Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majoie, Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mònica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Methods We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days in the pooled population and examine heterogeneity of this treatment effect across prespecified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome in the whole population (shift analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale score), site of occlusion (internal carotid artery *vs* M1 segment of middle cerebral artery *vs* M2 segment of middle cerebral artery), intravenous alteplase (yes *vs* no), baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Findings We analysed individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across prespecified subgroups for reduced disability ($p_{interaction}$=0·43). Effect sizes favouring endovascular thrombectomy over control were present in several strata of special interest, including in patients aged 80 years or older (cOR 3·68, 95% CI 1·95–6·92), those randomised more than 300 min after symptom onset (1·76, 1·05–2·97), and those not eligible for intravenous alteplase (2·43, 1·30–4·55). Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations.

Interpretation Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

Funding Medtronic.

Introduction

Endovascular thrombectomy for acute ischaemic stroke has evolved substantially; however, only after the 2015 publication of five clinical trials[1–5] has this procedure been accepted as the standard of care for patients with proximal anterior circulation occlusions.[6] Uncertainties remain about the benefit of endovascular thrombectomy in patient groups under-represented in these individual

trials, including those who presented to treatment late, are elderly, have mild deficits, and are not eligible for intravenous alteplase.[6] Moreover, because these trials were individually moderate in size, data pooling can provide more precise estimates of treatment effects. As investigators from the MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, and EXTEND IA trials, we seek to address these and other questions about the risks and

Departments of Clinical Neuroscience and Radiology, Hotchkiss Brain Institute, Cummings School of Medicine, University of Calgary, Calgary, AB, Canada (Prof M Goyal MD, B K Menon MD, Prof A M Demchuk MD, Prof M D Hill MD); **Maastricht University Medical Center, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands** (W H van Zwam MD, D Beumer MD, Prof R J van Oostenbrugge MD); **Erasmus MC University Medical Center, Rotterdam, Netherlands** (Prof D W J Dippel MD, Prof A van der Lugt MD); **Department of Radiology** (Prof P J Mitchell MBBS) **and Department of Medicine and Neurology, Melbourne Brain Centre** (Prof S M Davis MD, B C V Campbell MD), **Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia; Hospital Germans Trias y Pujol, Barcelona, Spain** (Prof A Dávalos MD); **Academic Medical Center, Amsterdam, Netherlands** (Prof C B L M Majoie MD, Prof Y B W E M Roos MD, O A Berkhemer MD, L A van den Berg MD); **Hospital de Bellvitge, Barcelona, Spain** (M A De Miquel MD); **Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia** (Prof G A Donnan MD); **Hospital Guy de Chaulliac, Montpellier, France** (Prof A Bonafe MD); **UCLA**

Medical Center, Los Angeles,
CA, USA (R Jahan MD);
Department of Neurology,
University Hospital Essen,
Essen, Germany
(Prof H-C Diener MD); State
University of New York,
Buffalo, Buffalo, NY, USA
(Prof E I Levy MD); University of
Toronto, Toronto, ON, Canada
(V Pereira MD); University of
Edmonton, Edmonton, AB,
Canada (J Rempel MD); Hospital
Germans Trials y Pujol,
Barcelona, Spain (M Millán MD);
CHUM Notre-Dame Hospital,
Montreal, QC, Canada
(Prof D Roy MD); Beaumont
Hospital, Dublin, Ireland
(J Thornton MD); Hospital
Clinic, Barcelona, Spain
(L San Román MD); Hospital Vall
d'Hebron, Barcelona, Spain
(M Ribó MD); Philadelphia
College of Osteopathic
Medicine, Philadelphia, PA,
USA (Prof B Stouch PhD); Altair
Biostatistics, St Louis Park,
MN, USA (S Brown PhD); David
Geffen School of Medicine,
University of Los Angeles,
Los Angeles, CA, USA
(Prof J L Saver MD); and
University of Pittsburgh
Medical Center Stroke
Institute, Presbyterian
University Hospital,
Pittsburgh, PA, USA
(T G Jovin MD)

Correspondence to:
Dr Tudor Jovin, University of
Pittsburgh Medical Center Stroke
Institute, Presbyterian University
Hospital, Pittsburgh, PA 15213,
USA
jovintg@upmc.edu

See Online for appendix

Research in context

Evidence before the study

Evidence to support endovascular therapy for stroke has previously been poor because randomised trials have used thrombectomy devices of low efficacy, insufficiently robust imaging selection criteria, and had long delays from hospital presentation to reperfusion. Five individual trials published in 2015 established that thrombectomy, when done with newer generation devices (mainly stent retrievers), more stringent imaging selection criteria, and more efficient workflow, significantly reduces disability rates after acute ischaemic stroke caused by proximal occlusion of large vessels in the anterior circulation. Because most of these studies were stopped prematurely, they were underpowered to provide convincing evidence of efficacy across some of the subgroups of great relevance to clinical practice. We did an extensive literature search of major online databases including PubMed and Embase for papers published from Jan 1, 2010, to Dec 23, 2015, and did not identify any other published randomised endovascular stroke studies that used modern thrombectomy devices. Study level meta-analyses have been reported but most included patients enrolled without definitive proof of vessel occlusion and who were treated with less effective reperfusion technology. Furthermore, study-level meta-analyses are considered less informative than patient-level meta-analytical approaches due to their inability to adjust for confounding baseline variables, which leads to less precise estimates of treatment effect. To our knowledge no patient-level meta-analyses have been reported.

