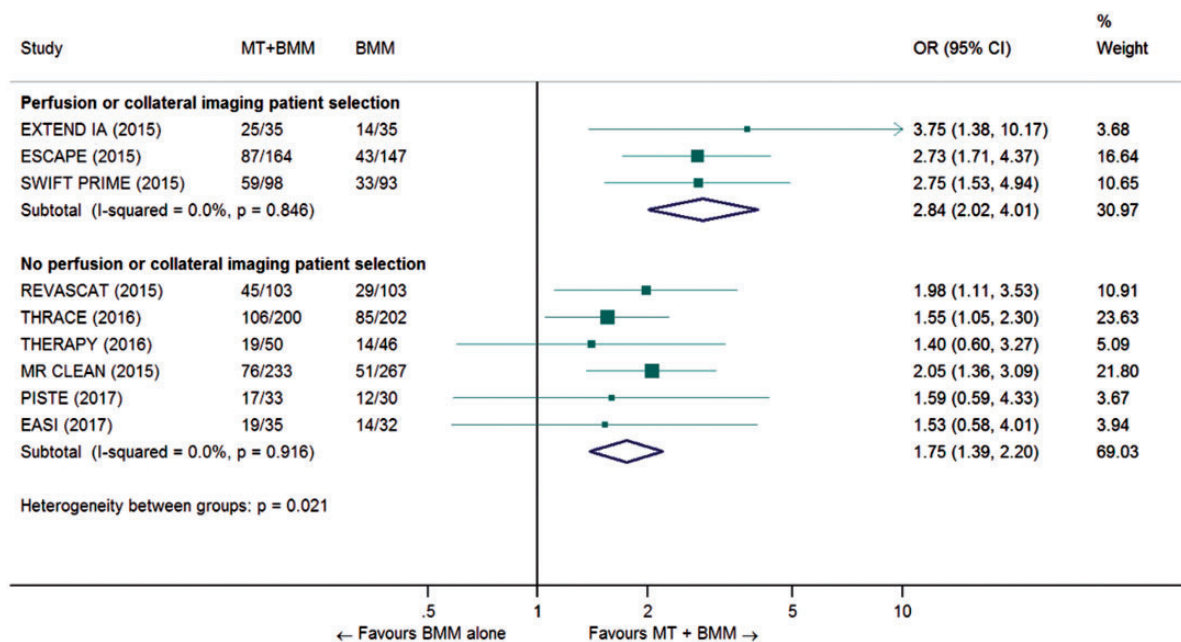


Figure 7. Therapy effect of MT + BMM vs. BMM alone on functional independence, according to advanced imaging patient selection. Unadjusted pooled odds ratios, fixed-effect meta-analysis.

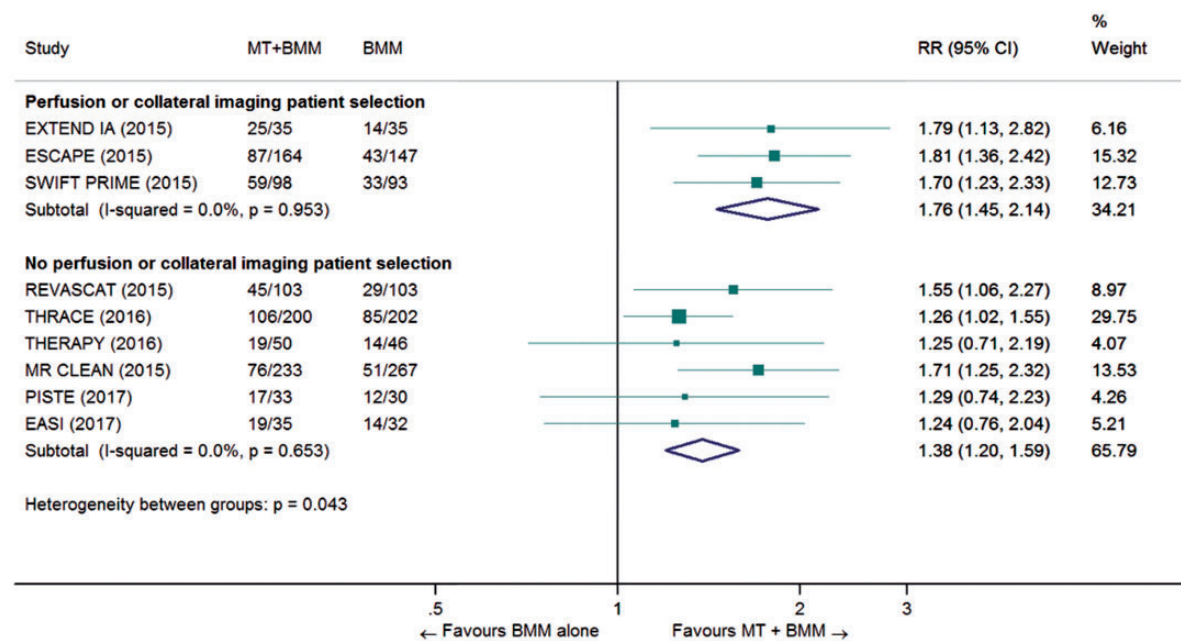


Figure 8. Therapy effect of MT + BMM vs. BMM alone on functional independence, according to advanced imaging patient selection. Unadjusted pooled risk ratios, fixed-effect meta-analysis.

Importantly, MT + BMM was clearly superior to BMM alone also in trials in which only a plain CT and CTA were required prior to randomisation, such as MR CLEAN.¹

Advanced imaging selection with automated software was mandatory for both RCTs randomising patients exclusively >6 h after symptom onset or last known well.^{9,10}

Recommendations

- In adult patients with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting from 0 to 6 h from time last known well, advanced imaging is not necessary for patient selection.

Quality of evidence: **Moderate** ⊕⊕⊕, Strength of recommendation: **Weak** ↓?

- In adult patients with anterior circulation large vessel occlusion-related acute ischaemic stroke presenting beyond 6 h from time last known well, advanced imaging selection is necessary.

Quality of evidence: **Moderate** ⊕⊕⊕, Strength of recommendation: **Strong** ↑↑

Additional information

Three of the 0–6 h RCTs initially required confirmation of salvageable brain tissue (ESCAPE,³ EXTEND-IA,² and SWIFT PRIME⁴) either by defining small ischaemic cores in combination with the presence of salvageable brain tissue (SWIFT PRIME and EXTEND-IA) and/or adequate collateral flow (ESCAPE). Within EXTEND-IA and SWIFT PRIME, detection of salvageable tissue was attempted by using an automated perfusion post-processing software in 100% and 81% of patients. SWIFT PRIME used the same software for the first 71 patients. After enrolment of the first 71 patients, the investigators added the alternate criterion of ASPECTS ≥ 6 for sites which did not have automated CTP capability. In ESCAPE, multiphase CTA was used to select patients with moderate to good collateral circulation (filling of $\geq 50\%$ pial arterial circulation visualised).⁹⁴

In the HERMES collaboration's individual patient data meta-analysis, there was no significant modification of treatment effect by collateral grade ($p_{\text{interaction}} = 0.30$). The adjusted cOR for better functional outcome was 1.49 (95% CI: 0.86–2.55) in the subgroup of patients with poor collaterals (grade 0–1; $n = 211/1278$).²³

Both RCTs exclusively enrolling patients beyond the 6-h time window mandated the use of automated software processing of either CTP or MRI (Table 3).^{9,10} The DAWN trial (0–24 h) used clinical-imaging (core) mismatch as the inclusion criterion, whereas DEFUSE-3 (0–16 h) used perfusion-core mismatch and maximum core size to select patients with LVO for enrolment. Both trials showed a significant improvement in functional outcome at 90 days with MT (see PICO question 2).

A subgroup analysis of CTP data from MR CLEAN suggested that this method could be useful for predicting functional outcome but not for reliable identification of patients who will not benefit from EVT.⁹⁵

It has been consistently shown that advanced perfusion imaging can identify the patients with good clinical prognosis and high therapy effect.^{96–101}

Expert opinion

Within the 0–6 h time window, patient selection with perfusion or collateral imaging does modify the expected therapy effect. However, patient selection with advanced imaging may exclude a substantial proportion of patients who have the potential to respond favourably to reperfusion. The possible enhanced benefit of advanced perfusion or collateral image processing using novel thresholds (i.e. larger core infarction volumes) for patient selection may justify further study, especially in the 0–6 h time window.

Within the 6–24 h time window, specific national and regional resources and their limitations need to be considered in choosing optimal imaging-based patient selection. Consequently, regions with limited MT resources should apply the most advanced imaging capabilities available for strict patient selection.

PICO 10: For adults with LVO-related acute ischaemic stroke, does MT performed in a CSC compared with MT performed outside of a CSC: Improve functional outcome? Reduce time to reperfusion? Reduce the rate of sICH?

Analysis of current evidence and evidence-based recommendation

The literature search did not identify RCTs of MT performed in a comprehensive stroke centre compared with MT performed outside of a comprehensive stroke centre. The RCTs that showed superiority of MT + BMM over BMM alone had following common minimum characteristics for centres appropriate to conduct MT.^{1–5,15}

- An established organisation to support rapidly instituted IV rt-PA use.
- Team organisation of a level sufficient to support clinical trial participation.
- Experience with acute CT interpretation including ASPECT scoring.
- Experience with CTA in acute stroke patients as a minimum additional imaging modality.

- A process for monitoring door-to-needle/groin puncture/reperfusion, and procedural duration times, and a governance process to ensure that these are reviewed.
- Implementation of door-to-needle time minimisation strategies as for IV rt-PA use.
- Minimum institutional and individual experience of cerebrovascular procedures in general, of thrombectomy for acute stroke, and of the specific device.

The generalisability of the trial findings to centres or interventional teams that do not fulfil these criteria is not established by the literature.

Table 8 summarises the centre requirements to participate in each RCT showing a benefit of MT + BMM vs. BMM alone.

A recent study based on administrative data assessed mortality rates among 8533 patients admitted

Table 8. Centre requirements to participate in the main positive MT trials.

