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Endovascular Therapy for Acute Ischemic Stroke: A Systematic Review and Meta-analysis

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Abstract

Objective—To consolidate the evidence from randomized trials for the use of endovascular therapy (ET) in patients with acute ischemic stroke.

Methods—We searched major databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus) from their inception to February 12, 2013, for randomized trials evaluating the efficacy of ET compared with standard of care for acute ischemic stroke. Pooled absolute and relative risk estimates were synthesized by using a random-effects model. Heterogeneity was assessed by using Q statistic and I^2 statistic. Subset analysis was performed for patients with severe stroke (National Institutes of Health Stroke Scale score ≥20). The study was conducted from January 15, 2013 to April 30, 2013.

Results—Of the 1252 retrieved articles, 5 randomized trials enrolling 1197 patients with acute ischemic stroke were included. Seven hundred eleven patients received ET, and 486 received intravenous (IV) tissue plasminogen activator. There was no significant improvement in any of the outcomes in patients receiving ET compared with those receiving IV thrombolysis. On subgroup analysis, ET was found to have better outcomes in patients with severe stroke (National Institutes of Health Stroke Scale score ≥20), showing a dose-response gradient and improving excellent, good, and fair outcomes by an additional 4%, 7%, and 13%, respectively, compared with IV thrombolysis.

Conclusion—Overall, ET is not superior to IV thrombolysis for acute ischemic strokes (level B recommendation). However, ET showed promise and improved outcomes in patients with severe strokes, but the evidence is limited due to sample size. There is a need for further trials evaluating the role of ET in this high-risk group.

Stroke is a leading cause of long-term severe disability and the fourth leading cause of death in the United States. Cost of care, lost productivity, and premature mortality are high for stroke survivors (the estimated cost in the United States in 2008 was $34.3 billion).[1] Intravenous (IV) thrombolysis with a recombinant tissue plasminogen activator (tPA) within the first 3 hours of stroke onset is the only therapy approved by the US Food and Drug Administration for acute ischemic stroke (AIS).[2] However, recanalization rates with IV tPA are low (14% for internal carotid arteries and 55% for middle cerebral arteries), which led to the exploration of endovascular therapies (ETs) in AIS.[3] The benefit of ET in AIS is not clear.[4] A meta-analysis found no clear benefit of ET over IV tPA in patients with AIS, but

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the strength of evidence was limited because of the small sample size of the 2 trials.[5] In the present study, we attempted to synthesize the available evidence by including 3 recently published randomized controlled trials (RCTs) of ET for AIS.[6–8]

The aim of our study was to perform a comprehensive systematic review and meta-analysis of all the published RCTs to compare the efficacy of ET (with or without IV tPA) with IV thrombolysis in patients with AIS by using different clinical outcomes (all-cause mortality, functional outcome, and symptomatic intracranial hemorrhage [sICH] rate).

METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses guidelines to report our study findings.[9] A protocol was designed a priori and was registered with PROSPERO.[10]

Eligibility Criteria

The study's eligibility criteria were as follows: (1) RCT, (2) comparison of ET with IV throm-bolysis, (3) report of a risk estimate (relative risk, odds ratio, or data from which it could be calculated), and (4) report of the following outcomes: all-cause mortality, functional outcome measured by the modified Rankin Scale (mRS), and/or the sICH rate.

Data Sources and Search Strategies

A comprehensive search was conducted from major databases (Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus) from earliest inception to February 12, 2013, irrespective of any language barrier (Supplemental Appendix, available online at http://www.mayoclinicproceedings.org). The search strategy (controlled vocabulary supplemented with keywords) was designed and conducted by an experienced librarian (L.J.P.) with input from the study team. Conference proceedings of major neurology, neurosurgery, and stroke organizations were searched manually to identify relevant abstracts and potential articles. Content experts were queried, and references of potentially eligible articles were reviewed to identify all potentially eligible articles. In the case of missing data, corresponding authors were contacted for additional information. The study was conducted from January 15, 2013 to April 30, 2013.

Study Selection

Two investigators (B.S. and M.K.M.) independently and in duplicate screened all the abstracts and titles to identify potentially eligible articles for full-text review, and then reviewed the full text of selected articles independently to identify the studies meeting eligibility criteria. The interreviewer agreement was assessed by using Cohen weighted κ,[11] and any disagreement was resolved with consensus in the presence of the third investigator (A.K.P.).