Added value of this study

In this individual patient meta-analysis of trials published in 2015, we provide additional relevant facts that will enable clinicians to better understand the degree of precision of adjusted effect size estimates, safety outcome estimates, and estimates by clinical subgroups. We show clinical benefits for thrombectomy across a wide range of age and initial stroke severity and for patients eligible and ineligible for intravenous alteplase. Smaller amounts of other baseline variables such as degree of early ischaemic changes on baseline CT or time to treatment were reported and therefore the observed effects should be interpreted within the context of the populations included.

Implications of all the available evidence

The consistent results across different patient populations suggest that benefit from thrombectomy is generalisable to a broad range of patients with large-vessel ischaemic stroke. By providing a more precise treatment effect estimate than each individual trial, our findings allow cost-effectiveness of this intervention at society level to be calculated with higher precision. Our study provides clear evidence that in clinical practice, endovascular therapy for stroke should not be withheld on the basis of advanced age, moderately extensive early ischaemic changes on baseline CT, and moderate or severe clinical deficit.

benefits of modern endovascular therapy by analysing pooled individual patient data for thrombectomy after acute ischaemic stroke.

Methods

Study inclusion and procedures

We searched major online databases including Medline and PubMed to identify controlled trials in endovascular stroke published between Jan 1, 2010, and Dec 23, 2015, that used vessel imaging to identify patients with anterior circulation ischaemic stroke and assessed treatment with modern neurothrombectomy devices. Five trials fit these criteria: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA.[1–5] These trials differed from all previously published trials of endovascular therapy in that the protocols emphasised fast treatment, had CT (or in some patients magnetic resonance) imaging criteria to include only patients with target large vessel occlusions who are most likely to benefit from endovascular therapy, and used second-generation neurothrombectomy devices, which have better recanalisation rates and lower complication rates than first-generation devices and techniques.[7,8] In all five studies, patients with acute ischaemic stroke were randomly assigned to receive endovascular neurothrombectomy treatment plus usual care or usual care alone (appendix p 1). All patients were treated with standard-dosing (0·9 mg per kg bodyweight) intravenous alteplase, if eligible, before randomisation.

We established a collaborative group to pool patient-level data from these trials: the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration. Differences from the TREAT meta-analysis protocol[9] include sampling frame and the primary research question.

The study statisticians from each trial extracted the patient-level data by direct access to the study databases. Independent statisticians (BS, SB) collated all data from the individual trials and cross-checked them against previous publications.

Outcomes

The prespecified primary outcome in this meta-analysis was the degree of disability on the modified Rankin Scale (mRS) at 90 days. The score on mRS ranges from normal (0) to death (6). In statistical modelling of the full modified Rankin scale, we merged scores of 5 (severe disability) and 6 (death) into a single category. Prespecified secondary outcomes were proportion of patients with functional independence (mRS 0–2) at 90 days; stroke severity as measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 h after stroke onset; proportion of patients with NIHSS

score 0–2 at 24 h; proportion of patients with major early neurological recovery at 24 h, defined as a reduction in NIHSS score from baseline of at least 8 points or reaching 0–1; and change in NIHSS score from baseline to 24 h. Technical efficacy was assessed through the degree of revascularisation at the end of the endovascular procedure, defined using the modified Thrombolysis in Cerebral Infarction (mTICI) scale score of 2b or 3—corresponding to reperfusion of at least 50% of the affected vascular territory. Safety outcomes were the proportion of patients with symptomatic intracranial haemorrhage (as defined by each trial), neuroradiological parenchymal haematoma type 2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days, and mortality within 90 days.

Statistical analysis

Details of the statistical analysis plan are available in the appendix (pp 12–15). To account for between-trial differences, we used mixed-effects modelling with fixed effects for parameters of interest such as treatment assignment and random effects for trial and treatment within trial. This model structure was used for all statistical analysis a priori, per the statistical analysis plan. With this approach, treatment effects for each trial (t_1, t_2, etc) are not assumed to be deterministically equal, but rather drawn from a common distribution centred on the overall effect across trials. This structure is captured by including "trial" and the interaction term "trial*treatment" as random effects variables in all mixed models. We report the overall treatment effect and all other effects using this model, which ensures that between-trial variance is incorporated in estimation for all parameters, their standard errors, and associated CIs.

