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Endovascular therapy for acute ischaemic stroke: a systematic review and meta-analysis of randomized trials

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Aims Evidence from randomized controlled trials (RCTs) evaluating possible benefits of endovascular therapy (EVT) for acute ischaemic stroke has shown conflicting results. The purpose of this meta-analysis was to systematically examine clinical outcomes in RCTs comparing the use of intravenous (IV) fibrinolysis alone to IV fibrinolysis plus EVT, for the treatment of acute ischaemic stroke.

Methods and results We selected English language RCTs, comparing EVT plus IV tissue-type plasminogen activator (tPA) (if eligible) with IV tPA alone in eligible patients for the treatment of acute ischaemic stroke. The primary endpoint was good functional outcome [modified Rankin Scale (mRS) of 0–2]. Other major endpoints of interest were all-cause mortality and symptomatic intracerebral haemorrhage (sICH). The meta-analysis included 8 RCTs that randomized 2423 patients with large-vessel, anterior-circulation stroke. EVT significantly improved the rate of functional independence (90-day mRS of 0–2) when compared with IV fibrinolysis [odds ratio (OR) 1.73, 95% confidence interval (CI) 1.18–2.53, number needed to treat (NNT) = 9.3]. The all-cause mortality was lower with EVT compared with the control group; however, the result did not reach statistical significance (OR 0.89, 95% CI 0.68–1.15). The rate of sICH was not higher with EVT (OR 1.07, 95% CI 0.73–1.56). Analyses from only the recent trials (reported in 2014–15) showed further benefit (OR of mRS 0–2: 2.42, 95% CI 1.91–3.08, NNT = 5) with similar safety results.

Conclusion In centres with advanced systems of stroke care, EVT significantly improved functional outcomes (without compromising safety) in patients with acute ischaemic stroke due to anterior circulation, large artery occlusion, compared with standard therapy.

Keywords Stroke • Endovascular • Thrombolytics • Meta-analysis • Outcomes

Introduction

Ischaemic stroke is a potentially devastating condition and is a leading cause of neurological morbidity and mortality worldwide.[1,2] Intravenous (IV) fibrinolytic therapy (tissue-type plasminogen activator, tPA) and treatment in a stroke unit are two proven treatments for acute ischaemic stroke. Use of IV tPA is limited to a time period of up to 4.5 h after the onset of symptoms. Some

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studies have shown limited response to IV tPA in specific circumstances such as large clots in the distal internal carotid artery or in the first segment of the middle cerebral artery. These patients are less likely to quickly recanalize their occlusions and thus respond poorly to IV thrombolysis.[1–4] Data from registries and observational studies showed recanalization rates after IV thrombolysis is only 40–50%.[2,4] Endovascular therapy (EVT) meets two primary needs: (i) an alternate therapeutic approach to salvage patients who respond poorly to IV agents and (ii) to treat patients who are otherwise ineligible for IV fibrinolysis because of systemic anticoagulation, recent surgery, or a variety of other reasons.[2,4] However, three large randomized controlled trials (RCTs) of EVT published in 2013 did not show any additional benefit with EVT compared with IV thrombolytics alone.[5–7] Subsequent trials were constructed using a more evolved understanding of the potential role for endovascular procedures. Thus, a more refined patient cohort was identified for the newer trials by using more sophisticated imaging techniques, and treatment was performed using next generation thrombectomy devices.[8–12] The care of most stroke victims including those receiving EVT requires intensive training on the part of the operator, close post-procedural monitoring in specialized neurological intensive care, rehabilitation, and allocation of significant health resources.[2,4,8] Recent evidence from randomized trials evaluating the effects of EVT for acute ischaemic stroke showed conflicting results.[5–13] In view of these conflicting results noted in available data, we performed a meta-analysis of contemporary trials and an up-to-date systematic review of the available evidence.

Methods

Data sources and searches

We searched PubMed, Cochrane CENTRAL, EMBASE, EBSCO, Web of Science, and CINAHL databases from 1 January 1995 (year of publication of the NINDS rt-PA Stroke trial)[14] through 15 May 2015, for English language, peer-reviewed publications. We identified published randomized trials that compared EVT (in the form of intra-arterial thrombolytic administration and/or thrombectomy) plus IV tPA (if eligible) with IV tPA alone or standard therapy (if not tPA eligible) for the treatment of acute ischaemic stroke. The following Medical Subject Heading terms and/or keywords were used for database searches: 'stroke', 'cerebrovascular accident', 'ischemic stroke', 'transient ischemic attack', 'cerebral ischemia', 'cerebrovascular disorder' , and 'thrombolysis', 'intravenous thrombolysis', 'intra-arterial therapy', 'intra-arterial thrombolysis', 'endovascular treatment', 'endovascular therapy', 'thrombectomy', and 'catheter-based treatment'. Related reviews, clinical trial databases, and the reference lists of all retrieved articles were also searched manually for relevant studies.