Data Collection

A predesigned data abstraction form was used by 2 investigators (B.S. and M.K.M.) to extract data in duplicate from the included studies. For each trial, we extracted the study characteristics (author, year, country, inclusion and exclusion criteria, baseline National Institutes of Health Stroke Scale [NIHSS] score, number of participantsdtotal and in each treatment armdand demographic characteristics of study participants), type of intervention, time to intervention, and outcome measures. Loss of follow-up and missing data were collected for quality assessment.

Outcome Measure

The mRS is a tool used to measure the poststroke functional outcome, with scores ranging from 0 to 6 (0, no symptoms at all; 1, no major disability; 2, slight disability; 3, moderate disability requiring some help but able to walk without assistance; 4, moderately severe disability; 5, severe disability; and 6, death). We defined 90-day mRS score of 1 or less as an excellent outcome, 2 or less as a good outcome, and 3 or less as a fair outcome.[12]

The primary outcome of interest for our study was improvement in the mRS score at 3 months. Secondary outcomes were all-cause mortality and the sICH rate.

Quality Assessment

The quality assessment of the included trials was evaluated by using the Jadad score.[13] The Jadad score consists of 3 items: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 points). Response to each question is either “yes” (1 point) or “no” (0/−1). The score ranges from 0 to 5 points, with higher scores indicating better reporting. Studies with a Jadad score of 2 or less are considered of low quality, and those with a Jadad score of 3 or more are considered of high quality.[14] The Cochrane Risk of Bias Tool was used to assess the quality of study methodology of eligible RCTs. Study quality was assessed independently and in duplicate by 2 investigators (B.S. and M.K.M.) following 7 criteria: (1) random sequence generation, (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias.[15] Time from stroke onset to recanalization has been described as an important confounding factor between recanalization and patient outcomes.[16,17] Each study was evaluated for adjustment for time from stroke onset to recanalization. Response for each criterion was reported as low risk of bias, high risk of bias, and unclear risk of bias. Any disagreement was resolved with mutual consensus in the presence of the third investigator (A.K.P.).

Subgroup/Subset Analysis

An a priori sensitivity analysis was performed in patients with severe strokes (NIHSS score ≥20) because a favorable trend was seen for ET in this subgroup in the Interventional Management of Stroke (IMS) III trial.[6] Further subgroup analyses of studies comparing ET with IV tPA were performed according to the country of origin (US vs non-US), duration of therapy from stroke onset (≤6 hours and >6 hours), and the study design (multicenter vs monocenter) to study the effect of different health care systems on patient outcome.

Levels of Evidence

We classified all the studies into class I to IV by using American Academy of Neurology’s (AAN’s) study classification scheme.[18] We further used AAN’s classification of recommendations for the strength of study findings.

Statistical Analyses

Continuous variables were reported as means ± SD or medians with interquartile range, and categorical variables were reported as frequency and proportions. Risk estimate was presented by using risk ratios (RRs) with 95% CI, calculated by using the random Der-Simonian and Laird effects model.[19] The heterogeneity among the studies was assessed by using the I^2 statistic and the Cochran Q statistic for each outcome.[20] A P value of less than . 10 of the Cochran Q test suggests that the heterogeneity is beyond random error or chance.[20] We calculated the absolute risk difference and number needed to treat with 95% CI for statistically significant outcomes. All other P values were considered significant for $P<.05$

except for subgroup analysis in which $P<.0125$ was considered significant after the Bonferroni correction for multiple comparisons. Statistical analyses were performed using Review Manager (RevMan) Version 5.1.

RESULTS

A total of 1252 unique records were identified through comprehensive database search, and 3 additional articles were identified from other sources (Figure 1).[6–8] The interobserver agreement was excellent for initial screening of the titles and abstracts (κ 0.93; 95% CI, 0.86–0.99) and full-text review (κ 0.89; 95% CI, 0.68–1.10).