For primary analyses we used mixed-effects ordinal logistic regression to answer the following research question: "Do patients with acute ischaemic stroke and proximal anterior circulation occlusions have reduced disability at 90 days with additional endovascular mechanical thrombectomy compared with standard care (including intravenous alteplase in eligible patients)?" For analyses of the full mRS, we report unadjusted and adjusted treatment effects using common odds ratios (cORs), which are derived from ordinal logistic regression and indicate the odds that the intervention would lead to improvement of 1 or more points on the mRS in a shift analysis. In the adjusted analyses we account for the following prespecified covariates: age, sex, baseline stroke severity (NIHSS score), site of occlusion (internal carotid artery vs M1 segment of middle cerebral artery vs M2 segment of middle cerebral artery), intravenous alteplase (yes vs no), baseline Alberta Stroke Program Early CT Score (ASPECTS), and time from stroke onset to randomisation. Missing data for baseline covariates are reported as percentages and dealt with using prespecified rules (appendix p 15). We report overall treatment effect as number needed to treat by calculating the geometric mean

of the values derived by the algorithmic joint outcome table method and the permutation test.[10,11]

For secondary analyses, we report rate ratios for prespecified efficacy and safety outcomes (unadjusted and adjusted for the above prespecified covariates) along with 95% CIs calculated with either mixed effects logistic or linear regression as appropriate.

We tested heterogeneity of treatment effect by prespecified clinically relevant variables on the primary outcome (mRS score distribution at 90 days) and two secondary outcomes (mRS score 0–2 at 90 days and death at 90 days) using a multiplicative interaction term (treatment*prespecified variable) and mixed methods modelling. Prespecified variables were age, sex, baseline stroke severity on NIHSS, time from symptom onset to randomisation, baseline ASPECTS, baseline site of thrombi, concomitant ipsilateral carotid artery occlusion or carotid artery stenosis, and whether a patient received (ie, was eligible for) alteplase. We report graphically using forest plots for stratum-specific treatment effects along with the p value for the interaction term. We reported main effects in the text if we found no

	Intervention population (n=634)	Control population (n=653)
Demographic characteristics		
Median age (years)	68 (57–77)	68 (59–76)*
Men	330 (52%)	352 (54%)
Women	304 (48%)	301 (46%)
Past medical history		
Hypertension	352 (56%)	388 (59%)
Diabetes mellitus	82 (13%)	88 (13%)
Atrial fibrillation	209 (33%)	215 (33%)
Smoking (recent or current)	194 (31%)	210 (32%)
Clinical characteristics		
Baseline NIHSS score	17 (14–20)†	17 (13–21)‡
Baseline blood glucose (mmol/L)	6·6 (5·9–7·8)§	6·7 (5·9–7·8)¶
Imaging characteristics		
ASPECTS on baseline CT	9 (7–10)§	9 (8–10)¶
Intracranial occlusion location		
Internal carotid artery	133 (21%)	144 (22%)
M1 segment middle cerebral artery	439 (69%)	452 (69%)
M2 segment middle cerebral artery	51 (8%)	44 (7%)
Other	11 (2%)	13 (2%)
Treatment details and process times		
Treatment with intravenous alteplase	526 (83%)	569 (87%)
Treatment with intravenous alteplase documented within 180 min	442 (70%)	462 (71%)
Process times (min)		
Onset to randomisation	195·5 (142–260)‖	196 (142–270)*
Onset to intravenous alteplase	100 (75–133)**	100 (74–140)††
Onset to reperfusion	285 (210–362)	NA

Data are median (IQR), n (%), or mean (SD). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. *n=650. †n=631. ‡n=648. §n=620. ¶n=644. ‖n=632. **n=598. ††n=618.

Table 1: Baseline characteristics in the pooled data

statistically significant interaction. All secondary analyses are reported as unadjusted and adjusted effects (adjusted for the same prespecified covariates as in primary analyses). Wherever appropriate, treatment effects are also reported as rate ratios. For graphical depiction of the effect of variation in age and presenting stroke severity on clinical outcome at 90 days based on treatment type, we estimated the mRS and the mRS transformed into utility scores (using standardised weightings) with adjusted mixed-methods linear regression (adjusted for the above prespecified covariates).[12] We did all statistical analyses with SAS version 9.2 and drew figures with Stata/MP version 14.0 and R software.

Figure 1: Scores on the modified Rankin Scale at 90 days
Distribution of scores at 90 days in the intervention and control groups in the overall trial population (A) and for patients treated with, or ineligible for, intravenous alteplase (B). Distributions for other subgroups shown in appendix pp 5–11.

Role of the funding source

The funding source was Medtronic through an unrestricted grant to the University of Calgary. Medtronic had no role in design, conduct, analysis, or reporting of this study. The corresponding author had full access to all the data. The steering committee had responsibility for the decision to submit for publication.