Trial	Criteria
MR CLEAN ¹	<ul style="list-style-type: none"> • The intervention team should have ample experience with endovascular interventions for cerebrovascular disease, peripheral artery disease, or coronary artery disease. At least one member of the intervention team should have sufficient experience with intra-arterial thrombolysis (IAT). • At least one member of the intervention team should have sufficient experience with the particular device (defined as completion of at least 5 full procedures with the particular device). Procedures that have been carried out by two team members (e.g. in a training setting) count. Procedures do not need to be successful, nor uncomplicated. Procedures consisting of mechanical thrombectomy combined with IAT count for both. • The possibility of treatment by an interventionalist with sufficient experience is listed as an inclusion criterion.
EXTEND-IA ²	Sites were required to have an established intravenous rt-PA programme with multimodal CT or MRI imaging as standard procedure
ESCAPE ³	Sites were required to employ CTA as standard of care for acute stroke patients and have effective systems for identification of patients. In addition, the protocol stated that 'the quality of intervention will be ensured by hand-selection of sites and only be approved by the executive committee after a site visit. All sites must submit evidence within the 2 years prior to commencement of the trial that they can meet the 90 minute target of CTA-to-recanalisation time. A key and critical component of the trial will be an ongoing quality assurance programme to ensure that sites can meet these targets for endovascular intervention. Training will be undertaken at the sites and continued on a quarterly basis. Monitoring of interval times will be collated and provided to sites on a quarterly basis so that regular feedback might induce appropriately fast treatment processes. Sites that fail to meet these objectives in the trial will be dropped from the trial.'
REVASCAT ⁵	Conducted in the setting of a regional network of acute stroke care, covering a population of 7.5 million in a compact geographical region of Catalonia. No trial specified the characteristics of a network, only of individual participating centres.
SWIFT-PRIME ⁴	In addition to general criteria related to GCP, other criteria were: <ul style="list-style-type: none"> • Previous experience with clinical research and mechanical thrombectomy procedures • Experience in conducting randomised, controlled, clinical studies • Currently treating subjects who meet the inclusion/exclusion criteria • Ability to enrol an adequate number of subjects • Ability and willingness to randomise study subjects • Ability to perform required clinical testing, including: angiography, CT, and MRI • Adequate staffing to conduct the study.
THRACE ¹⁵	No mention of specific centre requirements
DAWN ⁹	No mention of specific centre requirements
DEFUSE-3 ¹⁰	<ul style="list-style-type: none"> • No mention of specific centre requirements • Interventionalists had to meet the following requirements: Training: Satisfactory completion of a 7-year ACGME approved neurosurgical residency OR Board certification (ABMS) Board in Neurology with subspecialty certification from an ACGME-accredited Vascular/Stroke Neurology Fellowship OR Board certification (ABMS) Board (Radiology) with subspecialty certification in Neuroradiology AND Interventionalist has completed a minimum of 12 months of continuous training as a fellow in a dedicated Neuroendovascular fellowship <p>Experience: Interventionalist has performed a minimum of 200 cerebral angiograms AND Interventionalist has performed at least 20 stroke thrombectomy cases with stent retrievers and/or suction thrombectomy devices as a primary operator. (When a prospective interventionalist had extensive experience performing endovascular thrombectomies, but did not fully meet the training requirements, they could be approved by unanimous vote of the 4-member DEFUSE-3 Endovascular Committee.)</p>

for MT in 118 U.S. centres, showing a negative correlation between institutional procedural volume and mortality ($r = -0.24$, $p = 0.007$).¹⁰² Numeric cut-offs for institutional procedural volumes that yielded the greatest differences in mortality index were ≤ 7 procedures per year (low-volume thrombectomy centres) and > 35 procedures per year (high-volume thrombectomy centres). A lower mortality rate among patients treated with MT who were transferred to high-volume centres compared with those directly admitted to low-volume centres was observed (10.0% vs. 20.4%; $p = 0.005$). The authors concluded that the benefit of greater institutional procedural experience may mitigate the delay in reperfusion associated with hospital transfer.

Recommendation

- In adult patients with large vessel occlusion-related acute ischaemic stroke, we recommend treatment in a comprehensive stroke centre.

Quality of evidence: **Very low** ⊕, Strength of recommendation: **Strong** ↑↑

In the above recommendation, ‘comprehensive stroke centre’ refers to centres meeting the definition of ‘ESO stroke centre’ according to the ESO recommendations.¹⁰³

Expert opinion

The same organisational components that have been shown to achieve rapid door-to-needle times for IVT will be required also for provision of MT.¹⁰⁴ Process improvements have been documented in a number of publications and guidelines and these have been shown to improve treatment times when translated into a different healthcare environment.¹⁰⁵ The additional components required for implementation of MT should include early notification of the interventional team, and neuroradiology workflow that minimises acquisition, processing and interpretation of additional imaging to select patients for MT.^{7,8}

A group of international multi-disciplinary societies involved in MT for acute ischaemic stroke have put forth training guidelines. Formal neuroscience training, stringent peer review and quality assurance processes are critical to ensuring the best possible patient outcomes.¹⁰⁶ The key specifications are:

- The operator must have a training in radiology, neurology or neurosurgery, which should include documented training in the diagnosis and management of acute stroke, the interpretation

of cerebral arteriography and neuroimaging under the supervision of a neuroradiologist, neurologist or neurosurgeon with subsequent eligibility or certification. Those physicians who did not have adequate training during their residencies must spend an additional period (at least one year) by training in clinical neurosciences and neuroimaging.

and:

- Dedicated training in interventional neuroradiology (also termed endovascular neurosurgery or interventional neurology) under the direction of a neurointerventionalist (with neuroradiology, neurology or neurosurgical training background), at a high-volume centre. It is preferred that this is a dedicated time (minimum of one year), which occurs after graduating (i.e. a fellowship).

PICO 11: For adults with LVO-related acute ischaemic stroke, does reperfusion TICI Grade 3 compared with reperfusion TICI Grade 2b improve functional outcome?

Analysis of current evidence and evidence-based recommendation

The thrombolysis in cerebral infarction (TICI) grading system was described in 2003 as tool for grading the response of thrombolytic therapy for ischaemic stroke from Grade 0: no perfusion, to Grade 3: complete perfusion.^{107,108} In neurointerventions, it is the standard for patients post-endovascular revascularisation and successful reperfusion is currently defined as TICI score of 2b or 3.¹⁰⁹

The literature search did not identify RCTs comparing the effect of attempting a reperfusion result of a TICI Grade 3 vs. TICI Grade 2b. A dedicated systematic review and study-level meta-analysis included 14 studies with available follow-up.¹¹⁰ Eleven of the 14 studies were retrospective observational studies, while one currently unpublished study examined different degrees of successful reperfusion in the HERMES collaboration of recent endovascular trials.¹¹¹ TICI 3 and 2b were achieved in 1131 and 1248 patients, respectively.

In the meta-analysis, TICI 3 reperfusion was associated with higher rates of functional independence (mRS ≤ 2 : OR = 1.74, 95% CI: 1.44–2.10), also after including adjusted estimates. Due to the observational design of available studies, the QoE for the present recommendations was considered to be low (Table 9).

Table 9. Summary of findings for PICO 11.

Certainty assessment		No. of patients		Effect		Quality of evidence	Importance
No. of studies	Risk of bias	TICI 3	TICI 2b	Relative (95% CI)	Absolute (95% CI)		
mRS 0–2							
14	Observational studies	-/1131	-/1248	OR 1.74 (1.44–2.10)		⊕⊕○○ Low	Critical

CI: confidence interval; OR: odds ratio.

Recommendation

For adults with large vessel occlusion-related acute ischaemic stroke, we recommend that intervention-ists should attempt a TICI Grade 3 reperfusion, if achievable with reasonable safety.

Quality of evidence: **Low** ⊕⊕, Strength of recommendation: **Strong** ↑↑

Additional information

This effect superiority of TICI 3 over TICI 2b seems to be independent of time and collaterals.¹¹⁰ The safety profile of patients with TICI 3 was superior, as demonstrated by lower rates of mortality (OR = 0.59, 95% CI: 0.37–0.92) and symptomatic intracranial haemorrhages (OR = 0.42, 95% CI: 0.25–0.71).¹¹⁰

A low number of thrombectomy attempts leading to TICI 3 is additionally associated with better outcome. A recent analysis suggested a higher rate of functional independence with first pass effect (single pass, TICI 3, no rescue therapy) when compared with final TICI 3 with >1 pass, any TICI 2b, or TICI 2b from the first pass (61.3% vs. 45% ($p = 0.07$), 44.3% ($p = 0.02$), and 52.4% ($p = 0.35$)).¹¹²

Generally, novel scoring systems do not seem to be superior to traditional TICI.¹¹³ A mTICI scoring system has been suggested that includes an additional TICI score category (TICI 2c) comprising a near complete reperfusion except for slow flow or distal emboli in a few distal cortical vessels.¹¹⁴ Another group recently suggested the oTICI2c scale, which subdivides the grade 2b into 2b with 50–66% reperfusion and 2b with 67–90% reperfusion. Here, reperfusion of 90–99% is referred to as Grade 2c.¹¹⁵

Expert opinion

There is consensus that TICI 3 reperfusion is associated with better outcome and better safety profile than TICI 2b reperfusion. As reperfusion quality is the most important modifiable predictor of patients' outcome, a more conservative definition of reperfusion success and further evaluation of treatment approaches geared towards achieving TICI 3 reperfusion are desirable.^{110,116}

The key practical question is when to stop a procedure after incomplete reperfusion and when to pursue further reperfusion attempts that might increase complication risk. A dedicated study could randomise these approaches after a pre-defined number of reperfusion attempts.

The key research question is which method is associated with the highest rate of TICI 3 with the lowest number of passes, e.g. the highest first pass effect. The

methods to be investigated include the access material, the reperfusion devices and the combinations thereof.

PICO 12: For adults with LVO-related acute ischaemic stroke, does MT using direct aspiration compared with a stent retriever: Improve functional outcome? Increase the rate of complete reperfusion?

Analysis of current evidence and evidence-based recommendation

Stent retrievers were the devices of choice in the pivotal trials demonstrating the benefits of MT + BMM over BMM alone.^{1–5} Therefore, MT using stent retrievers should be considered as the current standard of care.

THERAPY was a RCT of non-ADAPT (a direct aspiration first-pass technique) aspiration thrombectomy after IVT compared with IVT alone in patients with large vessel ischaemic stroke because of a thrombus length of ≥ 8 mm.¹⁶ The primary efficacy end point was the rate of functional independence at 90 days (mRS ≤ 2 ; intention-to-treat analysis). Enrolment was halted after 108 patients (of 692 planned) because of external evidence of the added benefit of MT to IVT alone. THERAPY did not achieve its primary end point in this underpowered sample. Intention-to-treat common OR for better functional outcome was 1.76 (95% CI: 0.86–3.59; $p = 0.12$) in favour of aspiration thrombectomy.