The 5 studies meeting eligibility criteria included 6 study cohorts (the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR-RESCUE] trial, reported by Kidwell et al,[8] was divided into 2 cohorts: penumbra and nonpenumbra), comprising 1197 patients with AIS, of which 711 (59.4%) received ET with or without IV tPA and 486 (40.6%) received a control intervention (IV tPA).[6–8,21,22] The study sample size ranged from 7 patients[22] to 654 patients.[6] The study characteristics are described in Table 1. In the MR-RESCUE trial,[8] in which ET was compared with the standard of care, 43.8% of the patients received IV tPA in the ET arm and 29.6% received IV tPA in the control arm. The inclusion, exclusion, and interim analysis criteria are shown in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). Two studies were discontinued before their completion.[6,21] All studies except 1 had a treatment window of 6 hours or less.[8]

Quality Assessment

The quality assessment of the included trials using the Jadad score is shown in detail in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org), and the study quality, given as “high” or “low,” is shown in Table 1. The Supplemental Figure (available online at http://www.mayoclinicproceedings.org) shows the risk-of-bias summary. Performance bias was observed in all studies because none of the studies did a sham procedure in the control arm. Two studies (3 cohorts) had attrition bias,[6,8] and 1 study had selective reporting bias.[22] None of the studies adjusted the outcome for time from stroke onset to recanalization.[16,17]

Outcome

No significant difference was found in either primary or secondary outcome when ET (±IV tPA) was compared with IV tPA (Table 2). None to modest heterogeneity was noted for all outcomes (I^2, 0% for mRS score ≤3, mortality, and sICH; I^2, 1% for mRS score ≤1 and I^2, 21% for mRS score ≤2, respectively). The subgroup analysis according to the study enrollment time (within 6 hours vs >6 hours), study location (US vs non-US), or setting (multicenter vs monocenter) did not reveal any difference in patient outcomes (Table 3). A post hoc sensitivity analysis was conducted according to the treatments used in control and intervention groups. We did not observe any difference in outcomes when we compared trials in which only IV tPA was used as the control group[6,7,21,22] vs trials in which both IV tPA and standard of care were used as the control group.[8] Similarly, no difference was observed in outcomes when trials using ET only (no IV tPA) in the intervention arm[7,21,22] were compared with trials using IV tPA (for any number of patients) along with ET.[6,8]

Subset Analysis of Patients With Severe Strokes (NIHSS Score ≥20)

Only 1 study[6] had reported outcome data for patients with severe AIS (NIHSS score ≥20) initially. Outcome data were received for 2 additional studies after contacting the corresponding authors.[7,21] Of 1163 patients with AIS with reported primary outcome of improvement in the mRS score, 271 (23.3%) had severe stroke. Endovascular therapy was

found to have better outcomes in patients with severe stroke (NIHSS score ≥20), with ET showing a dose-response gradient and improving excellent, good, and fair outcomes by an additional 4%, 7%, and 13%, respectively, compared with IV thrombolysis. Compared with IV tPA, ET had favorable fair (RR, 1.41; 95% CI, 1.00–1.99), good (RR, 1.40; 95% CI, 0.86–2.28), and excellent (RR, 1.40; 95% CI, 0.72–2.71) outcomes; however, the effect estimate did not reach statistical significance (Figure 2).

Publication Bias

Publication bias could not be assessed because of the small number of studies (< 10 studies).[23,24]

DISCUSSION

This is the first meta-analysis that combined the results from all RCTs[6–8,21,22] to date comparing ET (±IV tPA) to IV tPA. By using the AAN classification scheme for therapeutic questions,[18] all 5 RCTs comparing ET with IV tPA[6–8,21,22] were graded as class II (because of lack of adjustment for time from stroke onset to recanalization, a major confounder).[17] On the basis of these 5 class II trials, we found that ET is not superior to IV tPA in improving mortality or functional outcome at 3 months (level B recommendation) with a similar rate of symptomatic hemorrhage (level B recommendation).

