Supplementary Online Content

Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. *JAMA*. doi:10.1001/jama.2015.13767.

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Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis

SUPPLEMENTARY MATERIAL

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STUDY PROTOCOL

OBJECTIVES

Our aim is to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to delineate the impact of endovascular therapy on clinical outcomes of patients with acute ischemic stroke compared to best medical care.

METHODS

We shall conduct a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[1] and the Cochrane Handbook for Systematic Reviews of Interventions.[2]

Search Strategy

Electronic Databases

A detailed search will be conducted of the MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, and Cochrane Library databases through August 2015 without language restrictions. We will use keywords/MeSH terms related to the medical condition (e.g., *cerebrovascular accident*, *stroke*, *ischemia*) and therapy (e.g., *embolectomy*, *endovascular*, *intraarterial*, *thrombectomy*, *thrombolysis*) of interest.

Searching Other Sources

The search will be supplemented by manually screening the references of relevant articles.

Study Selection

Selection of Studies

Three investigators will independently evaluate studies for eligibility. Disagreements between the reviewers concerning the decision to include or exclude a study will be resolved by consensus, and if necessary, consultation with a fourth reviewer.

Inclusion Criteria

Our inclusion criteria shall be:

- *Study design*: published RCT
- *Population*: adults (≥18 yrs) with acute ischemic stroke
- *Intervention*: endovascular therapy with mechanical clot retrieval (i.e., thrombectomy) with or without use of intraarterial thrombolytic agents
- *Control*: standard medical care, which includes intravenous (IV) administration of tissue plasminogen activator (t-PA, alteplase) in eligible patients
- *Outcome*: functional outcome, as assessed by the modified Rankin scale (mRS) score or other validated instrument, and/or mortality

Exclusion Criteria

For studies published more than once, we will include only the report with the most informative data. Pilot studies and post-hoc analyses will be excluded. Furthermore, we will exclude studies that did not include IV t-PA as part of the optimal medical therapy

control arm and studies that did not examine mechanical thrombectomy in the intervention group.

Data Collection and Analysis

Data Extraction and Management

Data from selected trials will be abstracted independently by the three primary reviewers and verified for accuracy by the fourth reviewer. Discrepancies are to be resolved by discussion and consensus. We will gather information from eligible articles using data abstraction forms that include fields for: trial name; article title; first author; journal; year of publication, number and countries of participating centers; sources of funding; details regarding study methods (e.g., blinding, outcome assessment), recruitment period; total number of patients randomized; eligibility criteria; baseline patient characteristics, including age, gender, underlying medical comorbidities (e.g., hypertension, atrial fibrillation, coronary artery disease, myocardial infarction, congestive heart failure, hyperlipidemia, diabetes mellitus, previous ischemic stroke), antiplatelet use, smoking, clinical stroke severity as assessed by the National Institute of Health Stroke Scale (NIHSS) score, and radiographic stroke severity as assessed by the Alberta Stroke Program Early CT Score (ASPECTS); imaging findings, including location of arterial occlusion; treatment time metrics, including time from stroke onset to enrolment and time from stroke onset to treatment; details regarding endovascular (e.g., mechanical devices/techniques and intraarterial thrombolytic agents with their dose) and control therapy, including use/dosing of IV t-PA; and primary, secondary, and tertiary outcomes, including modified Rankin scale scores, revascularization, quality of life (QOL) metrics, mortality, symptomatic ICH, serious adverse events, and procedure- and/or device-related complications.

Assessment of Methodological Quality

The three primary reviewers will independently perform quality assessment. The Cochrane Collaboration's tool[4] will be used to assess the risk of selection, performance, detection, attrition, and reporting biases among included randomized trials. Trials with more than two and four high-risk components will be judged as having a moderate and high risk of bias, respectively.

Statistical Analysis and Data Synthesis

All analyses will follow the intention-to-treat principle. The primary outcome will be modified Rankin scale (mRS) score at 90 days. This ordinal scale measures functional outcome with scores ranging from 0 to 6 (eTable 1). The treatment effect for each trial will be estimated using ordinal logistic regression to calculate the proportional odds ratio (OR), which measures the

eTable 1: The modified Rankin scale (mRS)[3]

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Death

likelihood of endovascular therapy leading to lower mRS scores than standard therapy (shift analysis). Secondary outcomes will include further measures of efficacy and also independence, defined as modified Rankin score of 0, 1, or 2, at 90 days. Moreover, we shall evaluate early revascularization, defined as restoration of blood flow at the site of arterial occlusion within 24 hours of stroke demonstrated on computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or digital subtraction angiography (DSA) according to the modified Thrombolysis in Cerebral Infarction (TICI) scale (eTable 2) or modified Arterial Occlusive Lesion (AOL) scale (eTable 3). Safety analyses will include the serious adverse events of 90-day all-cause mortality and symptomatic ICH. We will perform random-effects meta-analyses using the DerSimonian and Laird model[6] for each of the five outcomes of interest. We examined ORs with 95% confidence intervals (CIs) weighted by the inverse-variance method. Moreover, we will calculate the number needed to treat based on the outcome of functional independence using the following equation:[2]

eTable 2: The modified Thrombolysis in Cerebral Infarction (TICI) scale[5]

Grade	Description
0	No perfusion
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a	Perfusion of less than half of the vascular distribution of the occluded artery
2b	Perfusion of half or greater of the vascular distribution of the occluded artery
3	Full perfusion with filling of all distal branches

eTable 3: The modified Arterial Occlusive Lesion (AOL) scale[5]

Grade	Description
0	No recanalization of the occlusion
1	Incomplete or partial recanalization of the occlusion, with no distal flow
2	Incomplete or partial recanalization of the occlusion, with any distal flow
3	Complete recanalization of the occlusion with any distal flow

$$\text{NNT} = \frac{1}{\left| \text{ACR} - \frac{\text{OR} \times \text{ACR}}{1 - \text{ACR} + \text{OR} \times \text{ACR}} \right|}$$

The threshold type I error rate for statistical significance shall be $\alpha = 0.05$. We plan to Comprehensive Meta-Analysis version 2.2 (Biostat, Inc., Englewood, NJ) to conduct all statistical analyses.

Evaluation of Heterogeneity

Between-study heterogeneity will be evaluated by Cochran's *Q* test and measured by the I^2 statistic, with I^2 values exceeding 25%, 50%, and 75% being judged as low, moderate, and high heterogeneity, respectively.[7]

Evaluation of Reporting Bias

Publication bias will be evaluated visually by funnel plot analysis and quantified by Begg and Mazumdar's[8] and Egger's tests.[9]

Subgroup Analyses

We shall conduct subgroup analyses to examine if the treatment effect of endovascular therapy versus standard of care is influenced by key patient, treatment, or imaging

characteristics. We plan to examine subgroups stratified by age, sex, NIHSS score, ASPECTS, time to enrolment, use of vascular imaging (i.e., CTA and/or MRA) to confirm vessel occlusion prior to treatment, location of arterial occlusion, time to treatment, use of IV t-PA in the intervention group in addition to endovascular approach (i.e., combination therapy), endovascular technique used (mechanical +/- chemical), and type of mechanical device used for thrombectomy.

SEARCH STRATEGY

The following search strategy was employed for the MEDLINE database, using the Ovid interface:

1. exp Stroke/
2. exp Brain Ischemia/
3. exp Endovascular Procedures/
4. exp Thrombectomy/
5. exp Thrombolytic Therapy/
6. exp Embolectomy/
7. exp Infusions, Intra-Arterial/
8. exp Stents/
9. exp Clinical Trial/
10. 1 or 2
11. 3 or 4 or 5 or 6 or 7 or 8
12. 9 and 10 and 11