Study selection

We included trials with at least 12 weeks of follow-up. Single-arm phase I or II studies[15,16] were not included as they did not directly compare EVT of stroke with currently recommended IV tPA. We also did not include single-arm trials or trials with predominant use of urokinase (>50% patients) as the IV thrombolytic agent.[17,18] Both double-blind- and open-label trial designs were eligible for inclusion. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs for the protocol of our meta-analysis.[19]

Data extraction and quality assessment

Four physician reviewers (P. Sardar, S.C., A.K., and P. Sen) independently extracted data from relevant published articles, after determining the eligibility for inclusion. Disagreements regarding data incorporation were resolved by consensus among all authors. Methods specified in the Cochrane Handbook of Systematic Reviews were followed for objective assessment of the included trials.[20] Data were from published sources regarding total number of treated patients, duration of follow-up, and specifics of the intervention and control groups. The occurrence of the following events was abstracted for individual trials and separately for the endovascular treatment and comparator arms: population with modified Rankin Score (mRS)[21] of 0–2 (indicating reasonably good functional outcome at 90 days or at longest available follow-up), all-cause mortality, and symptomatic intracerebral haemorrhages (sICHs). EVT-related device or procedural complication data were also retrieved.

Data synthesis and analysis

To combine the data from each study, random-effects models of DerSimonian and Laird[22] were used to calculate a summary estimate across all included studies. Analysis using fixed-effects models was carried out in the absence of heterogeneity, as a sensitivity analysis. We calculated the odds ratio (OR) estimates and associated 95% confidence intervals (CIs) for each of the endpoints. Cochran's *Q*-test and the Higgins I^2-test were used for heterogeneity testing. A Cochran's Q $P < 0.10$ and $I^2 > 50\%$ were considered indicative of significant heterogeneity. Funnel plots graphically showing the logarithm of the standard error and the effect size to evaluate publication bias were also created. Sensitivity analyses planned a priori were performed to identify the effect of a single trial by sequential elimination of each trial from the pool and then to assess the overall outcomes. We performed a sensitivity analysis with data from newer trials (reported in 2014–15), which included well-selected patients and used modern imaging and state-of-the-art devices. We also conducted meta-regression analysis exploring the potential for effect modification by multiple variables, including age, female sex, stroke severity (NIHSS score at baseline), IV tPA use, time from stroke onset to randomization, stroke onset to groin puncture, stroke onset to reperfusion in EVT group, use of stent retrievers, and the rate of successful reperfusion (TICI score of 2b or 3). All tests were two-tailed with a *P*-value of <0.05 considered significant. Analyses were performed using the Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark) and Stata 12 (StataCorp LP, College Station, TX, USA) software. Objective evaluation of trial quality and risk of bias in reporting data for individual studies was carried out according to Cochrane metrics.[20]

Results

Description of study characteristics

The database search yielded 374 publications with an additional 32 reports found from other sources (Supplementary material online, *Figure S1*). Finally, eight randomized trials ($N = 2423$) were included in our meta-analysis.[5–12] We excluded conference abstracts, for which full text was not published, to ensure high-quality data.[13] The characteristics of the included trials are provided in *Table 1* and Supplementary material online, *Table S1*. Comparator groups in all the trials received IV thrombolytics if eligible for such therapy (IV tPA in seven trials and IV tPA or urokinase in only one trial). Five trials were discontinued before their completion: one because of