Time from stroke onset to intervention is an important factor in the management of patients with AIS, with a decline in favorable outcomes with an increase in picture to puncture time.[17] The ideal enrollment time needs to be taken into account in future trials of ET vs IV tPA. The REcanalisation using Combined intravenous Alteplase and Neurointerventional ALgorithm for acute Ischemic StrokE (RECANALISE) study reported that recanalization in less than 210 minutes, in 210 to 260 minutes, and in more than 260 minutes was associated with 93%, 67%, and 37% good outcome (mRS score ≤2) at 90 days, respectively.[16] The IMS-III trial reported the mean time from groin puncture to recanalization as 41 minutes.[6] On combining the information from these 2 studies, we found that the ideal onset to groin puncture time should be less than 3 hours and the recanalization should be finished within 3.5 hours for maximum benefit and within 4.3 hours for moderate benefit. The outcome data for patients who were treated with ET and underwent recanalization within 3.5 hours were not available from any of the published trials. Subgroup analysis of the IMS-III trial[6] and the Local Versus Systemic Thrombolysis for Acute Ischemic Stroke trial[7] may help clarify the effect of time from stroke onset to recanalization on patient outcome to some extent; however, it would be limited by sample size. There is much interest in the new stent retrievers that have been reported to have recanalization rates of more than 80%.[25,26] Even these studies reported time from onset to groin puncture as 4.7 to 5 hours with good outcome (mRS score ≤2 at 90 days) in only 37% to 40% of patients,[25,26] which is similar to the 40% rate reported in Prolyse in Acute Cerebral Thromboembolism II (PROACT-II). This observation suggests that patient outcome is not entirely dependent on the type of ET (intra-arterial thrombolysis or mechanical devices) but that other factors such as time to ET and collateral circulation also play important roles. We need system-based research to evaluate and eliminate the factors causing delay in ET initiation.[17]

One of the identified causes of delay in ET is multimodal imaging. However, the true value of these imaging techniques is uncertain as evident from the MR-RESCUE trial, which found that penumbra-based ET does not make a difference in patient outcome.[8] A retrospective study from 10 US centers reported that a computed tomography-based ET decision may shorten the stroke onset to groin puncture time to 2 hours.[27] Immediate transfer of patients to the angiography suite under bridging therapy and use of stent retrievers may also shorten the picture to puncture time,[28] and this approach may be

explored in future trials. System-based research standardizing the processes to eliminate intercenter variability in multicenter trials may further help to improve time to recanalization.

Endovascular Therapy vs IV tPA for Patients With Severe Stroke (NIHSS Score ≥20)

Around one-fourth of the patients with AIS with reported functional outcomes had severe stroke. Patients with severe AIS (NIHSS score ≥20) had a higher probability of good and excellent outcomes when treated with ET compared with IV tPA; however, these findings did not achieve statistical significance secondary to smaller sample size. These results were based on the pooled estimate of 3 RCTs with small sample size (all class II studies)[6,7,21]; therefore, they need to be interpreted with caution. However, we observed an internal and external consistency in this subgroup that warrants further exploration in future clinical trials.

Strengths and Limitations

Our meta-analysis had various strengths. We did a comprehensive search of all the major databases and manually searched the abstracts and proceedings of major conferences to avoid selection bias. Authors were contacted for missing data to reduce the attrition bias. Subgroup analyses provided similar results to the overall analysis, explaining the robustness of our study. The majority of the trials were multi-centered, strengthening the generalizability of our meta-analysis findings. Our meta-analysis has a few limitations. There was variability in the definition of “time to therapy” among the studies. Definition of time to ET was not clear and could mean stroke onset to groin puncture, stroke onset to microcatheter placement, or stroke onset to recanalization. Owing to lack of reported data, we could not study the following associations: effect of recanalization on patient outcome, effect of time to recanalization on patient outcome, effect of anterior vs posterior circulation stroke on patient outcome, and effect of ET vs IV tPA on patients’ activities of daily life using the Barthel index. The results of our meta-analysis cannot be generalized to those patients with stroke who are younger than 18 years or older than 85 years.

CONCLUSION

This meta-analysis failed to show any superiority of ET over IV tPA for patients with AIS. Endovascular therapy may lead to a better outcome for patients with severe strokes (NIHSS score ≥20); however, these results should be interpreted with caution and need to be confirmed in a double-blind, large, multicenter RCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

AAN	American Academy of Neurology

AIS	acute ischemic stroke
ET	endovascular therapy
IMS	Interventional Management of Stroke
IV	intravenous
mRS	modified Rankin Scale
MR-RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
NIHSS	National Institute of Health Stroke Scale
RCT	randomized controlled trial
RR	risk ratio
sICH	symptomatic intracranial hemorrhage
tPA	tissue plasminogen activator