SUPPLEMENTAL RESULTS

eTable 4: Descriptive characteristics of included randomized trials

Study (Year)	Country, No. of Centers	Recruitment Period	*N*	Study Design	Eligibility Criteria	Intervention	Control	Outcomes	Sources of Funding
SYNTHESIS (2013)[10]	Italy, 24 centers	Feb 2008 to Apr 2012	362	Phase 3; randomization within 4.5 hrs of stroke onset; open-label; blinded endpoint; analysis by intention-to-treat	18 yrs ≤ age ≤ 80 yrs; acute ischemic stroke; NIHSS score ≤ 25; no acute ICH or intracranial tumor; able to initiate IV t-PA within 4.5 hrs or endovascular therapy within 6 hrs of stroke onset; premorbid mRS score 0-1	*N* = 181 Pharmacologic thrombolysis with IA t-PA 0.9 mg/kg up to max 90 mg over max 1 hr, mechanical clot disruption/retrieval with micro-guidewire (*n* = 109) or with addition of a device (*n* = 56) (Solitaire FR Revascularization Device [*n* = 18], Penumbra System [*n* = 9], Trevo Retriever [*n* = 5], Merci Retriever [*n* = 5]), or combination; intra-procedural IV heparin (5,000 IU bolus then 500 IU/hr) (*n* = 57) * No IV t-PA	*N* = 181 IV t-PA 0.9 mg/kg up to max 90 mg with 10% as bolus and remaining 90% as constant infusion over 1 hr	Primary—survival free of disability at 90 days (mRS score 0-1) Secondary efficacy—mild neurologic deficit or none (NIHSS score ≤ 6) at 7 days Safety (7-day)—symptomatic ICH; symptomatic brain edema from original brain infarction; recurrent ischemic stroke; mortality; neurologic deterioration (increase of ≥ 4 points in NIHSS score); extracerebral events * Examiners trained in use of the NIHSS and mRS scores	Italian Medicines Agency (AIFA)
MR RESCUE (2013)[11]	USA and Canada, 22 centers	2004 to 2011	118	Phase 2b; randomization within 8 hrs of stroke onset; pretreatment multimodal CT or MRI brain; randomization stratified according to favorable penumbral pattern versus non-penumbral pattern on pretreatment neuroimaging; open-label; blinded endpoint; analysis by intention-to-treat	18 yrs ≤ age ≤ 85 yrs; acute ischemic stroke; 6 ≤ NIHSS score ≤ 29; no acute ICH; large vessel anterior circulation occlusion (distal ICA, M1 or M2 MCA) on CTA or MRA; able to initiate mechanical embolectomy within 8 hrs of stroke onset; premorbid mRS score 0-2 * Allowed, but not required—IV t-PA within 4.5 hrs of stroke onset with persistent target occlusion on post-treatment CT or MRI brain	*N* = 64 Mechanical embolectomy (Merci Retriever [*n* = 37], Penumbra System [*n* = 14], or both [*n* = 10]); adjunctive IA t-PA (up to max 14 mg) within 6 hrs of stroke onset (*n* = 8); intra-procedural IV heparin at the discretion of the treating physician (max 2,000 IU bolus then 500 IU/hr) * Participating neurointerventionalists had training or prior experience with devices	*N* = 54 Best conventional medical therapy; general medical management according to American Heart Association/American Stroke Association guidelines; admission to monitored or intensive care unit for at least 24 hrs; ASA 325 mg daily for 7 days (+/- clopidogrel if indicated for cardiac disease) then per discretion of the treating physician	Primary—mRS score at 90 days Secondary efficacy—good functional outcome (mRS score 0-2) at 90 days; partial or complete revascularization (TICI score 2a-3) on CTA or MRA at 7 days; reperfusion (≥ 90% reduction in volume of perfusion lesion from baseline) on perfusion MRI at 7 days; final infarct volume and change in ischemic lesion volume from baseline on CT or MRI brain at 7 days Safety—90-day mortality; symptomatic and/or asymptomatic ICH within 7 days * Examiners trained in use of the NIHSS score	National Institute of Neurological Disorders and Stroke (NINDS); Concentric Medical

eTable 4: Descriptive characteristics of included randomized trials (cont'd)

Study (Year)	Country, No. of Centers	Recruitment Period	*N*	Study Design	Eligibility Criteria	Intervention	Control	Outcomes	Sources of Funding
IMS III (2013)[12]	USA, Canada, Australia, and Europe, 58 centers	Aug 2006 to Apr 2012	656	Phase 3; randomization within 40 min of initiation of IV t-PA infusion to additional intraarterial treatment (IV t-PA plus endovascular therapy) or IV t-PA alone in 2:1 ratio; stratified by center and stroke severity (NIHSS score ≤ 19 or > 19); open-label; blinded endpoint; analysis by intention-to-treat	18 yrs ≤ age ≤ 82 yrs; acute ischemic stroke; receipt of IV t-PA within 3 hrs of stroke onset; NIHSS score ≥ 10 at time IV t-PA is begun or NIHSS score 8 or 9 with CTA evidence of occlusion in M1 MCA, ICA, or basilar artery at institutions where baseline CTA was standard of care; no acute ICH or intracranial neoplasm	*N* = 434 IV t-PA 0.9 mg/kg up to max 90 mg with 10% as bolus and remaining 90% as constant infusion over 1 hr; formal angiogram within 5 hrs of symptom onset to confirm treatable occlusion; mechanical thrombectomy (Merci Retriever [*n* = 95], Penumbra System [*n* = 54], Solitaire FR Revascularization Device [*n* = 5], EKOS MicroSonic SV Infusion System [*n* = 22], standard micro-catheter [*n* = 142], or other [Trevo Retriever or combination] [*n* = 16]); IA t-PA (up to max 22 mg) (*n* = 266); intra-procedural IV heparin 2000 IU bolus then 450 IU/hr * Participating neurointerventionalists had training or prior experience with devices	*N* = 222 IV t-PA 0.9 mg/kg up to max 90 mg with 10% as bolus and remaining 90% as constant infusion over 1 hr	Primary—functional independence (mRS score 0–2) at 90 days Safety—7- and 90-day mortality; symptomatic and/or asymptomatic ICH within 30 hrs; major complication due to non-intracerebral bleeding within 5 days; recurrent ischemic stroke within 90 days; device- or procedure-related complications * Examiners trained in use of the NIHSS and mRS scores	National Institutes of Health (NIH); National Institute of Neurological Disorders and Stroke (NINDS); Genentech; EKOS; Concentric Medical; Cordis Neurovascular; Boehringer Ingelheim
MR CLEAN (2015)[13]	Netherlands, 16 centers	Dec 2010 to Mar 2014	500	Phase 3; randomization stratified by center, use of IV t-PA (yes or no), planned treatment method (mechanical or other), and stroke severity (NIHSS score ≤ 14 or > 14); 445 (89.0%) patients received IV t-PA prior to randomization; open-label; blinded endpoint; analysis by intention-to-treat	Age ≥ 18 yrs; acute ischemic stroke; NIHSS score ≥ 2; no acute ICH; proximal arterial occlusion in anterior cerebral circulation (distal ICA, M1 or M2 MCA, or A1 or A2 ACA) on CTA, MRA, or DSA; able to initiate intraarterial therapy within 6 hrs of stroke onset	*N* = 233 Usual care plus IA thrombolysis (*n* = 25) with max 90 mg t-PA or 1,200,000 IU urokinase if no IV t-PA given, or max 30 mg t-PA or 400,000 IU urokinase if IV t-PA given; mechanical treatment (*n* = 195) with thrombus retraction, aspiration, wire disruption, or use of retrievable stent (*n* = 190); or both * Participating neurointerventionalists had training or prior experience with devices	*N* = 267 Usual care alone, may include IV t-PA 0.9 mg/kg up to max 90 mg within 4.5 hrs of stroke onset	Primary—mRS score at 90 days Secondary efficacy— mRS score 0–2 at 90 days; NIHSS score at 24 hrs and 5 to 7 days or discharge; ADLs (Barthel index) and health-related QOL (EQ-5D score) at 90 days; recanalization (mAOL score 3) on CTA or MRA at 24 hrs; final infarct volume on CT at 5 to 7 days; Safety—7- and 30-day mortality; symptomatic ICH; need for hemicraniectomy; progression of ischemic stroke; new ischemic stroke in different vascular territory * Examiners trained in use of the NIHSS score	Dutch Heart Foundation; AngioCare Covidien/EV3; Medac/Lamepro; Penumbra

eTable 4: Descriptive characteristics of included randomized trials (cont'd)

Study (Year)	Country, No. of Centers	Recruitment Period	*N*	Study Design	Eligibility Criteria	Intervention	Control	Outcomes	Sources of Funding
ESCAPE (2015)[14]	Canada, USA, South Korea, Ireland, and United Kingdom, 22 centers	Feb 2013 to Oct 2014	315	Phase 3; randomization within 12 hrs of stroke onset in 1:1 ratio; randomization stratified by age, sex, baseline NIHSS score, site of arterial occlusion, baseline ASPECTS, and status with respect to IV t-PA treatment; open-label; blinded endpoint; analysis by intention-to-treat	Age ≥ 18 yrs; acute ischemic stroke; NIHSS score > 5; proximal intracranial occlusion in anterior circulation (ICA, M1 MCA, or two or more M2 MCA segments) on CTA; pre-stroke independent functional status (modified Barthel index ≥ 90); able to initiate endovascular therapy within 60 min of CT with target CT to first recanalization of 90 min; small infarct core on CT (ASPECTS 6-10,); moderate-to-good collateral circulation (≥ 50% filling of MCA pial arterial circulation on CTA)	*N* = 165 Standard care, including IV t-PA within 4.5 hrs of stroke onset, if eligible, plus endovascular therapy, which may include IA t-PA (up to max 10 mg), balloon angioplasty, guidewire manipulation of thrombus, direct aspiration of thrombus through large bore access catheter, or use of an available thrombectomy device (retrievable stent [*n* = 130] - i.e., Solitaire FR Revascularization Device [*n* = 100])	*N* = 150 Standard care as described by Canadian or local guidelines for the management of acute stroke, including IV t-PA within 4.5 hrs of stroke onset, if eligible; admission to a stroke unit; ASA therapy within first 48 hrs after day +1 neuroimaging demonstrating no evidence of hemorrhage; appropriate rehabilitation	Primary—mRS score at 90 days Secondary efficacy—mRS score 0-2 at 90 days; NIHSS score at 24 hrs and 90 days; NIHSS score 0-2 at 90 days; Barthel index 95-100 at 90 days; EQ-5D score at 90 days; recanalization (TICI score 2b-3 or mAOL score 2-3) at final angiogram or on CTA at 2-8 hrs Safety—90-day mortality; large or malignant MCA stroke; symptomatic ICH; hematoma at access site; perforation of MCA * Examiners trained in use of the mRS score	Covidien; University of Calgary; Alberta Innovates-Health Solutions; Heart and Stroke Foundation of Canada; Alberta Health Services
EXTEND-IA (2015)[15]	Australia and New Zealand, 10 centers	Aug 2012 to Oct 2014	70	Phase 2; randomization in 1:1 ratio stratified by site of arterial occlusion (ICA, M1 MCA, or M2 MCA); open-label; blinded endpoint; analysis by intention-to-treat	Age ≥ 18 yrs; acute ischemic stroke; no acute ICH or intracranial neoplasm; has received, or eligible using standard criteria to receive, IV t-PA within 4.5 hrs of stroke onset; proximal arterial occlusion in ICA or M1 or M2 MCA on CTA; ischemic core < 70 mL on CT perfusion; able to initiate endovascular therapy within 6 hrs of stroke onset; mRS score 0-1 prior to stroke	*N* = 35 IV t-PA 0.9 mg/kg up to max 90 mg with 10% as bolus and remaining 90% as constant infusion over 1 hr within 4.5 hrs of stroke onset, plus mechanical thrombectomy with Solitaire FR Revascularization Device initiated within 6 hrs and completed within 8 hrs of stroke onset * no IA t-PA	*N* = 35 IV t-PA 0.9 mg/kg up to max 90 mg with 10% as bolus and remaining 90% as constant infusion over 1 hr within 4.5 hrs of stroke onset	Primary—reperfusion (% reduction in perfusion-lesion volume) on MR or CT perfusion at 24 hrs; early neurologic improvement (≥ 8 point reduction in NIHSS score or NIHSS score 0-1 at 3 days) Secondary efficacy—reperfusion > 90% on MR or CT perfusion at 24 hrs without symptomatic ICH; recanalization (TIMI score 2-3) on MRA or CTA at 24 hrs; infarct growth on MRI or CT at 24 hrs; NIHSS score at 24 hrs; independent outcome (mRS score 0-2) at 90 days Safety—90-day mortality; symptomatic ICH within 36 hrs * Examiners trained in use of the NIHSS and mRS scores	National Health and Medical Research Council of Australia; Royal Australian College of Physicians; Royal Melbourne Hospital Foundation; National Heart Foundation of Australia; state government of Victoria; Covidien