Results

By pooling data from the five trials, we obtained data for 1287 participants; 634 assigned to endovascular thrombectomy (intervention population) and 653 assigned to standard medical treatment (control population). Baseline characteristics were largely balanced between the populations (table 1), but slightly fewer patients in the intervention group were treated with intravenous alteplase before randomisation (p=0·04). The most common location of the target occlusion was the M1 segment of the middle cerebral artery, followed by the intracranial internal carotid artery. The median time from onset to the randomised decision to pursue or not pursue endovascular reperfusion was 3 h 16 min (IQR 2 h 22 min to 4 h 27 min)

Figure 1 shows distribution of mRS scores by treatment population at 90 days. For the primary outcome, pooled data showed reduced chance of disability at 90 days in patients assigned to thrombectomy versus those assigned to control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001; table 1). The number needed to treat for one patient to have reduced disability of at least 1 point on mRS was 2·6.

The proportion of patients with an mRS score 0–2 at 90 days was higher in the endovascular thrombectomy population than in the control population (table 2) and more patients in the intervention population achieved major neurological recovery (table 2). Of 570 patients assigned to thrombectomy who had persistent and accessible occlusions at the time of catheterisation, 402 (71%) had successful revascularisation (mTICI score 2b or 3). NIHSS score was significantly higher after

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
mRS score reduction (shift analysis; primary outcome)*	··	··	··	··	2·26* (1·67–3·06); p<0·0001	··	2·49* (1·76–3·53); p<0·0001
mRS score 0–1 at 90 days	26·9% (170/633)	12·9% (83/645)	14·0	2·00 (1·54–2·60); p<0·0001	2·49 (1·84–3·35); p<0·0001	2·06 (1·59–2·69); p<0·0001	2·72 (1·99–3·71); p<0·0001
mRS score 0–2 at 90 days	46·0% (291/633)	26·5% (171/645)	19·5	1·7 (1·41–2·05); p<0·0001	2·35 (1·85–2·98); p<0·0001	1·73 (1·43–2·09); p<0·0001	2·71 (2·07–3·55); p<0·0001
NIHSS score 0–2 at 24 h	21·0% (129/615)	8·3% (52/630)	12·7	2·47 (1·79–3·41); p<0·0001	2·91 (2·06–4·12); p<0·0001	2·66 (1·92–3·67); p<0·0001	3·77 (2·49–5·71); p<0·0001
Early neurological recovery at 24 h	50·2% (309/616)	21·2% (134/633)	29·0	2·34 (1·91–2·87); p<0·0001	4·04 (2·75–5·93); p<0·0001	2·34 (1·91–2·87); p<0·0001	4·36 (3·03–6·27); p<0·0001

Data show the proportion of patients with outcome (n/N), unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. *Common odds ratio indicating the odds of improvement of 1 point on the mRS.

Table 2: Efficacy outcomes from the pooled data

	Intervention population (n=615)	Control population (n=630)	Absolute difference (%)	β coefficient (95% CI)	Adjusted β coefficient (95% CI)
NIHSS at 24 h					
Mean score	10·4 (8·7)	14·2 (7·8)	3·8	3·6 (2·5–4·7); p<0·0001	3·8 (2·7–5·0); p<0·0001
Median score	8 (3 to 16)	15 (9 to 19)	..	..	..
Change in NIHSS score from baseline to 24 h					
Mean change	–6·4 (8·2)	–2·6 (6·6)	3·8	4·3 (2·7–5·9); p<0·0001	3·9 (2·7–5·1); p<0·0001
Median change	–7 (–12 to –1)*	–2 (–6 to 1)	..	..	..

Data in parentheses are SD or IQR, unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. *n=613.

Table 3: NIHSS score

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
Symptomatic intracranial haemorrhage	4·4% (28/634)	4·3% (28/653)	0·1	1·06 (0·63–1·80); p=0·82	1·07 (0·62–1·83); p=0·81	1·07 (0·62–1·80); p=0·81	1·07 (0·62–1·84); p=0·81
Parenchymal haematoma type 2	5·1% (32/629)	5·3% (34/641)	–0·2	0·99 (0·61–1·61); p=0·97	0·99 (0·60–1·63); p=0·97	1·04 (0·64–1·69); p=0·88	1·04 (0·63–1·72); p=0·88
Mortality	15·3% (97/633)	18·9% (122/646)	–3·6	0·82 (0·63–1·07); p=0·15	0·77 (0·54–1·10); p=0·16	0·82 (0·62–1·08); p=0·15	0·73 (0·47–1·13); p=0·16

Data show the proportion of patients with outcome (n/N), unless otherwise stated.

Table 4: Safety outcomes at 90 days

24 h and showed more improvement between baseline and 24 h after treatment in patients assigned to thrombectomy (table 3). Mortality at 90 days and risk of parenchymal haematoma type 2 and symptomatic intracranial haemorrhage did not differ between populations (table 4).