No RCT compared direct aspiration alone vs. stent retriever alone in LVO-related strokes. However, two RCTs (Interest of Direct Aspiration First Pass Technique for Thrombectomy Revascularisation of Large Vessel Occlusion in Acute Ischaemic Stroke (ASTER)¹¹⁷ and A comparison of direct aspiration vs. stent retriever as a first approach (COMPASS)¹¹⁸) compared direct aspiration vs. stent retriever as first-line therapeutic strategy, with the possibility to switch to another endovascular therapy (rescue treatment).

The ASTER trial compared direct contact aspiration technique (ADAPT) to stent-retriever thrombectomy as first-line therapeutic strategy, with the aim of successful reperfusion (mTICI $\geq 2b$) in 381 patients with LVO-related acute ischaemic stroke.¹¹⁷ Operators were required to perform at least three attempts at recanalisation using the assigned endovascular technique before switching to another endovascular therapy. At the end of all endovascular procedure, the rate of successful reperfusion was 85% in the first-line ADAPT group vs. 83% in the first-line stent retriever group ($p = 0.53$) and the rates of functional independence were not statistically different (90-day mRS ≤ 2 : 45% vs. 50%, $p = 0.38$). Successful reperfusion after first-line strategy alone was observed in

63% vs. 68% of patients in the ADAPT and stent retriever groups, respectively ($p = 0.34$). After first-line treatment with stent retriever, mTICI 3 was achieved in 35.4% vs. 28.6% with aspiration. The design of the ASTER trial was to demonstrate superiority of contact aspiration vs. stent retriever and in this regard the trial was unsuccessful. The authors concluded that the ASTER trial was not designed nor adequately powered to demonstrate the non-inferiority of ADAPT over stent retriever thrombectomy.

The COMPASS trial, recently presented at the International Stroke Conference 2018, was a prospective, randomised, multicentre non-inferiority trial of first-line aspiration thrombectomy (ADAPT) versus first-line stent retriever thrombectomy.^{118,119} The primary efficacy end point was functional independence at 90 days (mRS ≤ 2) with secondary endpoints of mTICI 2c-3 within 45 min of groin puncture and time to mTICI 2b or greater. There was no statistically significant difference in terms of clot location between the two groups. Using the primary modality, TICI $\geq 2b$ was achieved in 83.2% of patients in the aspiration group vs. 81.3% of the stent-retriever group ($p = 0.75$). Functional independence at 90 days was seen in 52% of patients in the first-line aspiration group vs. 49% of patients in the first-line stent retriever group ($p = 0.001$ for non-inferiority).

Despite the results of the ASTER and COMPASS trials (Figures 9 to 13 and Table 10), we believe that no evidence-based recommendation can be currently provided regarding the first-list contact aspiration vs. first-line stent retriever approaches. Indeed, the COMPASS trial has not been published yet and we feel that more detailed results are needed to make an evidence-based recommendation.

Recommendation

- There is currently no evidence that contact aspiration alone improves functional outcome compared with best medical management in patients undergoing mechanical thrombectomy.
- There is currently no evidence that contact aspiration alone increases the rate of reperfusion over thrombectomy using a stent retriever.
- Therefore, we suggest the use of a stent retriever over contact aspiration alone for mechanical thrombectomy in patients with acute ischaemic stroke.

Quality of evidence: **Very low** \oplus ; Strength of recommendation: **Weak** \uparrow ?

(see expert opinion below regarding first-line aspiration vs. first-line stent retriever, which have been specifically assessed in ASTER and COMPASS)

Additional information

In the ASTER trial, there was an uneven distribution of clots between the groups with a higher percentage of M2 occlusions in the aspiration cohort (27.6% vs. 17.6%) and fewer terminal ICA occlusion (12.6% vs. 18.7%).¹¹⁷ In a subgroup analysis of M2 occlusions,

the rate of mTICI 3 reperfusion when stent-retrievers were used as first-line devices was 38.7%, compared with 29.2% regarding first-line aspiration ($p=0.33$ for comparison).¹²⁰ Furthermore, in this subgroup analysis the 24-h change in NIHSS had a trend to better outcomes with stent retriever treatment as did the change in ASPECTS at 24 h. Similarly, there was a numerically higher mortality rate at 90 days in the aspiration group (19.6% vs. 3.3%, $p=0.078$) and a non-significantly higher rate of procedure related adverse events in the aspiration group (14.6% vs. 9.7%, $p=0.73$).

The proportion of patients in the aspiration group who required rescue therapy with a stente retriever in the ASTER and COMPASS trials were 32.8% and 20.9%, respectively.^{117,118} Retrospective studies have reported the requirement of rescue treatment with stent-retrievers to be as high as 40%.¹²¹ A difficulty in interpretation therefore arises since the results of these trials are presented as pooled data. Ideally, the results of patients requiring rescue treatment should be presented separately or a subgroup analysis should be performed similar to the results of the M2 subgroup analysis detailed above.

Balloon guide catheters. Many have advocated the use of balloon guide catheters (BGCs). However, there is no RCT to compare the outcomes between patients treated with MT in conjunction with BGC to those without. Observational studies have suggested that BGCs are associated with higher reperfusion rates and improved rates of good neurological outcome.^{122,123}

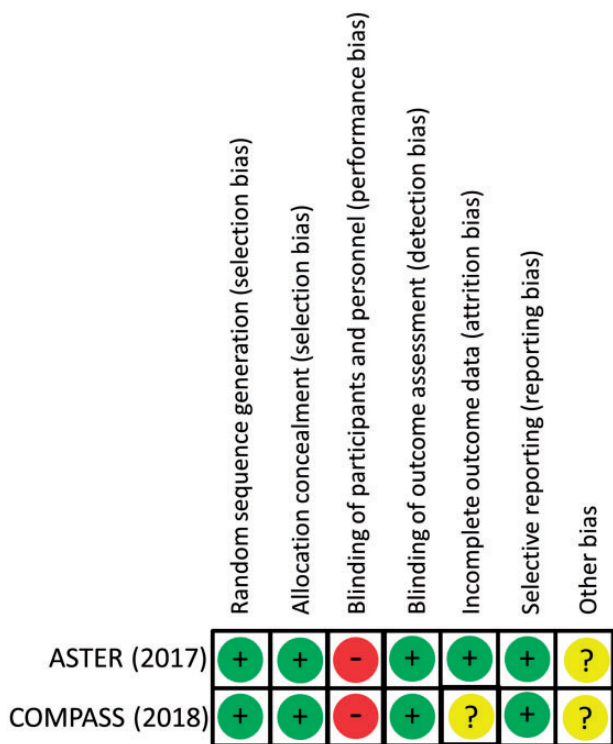


Figure 9. Risk of bias in each trial.

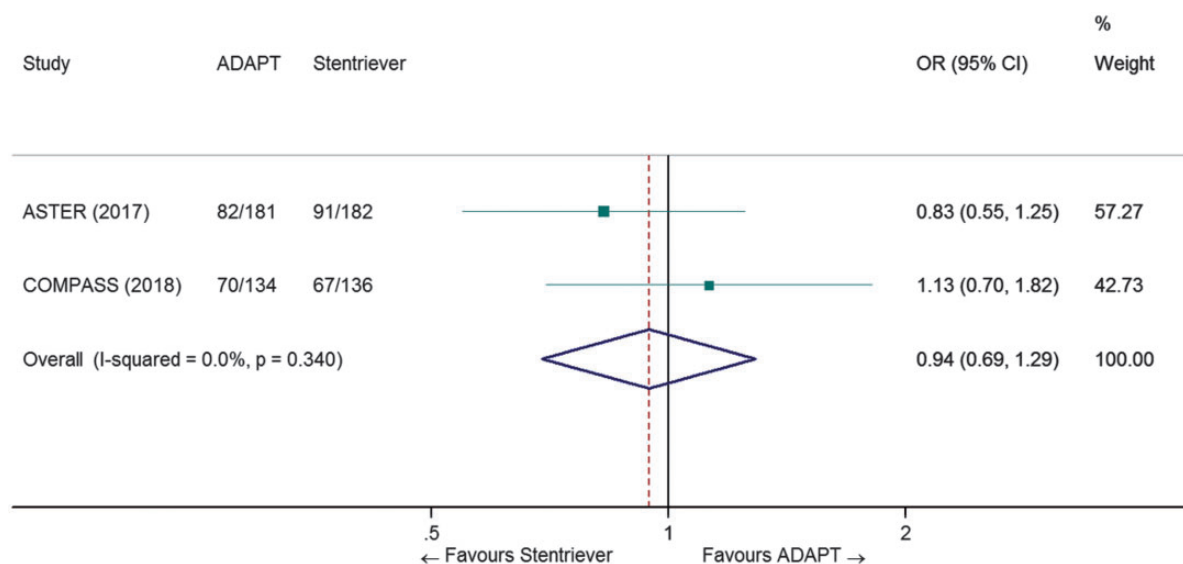


Figure 10. Pooled odds ratio for functional independence in patients treated with first-line ADAPT vs. first-line stent retriever. Random-effects meta-analysis.