eTable 4: Descriptive characteristics of included randomized trials (cont'd)

Study (Year)	Country, No. of Centers	Recruitment Period	*N*	Study Design	Eligibility Criteria	Intervention	Control	Outcomes	Sources of Funding
SWIFT-PRIME (2015)[16]	USA and Europe, 39 centers	Dec 2012 to Nov 2014	196	Randomization in 1:1 ratio; open-label; blinded endpoint; analysis by intention-to-treat	18 ≤ age ≤ 80; acute ischemic stroke; 8 ≤ NIHSS score ≤ 29; ASPECTS 6–10; no acute ICH; large vessel (intracranial ICA, carotid terminus, or M1 MCA) occlusion (TICI score 0-1) on CTA or MRA; pre-stroke mRS score 0–1; has received, or eligible to receive, IV t-PA within 4.5 hrs of stroke onset; able to initiate endovascular therapy within 6 hrs of stroke onset and 90 min of qualifying imaging	*N* = 98 IV t-PA plus mechanical thrombectomy using Solitaire FR or Solitaire 2 Revascularization Device	*N* = 98 IV t-PA alone	Primary—mRS score at 90 days Secondary efficacy—functional independence (mRS score 0–2) at 90 days; change in NIHSS score at 27 hrs; infarct volume at 27 hrs; reperfusion measured by reperfusion ratio on CT or MRI at 27 hrs; recanalization (TICI score 2b–3) after endovascular procedure; EQ-5D score at 90 days Safety—90-day mortality; symptomatic ICH within 27 hrs	Covidien
REVASCAT (2015)[17]	Spain, 4 centers	Nov 2012 to Dec 2014	206	Randomization in 1:1 ratio; open-label; blinded endpoint; analysis by intention-to-treat	18 ≤ age ≤ 85; acute ischemic stroke; proximal anterior circulation occlusion (intracranial ICA, M1 MCA, or tandem ICA-M1 MCA with TICI scale score 0-1); pre-stroke mRS score 0-1; baseline NIHSS score ≥ 6; baseline ASPECTS 7-10; received, or eligible to receive, IV t-PA within 4.5 hrs of stroke onset; no acute ICH	*N* = 103 Standard care, including IV t-PA within 4.5 hrs of stroke onset, if eligible, plus mechanical thrombectomy using Solitaire FR Revascularization Device	*N* = 103 Standard care, including IV t-PA within 4.5 hrs of stroke onset, if eligible	Primary—mRS score at 90 days Secondary efficacy—infarct volume on CT or MRI at 24 hrs, vessel revascularization on CTA or MRA at 24 hrs, NIHSS score at 24 hours, NIHSS score at 90 days, Barthel index at 90 days, EQ-5D score at 90 days Safety—90-day mortality; symptomatic ICH at 90 days, procedure-related complications, serious adverse events	Covidien; Spanish Ministry of Health; Fondo Europeo De Desarrollo Regional; Generalitat de Catalunya

Abbreviations: ACA, anterior cerebral artery; ADLs, activities of daily living; ASA, acetylsalicylic acid; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; IA, intraarterial; ICA, internal carotid artery; ICH, intracranial hemorrhage; IV, intravenous; mAOL, modified Arterial Occlusive Lesion; MCA, middle cerebral artery; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; QOL, quality of life; TICI, Thrombolysis in Cerebral Infarction; TIMI, Thrombolysis in Myocardial Infarction; t-PA, tissue plasminogen activator

eTable 5: Detailed secondary efficacy and safety outcomes by treatment group as reported by individual included randomized trials

Study (Year)	Treatment Group	Secondary Efficacy Outcomes	Safety Outcomes		
			Mortality	Intracranial Hemorrhage	Other Morbidity
SYNTHESIS (2013)[10]	Endovascular Therapy (*N* = 181)	- NIHSS score ≤ 6 at 7 days: 97 (53.6)	- 7-day mortality: 14 (7.7) - 90-day mortality: 26 (14.4)	- Symptomatic ICH within 7 days: 10 (5.5)	- Symptomatic edema from original brain infarction within 7 days: 37 (20.4) - Recurrent ischemic stroke within 7 days: 4 (2.2) - Neurologic deterioration (increase of ≥ 4 points in NIHSS score) within 7 days: 16 (8.8) - Severe extracranial bleeding (groin hematoma) within 7 days: 2 (1.1) - PE within 7 days: 1 (0.6) - MI within 7 days: 4 (2.2) - Sepsis within 7 days: 1 (0.6) - DVT within 7 days: 1 (0.6) - Pulmonary edema within 7 days: 2 (1.1)
	Standard Therapy (*N* = 181)	- NIHSS score ≤ 6 at 7 days: 100 (55.2)	- 7-day mortality: 11 (6.1) - 90-day mortality: 18 (9.9)	- Symptomatic ICH within 7 days: 10 (5.5)	- Symptomatic edema from original brain infarction within 7 days: 32 (17.7) - Recurrent ischemic stroke within 7 days: 4 (2.2) - Neurologic deterioration (increase of ≥ 4 points in NIHSS score) within 7 days: 12 (6.6) - Severe extracranial bleeding within 7 days: 2 (1.1) - PE within 7 days: 0 (0) - MI within 7 days: 2 (1.1) - Sepsis within 7 days: 0 (0) - DVT within 7 days: 0 (0) - Pulmonary edema within 7 days: 2 (1.1)
MR RESCUE (2013)[11]	Endovascular Therapy (*N* = 64)	- Good functional outcome (mRS score 0–2) at 90 days: 12 (18.8) - Partial or complete revascularization (TICI score 2a–3) at 7 days: 40/56 (71.4) - Reperfusion (≥ 90% reduction in volume of perfusion lesion from baseline) at 7 days: 23/47 (48.9)	- 90-day mortality: 12 (18.8)	- Symptomatic ICH within 7 days: 3 (4.7) - Asymptomatic ICH within 7 days: 42 (65.6) - Asymptomatic SAH: 5 (7.1) - Symptomatic SAH: 2 (2.9)	- Groin hematoma requiring transfusion or surgery: 0 (0) - Procedural complications within 90 days (*N* = 70) - Vessel dissection: 1 (1.4) - Vessel perforation: 7 (10.0) - Emboli in previously uninvolved territory: 1 (1.4) - Device fracture: 1 (1.4)
	Standard Therapy (*N* = 54)	- Good functional outcome (mRS score 0–2) at 90 days: 11 (20.4) - Partial or complete revascularization (TICI score 2a–3) at 7 days: 39/45 (86.7) - Reperfusion (≥ 90% reduction in volume of perfusion lesion from baseline) at 7 days: 20/39 (51.3)	- 90-day mortality: 13 (24.1)	- Symptomatic ICH within 7 days: 2 (3.7) - Asymptomatic ICH within 7 days: 26 (48.1)	

eTable 5: Detailed secondary efficacy and safety outcomes by treatment group as reported by individual included randomized trials (cont'd)