For subgroup analysis of mRS distribution shift at 90 days, there was no evidence of heterogeneity of treatment effect across any of the prespecified variables: age, sex, NIHSS, site of intracranial occlusion, intravenous alteplase received or ineligible, ASPECTS, time from onset to randomisation, and presence of tandem cervical carotid occlusion (figure 1, appendix pp 5–11). The direction of effect favoured endovascular treatment across all strata, although the adjusted cORs for treatment were not significant for patients younger than 50 years, those with a low ASPECTS or NIHSS score, and in those with an M2 segment thrombus (figure 2). Effects favouring the intervention were significant in several subgroups of special interest, including patients older than 80 years, those randomised more than 300 min after symptom onset, and in those not receiving intravenous alteplase (figure 2).

We also noted no evidence of heterogeneity of treatment effect across the prespecified subgroups for achievement of functional independence (mRS 0–2) at 90 days (appendix p 2). However, patients randomised after 300 min and patients with tandem lesions also did not show significant benefit on functional independence after thrombectomy. No heterogeneity of treatment effect was noted for mortality ($p_{interaction}$=0·33) but rate ratios were rarely significant in any of the subgroups. Patients older than 80 years assigned to thrombectomy had a slightly reduced risk of death (41 [45%] of 91 patients died *vs* 30 [28%] of 107 assigned to control; adjusted rate ratio 0·60, 95% CI 0·36–0·99; appendix p 3).

Older age and higher baseline NIHSS score were positively correlated with high mRS score at 90 days in both the treatment and control groups (figure 3). Utility weighted mRS scores by age and NIHSS score show worse clinical outcome with older age and higher NIHSS score, but the difference between intervention and control groups remains constant, indicating a consistent treatment effect over the entire range (appendix p 4).

Discussion

In this pooled analysis of patient-level data we show that modern endovascular thrombectomy added to best medical therapy more than doubles the odds of a higher mRS score compared with best medical therapy alone in patients with acute ischaemic stroke due to anterior circulation large vessel occlusion. This analysis confirms benefit of endovascular thrombectomy across a range of subgroups, including in groups of interest such as the elderly, patients not receiving intravenous alteplase, and patients who present later than 300 min from stroke symptom onset. The degree of benefit conferred by endovascular thrombectomy is substantial: for every 100 patients treated, 38 will have a less disabled outcome than with best medical management, and 20 more will
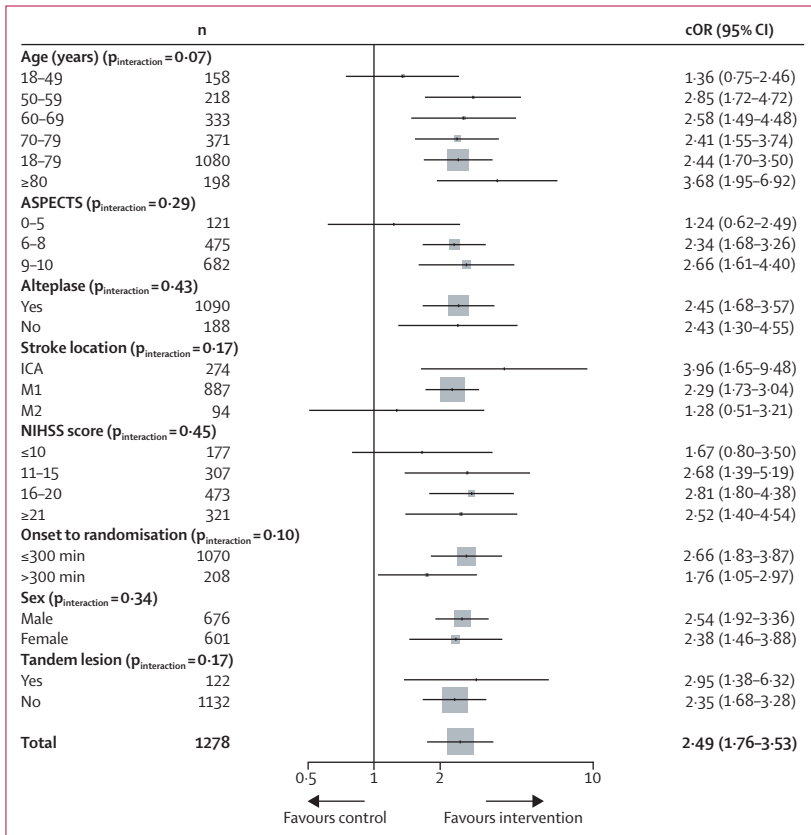
Figure 2: Forest plot showing adjusted treatment effect for mRS at 90 days in prespecified subgroups with p values for heterogeneity across subgroups
cOR=common odds ratio. mRS=modified Rankin Scale. ASPECTS=Alberta Stroke Program Early CT score. ICA=internal carotid artery. M1=M1 segment of middle cerebral artery. M2=M2 segment of middle cerebral artery. NIHSS=National Institutes of Health Stroke Scale.

achieve functional independence (mRS 0–2) as a result of treatment. The rates of symptomatic intracranial haemorrhage and radiological intracerebral haematoma (parenchymal haematoma type 2) are no higher with endovascular thrombectomy than with best medical therapy alone and mortality risk did not significantly differ between groups (table 4).