Table 1 Characteristics of included trials

Variable	IMS III 2013	MR RESCUE 2013		SYNTHESIS Expansion 2013	MR CLEAN 2015	ESCAPE 2015	EXTEND-IA 2015	SWIFT PRIME 2015	REVASCAT 2015
		Penumbral	Non-penumbral						
	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control
Total	434/222	34/34	30/20	181/181	233/267	165/ 150	35/35	98/98	103/103
Follow-up (days)	90	90	90	90	90	90	90	90	90
Location	58 centres in USA, Canada, Australia, and Europe	22 sites, North America		24 sites, Italy	16 sites, The Netherlands	22 centres worldwide in USA, Canada, UK, and South Korea	14 centres in Australia and New Zealand	39 sites, USA and Europe	4 centres in Spain
Trial design	PROBE design	PROBE design		PROBE design	PROBE design	PROBE design	PROBE design	PROBE design	PROBE design
IV tPA in EVT group	Yes	Yes		No	Yes	Yes	Yes	Yes	Yes
Maximum delay for initiation of EVT (h)	5	8		6	6	12	6	6	8
Premature termination and reason	Yes, because of futility	No		No	No	Yes, because of external evidence/ efficacy	Yes, because of external evidence/efficacy	Yes, because of external evidence/ efficacy	Yes, because of external evidence/ efficacy
Vessel imaging required CTA/MRA/ DSA	Not required in initial protocol, later amendment	Yes		No	Yes	Yes	Yes	Yes	Yes
Other imaging modality for trial inclusion	NCCT	NCCT		NCCT	NCCT	NCCT, collateral assessment on multiphase CTA	NCCT, CT perfusion imaging	NCCT, CT perfusion imaging (81%), MRI (in few patients)	NCCT, MRI
Control group therapy	IV tPA	IV tPA		IV tPA	IV alteplase or urokinase	IV alteplase	IV alteplase	IV tPA	IV alteplase (when eligible)
Primary efficacy outcome	mRS of 2 or less at 90 days	mRS at 90 days		mRS at 90 days	mRS at 90 days	mRS at 90 days	Median reperfusion at 24 h and early neurological improvement	mRS at 90 days	Severity of global disability at 90 days on mRS

Continued

Table 1 *Continued*

Variable	IMS III 2013	MR RESCUE 2013		SYNTHESIS Expansion 2013	MR CLEAN 2015	ESCAPE 2015	EXTEND-IA 2015	SWIFT PRIME 2015	REVASCAT 2015
		Penumbral	Non-penumbral						
	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control	EVT/control
Total	434/222	34/34	30/20	181/181	233/267	165/ 150	35/35	98/98	103/103
Other efficacy outcomes	NIHSS, Barthel Index, Trail Making Test, and the EuroQoL EQ-5D	Final infarct volume		NIHSS Score	NIHSS Score, Barthel Index, EQ-5D Score	NIHSS Score, Barthel Index, Modified AOL Score, EQ-5D visual-analogue scale score	mRS at 90 days	NIHSS, functional independence	Infarct volumes, NIHSS Score, Barthel Index

CTA, computed tomographic angiography; CT, computed tomography; DSA, digital-subtraction angiography; EVT, endovascular therapy; EQ-5D, the EuroQoL Group 5-Dimension Self-Report Questionnaire; IV tPA, intravenous tissue-type plasminogen activator; MRA, magnetic resonance angiography; mRS, modified Rankin Score; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NCCT, non-contrast CT; PROBE, Prospective Randomized Open Blinded End-point.

futility[5] and four because of efficacy or external evidence of benefit with EVT.[9–12] The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) trial[7] had two cohorts: penumbra and non-penumbra; we combined the data from these two cohorts for our analysis. All trials included patients with large-vessel, anterior-circulation ischaemic stroke. Average duration of follow-up was 3 months. Mean duration from the stroke onset to randomization was 223 ± 67 min in the EVT group and 231 ± 81 min in the control group (Supplementary material online, *Table S2*). Mean duration from the stroke onset to groin puncture was 248 ± 58 min. Risk of bias assessments for randomized clinical trials included is presented in Supplementary material online, *Table S3*. All trials followed PROBE (Prospective Randomized Open Blinded End-point) design.

Meta-analysis

EVT significantly improved the rate of functional independence (90-day mRS of 0–2) when compared with IV thrombolytics [42.4 vs. 31.7% in the control group; OR 1.73, 95% CI 1.18–2.53; $P = 0.005$, number needed to treat (NNT) = 9.3] for the treatment of acute ischaemic stroke (*Figure 1A*). There was non-significant lower mortality with EVT (16.2 vs. 17.3% in the control group; OR 0.89, 95% CI 0.68–1.15) (*Figure 1B*). The rate of sICH was similar with EVT and conventional IV thrombolytics (5.1 vs. 4.8% in the control group; OR 1.07, 95% CI 0.73–1.56) (*Figure 1C*).