Study (Year)	Treatment Group	Secondary Efficacy Outcomes	Safety Outcomes		
			Mortality	Intracranial Hemorrhage	Other Morbidity
IMS III (2013)[12]	**Endovascular Therapy (*N* = 434)**		**- 7-day mortality: 52 (12.0)** **- 90-day mortality: 83 (19.1)**	**- Symptomatic ICH within 30 hrs: 27 (6.2)** **- Asymptomatic ICH within 30 hrs: 119 (27.4)** **- Major complication due to non-intracerebral bleeding within 5 days: 13 (3.0)**	**- Recurrent stroke within 90 days: 22 (5.1)** **- Device- or procedure-related complication (i.e., groin hematoma, vessel dissection, vessel perforation, and/or emboli in previously uninvolved territory): 70 (16.1)**
	Standard Therapy (*N* = 222)		- 7-day mortality: 24 (10.8) - 90-day mortality: 48 (21.6)	- Symptomatic ICH within 30 hrs: 13 (5.9) - Asymptomatic ICH within 30 hrs: 42 (18.9) - Major complication due to non-intracerebral bleeding within 5 days: 5 (2.3)	- Recurrent stroke within 90 days: 14 (6.3)
MR CLEAN (2015)[13]	Endovascular Therapy (*N* = 233)	- mRS score 0–2 at 90 days: 76 (32.6) - NIHSS score at 24 hrs: 13 (6–20) - NIHSS score at 5 to 7 days or discharge: 8 (2–17) - Barthel index 19 or 20 at 90 days: 99/215 (46.0) - EQ-5D score at 90 days: 0.69 (0.33–0.85) - No intracranial occlusion on CTA at 24 hrs: 141/187 (75.4) - Final infarct volume on non-contrast CT at 3 to 9 days (*n* = 138): 49 mL (22-96 mL)	- 7-day mortality: 27 (11.6) - 30-day mortality: 44 (18.9) - 90-day mortality: 49 (21.0)	- Symptomatic ICH: 18 (7.7)	- Required hemicraniectomy: 14 (6.0) - New ischemic stroke in different vascular territory: 13 (5.6) - Progressive ischemic stroke: 46 (19.7) - Pneumonia: 25 (10.7) - Other infection: 16 (6.9) - Cardiac ischemia: 1 (0.4) - Extracranial hemorrhage: 0 (0) - Allergic reaction: 1 (0.4) - Other complication: 22 (9.4)
	Standard Therapy (*N* = 267)	- mRS score 0–2 at 90 days: 51 (19.1) - NIHSS score at 24 hrs: 16 (12–21) - NIHSS score at 5 to 7 days or discharge: 14 (7–18) - Barthel index 19 or 20 at 90 days: 73/245 (29.8) - EQ-5D score at 90 days: 0.66 (0.30–0.81) - No intracranial occlusion on CTA at 24 hrs: 68/207 (32.9) - Final infarct volume on non-contrast CT at 3 to 9 days (*n* = 160): 79 mL (34-125 mL)	- 7-day mortality: 33 (12.4) - 30-day mortality: 49 (18.4) - 90-day mortality: 59 (22.1)	- Symptomatic ICH: 17 (6.4)	- Required hemicraniectomy: 13 (4.9) - New ischemic stroke in different vascular territory: 1 (0.4) - Progressive ischemic stroke: 47 (17.6) - Pneumonia: 41 (15.4) - Other infection: 9 (3.4) - Cardiac ischemia: 4 (1.5) - Extracranial hemorrhage: 2 (0.7) - Allergic reaction: 0 (0) - Other complication: 33 (12.4)

eTable 5: Detailed secondary efficacy and safety outcomes by treatment group as reported by individual included randomized trials (cont'd)

Study (Year)	Treatment Group	Secondary Efficacy Outcomes	Safety Outcomes		
			Mortality	Intracranial Hemorrhage	Other Morbidity
ESCAPE (2015)[14]	**Endovascular Therapy (*N* = 165)**	- mRS score 0-2 at 90 days: 87/164 (53.0) - NIHSS score at 24 hrs: 6 (3-14) - NIHSS score at 90 days: 2 (1-8) - NIHSS score 0-2 at 90 days: 79/153 (51.6) - Barthel index 95-100 at 90 days: 94/163 (57.7) - EQ-5D score at 90 days: 80 (60-90) - Recanalization (TICI score 2b-3) at final angiogram: 113/156 (72.4)	- 90-day mortality: 17/164 (10.4)	- Symptomatic ICH: 6 (3.6)	- Required hemicraniectomy: 1 (0.6) - Large or malignant MCA stroke: 8 (4.8) - Hematoma at access site: 3 (1.8) - Perforation of MCA: 1 (0.6) - Angioedema: 0 (0) - Atrial fibrillation: 3 (1.8) - Cancer: 2 (1.2) - Carotid endarterectomy: 2 (1.2) - CHF/pulmonary edema: 4 (2.4) - Fall: 1 (0.6) - GI bleed: 2 (1.2) - MI: 2 (1.2) - Pneumonia: 7 (4.2) - DVT/PE: 2 (1.2) - Recurrent stroke: 8 (4.9) - Sepsis: 1 (0.6) - Systemic embolus: 1 (0.6) - Seizure 0 (0)
	Standard Therapy (*N* = 150)	- mRS score 0-2 at 90 days: 43/147 (29.3) - NIHSS score at 24 hrs: 13 (6-18) - NIHSS score at 90 days: 8 (3-19) - NIHSS score 0-2 at 90 days: 31/134 (23.1) - Barthel index 95-100 at 90 days: 49/146 (33.6) - EQ-5D score at 90 days: 65 (50-80) - Recanalization (mAOL score 2-3) on CTA at 2-8 hrs: 43/138 (31.2)	- 90-day mortality: 28/147 (19.0)	- Symptomatic ICH: 4 (2.7)	- Required hemicraniectomy: 1 (0.7) - Large or malignant MCA stroke: 16 (10.7) - Angioedema: 1 (0.7) - Atrial fibrillation: 1 (0.7) - Cancer: 2 (1.3) - Carotid endarterectomy: 0 (0) - CHF/pulmonary edema: 3 (2.0) - Fall: 1 (0.7) - GI bleed: 1 (0.7) - MI: 1 (0.7) - Pneumonia: 9 (6.0) - DVT/PE: 2 (1.3) - Recurrent stroke: 3 (2.0) - Sepsis: 2 (1.3) - Systemic embolus: 0 (0) - Seizure: 1 (0.7)

eTable 5: Detailed secondary efficacy and safety outcomes by treatment group as reported by individual included randomized trials (cont'd)

Study (Year)	Treatment Group	Secondary Efficacy Outcomes	Safety Outcomes		
			Mortality	Intracranial Hemorrhage	Other Morbidity
EXTEND-IA (2015)[15]	Endovascular Therapy (*N* = 35)	**- Reperfusion (% reduction in perfusion-lesion volume) on MR or CT perfusion at 24 hrs: 100 (100-100)** **- Early neurologic improvement (≥ 8 point reduction in NIHSS score or NIHSS score 0-1 at 3 days): 28 (80.0)** **- mRS score 0-2 at 90 days: 25 (71.4)** **- > 90% reperfusion on MR or CT perfusion at 24 hrs without symptomatic ICH: 31 (88.6)** **- Recanalization (TIMI score 2-3) on CTA or MRA at 24 hrs: 33 (94.3)** **- Infarct growth on MRI or CT at 24 hrs: 10.9 mL (0-23.6 mL)** **- Days spent at home during first 90 days after stroke: 73 (47-86)** **- Reduction in NIHSS score at 24 hrs: 11 (5-16)** **- Reduction in NIHSS score at 3 days: 12 (6-17)** **- Neurologic improvement (≥ 8 point reduction in NIHSS score or NIHSS score 0-1) at 90 days: 30 (85.7)**	**- 90-day mortality: 3 (8.6)**	**- Symptomatic ICH: 0 (0)** **- Parenchymal hematoma: 4 (11.4)**	**- Vessel perforation: 1 (2.9)** **- Groin hematoma: 1 (2.9)** **- Embolization into another vessel territory: 2 (5.7)**
	Standard Therapy (*N* = 35)	- Reperfusion (% reduction in perfusion-lesion volume) on MR or CT perfusion at 24 hrs: 37 (-0.5–96) - Early neurologic improvement (≥ 8 point reduction in NIHSS score or NIHSS score 0–1 at 3 days): 13 (37.1) - mRS score 0–2 at 90 days: 14 (40.0) - > 90% reperfusion on MR or CT perfusion at 24 hrs without symptomatic ICH: 12 (34.3) - Recanalization (TIMI score 2–3) on CTA or MRA at 24 hrs: 15 (42.9) - Infarct growth on MRI or CT at 24 hrs: 35.3 mL (6.3–73.4 mL) - Days spent at home during first 90 days after stroke: 15 (0–69) - Reduction in NIHSS score at 24 hrs: 1 (-1–7) - Reduction in NIHSS score at 3 days: 3 (-2–10) - Neurologic improvement (≥ 8 point reduction in NIHSS score or NIHSS score 0–1) at 90 days: 21 (60.0)	- 90-day mortality: 7 (20.0)	- Symptomatic ICH: 2 (5.7) - Parenchymal hematoma: 3 (8.6)	- Angioedema: 1 (2.9)
SWIFT-PRIME (2015)[16]	Endovascular Therapy (*N* = 98)	- Improvement NIHSS score at 27 hrs (*N* = 97): 8.5 ± 7.1 - Reperfusion ≥ 90% on CT or MRI at 27 hrs: 53/64 (82.8) - 50-99% reperfusion on angiography immediately after thrombectomy: 16/83 (19.3) - 100% reperfusion on angiography immediately after thrombectomy: 57/83 (68.7) - 90-day NIHSS (*N* = 88): 1 (0-22) - Barthel Index at 90 days (*N* = 88): 100 (10-100) - Infarct volume at 27hours (*N* = 97): 32 mL (0 – 530.5 mL) - Infarct growth at 27hours (*N* = 82): 14.8 mL (-17.5 – 516.5 mL)	- 90-day mortality: 9 (9.2)	- Symptomatic ICH within 27 hrs: 0 (0) - Parenchymal hematoma within 27 hrs: 5 (5.1) - SAH within 27 hrs: 4 (4.1)	- Any serious adverse event: 35 (35.7) - Procedure related adverse events: Cerebral vasospasm: 4; IVH: 1; SAH: 1
	Standard Therapy (*N* = 97)	- Improvement NIHSS score at 27 hrs (*N* = 92): 3.9 ± 6.2 - Reperfusion ≥ 90% on CT or MRI at 27 hrs: 21/52 (40.4) - 90-day NIHSS (*N* = 75): 5 (0-32) - Barthel Index at 90 days (*N* = 77): 90 (0-110) - Infarct volume at 27hours (*N* = 94): 35.3 mL (0 – 406.6 mL) - Infarct growth at 27hours (*N* = 72): 25.7 mL (-7.4 – 276.7 mL)	- 90-day mortality: 12 (12.4)	- Symptomatic ICH within 27 hrs: 3 (3.1) - Parenchymal hematoma within 27 hrs: 7 (7.2) - SAH within 27 hrs: 1 (1.0)	- Any serious adverse event: 30 (30.9)