Our analysis distinguishes itself from study-level meta-analyses[13–17] by using individual patient data. By permitting adjustment for prognostic variables at the level of individual participants, patient-level pooled analyses provide a more powerful and reliable method of addressing questions that have not been satisfactorily resolved by individual trials.[18] Another strength of this analysis is that it includes only trials that incorporated key elements of current clinical practice, including universal requirement for proven large artery occlusion; timely treatment; and use of second-generation, more effective, devices (mainly stent retrievers). Most of the included trials also emphasised workflow to reduce time to reperfusion, compared with previous trials,[19,20] and several excluded patients with large regions of irreversibly injured brain at initial imaging.

Most (five of every six) patients enrolled across all five trials were eligible for and received intravenous alteplase. The benefit of endovascular thrombectomy in alteplase-treated patients shown in every individual trial analysed is reinforced by our pooled analysis comprising 1090 alteplase-treated patients. By contrast, previous trials individually did not have adequate power to reliably assess the benefit of endovascular therapy in alteplase-ineligible patients. Our pooled analysis of 188 alteplase-ineligible patients showed substantial benefit in this subgroup (figure 2). This finding does not mean that alteplase should be withheld before thrombectomy in alteplase-eligible patients. Rather, endovascular reper-fusion should be pursued for large anterior vessel occlusions, irrespective of eligibility for alteplase.

Our study provides evidence of consistent benefit for endovascular treatment on disability across all age groups, including in octogenarians. Our results suggest that there is no reason to withhold thrombectomy solely on the basis of age. Although age does not modify the treatment effect, it remains a strong independent predictor of final outcome (figure 3A, appendix p 4).

Our analysis confirms benefit from endovascular thrombectomy for patients with occlusions of the intracranial arterial circulation segment, with or without concomitant (tandem) occlusions of the extracranial internal carotid artery, indicating that patients with tandem occlusions should not be excluded from treatment (figure 2, appendix p 11). However, the heterogeneity of treatment methods given with respect to the proximal extracranial carotid occlusion in this group of patients (no revascularisation of the proximal lesion vs angioplasty vs stenting) does not allow for any conclusions about the optimum treatment approach for patients with tandem occlusions. This strategy remains to be refined through future studies.

The question of benefit with more distally located occlusions in the M2 middle cerebral artery segment is only partially addressed by our analysis. Three of the five trials restricted enrolment to patients with more proximal occlusions and the remaining two enrolled only a few patients with distal occlusions. Although we noted no statistical heterogeneity in treatment effect, our analysis does not have power to fully confirm benefit or harm in this patient subgroup. Furthermore, most of the patients with M2 occlusions included in this analysis were misclassified as having M1 occlusion at the time of enrolment, having subsequently been adjudicated by the core lab as M2 occlusion. These adjusted patients are probably a disproportionate sample of proximal and large M2 occlusions. These off-target enrolments highlight the challenge associated with poor standardisation in distinguishing between M1 and M2 segment stroke. Patients with basilar artery occlusion were not included in these studies. A randomised trial is now assessing the effect of endovascular thrombectomy in this patient group (NCT01717755).[21]

Contrary to previous studies that have identified patients with most severe strokes (baseline NIHSS score ≥20) as deriving most benefit from embolectomy,[22] our analysis shows a similar effect on disability across the entire NIHSS severity range. However, few patients with minor strokes were available for analysis. In clinical practice, treatment of patients with mild strokes and confirmed large vessel occlusion should be determined based on specific clinical and radiological features of the individual case, bearing in mind the risk of subsequent clinical deterioration with best medical therapy in patients with large vessel occlusion.[23]

The extent of pretreatment infarction on baseline imaging has been recognised as a critical determinant of clinical outcome in patients treated with reperfusion therapies.[24] For that reason, most studies have excluded from enrolment patients who present with signs of a large infarct on baseline brain imaging. Different trials have assessed this variable with methods of different degrees of sophistication but baseline ASPECTS[25] is an element common to all trials. Our analysis suggests that although lower baseline ASPECTS (more extensive irreversible injury) is strongly associated with lower rates of favourable outcomes, similar benefit is conferred in patients with high baseline ASPECTS (9–10) and those with moderate baseline ASPECTS (6–8). Because most trials excluded patients with an ASPECTS of 5 or lower, the effect of endovascular thrombectomy in this category of patients could not be established by our analysis. In this subgroup the treatment effect on functional outcome was not significant (cOR 1·24, 95% CI 0·62–2·49) and further clarification is needed from future studies. Clinically, an important distinction should be made between low ASPECTS as an indicator of a very poor prognosis and any possible treatment effect of reperfusion. If the prognosis is extremely poor, even a small treatment effect might not represent a useful intervention.