Analysis limited to newer trials

Five trials including 1287 patients were published between the end of 2014 and early 2015 (MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME, and REVASCAT).[8–12] These trials selected patients meticulously with the use of computed tomographic angiography (CTA) or perfusion imaging and used modern stent-retriever procedures for reperfusion. Notably, there was a marked improvement in functional independence (90-day mRS of 0–2) with EVT (46.1 vs. 26.2% in the control group; OR 2.42, 95% CI 1.91–3.08; $P < 0.001$, NNT = 5.0) (*Figure 2A*). There was no significant heterogeneity between the five studies (I^2 statistic = 0%) noted with analysis of this outcome. We observed a non-significant lower mortality with EVT when limiting the analysis to the newer trials (14.5 vs. 17.3% in the control group; OR 0.80, 95% CI 0.54–1.18); the rate of sICH was also not increased with EVT (4.1 vs. 4.3% in the control group; OR 1.08, 95% CI 0.62–1.88) (*Figure 2B* and *C*).

Sensitivity analyses and meta-regression

Sensitivity analyses by sequentially dropping individual trials and then evaluating the overall outcomes failed to identify any of the individual trials as having influenced the outcomes to a significant extent (Supplementary material online, *Table S4*). Fixed-effects analyses showed consistent benefit with EVT in all sensitivity analyses for the rate of functional independence. Meta-regression with multiple covariates (as mentioned before) showed that the use of stent retrievers and the rate of successful reperfusion (TICI score of 2b or 3) were significantly related to the rate of functional independence (Supplementary material online, *Figure S2*). However, data related to different 'time windows' including stroke onset to randomization and interventions were not consistently reported (Supplementary material online, *Table S2*). There was also no significant publication