eTable 5: Detailed secondary efficacy and safety outcomes by treatment group as reported by individual included randomized trials (cont'd)

Study (Year)	Treatment Group	Secondary Efficacy Outcomes	Safety Outcomes		
			Mortality	Intracranial Hemorrhage	Other Morbidity
REVASCAT (2015)[17]	Endovascular Therapy (*N* = 103)	- mRS score 0-2 at 90 days: 45 (43.7) - NIHSS score at 90 days: 2 (0 – 8) - Barthel Index score of 95-100 at 90 days: 47/82 (57.3) - EQ-5D score at 90 days: 0.65 (0.21 – 0.79) - Infarct volume at 24 hrs: 16.3 mL (8.3 – 58.5 mL) - 50-99% reperfusion on angiography immediately after thrombectomy: 48/102 (47.1) - 100% reperfusion on angiography immediately after thrombectomy: 19/102 (18.6)	90-day mortality: 19 (18.4)	- Symptomatic ICH at 90 days: 5 (4.9) - Asymptomatic ICH at 90 days: 17 (16.5) - SAH at 90 days: 5 (4.9)	- Acute pulmonary edema: 1 (1.0) - Aspiration pneumonia: 15 (14.6) - Metastatic cancer: 2 (1.9) - Seizures: 7 (6.8) - Shock: 1 (1.0) - Stent thrombosis: 1 (1.0) - Neurological worsening (>4 points NIHSS within 5 days not attributable to ICH or edema): 16 (15.5) - Malignant cerebral edema: 11 (10.7) - Recurrent stroke: 4 (3.9) - Distal embolization to new territory: 5 (4.9) - Arterial dissection: 4 (3.9) - Arterial perforation: 5 (4.9) - Groin hematoma: 11 (10.7) - Groin pseudoaneurysm: 1 (1.0) - Vasospasm requiring treatment: 4 (3.9)
	Standard Therapy (*N* = 103)	- mRS score 0-2 at 90 days: 29 (28.2) - NIHSS score at 90 days: 6 (2 – 11) - Barthel Index score of 95-100 at 90 days: 23/87 (26.4) - EQ-5D score at 90 days: 0.32 (0.13 – 0.70) - Infarct volume at 24 hrs: 38.6 mL (11.9– 86.8 mL)	90-day mortality: 16 (15.5)	- Symptomatic ICH at 90 days: 2 (1.9) - Asymptomatic ICH at 90 days: 11 (10.7) - SAH at 90 days: 2 (1.9)	- Aspiration pneumonia: 9 (8.7) - Cardiogenic shock: 1 (1.0) - Extracranial hemorrhage: 5 (4.9) - Heart failure: 1 (1.0) - Metastatic cancer: 1 (1.0) - Seizures: 3 (2.9) - Neurological worsening (>4 points NIHSS within 5 days not attributable to ICH or edema): 13 (12.6) - Malignant cerebral edema: 10 (9.7) - Recurrent stroke: 3 (2.9)

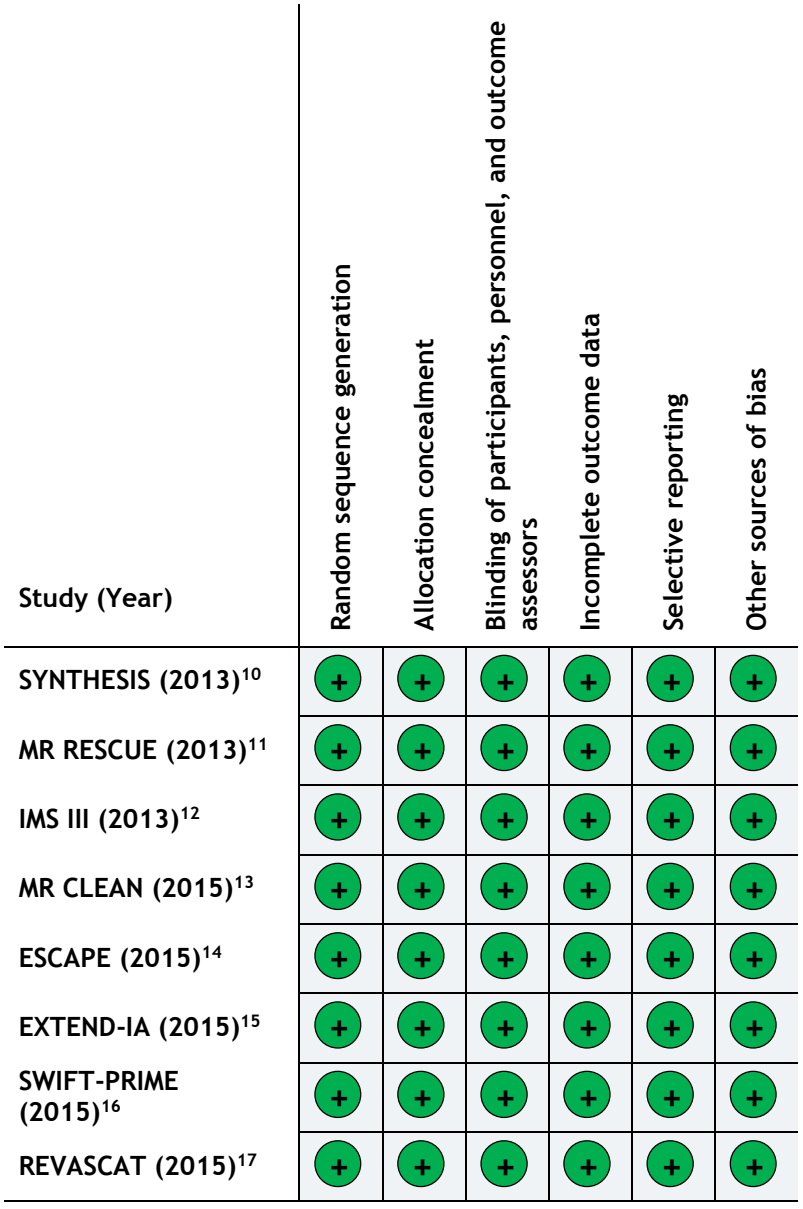
Data are presented as *n/N* (%), mean ± SD, or median (IQR), unless otherwise specified. *Abbreviations:* CHF, congestive heart failure; CT, computed tomography; CTA, computed tomography angiography; DVT, deep vein thrombosis; EQ-5D, EuroQoL Group 5-Dimension Self Report Questionnaire; GI, gastrointestinal; ICH, intracranial hemorrhage; mAOL, modified Arterial Occlusive Lesion; MCA, middle cerebral artery; MI, myocardial infarction; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PE, pulmonary embolism; SAH, subarachnoid hemorrhage; TICI, Thrombolysis in Cerebral Infarction; TIMI, Thrombolysis in Myocardial Infarction

eTable 6: Quality of evidence as rated using the GRADE[18]