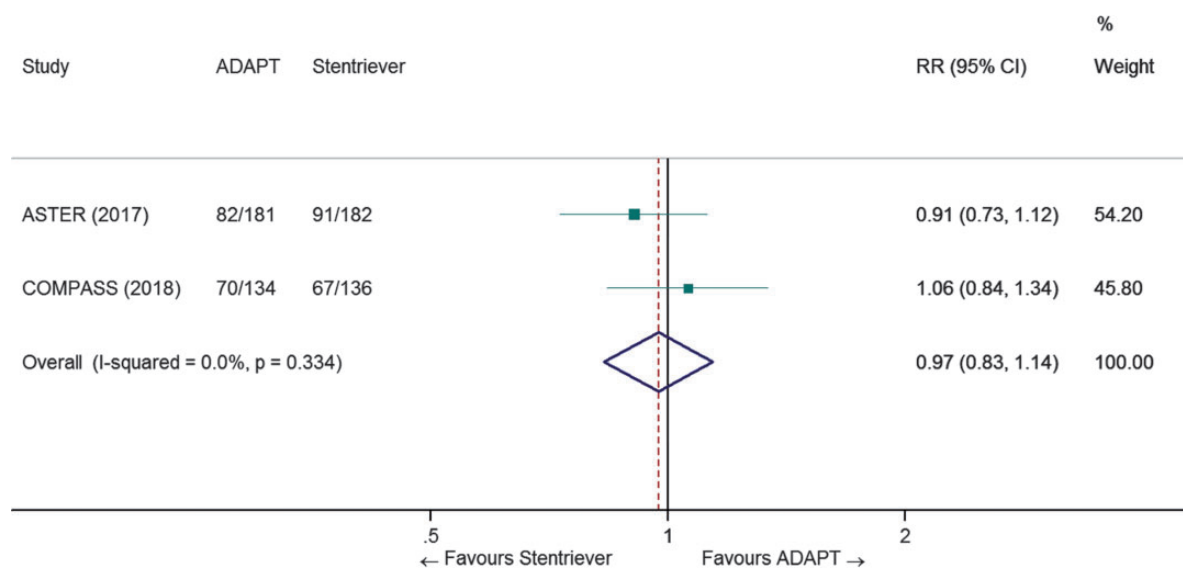


Figure 11. Pooled risk ratio for functional independence in patients treated with first-line ADAPT vs. first-line stent retriever. Random-effects meta-analysis.

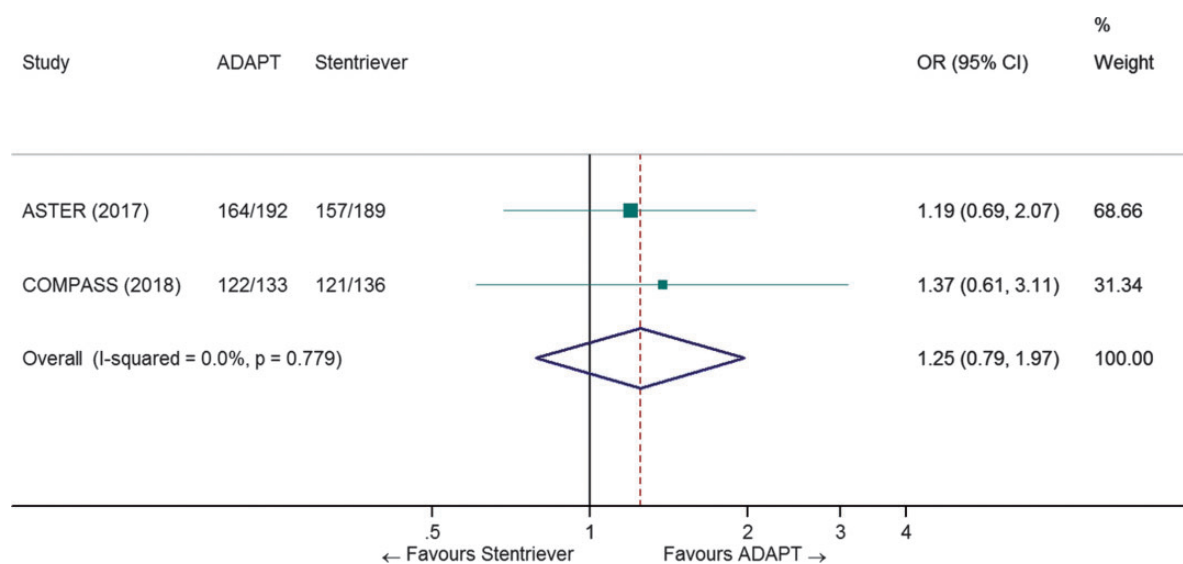


Figure 12: Pooled odds ratio for successful reperfusion in patients treated with first-line ADAPT vs. first-line stent retriever. Random-effects meta-analysis.

A systematic review and meta-analysis on the use of BGC during MT was recently conducted.¹²⁴ The authors identified five non-randomised studies of 2022 patients (1083 BGC group and 939 non-BGC group) all of whom were treated with stent retrievers. Patients treated with BGC had higher rates of functional independence (mRS ≤ 2): 59.7% compared with 43.8% for non-BGC-treated patients (OR = 1.84, 95% CI: 1.52–2.22, $p < 0.01$). Mortality rates were significantly lower in the BGC-treated patients (13.7%)

compared with those in non-BGC-treated patients (24.8%; OR = 0.52, 95% CI: 0.37–0.73, $p < 0.01$). Similarly, the overall first pass reperfusion rate for the BGC group was 63.1% compared with 45.2% for the non-BGC group (OR = 2.05, 95% CI: 1.65–2.55, $p < 0.01$). The TICI 3 rate was also higher in the BGC group (57.9%) compared with the non-BGC group (38.2%; OR = 2.13, 95% CI: 1.43–3.17, $p < 0.01$) with higher rates of TICI 2b-3 also seen (78.9% vs. 67.0%, OR = 1.54, 95% CI: 1.21–1.97,

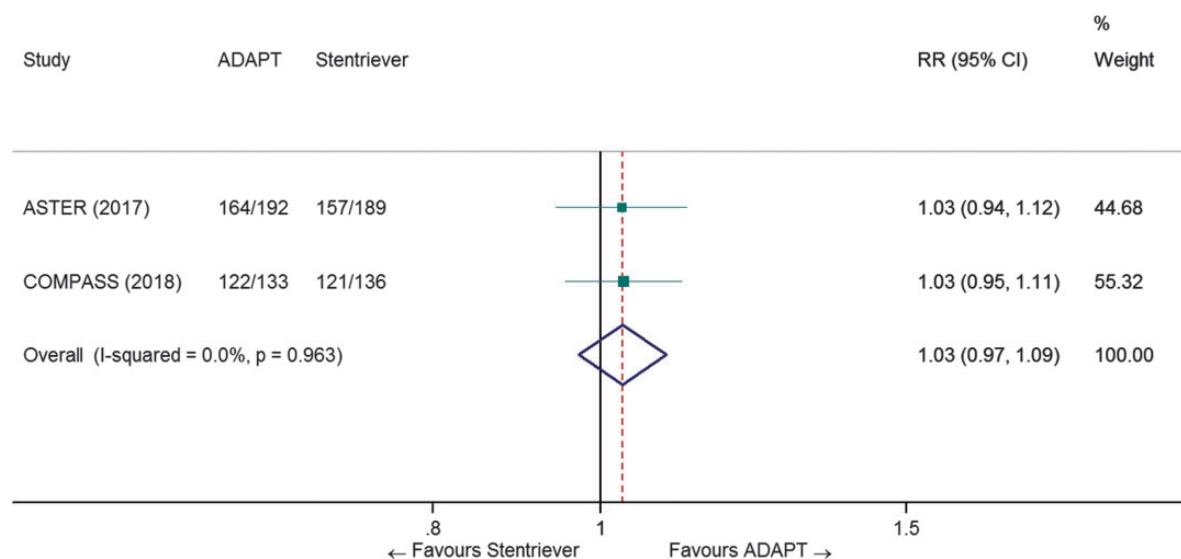


Figure 13: Pooled risk ratio for successful reperfusion in patients treated with first-line ADAPT vs. first-line stent retriever. Random-effects meta-analysis.

$p < 0.001$). The mean number of passes was lower for BGC patients (1.7 vs. 2, $p < 0.01$) and the mean procedure time was shorter (70.5 min vs. 90.9 min, $p < 0.01$).

Optimising MT. Several advanced MT techniques have been described in the literature and these include:

- Solumbra – complete retraction of stent retriever into distal aspiration catheter under aspiration.¹²⁵
- Aspiration retriever technique for stroke (ARTS) – stent retriever locked and removed under continuous aspiration with additional flow arrest.¹²⁶
- Stent retriever-assisted vacuum locked extraction (SAVE) – removal of stent-retriever with aspiration catheter as a vacuum locked unit.¹²⁷
- Continuous aspiration prior to intracranial vascular embolectomy (CAPTIVE) – local aspiration catheter connected to the continuous aspiration pump prior to deployment of the stent retriever.¹²⁸

Details on reperfusion rates using these techniques is provided in the Supplementary appendix.

Expert opinion

Expert opinion on aspiration, stent retriever and proximal balloon guide catheter

9/11 experts believe that ADAPT may be used as standard first-line treatment, followed by stent retriever thrombectomy as rescue therapy if needed.

Besides,

- We did not reach a majority vote on that distal aspiration should be used only in combination with a stent-retriever (3/11 experts)
- 8/11 experts believe that any mechanical thrombectomy procedure should be performed preferably in conjunction with a proximal balloon guide catheter.

PICO 13: For adults with LVO-related acute ischaemic stroke undergoing MT, does conscious sedation compared with general anaesthesia improve functional outcome?

Analysis of current evidence and evidence-based recommendation

Three randomised trials of conscious sedation (CS) versus general anaesthesia (GA) in patients receiving MT for acute stroke were identified: SIESTA,¹³⁰ AnSTROKE¹³¹ and GOLIATH.¹³² The trials recruited 128, 90 and 150 patients ($N = 368$ in total), respectively. One hundred and eighty-five patients received CS and 183 patients received GA. The risk of bias in each trial was considered low (Figure 14). There was no blinding of patients or staff for treatment arm but the endpoint of interest for the present meta-analysis (mRS at 90 days, figure 15) was assessed in a blinded fashion. There was a statistically non-significant trend in favour of GA with a RR for an independent outcome

Table 10. Summary of findings for the comparison of first-line ADAPT vs. first-line stent retriever.

Certainty assessment		No. of patients		Effect		Quality of evidence	Importance
No. of studies design	Risk of bias	First-line ADAPT	first-line stent retriever	Relative (95% CI)	Absolute (95% CI)		
mRS 0-2							
2	Randomised trials Serious ^a Not serious Indirectness Imprecision Not serious	152/315 (48.3%)	158/318 (49.7%)	RR 0.97 (0.83–1.14) OR 0.94 (0.69–1.29)	15 fewer per 1000 (from 70 more to 84 fewer)	⊕⊕○○ Low	Critical
mTICI 2b-3							
2	Randomised trials Serious ^a Not serious Indirectness Imprecision Not serious	286/325 (88.0%)	278/325 (85.5%)	RR 1.03 (0.97–1.09) OR 1.25 (0.79–1.97)	26 more per 1000 (from 26 fewer to 77 more)	⊕⊕○○ Low	Critical

CI: confidence interval; RR: risk ratio.

^aASTER was not designed nor powered to demonstrate non-inferiority.