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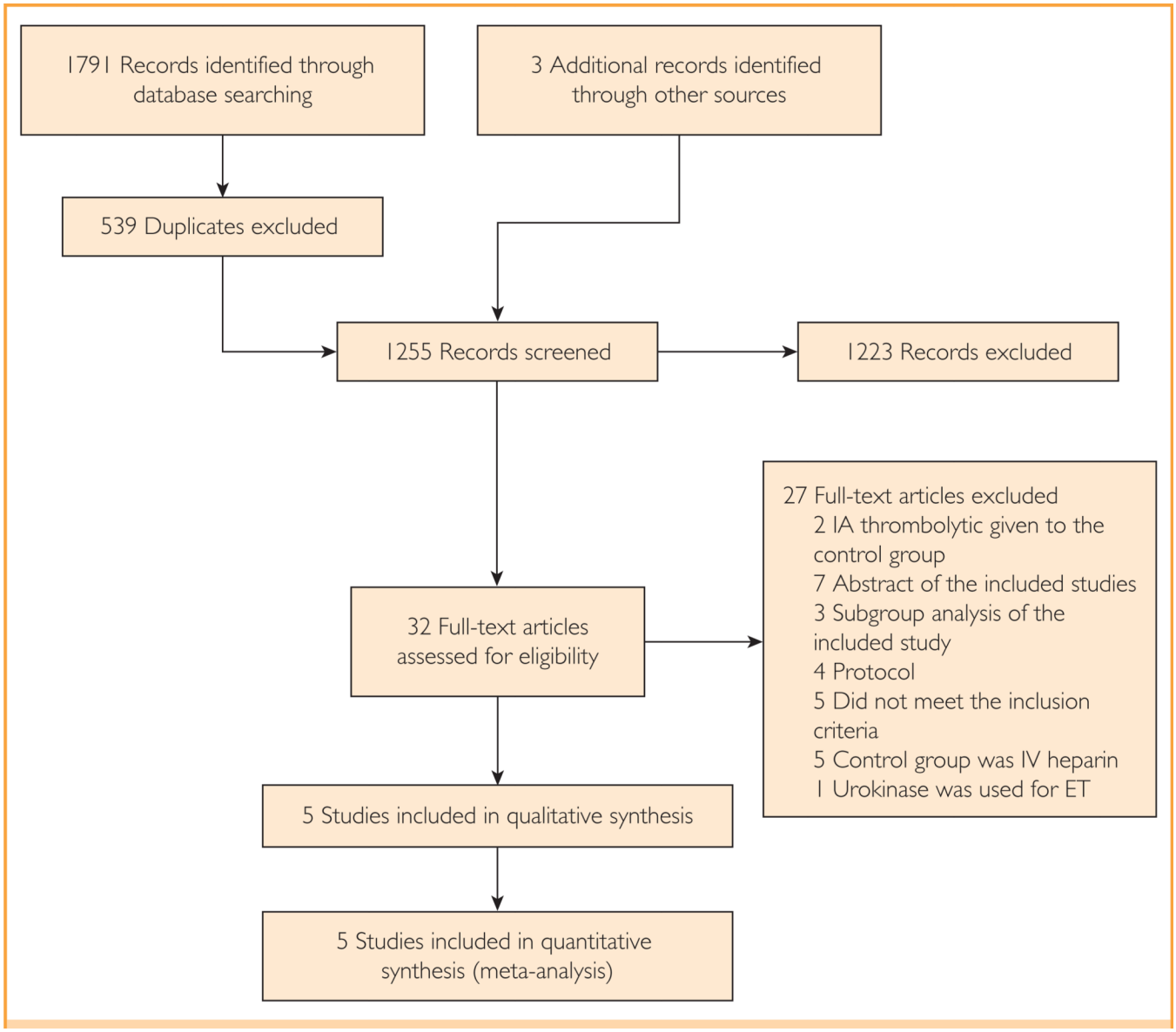

FIGURE 1.
The study flow diagram. ET = endovascular therapy; IV = intravenous.