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Endovascular Therapy	Standard Therapy	Relative (95% CI)	Absolute (95% CI)		
Proportional treatment benefit across all mRS scores (follow up: mean 90 days; assessed with: mRS)												
8	randomized trials	not serious	not serious[1]	not serious	not serious	none[2]	N/A	N/A	**OR 1.56** (1.14 to 2.13)	N/A	⨁⨁⨁⨁ HIGH	CRITICAL
Functional independence, mRS 0–2 (follow up: mean 90 days; assessed with: mRS)												
8	randomized trials	not serious	not serious[3]	not serious	not serious	none[2]	557/1293 (43.1%)	351/1094 (32.1%)	**OR 1.71** (1.18 to 2.49)	126 more per 1000 (from 37 more to 220 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Mortality (follow up: mean 90 days)												
8	randomized trials	not serious	not serious[4]	not serious	serious[5]	none[2]	218/1312 (16.6%)	201/1106 (18.2%)	**OR 0.87** (0.68 to 1.12)	20 fewer per 1000 (from 17 more to 51 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT
Revascularization (follow up: mean 24 hours; assessed with: Angiogram)												
4	randomized trials	not serious	not serious	not serious	not serious	none[2]	340/442 (76.9%)	147/432 (34.0%)	**OR 6.49** (4.79 to 8.79)	430 more per 1000 (from 372 more to 479 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Symptomatic intracranial hemorrhage (follow up: mean 7 days)												
8	randomized trials	not serious	not serious	not serious	serious[6]	none[2]	70/1313 (5.3%)	53/1109 (4.8%)	**OR 1.12** (0.77 to 1.63)	5 more per 1000 (from 11 fewer to 28 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

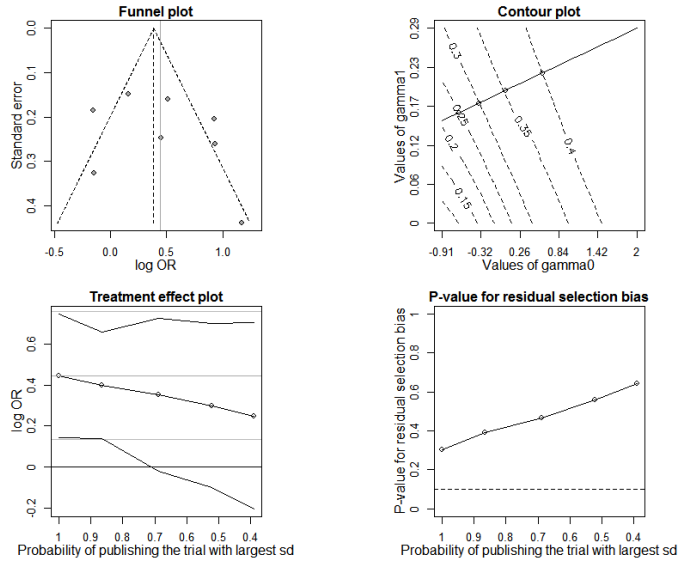
1. Although I^2=75.9% suggesting significant heterogeneity, we did not downgrade for inconsistency since heterogeneity is well explained by subgroup analyses.
2. Although number of included trials is less than 10, we used multiple methods to assess publication bias including funnel plots and Egger, Begg-Mazumdar, and Copas tests which did not suggest presence of publication bias.
3. Although I^2=75.4% suggesting significant heterogeneity, we did not downgrade for inconsistency since heterogeneity is well explained by subgroup analyses.
4. I^2=17.7% suggesting insignificant inconsistency.
5. We downgraded by one point for imprecision. Although point estimate suggest treatment benefit, the 95% confidence interval contained both benefit and harm.
6. We downgraded by one point for imprecision as the 95% confidence interval is wide (95% CI 0.77–1.63).

eFigure 1: Assessment of the methodological quality of included randomized trials using the Cochrane Collaboration's tool[4]



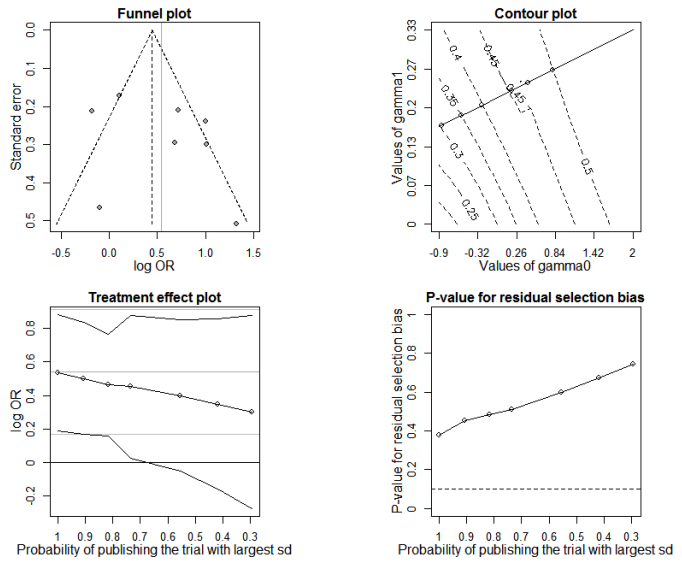
eFigure 2: Analysis of publication bias for meta-analyses of endovascular therapy versus standard therapy

A



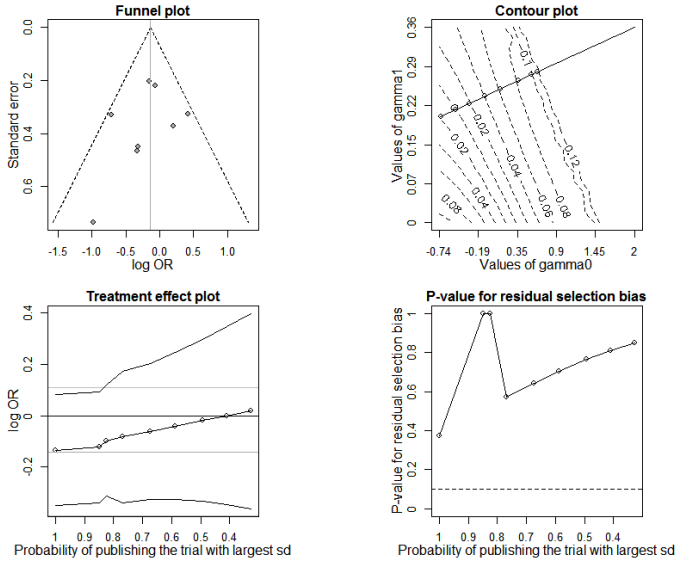
Begg-Mazumdar: Kendall's tau = 0.18, p = 0.54
Egger: bias = 2.11 (95% CI -3.83–8.04), p = 0.42

B



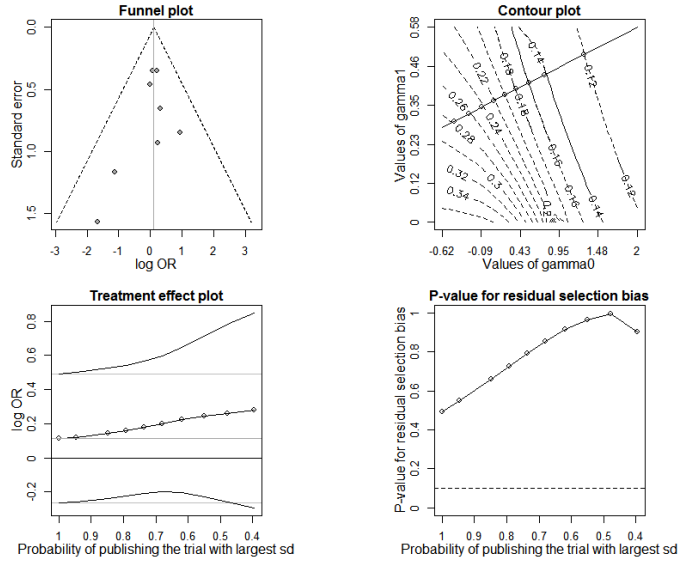
Begg-Mazumdar: Kendall's tau = 0.18, p = 0.54
Egger: bias = 2.37 (95% CI -3.15–7.88), p = 0.33

C



Begg-Mazumdar: Kendall's tau = -0.32, p = 0.27
Egger: bias = -0.89 (95% CI -3.66–1.88), p = 0.46