^bRescue therapy with another type of device was allowed in both trials.

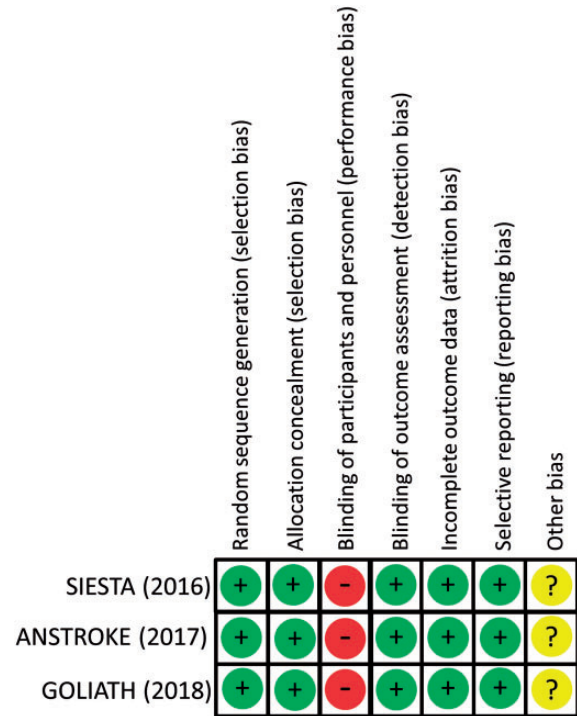


Figure 14. Risk of bias in each randomised trial.

(mRS ≤ 2) of 0.74 (95% CI: 0.54–1.01, $p = 0.056$; $I^2 = 37\%$, Figure 15) and a significant OR of 0.55 (95% CI: 0.34–0.89, $p = 0.01$; $I^2 = 15\%$, Figure 16), both analyses showing low heterogeneity.

Using the RR as summary measure, the absolute effect was 91 fewer (from 4 more to 162 fewer) patients being dependent or dead for 1000 patients treated. Despite the randomised design of these single centre trials, the overall QoE was downgraded to low, due to serious indirectness and imprecision (Table 11).

The HERMES collaboration performed a pooled analysis of individual patient data from seven RCTs of MT,¹³³ in which the use of GA was either discouraged (ESCAPE³ and REVASCAT⁵ trials) or left at the discretion of the investigators.^{1,2,4,15,17} Two-hundred and thirty-six (30%) of 797 patients who had MT procedures were treated under GA. The protocol for GA or CS was left at the discretion of each investigator. Three-month functional outcome, evaluated in a blinded fashion, was significantly better for patients who did not receive GA versus those who received GA (adjusted common OR for better outcome: 1.53, 95% CI: 1.14–2.04). The proportion of patients with functional independence was also higher in patients treated without GA (50% vs. 40%, adjusted OR = 1.65, 95% CI: 1.14–2.38). Still both outcomes were significantly better for patients treated with MT and GA versus patients in the BMM control arms.¹³³

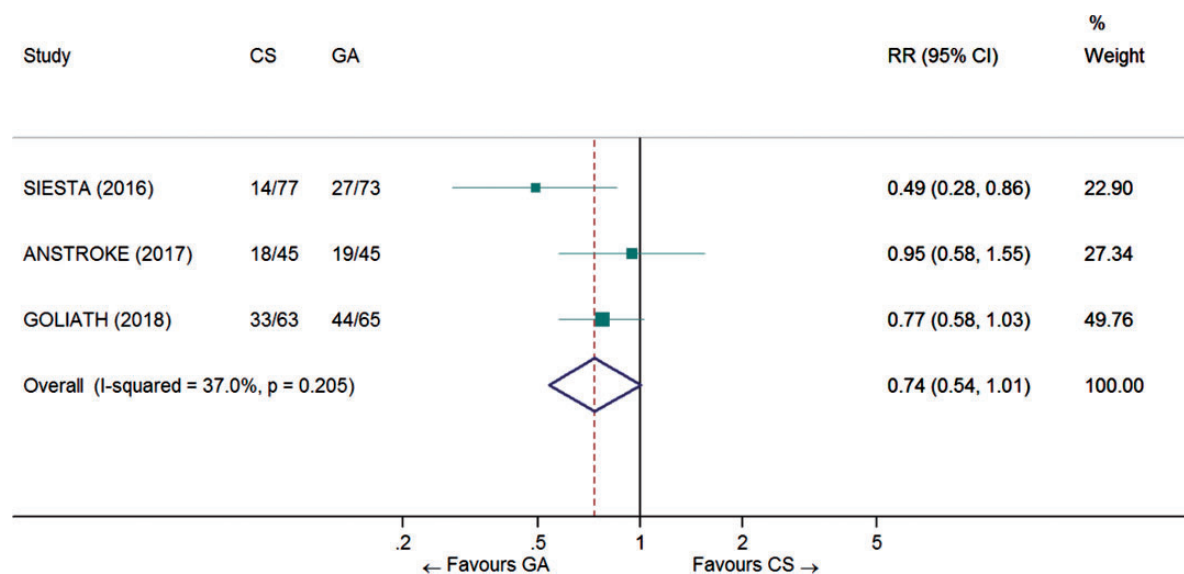


Figure 15. Pooled risk ratio for functional independence in patients undergoing conscious sedation (CS) vs. general anaesthesia (GA) for mechanical thrombectomy. Random-effects meta-analysis restricted to randomised controlled trials.

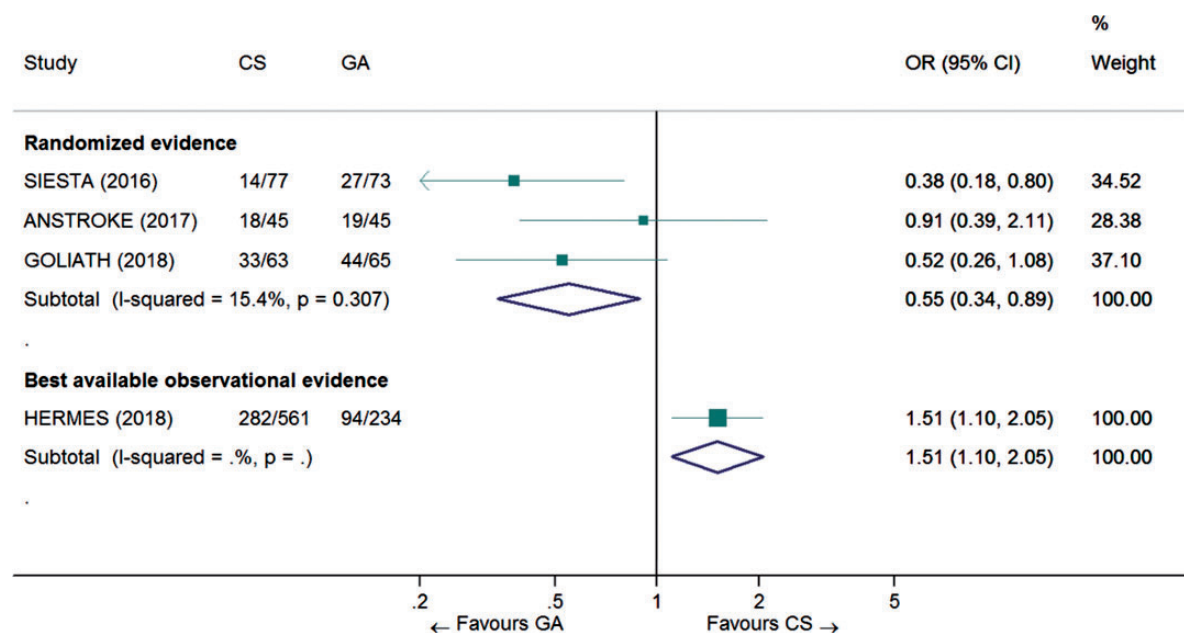


Figure 16. Unadjusted odds ratio for functional independence in patients undergoing conscious sedation (CS) vs. general anaesthesia (GA) for mechanical thrombectomy. Random-effects meta-analysis.

We consider that this analysis represents the best available observational evidence for the present PICO question, because high-quality data were prospectively collected and monitored in large multi-centre trials, allowing adjustment for several confounders. However, a major limitation of the HERMES data is the high likelihood of confounding

by indication. It is likely that patients who underwent GA had more frequently a medically required GA rather than an 'elective' GA. The QoE for the HERMES collaboration analysis was therefore considered very low (Table 11). Unfortunately, no information on the indication for GA is available in the HERMES database.

Table 11. Summary of findings for PICO 13.

Certainty assessment		No. of patients		Effect		Quality of evidence	Importance
No. of studies design	Risk of bias	GA	CS	Relative (95% CI)	Absolute (95% CI)		
mRS 0–2 (dedicated RCTs)							
3 Randomised trials	Not serious Not serious	90/183 (49.2%)	65/185 (35.1%)	RR 0.74 (0.54–1.01)	91 fewer per 1000 (from 4 more to 162 fewer)	⊕⊕○○ Low	Critical
mRS 0-2 (HERMES)							
7 Observational studies	Serious ^c Not serious	94/234 (40.2%)	282/561 (50.3%)	OR 1.65 (1.14–2.38)	122 more per 1000 (from 33 more to 204 more)	⊕○○○ Very low	Critical

CI: confidence interval; RR: risk ratio; OR: odds ratio.

^aWe believe that the setting in which the interventions in the three RCTs were performed cannot easily be implemented with the same sophistication in daily practice in many centres.

^bClinical action would differ if the upper versus the lower boundary of the 95% CI of the risk ratio represents the truth: GA would be recommended if the true RR is 0.54; GA would not be recommended if the true RR is 1.01.

^cProbable indication bias (confounding by indication): it is likely that patients who underwent GA had more frequently a medically required GA rather than an 'elective' GA.

Recommendation

We cannot provide recommendations to use general anaesthesia or conscious sedation in patients undergoing mechanical thrombectomy, due to a low quality of evidence and conflicting results between three small single-centre randomised clinical trials and the best available observational evidence. Therefore, we recommend the enrolment of patients in multicentre randomised controlled trials addressing this question.