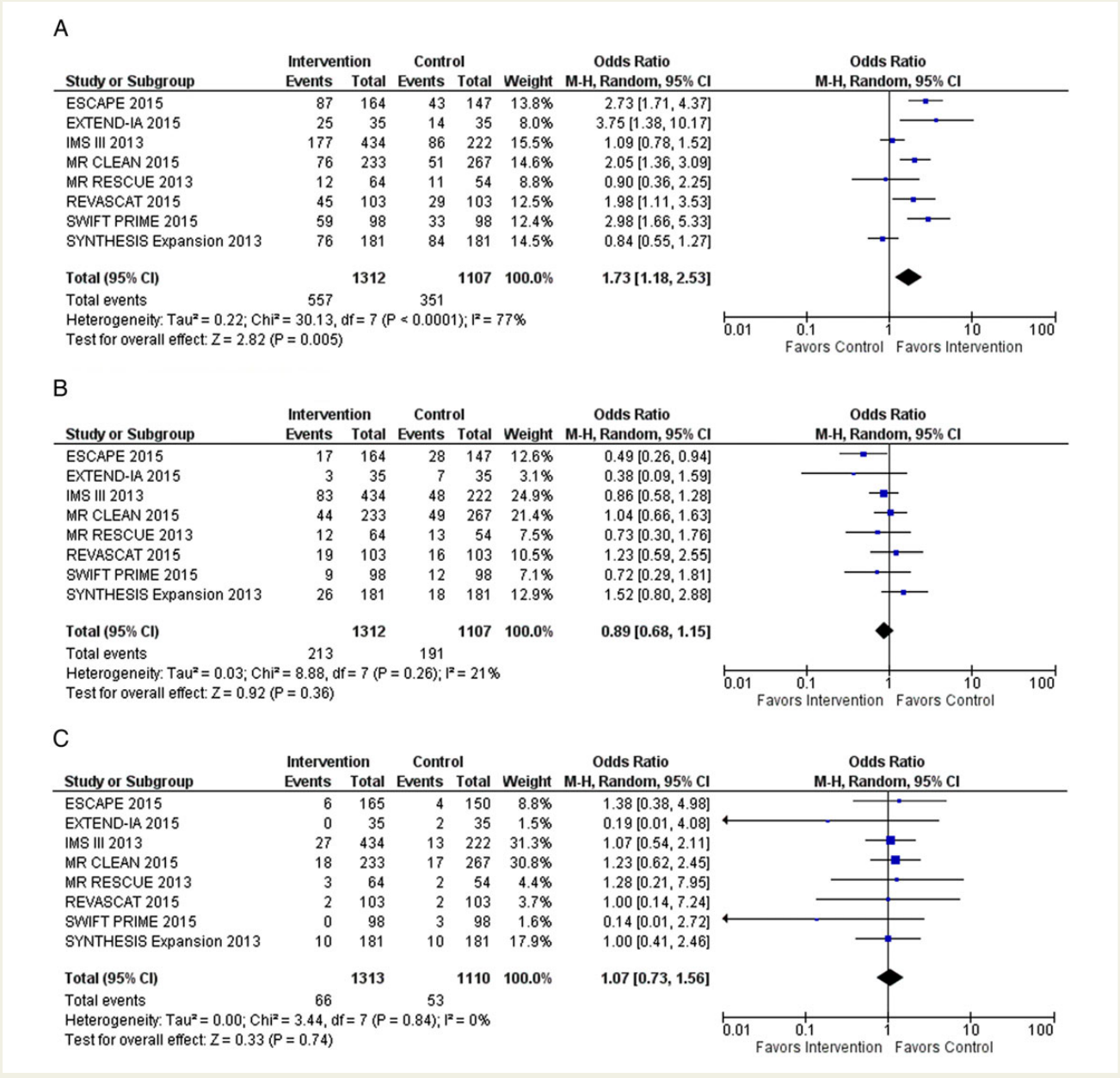

Figure 1 Analysis of all trials: (*A*) functional independence (90-day mRS of 0–2) with EVT; (*B*) all cause-mortality with EVT; and (*C*) sICH with EVT.

bias detected with the examination of funnel plots for the clinical outcomes or with Egger's regression test (Supplementary material online, *Figure S3*).

Device or procedural complications

Device or procedure-related complications occurred in 12.6% patients in the intervention group. Embolization into new territories outside the target downstream territory of the occluded vessel occurred in 3.9% patients, access site/groin haematoma was reported in 3.8% of the cases, procedure-related vessel dissections in 1.6% patients, and vessel perforations in 2.6% patients (Supplementary material online, *Table S5*).

Discussion

Our meta-analysis of meticulously performed RCTs that compared EVT with or without IV tPA with conventional IV thrombolytics alone in patients with anterior-circulation, large-artery acute ischaemic stroke showed significant benefit of 90-day functional independence with EVT. The risk of all-cause mortality was also lower with EVT (statistically non-significant), without any increase in rates of intracerebral haemorrhage.

Initial large RCTs evaluating EVT showed negative or inconclusive results.[5–7] These trials were criticized for their use of older recanalization devices that were associated with lower recanalization rates (in contrast to newer devices such as retrievable stents), for the long