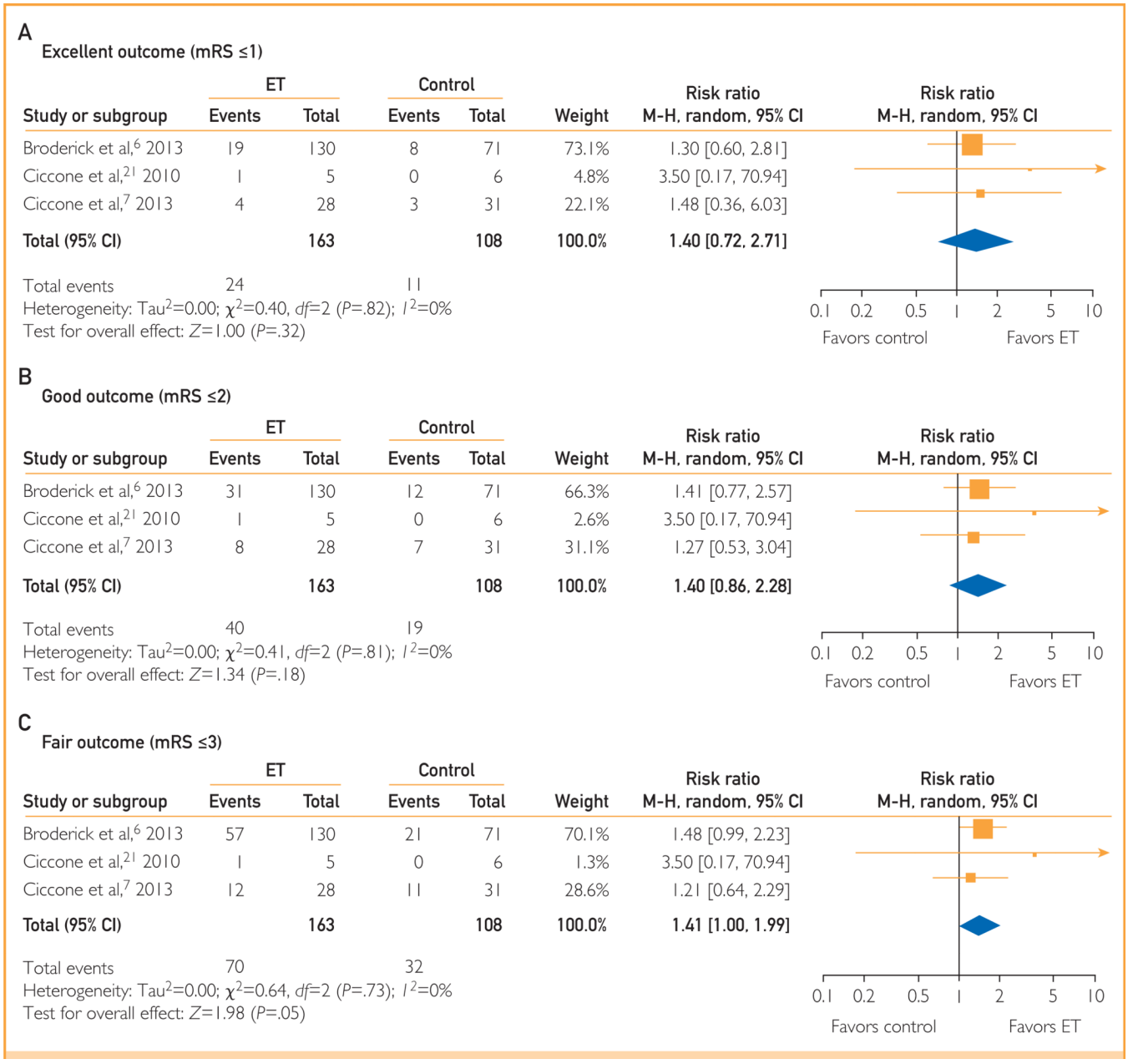

FIGURE 2.

Outcomes in patients with severe stroke. A, Excellent outcome (mRS score ≤1). B, Good outcome (mRS score ≤2). C, Fair outcome (mRS score ≤3). ET = endovascular therapy; M-H = Mantel-Haenszel; mRS = modified Rankin Scale.