Quality of evidence: **Very low** ⊕, Strength of recommendation: -

Additional information

Several ongoing RCTs are comparing CS or local anesthesia versus GA (Sedation Versus General Anesthesia for Endovascular Therapy in Acute Ischemic Stroke (SEGA): NCT03263117; General Anesthesia Versus Sedation During Intra-arterial Treatment for Stroke (GASS): NCT02822144; Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS): NCT03229148; Impact of Anesthesia Type on Outcome in Patients With Acute Ischemic Stroke Undergoing Endovascular Treatment (CANVAS): NCT02677415). The conflicting results of the three RCTs and the HERMES analysis are partially counterintuitive, albeit partially explained by a strictly standardised anaesthesia protocol in the RCTs versus standard of care procedures in patients recruited into the trials analysed in the HERMES collaboration.

Expert opinion

Expert opinion on anaesthesia modalities for mechanical thrombectomy

We suggest that further randomised multicentric data with less bias should be generated. However, if inclusion of the patient in a randomised controlled trial is not possible, 11/11 experts suggest that local anaesthesia or conscious sedation may be favoured over general anaesthesia, if the patient is able to undergo mechanical thrombectomy without general anaesthesia. On the other hand, general anaesthesia does not need to be avoided if indicated. The decision for or against general anaesthesia should be made rapidly and delays to induction of general anaesthesia should be minimised. We suggest, that according to the three randomised controlled trials, a specialised neuro-

Table 12. Summary of PICO questions, recommendations and expert opinion.

PICO question	Recommendations	Expert opinion
PICO 1: For adults with LVO-related acute ischaemic stroke within 6 h of symptom onset, does MT plus BMM compared with BMM alone improve functional outcome?	In adults with anterior circulation LVO-related acute ischaemic stroke presenting within 6 h after symptom onset, we recommend MT plus BMM – including IVT whenever indicated – over BMM alone to improve functional outcome. Quality of evidence: High ⊕⊕⊕⊕ Strength of recommendation: Strong ↑↑	There is a consensus among the guideline group (11/11 votes) that patients with M2 occlusion fulfilled the inclusion criteria in most randomised trials and therefore mechanical thrombectomy is reasonable in this situation. There is a consensus among the panel (11/11 votes) that in analogy to anterior circulation LVO and with regard to the grim natural course of basilar artery occlusions, the therapeutic approach with IVT plus MT should strongly be considered. Patients should be treated with MT plus BMM up to approximately 7 h 18 min after stroke onset, without the need of perfusion imaging-based selection. 10/11 experts agree that patients can be treated in the 6–12 h time window if they fulfil the ESCAPE criteria, notably ASPECTS ≥ 6 and moderate-to-good collateral circulation. However, such patients should preferably be treated in the context of clinical studies. Also, concurrent software applications utilising similar perfusion algorithms and rendering equivalent volumetry results as those used in the DAWN and DEFUSE-3 trials may be options, as well as simple volumetry on a high quality DWI scan for core volume when applying DAWN criteria. Therefore we advocate further research, inclusion of patients into late window trials, and implementation of institutional imaging standard operating procedures.
PICO 2: For adults with LVO-related acute ischaemic stroke 6–24 h from time last known well, does MT plus BMM compared with BMM alone improve functional outcome?	In adults with anterior circulation LVO-related acute ischaemic stroke presenting between 6 and 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3* or DAWN**, we recommend MT + BMM over BMM alone to improve functional outcome. Quality of evidence: Moderate ⊕⊕⊕ Strength of recommendation: Strong ↑↑	In LVO-related ischaemic stroke patients eligible for IVT before MT, 7/11 experts suggest the use of tenecteplase (0.25 mg/kg) over alteplase (0.9 mg/kg) if the decision on IVT is made after vessel occlusion status is known.
PICO 3: For adults with LVO-related acute ischaemic stroke, does IVT plus MT compared with MT alone improve functional outcome?	• In LVO-related ischaemic stroke patients eligible for both treatments, we recommend IVT plus MT over MT alone. Both treatments should be performed as early as possible after hospital arrival. MT should not prevent the initiation of IVT and IVT should not delay MT. Quality of evidence: Very low ⊕, Strength of recommendation: Strong ↑↑ • In LVO-related ischaemic stroke patients not eligible for IVT, we recommend MT as stand-alone treatment. Quality of evidence: Low ⊕⊕, Strength of recommendation: Strong ↑↑	• 11/11 experts concluded that there is currently not enough evidence to use a clinical scale in routine care to help triage of potential thrombectomy candidates in the pre-hospital field. • All patients suspected of having an acute stroke, irrespective of the time of onset, should undergo emergency imaging of the brain, including vascular imaging.
PICO 4: For adults with suspected acute stroke, does the use of a pre-hospital scale compared with no pre-hospital scale: - improve identification of patients eligible for MT? - reduce time to reperfusion?	In patients with suspected stroke, we cannot make a recommendation on the use of a pre-hospital scale for improving identification of patients eligible for MT. We suggest enrolling patients in a dedicated randomised controlled trial, whenever possible. Quality of evidence: Very low ⊕, Strength of recommendation: -	

(continued)

Table 12. Continued

PICO question	Recommendations	Expert opinion
PICO 5: For adults identified as potential candidates for MT in the pre-hospital field, does the mothership model, compared with the drip-and-ship model, improve functional outcome?	<p>We cannot make recommendations on whether for adults identified as potential candidates for MT in the pre-hospital field, the mothership or the drip-and-ship model should be applied to improve functional outcome.</p> <p>Quality of evidence: Very Low ⊕, Strength of recommendation: -</p>	<p>- As there is lack of strong evidence for superiority of one organisational model, the choice of model should depend on local and regional service organisation and patient characteristics. (Vote: 11/11 experts agree.)</p> <p>- The mothership model might be favoured in metropolitan areas, with transportation time to a comprehensive stroke centre of less than 30–45 min and the use of the drip-and-ship model when transportation times are longer (vote: 11/11 experts agree).</p> <p>- As there is limited experience with the other two models (drip-and-drive and mobile stroke unit) no expert opinion can be provided when to use these models (vote: 11/11 experts agree).</p>
PICO 6: For patients aged 80 years or more with LVO-related acute ischaemic stroke, does MT plus BMM compared with BMM alone improve functional outcome?	<ul style="list-style-type: none"> We recommend that patients aged 80 years or more with LVO-related acute ischaemic stroke within 6 h of symptom onset should be treated with MT plus BMM, including IVT whenever indicated. Application of an upper age limit for MT is not justified. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Strong ↑↑</p> <ul style="list-style-type: none"> We suggest that patients aged 80 years or more with LVO-related acute ischaemic stroke between 6 and 24 h from time last known well should be treated with MT plus BMM if they meet the eligibility criteria of the DEFUSE-3* or DAWN[†]** trials. <p>Quality of evidence: Low ⊕⊕, Strength of recommendation: Weak ↑?</p>	
PICO 7: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on a particular NIHSS score threshold compared with no specific threshold improve functional outcome ?	<ul style="list-style-type: none"> We do not recommend an upper NIHSS score limit for decision-making on MT. We recommend that patients with high stroke severity and LVO-related acute ischaemic stroke be treated with MT plus BMM, including IVT whenever indicated. These recommendations also apply for patients in the 6–24 h time window, provided that they meet the inclusion criteria for the DAWN* or DEFUSE-3** studies. <p>Quality of evidence: High ⊕⊕⊕⊕, Strength of recommendation: Strong ↑↑.</p> <ul style="list-style-type: none"> We recommend that patients with low stroke severity (NIHSS 0–5) and LVO-related acute ischaemic stroke within 24 h from time last known well be included in randomised controlled trials 	<p>In patients with a low NIHSS score (≤ 5) who are not eligible for a dedicated randomised controlled trial, we suggest that treatment with mechanical thrombectomy in addition to intravenous thrombolysis (or alone in case of contraindication to intravenous thrombolysis) may be reasonable:</p> <ul style="list-style-type: none"> - in patients with deficits that appear disabling (e.g. significant motor deficit or aphasia or hemianopia) at presentation (vote: 9/11 experts) - in the case of clinical worsening despite intravenous thrombolysis (vote: 9/11 experts) - we did not reach majority vote to suggest mechanical

(continued)

Table 12. Continued

PICO question	Recommendations	Expert opinion
<p>PICO 8: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on a particular ASPECTS or infarct core volume threshold compared with no specific threshold:</p> <ul style="list-style-type: none"> - improve identification of patients with a therapy effect of MT on functional outcome? - decrease the risk of symptomatic intracerebral haemorrhage? 	<p>comparing MT plus BMM versus BMM alone. Quality of evidence: Very Low ⊕, Strength of recommendation: -</p> <ul style="list-style-type: none"> • In the 0–6 h time window, we recommend MT plus BMM (including IVT whenever indicated) over BMM alone in LVO-related anterior circulation stroke patients without evidence of extensive infarct core (e.g. ASPECTS ≥6 on non-contrast CT scan or infarct core volume ≤70 mL). <p>Quality of evidence: High ⊕⊕⊕⊕, Strength of recommendation: Strong ↑↑.</p> <ul style="list-style-type: none"> • In the 6–24 h time window, we recommend MT plus BMM (including IVT whenever indicated) over BMM alone in LVO-related anterior circulation stroke patients fulfilling the selection criteria of DEFUSE-3* or DAWN[†]*, including estimated volume of infarct core. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Strong ↑↑.</p> <ul style="list-style-type: none"> • We recommend that anterior circulation stroke patients with extensive infarct core (e.g. ASPECTS <6 on non-contrast CT scan or core volume >70 mL or >100 mL) be included in RCTs comparing mechanical thrombectomy plus best medical management versus best medical management alone. <p>Quality of evidence: Very low ⊕, Strength of recommendation: -</p> <ul style="list-style-type: none"> - In adult patients with anterior circulation LVO-related acute ischaemic stroke presenting from 0 to 6 h from time last known well, advanced imaging is not necessary for patient selection. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Weak ↓?</p> <ul style="list-style-type: none"> - In adult patients with anterior circulation LVO-related acute ischaemic stroke presenting beyond 6 h from time last known well, advanced imaging selection is necessary. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Strong ↑↑</p>	<p>thrombectomy in patients with deficits that appear non-disabling (e.g. mild hypoesthesia) at presentation (vote: 5/11 experts)</p> <p>If inclusion of the patient in a dedicated randomised controlled trial is not possible, we suggest that treatment with MT may be reasonable on an individual basis in selected cases with ASPECTS <6 or core volume >70 mL (11/11 experts agree). Patient selection criteria might include age, severity and type of neurological impairment, time since symptom onset, location of the ischaemic lesion on plain CT scanner or MRI and results of advanced imaging, notably perfusion-core mismatch.</p>
<p>PICO 9: For adults with LVO-related acute ischaemic stroke, does selection of MT candidates based on advanced perfusion, core or collateral imaging compared with no advanced imaging</p> <ul style="list-style-type: none"> - improve identification of patients with a therapy effect of thrombectomy on functional outcome? - decrease the risk of symptomatic intracerebral haemorrhage? 	<p>Quality of evidence: Very low ⊕, Strength of recommendation: -</p> <ul style="list-style-type: none"> - In adult patients with anterior circulation LVO-related acute ischaemic stroke presenting from 0 to 6 h from time last known well, advanced imaging is not necessary for patient selection. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Weak ↓?</p> <ul style="list-style-type: none"> - In adult patients with anterior circulation LVO-related acute ischaemic stroke presenting beyond 6 h from time last known well, advanced imaging selection is necessary. <p>Quality of evidence: Moderate ⊕⊕⊕, Strength of recommendation: Strong ↑↑</p>	<p>(continued)</p>