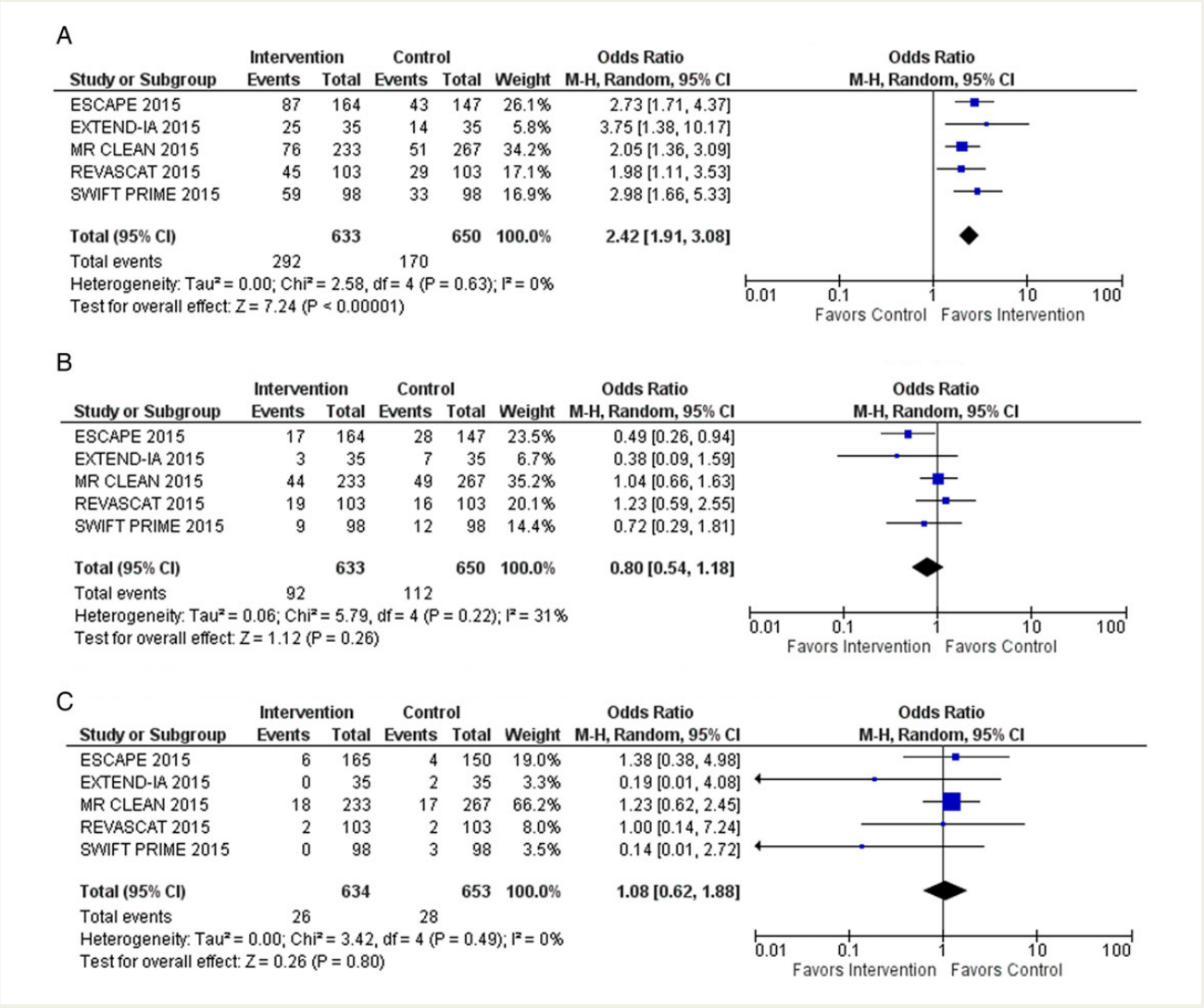

Figure 2 Analysis limited to newer (2014–15) trials: (*A*) functional independence (90-day mRS of 0–2) with EVT; (*B*) mortality with EVT; and (*C*) sICH with EVT.

interval between the onset of stroke and timing of intervention, and a disappointingly low recruitment rate, which suggested that many eligible patients were not included in the trials. Subgroup analyses suggested that there were benefits for patients treated in shorter time windows.[23,24] Moreover, two of these trials[5,6] did not require evidence of an occluded vessel prior to randomization, thereby making EVT futile from the very beginning. Key lessons learnt from these previous trials were that studies involving EVT ought to enroll patients with severe strokes, have confirmation of proximal vessel occlusion, have rapid and effective imaging methods, be able to initiate treatment as early as possible, and incorporate the usage of modern thrombectomy devices.[25] The five new trials[8–12] published thereafter (2014–15) followed modified strategies. Despite inclusion and procedural strategies varying across the trials, our pooled sensitivity analysis with only these five trials showed consistent and profound benefits in the functional outcomes of patients with EVT (NNT was only 5.0 vs. 9.3 with all eight trials), without an increased risk of sICH.

Time to randomization and intervention

Although the newer trials included patients who presented within 6 h after symptom onset, mean duration from the stroke onset to randomization was still only 3.7 h in the EVT group and 3.8 h in the control group. Mean duration from stroke onset to groin puncture was 4.1 h. In the ESCAPE trial,[10] eligibility criteria allowed enrolment up to 12 h after symptom onset; however, data on patients presented beyond 6 h were limited.[10] Due to data limitation from previous (published in 2013) trials, our meta-regression analysis for the effect of time to randomization on patient outcomes remains inconclusive.

Type of devices and successful reperfusion

Recent studies have shown the superiority of stent retrievers over the previous generation of thrombectomy devices. All five newer trials (2014–15) used stent retrievers in the majority of patients and showed consistent benefit with EVT. Three trials used a specific

technology, the Solitaire FR revascularization device, in all patients.[9,11,12] MR CLEAN[8] and ESCAPE[10] trials were pragmatic in allowing the usage of any FDA-approved devices. Consistent and additional benefits in pooled analysis from 2014–15 trials and meta-regression analysis suggest that retrievable stents might be the preferable endovascular device type for better outcomes. Successful reperfusion (TICI score of 2b or 3) in the EVT group was achieved in 78% of the patients in 2014–15 trials and in 67% of the patients in the rest of the trials, which might explain the additional clinical benefit in 2014–15 trials ($P = 0.04$ in meta-regression analysis).