TABLE 1

Characteristics of the Included RCTs[a]

Reference, year	Intervention (maximum dosage)	No. of patients (male %)	Age (y), mean ± SD or median (range)	Primary outcome	NIHSS score, mean/ median	NIHSS score ≥20	Occlusion	Time from symptom onset to treatment (min), median/mean ± SD	Recanalization (TICI)	Quality of studies[b]
Ciccone et al,[7] 2013	I = IA tPA (0.9 mg/kg)[c] + IV heparin ± MT	181 (59)	66±11	mRS score ≤ 1 at 90 d	13	NA	Anterior and posterior circulation—complete data NA	Median = 225	NA	+
	C = IV tPA (0.9 mg/kg)	181 (57)	67±11		13	NA		Median = 165	NA	
Broderick et al,[6] 2013	I = IV[d] + IA tPA (22 mg) + IV heparin ± MT	434 (50)	69 (23–89)	mRS score ≤2 at 90 d	17	132	M1 = 135, ICA = 65, single M2 = 61, multiple M2 = 22, basilar occlusion = 4	Mean time to IV tPA = 122±38, mean time to groin puncture = 208±47, mean time to IA therapy = 249±51 Mean =121 ±34	Grade 2b–3; ICA (38%), M1 (41%), single M2 (44%), multiple M2 (23%)	+
	C = IV tPA (0.9 mg/kg)	222 (55)	68 (23–84)		16	72	NA		NA	
Kidwell et al,[8] 2013, penumbra[e]	I = MT ± IA/IV tPA[f](14 mg)	34 (50)	66±13	Improvement in mRS score level	16	NA	ICA = 6, M1 = 18, M2 = 10	Mean time to groin puncture = 381 ±74	Grade 2a–3 at day 7 = 67%	+
	C = standard medical care ± IV tPA	34 (44)	66±17		16	NA	ICA = 5, M1 = 23, M2 = 6	NA	Grade 2a–3 at day 7 = 93%	
Kidwell et al,[8] 2013, nonpenumbra	I = MT ± IA/IV tPA (14 mg)	30 (43)	62±12		19	NA	ICA = 7, M1 = 21, M2 = 2	Mean time to groin puncture = 381 ±74	Grade 2a–3 at day 7 = 77%	+
	C = standard medical care ± IV tPA	20 (60)	69±16		21	NA	ICA = 2, M1 = 16, M2 = 2	NA	Grade 2a–3 at day 7 = 78%	

Reference, year	Intervention (maximum dosage)	No. of patients (male %)	Age (y), mean ± SD or median (range)	Primary outcome	NIHSS score, mean/ median	NIHSS score ≥20	Occlusion	Time from symptom onset to treatment (min), median/mean ± SD	Recanalization (TICI)	Quality of studies[b]
Ciccone et al,[21] 2010	I = IA tPA (0.9 mg/kg)[g] + IV heparin ± MT	29 (76)	61 ±14	mRS score ≤1 at 90 d	17	NA	Anterior and posterior circulation—complete data NA	Median time to start of treatment = 195	NA	−
	C = IV tPA (0.9 mg/kg)	25 (75)	64±12		16	NA		Median time to start of treatment = 195	NA	
Sen et al,[22] 2009	I = IA tPA (22mg)	3	68±16	**1** To test the feasibility of enrollment and randomization of eligible patients with AIS (<3 h) with LVO **2** Safety (sICH at 24 h)	16	NA	M1 = 5, M2 = 1, terminal ICA = 1	Mean time to thrombolysis = 236	Grade 2a–3 = 3	+
	C = IV tPA (0.9 mg/kg)	4				NA		Mean time to thrombolysis = 170	Grade 2a–3 = 0	

[a] AIS = acute ischemic stroke; C = control; I = intervention; IA = intra-arterial; ICA = internal carotid artery; IQR = interquartile range; IV = intravenous; LVO = large vessel occlusion; MCA = middle cerebral artery; MI = first segment of MCA (horizontal); M2 = second segment of MCA (insular); mRS = modified Rankin Scale; MT = mechanical thrombolysis; NA = not available; NIHSS = National Institutes of Health Stroke Scale; RCT = randomized controlled trial; sICH = symptomatic intracranial hemorrhage; TICI = thrombolysis in cerebral infarction; tPA = tissue plasminogen activator.

[b] Represents quality of studies measured by the Jadad score; + = high quality; − = low quality.

[c] Median tPA dose used = 40 mg (IQR, 20–50 mg).