Table 12. Continued

PICO question	Recommendations	Expert opinion
<p>PICO 10: For adults with LVO-related acute ischaemic stroke, does MT performed in a comprehensive stroke centre compared with MT performed outside of a comprehensive stroke centre:</p> <ul style="list-style-type: none"> - improve functional outcome? - reduce time to reperfusion? - reduce the rate of symptomatic intracerebral haemorrhage? <p>PICO 11: For adults with LVO-related acute ischaemic stroke, does reperfusion TICI Grade 3 compared with reperfusion TICI Grade 2b improve functional outcome?</p> <p>PICO 12: For adults with LVO-related acute ischaemic stroke, does MT using direct aspiration compared with a stent retriever improve functional outcome?</p> <ul style="list-style-type: none"> - increase the rate of complete reperfusion? <p>PICO 13: For adults with LVO-related acute ischaemic stroke undergoing MT, does conscious sedation compared with general anaesthesia improve functional outcome?</p>	<p>• In adult patients with LVO-related acute ischaemic stroke, we recommend treatment in a comprehensive stroke centre. Quality of evidence: Very low ⊕, Strength of recommendation: Strong ↑↑</p> <p>For adults with LVO-related acute ischaemic stroke, we recommend that interventionalists should attempt a TICI Grade 3 reperfusion, if achievable with reasonable safety. Quality of evidence: Low ⊕⊕, Strength of recommendation: Strong ↑↑</p> <p>- There is currently no evidence that contact aspiration alone improves functional outcome compared with BMM in patients undergoing MT. - There is currently no evidence that contact aspiration alone increases the rate of reperfusion over thrombectomy using a stent retriever. - Therefore, we suggest the use of a stent retriever over contact aspiration alone for MT in patients with acute ischaemic stroke. Quality of evidence: Very low ⊕; Strength of Recommendation: Weak↑?</p> <p>We cannot provide recommendations to use general anaesthesia or conscious sedation in patients undergoing MT, due to a low quality of evidence and conflicting results between 3 small single-centre randomised clinical trials and the best available observational evidence. Therefore, we recommend the enrollment of patients in multicentre randomised controlled trials</p>	<p>9/11 experts believe that ADAPT may be used as standard first-line treatment, followed by stent retriever thrombectomy as rescue therapy if needed. Besides, - we did not reach a majority vote on that distal aspiration should be used only in combination with a stent-retriever (3/11 experts) - 8/11 experts believe that any MT procedure should be performed preferably in conjunction with a proximal balloon guide catheter. We suggest that further randomised multicentric data with less bias should be generated. However, if inclusion of the patient in a randomised controlled trial is not possible, I/II experts suggest that local anaesthesia or conscious sedation may be favoured over general anaesthesia, if the patient is able to undergo MT without general anaesthesia. On the other hand,</p>

(continued)

Table 12. Continued

PICO question	Recommendations	Expert opinion
	<p>addressing this question.</p> <p>Quality of evidence: Very low ⊕, Strength of recommendation: -</p>	<p>general anaesthesia does not need to be avoided if indicated. The decision for or against general anaesthesia should be made rapidly and delays to induction of general anaesthesia should be minimised. We suggest, that according to the three randomised controlled trials, a specialised neuro-anaesthesiological or neurocritical care team should perform the general anaesthesia procedure, whenever possible. Excessive blood pressure drops should be avoided (see PICO question 14). Adequate monitoring of vital parameters also of patients under conscious sedation or local anaesthesia is advised.</p>
<p>PICO 14: For adults with LVO-related acute ischaemic stroke undergoing MT, does maintaining blood pressure to a particular target compared with an alternative target improve functional outcome?</p>	<ul style="list-style-type: none"> We suggest to keep blood pressure below 180/105 mmHg during and 24 h after MT. No specific blood pressure-lowering drug can be recommended. <p>Quality of evidence: Very low ⊕, Strength of recommendation: Weak ↑</p> <ul style="list-style-type: none"> During MT systolic blood pressure drops should be avoided. <p>Quality of evidence: Very low ⊕, Strength of recommendation: Strong ↓↓</p> <ul style="list-style-type: none"> No recommendation can be provided regarding which treatment modality should be favoured in patients with LVO-related acute ischaemic stroke and associated extracranial carotid artery stenosis or occlusion. We recommend the inclusion of such patients in dedicated randomised controlled trials. <p>Quality of evidence: Very low ⊕, Strength of recommendation: -</p>	<p>I/II experts think that the degree of reperfusion should be taken into account in the choice of a blood pressure target after MT, with a lower blood pressure target in case of complete reperfusion.</p>
<p>PICO 15: For adults with LVO-related acute ischaemic stroke and high-grade ipsilateral extracranial carotid stenosis, does cervical stenting in addition to MT compared with MT alone improve functional outcome ?</p>	<ul style="list-style-type: none"> No recommendation can be provided regarding which treatment modality should be favoured in patients with LVO-related acute ischaemic stroke and associated extracranial carotid artery stenosis or occlusion. We recommend the inclusion of such patients in dedicated randomised controlled trials. <p>Quality of evidence: Very low ⊕, Strength of recommendation: -</p>	<p>9/II experts suggest that if inclusion in a dedicated randomised controlled trial is not possible, patients with high-grade stenosis or occlusion may be treated with intra-procedural stenting if unavoidably needed.</p>

IVT: intravenous thrombolysis; LVO: large vessel occlusion; MT: mechanical thrombectomy.

*6–16 h since time last known well:

- Age ≤90 years and NIHSS ≥6: infarct core volume <70 mL and penumbra volume >15 mL and penumbra volume/core volume >1.8.

**6–24 h since time last known well:

- Age <80 years: infarct core 30 mL if NIHSS ≥10; infarct core 51 mL if NIHSS ≥20.

- Age ≥80 years: infarct core 20 mL and NIHSS ≥10.

anaesthesiological or neurocritical care team should perform the general anaesthesia procedure, whenever possible. Excessive blood pressure drops should be avoided (see PICO question 14).¹³⁴ Adequate monitoring of vital parameters also of patients under conscious sedation or local anaesthesia is advised.

PICO 14: For adults with LVO-related acute ischaemic stroke undergoing MT, does maintaining blood pressure to a particular target compared with an alternative target improve functional outcome?

Analysis of current evidence and evidence-based recommendation

Blood pressure (BP) targets, for patients with LVO-related acute ischaemic stroke undergoing MT, were not specifically evaluated in RCTs. Post-hoc analyses from MR CLEAN indicated a U-shaped correlation between baseline systolic blood pressure (SBP) and functional outcome.¹³⁵ Both low and high baseline SBP were associated with three-month poor functional outcome, whereas higher SBP levels were associated with symptomatic intracranial haemorrhage (adjusted OR = 1.25 for every 10 mmHg increment in SBP, 95% CI: 1.09–1.44). Retrospective studies suggest also an association between baseline SBP and mortality following a similar U-shaped correlation. During the first 24 hours following MT, each 10 mmHg increment in SBP is associated with increased three months poor functional outcome (OR = 0.70; 95% CI: 0.56–0.87) and mortality (OR = 1.49; 95% CI: 1.18–1.88).¹³⁶ Retrospective data support also that achieving a BP goal below 160/90 mmHg is associated with decreased three-month mortality rates (OR = 0.08; 95% CI: 0.01–0.54).¹³⁷ Additionally, mean arterial BP falls during MT procedures, as low as 10%, were reported to be a risk factor for poor outcome in patients eligible to MT.¹³⁴ Interpretation of these pieces of evidence should be done keeping in mind that studied populations are often heterogenous, mixing patients with different reperfusion statuses (i.e. complete vs. incomplete or no reperfusion) and medical histories (e.g. with or without history of hypertension). In fact, the impact of BP reduction may be different considering different patient characteristics. There is no strong evidence to support the use of a specific BP-lowering drug in the setting of MT.

According to the GRADE methodology, the QoE of these recommendations based on observational data

was downgraded from low to very low due to indirectness.

Recommendations

- We suggest to keep blood pressure below 180/105 mmHg during and 24 h after mechanical thrombectomy. No specific blood pressure-lowering drug can be recommended.
Quality of evidence: **Very low** ⊕, Strength of recommendation: **Weak** ↑?
- During mechanical thrombectomy systolic blood pressure drops should be avoided.
Quality of evidence: **Very low** ⊕, Strength of recommendation: **Strong** ↓↓

Expert opinion

The quality of available studies does not allow the guidelines writing group to provide evidence-based recommendations for a different BP target in patients with versus without successful reperfusion. There is evidence from observational studies that patients with successful reperfusion (TICI 2b or 3) following MT are at risk of reperfusion haemorrhage and may therefore warrant a tight BP control, such as a target below 160/90 mmHg.^{137,138} Conversely, some authors advocated for permissive hypertension in patients with incomplete reperfusion because it may help optimise collateral blood flow and maintain brain perfusion pressure.^{139,140} In one observational study, symptomatic intracranial haemorrhage was observed at lower mean values of maximum SBP in patients with successful reperfusion compared with patients without (170 ± 9.1 vs. 196 ± 8.1 mmHg, $p = 0.05$).¹³⁸

Expert opinion on blood pressure targets after mechanical thrombectomy

11/11 experts think that the degree of reperfusion should be taken into account in the choice of a blood pressure target after mechanical thrombectomy, with a lower blood pressure target in case of complete reperfusion.