D

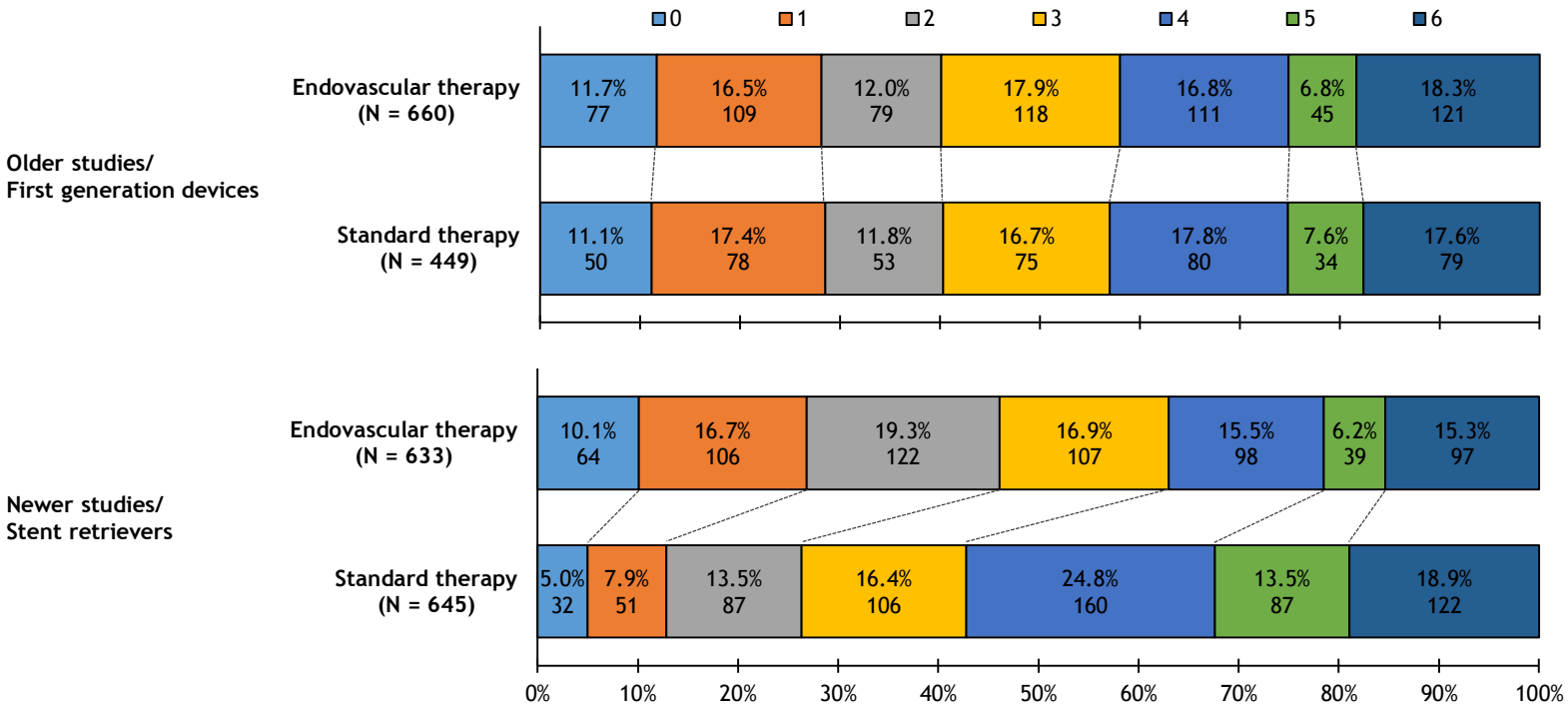


Begg-Mazumdar: Kendall's tau = -0.25, p = 0.39
Egger: bias = -0.54 (95% CI -1.95–0.87), p = 0.38

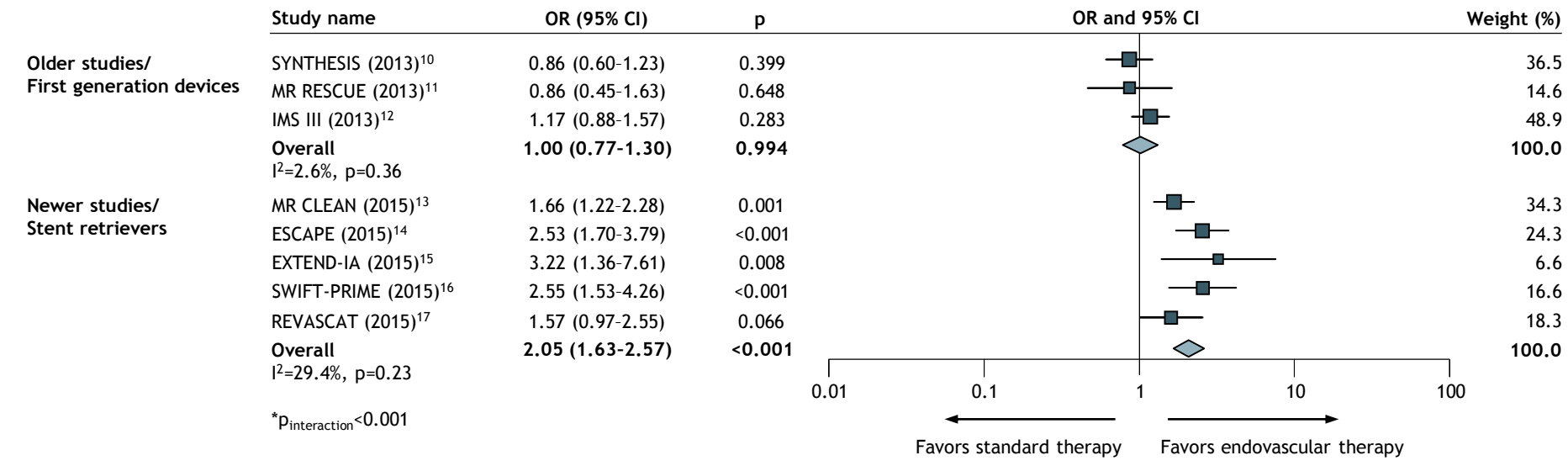
Outcomes assessed are: **(A)** proportional odds ratio for modified Rankin scale score (shift analysis); **(B)** functional independence (modified Rankin scale score 0–2); **(C)** mortality; and **(D)** symptomatic ICH

eFigure 3: Functional outcomes of endovascular therapy versus standard therapy stratified by year of publication/device use

A Degree of Disability at 90 days (modified Rankin scale)



B Reduced Disability at 90 days



Pooled distribution of modified Rankin scale scores at 90 days stratified by treatment group **(A)**. Meta-analysis of endovascular therapy versus standard therapy for outcomes of proportional treatment benefit across modified Rankin scale scores at 90 days **(B)**

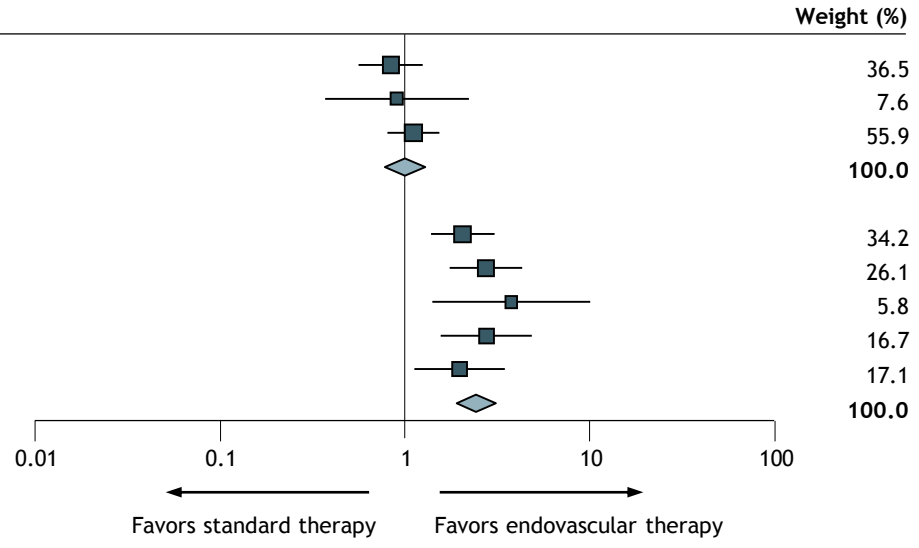
Size of data marker for each study is proportional to its sample size. Data on modified Rankin scale score at 90 days was not available for 19 patients in the endovascular therapy group and 8 patients in the standard medical treatment group in IMS III,[12] 1 patient in the endovascular therapy group and 3 patients in the standard medical treatment group in ESCAPE,[14] and 5 patients in the standard medical treatment group in SWIFT-PRIME[16] due to losses to follow-up in these trials. The modified Rankin scale[3] measures functional outcome on a 7-point ordinal scale: 0, no symptoms at all; 1, no significant disability despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; 6, death

eFigure 4: Secondary efficacy and safety outcomes of endovascular therapy versus standard therapy stratified by year of publication/device use

A Functional Independence (modified Rankin scale score 0-2) at 90 days

	Study name	Endovascular Therapy Events / *N*	Standard Therapy Events / *N*	OR (95% CI)	p	Weight (%)
Older studies/ First generation devices	SYNTHESIS (2013)[10]	76 / 181	84 / 181	0.84 (0.55-1.27)	0.397	36.5
	MR RESCUE (2013)[11]	12 / 64	11 / 54	0.90 (0.36-2.25)	0.825	7.6
	IMS III (2013)[12]	177 / 415	86 / 214	1.11 (0.79-1.55)	0.553	55.9
	Overall I^2=0.0%, p=0.58	**265 / 660**	**181 / 449**	**0.98 (0.77-1.26)**	**0.898**	**100.0**
Newer studies/ Stent retrievers	MR CLEAN (2015)[13]	76 / 233	51 / 267	2.05 (1.36-3.09)	0.001	34.2
	ESCAPE (2015)[14]	87 / 164	43 / 147	2.73 (1.71-4.37)	<0.001	26.1
	EXTEND-IA (2015)[15]	25 / 35	14 / 35	3.75 (1.38-10.17)	0.009	5.8
	SWIFT-PRIME (2015)[16]	59 / 98	33 / 93	2.75 (1.53-4.94)	0.001	16.7
	REVASCAT (2015)[17]	45 / 103	29 / 103	1.98 (1.11-3.53)	0.021	17.1
	Overall I^2=0.0%, p=0.69	**292 / 633**	**170 / 645**	**2.39 (1.88-3.04)**	**<0.001**	**100.0**