[d] From March 2006 to June 2011, two thirds of the total approved tPA dose was administered intravenously in the intervention arm (all patients were randomized within 40 min of starting IV tPA); after June 2011, the full dose of IV tPA was used even in the intervention arm. The mean dose of tPA received in the intervention arm = 60.3 ± 14.2 mg (IV tPA = 52.1 ± 12 and IA tPA = 13.3±6.7) and in the control arm = 72.5 ± 14.3 mg.

[e] Penumbra was defined as predicted infarct core of ≤90 mL and a proportion of predicted infarct tissue within the at-risk region of ≤70%.

[f] Mean IA tPA dose = 5.1 mg; overall, 44 (37%) patients received IV tPA.

[g] Median IA tPA dose = 50 mg (IQR, 45–70 mg); median IV tPA dose in the control arm = 66.5 mg (IQR, 58–72 mg).

TABLE 2

Outcomes in Patients With Acute Ischemic Stroke Comparing ET vs IV tPA

	ET vs IV tPA			
Outcome at 90 d	**ET (n/N)**	**Control (n/N)**	**RR (95% CI)**	**I^2 statistic (%)**
mRS score ≤1	194/685	135/478	1.02 (0.84–1.23)	1
mRS score ≤2	275/685	189/478	1.02 (0.84–1.24)	21
mRS score ≤3	397/685	270/478	1.03 (0.93–1.14)	0
Mortality	127/707	84/490	0.98 (0.76–1.25)	0
sICH	42/707	30/490	0.99 (0.62–1.58)	0

ET = endovascular therapy; IV = intravenous; mRS = modified Rankin Scale; n/N = No. of patients with stroke/total No. of patients with outcome; RR = risk ratio; sICH = symptomatic intracranial hemorrhage; tPA = tissue plasminogen activator.

TABLE 3

Subgroup Analysis[a]

Subgroup analysis	No. of cohorts	RR	95% CI	*P* value for difference between the subgroups[b]
Mortality				
Duration of therapy from stroke onset				
≤6 h	4	1.07	0.75–1.50	.39
≥6 h	2	0.76	0.38–1.51	
Study location				
US	4	0.86	0.65–1.15	.08
Non-US	2	1.43	0.87–2.36	
Study setting				
Multicenter	5	0.98	0.76–1.25	NA
Monocenter[c]	1	NA	NA	
mRS score ≤1				
Duration of therapy from stroke onset				
≤6 h	3	1.05	0.80–1.38	.56
>6 h	2	0.73	0.23–2.36	
Study location				
US	3	1.06	0.82–1.38	.85
Non-US	2	1.14	0.59–2.19	
Study setting				
Multicenter	5	1.02	0.84–1.23	NA
Monocenter[c]	1	NA	NA	
mRS score ≤2				
Duration of therapy from stroke onset				
≤6 h	3	1.06	0.83–1.35	.38
>6 h	2	0.71	0.30–1.69	
Study location				
US	3	1.04	0.86–1.26	70
Non-US	2	1.19	0.61–2.32	
Study setting				
Multicenter	5	1.02	0.84–1.24	NA
Monocenter[c]	1	NA	NA	
mRS score ≤3				
Duration of therapy from stroke onset				
≤6 h	3	1.05	0.94–1.16	26
>6 h	2	0.78	0.48–1.28	
Study location				
US	3	1.03	0.90–1.18	.88

Subgroup analysis	No. of cohorts	RR	95% CI	*P* value for difference between the subgroups[b]
Non-US	2	1.03	0.89–1.20	
Study setting				
Multicenter	5	1.03	0.93–1.14	NA
Monocenter[c]	1	NA	NA	
sICH				
Duration of therapy from stroke onset				
≤6 h	4	0.96	0.62–1.58	.63
>6 h	2	1.50	0.27–8.42	
Study location				
US	3	1.06	0.59–1.92	77
Non-US	3	0.89	0.42–1.89	
Study setting				
Multicenter	5	1.02	0.64–1.63	.55
Monocenter[c]	1	0.42	0.02–7.71	

[a] mRS = modified Rankin scale; NA = not applicable/available; RCT = randomized controlled trial; RR = risk ratio; sICH = symptomatic intracranial hemorrhage.

[b] $P<.10$ implies that difference between the 2 subgroups is significant, and it may explain the heterogeneity observed in the overall analysis.

[c] Sen et al[22]; in this RCT, no patient died and authors did not report the mRS score as an outcome.