This was a common viewpoint in a recent U.S. survey as well.¹⁴¹ However, further prospective and randomised data are needed to further inform clinical decision-making.

PICO 15: For adults with LVO-related acute ischaemic stroke and high-grade ipsilateral extracranial carotid stenosis, does cervical stenting in addition to MT compared with MT alone improve functional outcome?

Analysis of current evidence and evidence-based recommendation

The only trial in which LVO-related acute stroke patients underwent a randomisation regarding the treatment of an associated cervical carotid stenosis or occlusion was the EASI care trial.¹⁸ However, that study was not primarily designed nor powered to address that question, but rather to evaluate MT plus BMM versus BMM alone. The very small numbers of patients simultaneously randomised to treatment or no treatment of a cervical carotid stenosis or occlusion ($n=8$) does not allow to draw any conclusion on the potential benefits of cervical stenting.

Four of the pivotal RCTs of MT allowed the inclusion of patients with extracranial cervical carotid stenosis or occlusion: MR CLEAN,¹ EXTEND-IA,² ESCAPE³ and REVASCAT.⁵ In SWIFT-PRIME, carotid occlusion requiring stenting was an exclusion criteria but angioplasty could be performed.⁴ In all trials, the treatment of a tandem lesion was left at the discretion of the interventionalist, with a wide panel of available endovascular approaches, namely no treatment of the cervical lesion, angioplasty, stenting, angioplasty and stenting. It was also left at the discretion of the interventionalist whether the cervical lesion or the intracranial occlusion should be treated first. Hence, those trials do not allow to draw any conclusion regarding the best strategy to treat extracranial stenosis or occlusion.

Importantly, benefit from MT was observed for patients with or without extracranial cervical carotid stenosis or occlusion: in an individual patient data meta-analysis of the first five RCTs conducted by the HERMES collaboration, common ORs for a better functional outcome were 2.95 (95% CI: 1.38–6.32) and 2.35 (95% CI: 1.68–3.28) in patients with and without tandem lesion, respectively ($p_{\text{interaction}}=0.17$).⁶

Recommendation

- No recommendation can be provided regarding which treatment modality should be favoured in patients with large vessel occlusion-related acute ischaemic stroke and associated extracranial carotid artery stenosis or occlusion. We recommend the inclusion of such patients in dedicated randomised controlled trials.

Quality of evidence: **Very low**⊕, Strength of recommendation: -

Additional information

A recently published systematic review and meta-analysis aimed to compare the following therapeutic approaches in adults with LVO-related acute ischaemic stroke and extracranial carotid occlusion (i.e. tandem occlusion): (a) stenting versus angioplasty alone for the extracranial lesion and (b) treatment of the intracranial versus extracranial lesion first.¹⁴² However, the number of patients in each study were very small and most importantly only indirect comparisons could be performed, without adjustment for potential confounding factors. A total of 13 studies provided data in patients undergoing extracranial stenting, with a pooled rate of functional independence (mRS ≤ 2) of 49% (95% CI: 42–56%; $I^2=54\%$), while three studies provided data in patients solely treated with angioplasty, with a pooled rate of functional independence of 49% (95% CI: 33–65%; $I^2=50\%$). There was no significant heterogeneity between the two groups ($p=0.39$). There was also no evidence of significant heterogeneity in the pooled rates of functional independence in patients treated with the ‘intracranial first’ (7 studies; 49%, 95% CI: 39–60%; $I^2=31\%$) or ‘extracranial first’ (8 studies; 53%, 95% CI: 44–61%; $I^2=11\%$) therapeutic approaches ($p=0.58$ for heterogeneity between the two groups).

Another recent systematic review and meta-analysis, including predominantly retrospective multicentre studies, reported that stenting for extracranial cervical carotid stenosis or occlusion was associated with a pooled rate of functional independence of 53% (95% CI: 43–62%), a mTICI $\geq 2b$ rate of 80% (95% CI: 73–87%), a 90-day mortality rate of 14% (95% CI: 9–19%), and a symptomatic intracranial haemorrhagic rate of 7% (95% CI: 4–12%).¹⁴³

Expert opinion

Overall, the above-mentioned results are comparable to those of patients without extracranial cervical carotid stenosis who undergo MT. Emergency stenting in patients undergoing thrombectomy also seemed to be reasonably safe without an increase of sICH, especially if glycoprotein IIb/IIIa inhibitors are avoided.¹⁴⁴

Expert opinion on carotid artery stenting in mechanical thrombectomy patients with high-grade cervical stenosis or occlusion

9/11 experts suggest that if inclusion in a dedicated randomised controlled trial is not possible, patients

with high-grade stenosis or occlusion may be treated with intra-procedural stenting if unavoidably needed.

Restoration to normal calibre (100%) of the carotid stenosis should probably be avoided in the acute stage as it might increase the risk of reperfusion injury and intracerebral haemorrhage.

Discussion

This Guideline document was developed following the GRADE process and is aimed to assist physicians in decision making in patients with LVOs and potential MT therapy.^{11,12} It includes new scientific evidence from the last two years and supersedes the previously published EROICAS recommendations.⁸ All recommendations and expert opinions are summarized in table 12.

Although the number of studies with highest scientific quality in the field has increased impressively over the last few years, 14 out of 22 recommendations are based on low or very low QoE. Still, much of the evidence was derived from observational studies, and the influence of bias from such studies on efficacy is well known.¹⁴⁵ For ethical and practical reasons, not all open questions in medical science can be answered by randomised trials, specifically in surgical innovations and in the field of medical devices.^{146,147} Other multi-centre academic collaboration is a key element to improve our knowledge on MT. Registries, observational studies and treatment trials contribute valuable supplementary information.¹⁴⁸

To support physicians in their practical decision making, expert opinions are given in a dedicated paragraph. Whenever appropriate, these opinions were systematically collected as polls. About half of these polls lead to a good agreement of 9–11 of the 11 experts. In the remaining questions, the experts' opinions varied considerably. The recommendations with very low evidence background and poor agreement among experts were on the subjects of 'IVT plus MT compared with MT alone' (PICO 3) and 'direct aspiration compared with a stent retriever' (PICO 12). Fortunately, trials are under way to increase the scientific evidence to better answer these questions.

Enrolling patients in a dedicated RCT, whenever possible, was specifically recommended for PICO 4 (pre-hospital scales), PICO 8 (extensive infarct core), PICO 13 (type of anaesthesia), and PICO 15 (acute carotid stenting). Several trials on these and other subjects are currently under way. Trials studying subjects such as type of anaesthesia compete with studies on new therapies and devices, some of them with generous

industry support. National and international societies are starting to get involved. All these trials will increase the experience and knowledge of interventionalists in conducting trials in the neurointerventional field. These developments are very positive for the progress of science and the welfare of patients. The authors of this guideline are convinced that several current gaps in our knowledge about MT will be closed by high quality studies during the next few years.

There is a large gap between the state of the art as described in these guidelines and the reality of care in many European countries, leaving many patients untreated.¹⁴⁹ ESO and ESMINT will help to support governments, health care providers and European politicians to develop strategies to implement MT to further reduce stroke-related mortality and morbidity in Europe.¹⁵⁰ This guideline document will hopefully play a central role in this process.

Plain language summary

The ESO-ESMINT guidelines on mechanical thrombectomy (MT) strongly recommend MT plus best medical treatment (BMT) including intravenous thrombolysis in stroke patients with the occlusion of a large brain supplying artery (LVO). Based on the quality of the scientific evidence, the committee was able to make weak or strong recommendations for different patient groups and different therapy approaches. There is a high quality of evidence (QoE) and strong recommendation for MT in combination with BMT within the 6 hours after stroke symptom onset and a moderate QoE up to 24 h. With moderate to low QoE this applies also to patients aged over 80 years for the early and the late time window, respectively. There is no evidence for an upper stroke severity limit. However, LVO patients with low severity (NIHSS scores lower than 6) should be included into clinical trials whenever possible. If imaging prior to therapy shows a very large infarct already, the participation in a clinical study is recommended.

Whether MT alone is not inferior to combined IVT/MT is a matter of debate and ongoing trials. With a low level of evidence it is strongly recommended to perform both treatments whenever indicated without the one or the other causing treatment delays for either one.

Complete reperfusion of the entire brain tissue is related to improved outcomes compared with incomplete reperfusion and if safely achievable should be the treatment goal. While the recommendation has low QoE, this recommendation is strong.

Furthermore there is currently no evidence that contact aspiration of the blood clot alone improves reperfusion rates or good outcomes over MT with a stent

retriever; however, the initial use of this aspiration technique followed by MT with a stent retriever is deemed appropriate. There is no evidence to provide a recommendation for or against stenting of the brain supplying artery of the neck (carotid artery) if occluded on the way up to the brain. Intraprocedural stenting may be performed if unavoidable for successful MT. There is no evidence for any recommendation in terms of general anaesthesia versus conscious sedation or local anaesthesia for the MT procedure. General anaesthesia should neither be favoured if not needed nor be avoided, if necessary, trying to prevent severe drops in blood pressure. Besides the general recommendation to keep blood pressure below 180/105 mmHg within the first 24 h, there is no evidence or recommendation for a specific target blood pressure.

It is not recommended to select patients for MT based on advanced imaging methods within 6 h after symptom onset. At later times from symptom onset, MT requires advanced imaging showing small brain lesion volume or a clinical/imaging-based mismatch with a neurological deficit exceeding the small lesion volume.

There is no evidence for the benefit of a pre-hospital method to identify patients eligible for MT by clinical judgment alone. Also there is no evidence-based recommendation with regard to the preferred organisational model of how to get the patient to the MT, the typical two of these known as drip-and-ship or mothership. Generally speaking, as there is lack of strong evidence for superiority of one organisational model, the choice of model should depend on local and regional service organisation and patient characteristics. Both of these questions are matter of debates and also clinical trials. While the QoE is very low, the guidelines strongly recommend that MT is performed in a comprehensive stroke center.

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GT and JF drafted the PICO questions, which were refined by all authors (GT, PB, UF, PK, KL, MM, PDS, DT, JdV, PW, JF). GT and JF conducted the literature search. GT conducted data extraction and performed meta-analyses. All authors (GT, PB, UF, PK, KL, MM, PDS, DT, JdV, PW and JF) participated in the writing of the first draft of the manuscript. All authors reviewed and edited the manuscript for important intellectual content and approved the final version of the manuscript.

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