

EVMS JC: Critical Appraisal Worksheet: Systematic Review/Meta-analysis

Resident: Whitty

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Citation: Roaldsen MB, et al., [Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke](#). Cochrane Database Syst Rev. 2021 Dec 1;12(12)

Guide	
1. Did the review explicitly address a sensible question?	Yes, 'Do patients with wake-up-stroke symptoms benefit from recanalization therapy without appreciably increasing mortality risk?'
2. Was the search for relevant studies details and exhaustive?	<p>Yes, searched Cochrane stroke group trials register as well as:</p> <ul style="list-style-type: none"> • Cochrane central register of controlled trials • MEDLINE Ovid • Embase Ovid • US NIH ongoing trials register • WHO international clinical trials registry • Stroke trials registry <p>In addition, the authors:</p> <ul style="list-style-type: none"> • Screened reference lists of relevant trials • Contacted PIs of identified trials • Used science citation index cited reference search • Contacted manufacturers of relevant devices
3. Were the primary studies of high methodological quality?	<p>Yes, authors followed GRADE guidelines for systematic reviews. Therefore, studies were independently assessed for risk of bias and were assessed according to the following:</p> <ul style="list-style-type: none"> • Random sequence generation • Allocation concealment • Blinding of both participants and personnel • Blinding of outcome assessment • Whether or not there was incomplete outcome data • Selective outcome reporting • "Other bias" <p>Studies were deemed to be low or high risk for bias..</p> <p>The seven included studies were assessed as having low risk of bias with regard to selection</p>

	<p>bias, low or unclear risk of attrition bias, low risk of reporting bias. 6 of 7 trials were prematurely terminated d/t lack of funding, slow enrollment, lack of equipoise, or interim analyses showing efficacy -> assessed as unclear for other bias with regard to these six studies. (ECASS-4, EXTEND, THAWS, WAKE-UP, DAWN and DEFUSE3)</p>
<p>4. Were the criteria for study inclusion pre-determined and clearly stated?</p>	<p>Yes. authors applied GRADE and PRISMA guidelines for systematic reviews.</p> <p>Inclusion Criteria: Randomised controlled trials (RCTs) of intravenous thrombolytic drugs or endovascular thrombectomy treatments in people with acute ischaemic stroke presenting upon awakening.</p> <p>The authors did, complete a prisma diagram [Figure 1] and document reasons for exclusion.</p> <ul style="list-style-type: none"> • 355 duplicate references were excluded • 1709 records assessed, 1698 excluded d/t not being randomized trials of wake-up stroke • 11 studies assessed in full, and 7 included • 2 ongoing trials excluded, as well as POSITIVE trial, whose investigators failed to reply to request to share data. • NCT01455935 was put on hold and was excluded for that reason.
<p>5. Did the authors adequately assess the quality of the included studies?</p>	<p>Yes, they assessed for bias in allocation, blinding, attrition, selective reporting, and “other potential sources of bias.”</p> <p>The authors also looked at effects of interventions in each study with regard to patient important outcomes. The authors also conducted subgroup analyses.</p>
CLINICAL IMPORTANCE	
<p>6. What were the overall results of the review?</p> <p><i>(Are the results of all included studies clearly displayed? Are the results similar from study to study? Is there a clinical bottom line? If the study results combined, was it appropriate to do so?)</i></p>	<p>Intravenous thrombolytic treatment (mRS 0-2) N=775 5 RCT's 66% (TPA) vs. 58% (control) (risk ratio (RR) 1.13, 95% confidence interval (CI) 1.01 to 1.26; P = 0.03; 763 participants, 5 RCTs; high-certainty evidence</p> <p>Endovascular thrombectomy (mRs 0-2) N=205 2 studies 46% (thrombectomy) vs. 9% (control) (RR 5.12, 95% CI 2.57 to 10.17; P <0.001; 205 participants, 2 RCTs; high-certainty evidence).</p>

	<p>No differences in 90 day mortality</p> <p>“Recanalization therapies with endovascular thrombectomy of large vessel occlusion in the anterior circulation and thrombolytic treatment with intravenous alteplase seem to be safe and effective treatments in highly selected patients with wake-up stroke”</p> <p>Results of all studies are clearly displayed, (not necessarily the numbers but the authors analyses and their overall conclusions, though references to each study are provided and easily accessible) results are similar from study to study. It is important to note that the effect of these interventions is somewhat reduced when studies combined vs individually, though still significant.</p> <p>Clinical Bottom Line: wake up stroke arriving in the ED between 6 and 24 hours of onset still likely to benefit from one of the two interventions (thrombectomy RR 5.12 vs thrombolytics, RR 1.13).</p>
<p>8. Were the results similar from study to study?</p>	<p>Yes, there seems to be study to study agreement, with very little exception.</p>
APPLICABILITY	
<p>9. How can I best interpret the results to apply them to the care of my patients?</p>	<p>The authors did not discuss or compare the demographics of the patient populations in each study, so without looking at the demographics for each one individually, it’s difficult to know how generalizable the data is to our patient populations.</p> <p>However, overall the data reviewed in this systematic review supports intervention with either thrombolysis or thrombectomy (favoring thrombectomy) for patients with wake up stroke coming into the ED between 6 and 24 hours from last known normal.</p>
<p>10. Were all patient important outcomes considered?</p>	<p>I believe so. They included analysis based on good functional outcomes (using modified Rankin scale), Death at 90 days and also looked at patient important adverse effects such as intracranial hemorrhage incidence as well as subgroup analysis grouped by demographics (age, sex)</p>

<p>11. Are the benefits worth the costs and potential risks?</p>	<p>Yes, there is a clear benefit to intervention for wake-up-strokes, up to the studied upper limit of 24 hours from last known normal. Thrombectomy seems to perform better than thrombolysis, but both produce reliable good functional outcomes at acceptable levels of risk of death at 90 days or symptomatic intracranial hemorrhage. Costs of long term care likely significant.</p>
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Limitations:

- Some included studies were small
 - DAWN and DEFUSE -> no # in characteristics table
 - ECASS4 – 63 wake up strokes plus unpublished data
 - Michel 2012 – 9 wake up strokes and 3 non-wake up with unknown onset
 - THAWS – 89 wake up strokes plus unpublished
 - WAKE-UP – 449 wake up strokes plus unpublished.
- Some included studies included differing types of advanced imaging criteria for selection of patients to treatment
- Participants and investigators in three of the included trials were not blinded (DAWN, DEFUSE 3 and THAWS)
- All included trials terminated prematurely except Michel 2012 and may lack statistical power
- Most of patients from WAKE-UP (449) – could skew data

Clinical Bottom Line:

Data in this review seems to support thrombectomy and thrombolytics for patients with wake up stroke arriving in the ED between 6 and 24 hours of onset, thrombectomy numbers are better (RR 5.12 for good functional outcome; vs RR 1.13 for thrombolysis), but both improve functional outcomes without significantly increasing risk of death at 90 days (both interventions with RR 0.68) for selected patients.

Authors conclusions -> “There is good evidence that intravenous thrombolytic treatment improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke. There is also good evidence that endovascular thrombectomy treatment substantially improves functional and neurological outcomes without increasing death in selected patients with wake-up stroke”