Type of pre-selection imaging

Trial selection criteria evolved across the trials, becoming more selective over time. All trials required an initial non-contrast CT (NCCT) to rule out ICH. This was all that was required in SYNTHESIS Expansion[6] and in the initial IMS-III protocol.[5] All other studies required additional neck and brain vessel imaging to select patients with proximal intracranial thrombus (primarily CTA but also magnetic resonance angiography or digital subtraction angiography). In recent trials, enrolment additionally required measurement of the extent of early ischaemic changes with an NCCT and quantified via the Alberta Stroke Program Early CT Score (ASPECTS).[8,10–12] MR RESCUE[7] used multimodal CT or magnetic resonance imaging (MRI) to identify patients with a favourable penumbral imaging pattern. ESCAPE,[10] EXTEND-IA,[9] and SWIFT PRIME[11] trials also required proof of either adequate collaterals (using CTA)[10] or salvageable brain (using CT perfusion[9] or CTP/MRI[11]). The SWIFT PRIME trial[11] later allowed use of only CT-based ASPECTS score in order to include sites without penumbral imaging capabilities and to shorten imaging duration. Inclusion of patients based on imaging findings significantly narrowed the eligible patients for EVT and helped to identify patients who could potentially benefit from reperfusion therapy. However, this method of selection requires fast and experienced neuroradiology or stroke neurology input into a case; such expertise is typically not available at smaller facilities and may limit applicability of these findings to community hospitals.

Recommendations for the acute stroke treatment team

In appropriately selected patients with acute ischaemic stroke caused by proximal intra- or extracranial occlusions, EVT as an adjunct to IV fibrinolysis with tPA or as a standalone procedure in patients ineligible for IV fibrinolysis, administered within approximately 6 h (mean duration in our analysis 4.9 $\pm$ 0.9 h) after symptom onset, is both effective and safe. Our pooled analysis from recent trials showed benefits and low complication rates with EVT that was performed predominantly with retrievable stents. Advanced imaging modalities such as CTA and CT perfusion imaging are beneficial to properly select the eligible patients. The most significant factor that can influence positive outcomes is development of a multidisciplinary stroke team and a high level of communication between the emergency room, the neurointerventional team, and the neurology team, along with a concurrent rapid, highly efficient, protocol-based approach to acute stroke management.[25,26] It will be critical to first improve hospital-based stroke care systems and to develop regional systems of care, including transfer policies for hospitals without experienced stroke teams. Although the time targets for endovascular intervention in our analysis may appear daunting, the history of intervention for acute coronary syndromes suggests that similar efficiency in workflow is widely attainable in the near future.[27]

Limitations

As this study used only published data, we could not explore the results using individual, patient-level data. There was variability in the definition of 'time to therapy/intervention' among the trials. The analysed studies included very few patients (<1%) with posterior-circulation strokes. The results of our meta-analysis cannot be generalized to patients younger than 18 years or very old patients. Five trials were stopped prematurely because of evidence of significant benefit or futility in planned or unplanned interim analysis.[5,9–12] This may have precluded confident assessment of the true effect size that the intervention could potentially provide. Clinical factors, including the time to onset, exclude the vast proportion of stroke patients from EVT, as this intervention is appropriate only for those with persistent large artery occlusions who present to medical attention quickly.[26,28] The included trials were conducted at select endovascular centres with highly experienced neurointerventionalists and with efficient stroke evaluation systems in place. At present, this level of stroke expertise, neurointerventional experience, and systems efficiency are not uniformly available in all community hospitals, which might limit the immediate generalizability of our results.

Conclusion

EVT significantly improved functional outcomes in a selected group of patients with acute large-vessel ischaemic strokes. Proper patient selection to identify large-vessel occlusions with limited completed stroke volumes using CTA with or without perfusion imaging is critical to treatment success. Use of modern stent-retriever devices during procedures achieving high rates of complete or near-complete revascularization may provide additional safety and efficacy. Although these data support wider implementation of an endovascular approach to acute stroke management, ongoing efforts are needed to improve early stroke recognization, rapid triage, and patient access to designated comprehensive stroke centres to further improve outcomes in patients through both pharmacological and endovascular means.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: none declared.

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