Intervention benefited patients randomised later than 300 min (and generally less than 420 min) from stroke symptom onset. This generally corresponds to start of the endovascular procedure less than 8 h from symptom onset. Definitive proof of benefit in imaging-selected patients treated beyond 6 h remains to be established and is being addressed by ongoing trials (NCT02142283, NCT02586415).

Stent retrievers were the main device used across all five trials and treatment benefit with endovascular thrombectomy is most robust with this technology. Thus, stent retrievers constitute the benchmark against which future thrombectomy approaches should be measured. Among patients with persistent occlusions at catheterisation, 71% had reperfusion to at least half of the affected vascular territory. Although considerably better than the results with older technology,[7,8] further increases in the rate of successful and complete reperfusion and reduced procedural time are needed, justifying ongoing
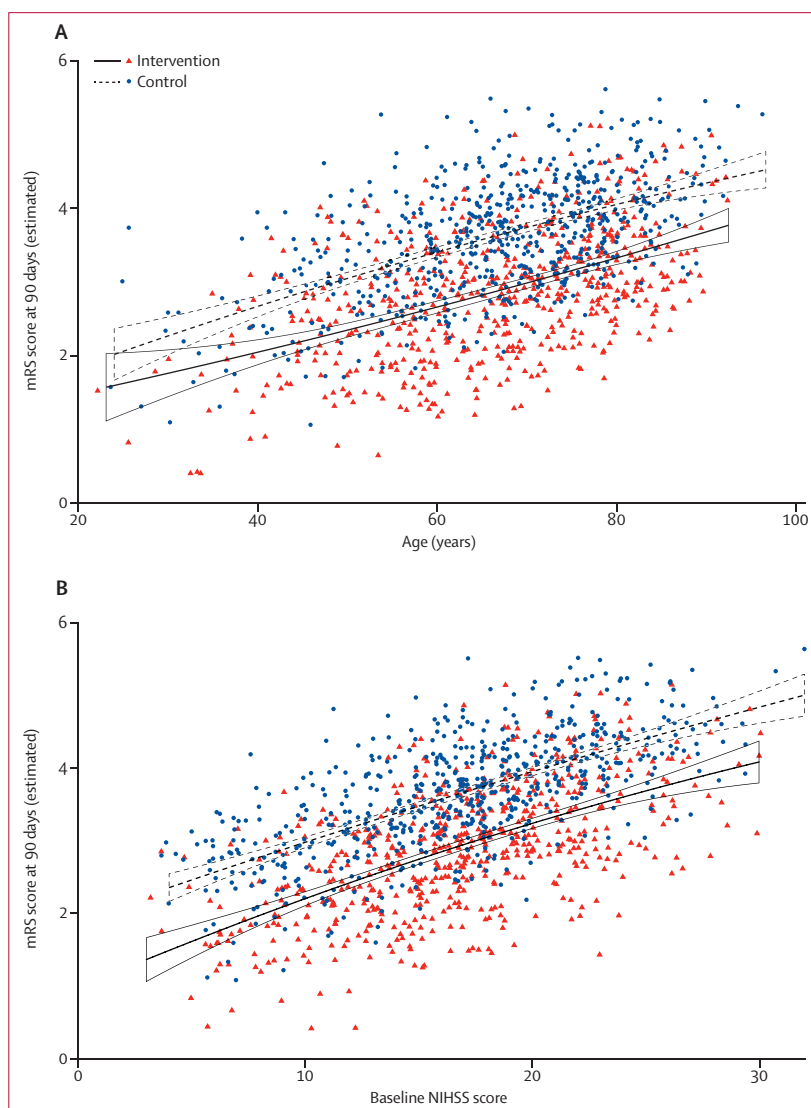
Figure 3: mRS score at 90 days estimated with a mixed methods linear regression versus age (A) and baseline NIHSS (B)

Data are stratified by intervention versus control. Models adjust for covariates (age, sex, baseline stroke severity, site of occlusion, intravenous alteplase [yes vs no], Alberta Stroke Program Early CT Score, and time from onset to randomisation). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale.

efforts to improve technological aspects of endovascular thrombectomy.

A strength of this study was that, although the individual trial populations were similar in many respects, they varied in some entry criteria and in diversity of the patient population with respect to geography and ethnic origin (appendix p 1). These differences allowed us to explore and confirm consistent benefit across wide ranges of age, baseline stroke severity, and additional patient characteristics. The consistency of results across all five trials suggests that our findings are generalisable to a broad range of patients with large vessel ischaemic stroke.