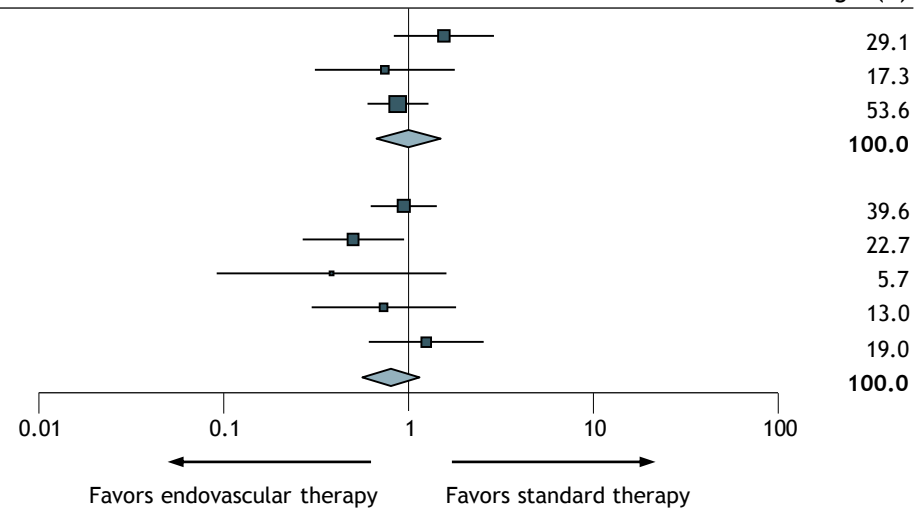
*$p_{interaction}$<0.001



B Mortality at 90 days

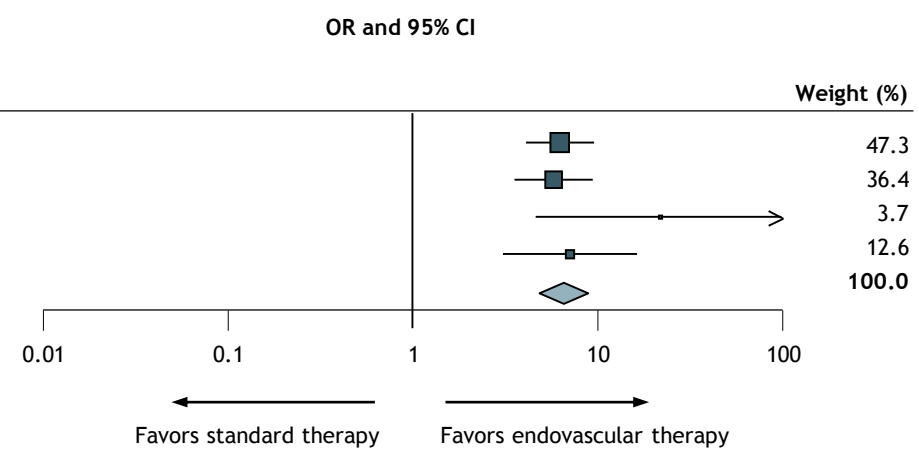
	Study name	Endovascular Therapy Events / *N*	Standard Therapy Events / *N*	OR (95% CI)	p	Weight (%)
Older studies/ First generation devices	SYNTHESIS (2013)[10]	26 / 181	18 / 181	1.52 (0.80-2.88)	0.200	29.1
	MR RESCUE (2013)[11]	12 / 64	13 / 54	0.73 (0.30-1.76)	0.482	17.3
	IMS III (2013)[12]	83 / 434	48 / 222	0.86 (0.58-1.28)	0.449	53.6
	Overall I^2=24.8%, p=0.26	**121 / 679**	**79 / 457**	**0.98 (0.66-1.47)**	**0.938**	**100.0**
Newer studies/ Stent retrievers	MR CLEAN (2015)[13]	49 / 233	59 / 267	0.94 (0.61-1.44)	0.772	39.6
	ESCAPE (2015)[14]	17 / 164	28 / 147	0.49 (0.26-0.94)	0.032	22.7
	EXTEND-IA (2015)[15]	3 / 35	7 / 35	0.38 (0.09-1.59)	0.183	5.7
	SWIFT-PRIME (2015)[16]	9 / 98	12 / 97	0.72 (0.29-1.79)	0.474	13.0
	REVASCAT (2015)[17]	19 / 103	16 / 103	1.23 (0.59-2.55)	0.578	19.0
	Overall I^2=22.3%, p=0.27	**97 /633**	**122 / 649**	**0.78 (0.55-1.12)**	**0.175**	**100.0**

*$p_{interaction}$=0.398



C Revascularization at 24 hours

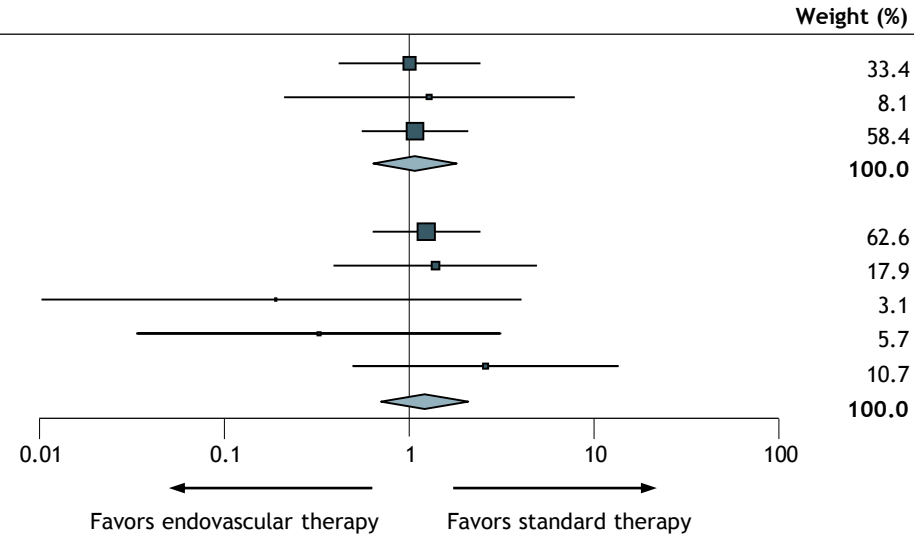
	Study name	Endovascular Therapy Events / *N*	Standard Therapy Events / *N*	OR (95% CI)	p	Weight (%)
Newer studies/ Stent retrievers	MR CLEAN (2015)[13]	141 / 187	68 / 207	6.27 (4.03-9.74)	<0.001	47.3
	ESCAPE (2015)[14]	113 / 156	43 / 138	5.81 (3.51-9.60)	<0.001	36.4
	EXTEND-IA (2015)[15]	33 / 35	15 / 35	22.00 (4.55-106.43)	<0.001	3.7
	SWIFT-PRIME (2015)[16]	53 / 64	21 / 52	7.11 (3.03-16.70)	<0.001	12.6
	Overall I^2=0.0%, p=0.46	**340 / 442**	**147 / 432**	**6.49 (4.79-8.79)**	**<0.001**	**100.0**



D Symptomatic intracranial hemorrhage within 90 days

	Study name	Endovascular Therapy Events / *N*	Standard Therapy Events / *N*	OR (95% CI)	p	Weight (%)
Older studies/ First generation devices	SYNTHESIS (2013)[10]	10 / 181	10 / 181	1.00 (0.41-2.46)	1.000	33.4
	MR RESCUE (2013)[11]	3 / 64	2 / 54	1.28 (0.21-7.95)	0.792	8.1
	IMS III (2013)[12]	27 / 434	13 / 222	1.07 (0.54-2.11)	0.853	58.4
	Overall I^2=0.0%, p=0.97	**40 / 679**	**25 / 457**	**1.06 (0.63-1.78)**	**0.828**	**100.0**
Newer studies/ Stent retrievers	MR CLEAN (2015)[13]	18 / 233	17 / 267	1.23 (0.62-2.45)	0.553	62.6
	ESCAPE (2015)[14]	6 / 165	4 / 150	1.38 (0.38-4.98)	0.625	17.9
	EXTEND-IA (2015)[15]	0 / 35	2 / 35	0.19 (0.01-4.08)	0.288	3.1
	SWIFT-PRIME (2015)[16]	1 / 98	3 / 97	0.32 (0.03-3.16)	0.332	5.7
	REVASCAT (2015)[17]	5 / 103	2 / 103	2.58 (0.49-13.59)	0.265	10.7
	Overall I^2=0.0%, p=0.47	**30 / 634**	**28 / 652**	**1.19 (0.69-2.05)**	**0.535**	**100.0**

*$p_{interaction}$=0.766



Meta-analyses of endovascular therapy versus standard therapy for outcomes of functional independence (modified Rankin scale score 0-2) at 90 days **(A)**, mortality at 90 days **(B)**, revascularization at 24 hours **(C)**, and symptomatic intracranial hemorrhage within 90 days **(D)**
Size of data marker for each study is proportional to its sample size. Revascularization was defined as angiographic restoration of blood flow at the site of arterial occlusion within 24 hours of stroke. Revascularization was evaluated at only 7 days in MR RESCUE,[11] and therefore this data could not be included in our analysis. Revascularization was assessed at 27 hours in the SWIFT-PRIME[16] trial, and this was considered equivalent to 24 hours for the purposes of the present analysis. The revascularization outcome in this trial was based on successful reperfusion (reperfusion ratio ≥ 90%) on CT or MR perfusion imaging

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