Our meta-analysis had some limitations. The five trials were done at experienced, comprehensive stroke centres;[1–5] registry studies in a larger group of hospitals are needed to confirm applicability to less experienced centres. Across all five trials, procedural, imaging, and clinical outcome measures (mTICI, ASPECTS, mRS, etc) were all ascertained in a blinded manner, but using different core labs and operationalised approaches (appendix p 1). Although the sample size was large (n=1287), the ability to provide adjusted treatment effect estimates for all subgroups analysed was limited by the number of people in each group. Although multiple comparisons inflate type I error, the analyses for the primary outcome were all significant at an α level of 0·0001 (table 2) or non-significant without adjustment for multiplicity, as in table 4. Hence, the resulting statistical inferences would be the same even with techniques adjusting for multiple comparisons. Subgroup analyses, for which the full sample size was by definition not used, remain potentially subject to type I error due to multiplicity of testing; however, no evidence of interaction effects was found (appendix). Finally, the potential for bias was minimised by the pre-specification of analysis objectives and methods, and the variance in resulting estimates was modelled appropriately by the inclusion of random effects in the statistical models.

Some patient populations, particularly those with large infarcts at baseline, those with posterior circulation occlusions, those presenting beyond 12 h, and those with substantial disability (mRS score ≥2) before stroke were excluded from all the analysed trials. Our results cannot be extrapolated to these patient populations. Finally, since the meta-analysis included some trials that were stopped early, the possibility exists of over-estimation of treatment effect. Establishing broad applicability will need careful systematic collection of registry data.

In conclusion, endovascular thrombectomy reduces disability for patients with large vessel anterior circulation ischaemic stroke. Benefits are seen across a wide range of age and initial stroke severity, and apply to patients irrespective of eligibility for intravenous alteplase.

Contributors

Declaration of interests

References

1 Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; **372:** 11–20.

2 Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; **372:** 1019–30.

3 Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015; **372:** 2285–95.

4 Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; **372:** 1009–18.

5 Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; **372:** 2296–306.

6 Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015; **46:** 3020–35.

7 Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; **380:** 1241–49.

8 Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012; **380:** 1231–40.

9 MacIsaac RL, Khatri P, Bendszus M, et al. A collaborative sequential meta-analysis of individual patient data from randomized trials of endovascular therapy and tPA vs. tPA alone for acute ischemic stroke: ThRombEctomy And tPA (TREAT) analysis: statistical analysis plan for a sequential meta-analysis performed within the VISTA-Endovascular collaboration. *Int J Stroke* 2015; **10** (suppl A100): 136–44.

10 Saver JL, Gornbein J, Grotta J, et al. Number needed to treat to benefit and to harm for intravenous tissue plasminogen activator therapy in the 3- to 4·5-hour window: joint outcome table analysis of the ECASS 3 trial. *Stroke* 2009; **40:** 2433–7.

11 Howard G, Waller JL, Voeks JH, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified Rankin outcomes. *Stroke* 2012; **43:** 664–69.

12 Chaisinanunkul N, Adeoye O, Lewis RJ, et al. Adopting a patient-centered approach to primary outcome analysis of acute stroke trials using a utility-weighted modified Rankin scale. *Stroke* 2015; **46:** 2238–43.

13 Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA* 2015; **314:** 1832–43.

14 Balami JS, Sutherland BA, Edmunds LD, et al. A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. *Int J Stroke* 2015; **10:** 1168–78.

15 Chen CJ, Ding D, Starke RM, et al. Endovascular vs medical management of acute ischemic stroke. *Neurology* 2015; **85:** 1980–90.

16 Elgendy IY, Kumbhani DJ, Mahmoud A, Bhatt DL, Bavry AA. Mechanical thrombectomy for acute ischemic stroke: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2015; **66:** 2498–505.

17 Yarbrough CK, Ong CJ, Beyer AB, Lipsey K, Derdeyn CP. Endovascular thrombectomy for anterior circulation stroke: systematic review and meta-analysis. *Stroke* 2015; **46:** 3177–83.

18 Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993; **341:** 418–22.

19 Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368:** 893–903.

20 Goyal M, Almekhlafi MA, Fan L, et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the Interventional Management of Stroke III trial. *Circulation* 2014; **130:** 265–72.

21 van der Hoeven EJ, Schonewille WJ, Vos JA, et al. The Basilar Artery International Cooperation Study (BASICS): study protocol for a randomised controlled trial. *Trials* 2013; **14:** 200.

22 Broderick JP, Berkhemer OA, Palesch YY, et al. Endovascular therapy is effective and safe for patients with severe ischemic stroke: pooled analysis of interventional management of stroke III and multicenter randomized clinical trial of endovascular therapy for acute ischemic stroke in the Netherlands data. *Stroke* 2015; **46:** 3416–22.

23 Coutts SB, Modi J, Patel SK, et al. CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study. *Stroke* 2012; **43:** 1013–17.

24 Jovin TG, Yonas H, Gebel JM, et al. The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion. *Stroke* 2003; **34:** 2426–33.

25 Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000; **355:** 1670–74.