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Summary

Background Evidence regarding whether imaging can be used effectively to select patients for endovascular thrombectomy (EVT) is scarce. We aimed to investigate the association between baseline imaging features and safety and efficacy of EVT in acute ischaemic stroke caused by anterior large-vessel occlusion.

Methods In this meta-analysis of individual patient-level data, the HERMES collaboration identified in PubMed seven randomised trials in endovascular stroke that compared EVT with standard medical therapy, published between Jan 1, 2010, and Oct 31, 2017. Only trials that required vessel imaging to identify patients with proximal anterior circulation ischaemic stroke and that used predominantly stent retrievers or second-generation neurothrombectomy devices in the EVT group were included. Risk of bias was assessed with the Cochrane handbook methodology. Central investigators, masked to clinical information other than stroke side, categorised baseline imaging features of ischaemic change with the Alberta Stroke Program Early CT Score (ASPECTS) or according to involvement of more than 33% of middle cerebral artery territory, and by thrombus volume, hyperdensity, and collateral status. The primary endpoint was neurological functional disability scored on the modified Rankin Scale (mRS) score at 90 days after randomisation. Safety outcomes included symptomatic intracranial haemorrhage, parenchymal haematoma type 2 within 5 days of randomisation, and mortality within 90 days. For the primary analysis, we used mixed-methods ordinal logistic regression adjusted for age, sex, National Institutes of Health Stroke Scale score at admission, intravenous alteplase, and time from onset to randomisation, and we used interaction terms to test whether imaging categorisation at baseline modifies the association between treatment and outcome. This meta-analysis was prospectively designed by the HERMES executive committee but has not been registered.

Findings Among 1764 pooled patients, 871 were allocated to the EVT group and 893 to the control group. Risk of bias was low except in the THRACE study, which used unblinded assessment of outcomes 90 days after randomisation and MRI predominantly as the primary baseline imaging tool. The overall treatment effect favoured EVT (adjusted common odds ratio [cOR] for a shift towards better outcome on the mRS 2·00, 95% CI 1·69–2·38; p<0·0001). EVT achieved better outcomes at 90 days than standard medical therapy alone across a broad range of baseline imaging categories. Mortality at 90 days (14·7% *vs* 17·3%, p=0·15), symptomatic intracranial haemorrhage (3·8% *vs* 3·5%, p=0·90), and parenchymal haematoma type 2 (5·6% *vs* 4·8%, p=0·52) did not differ between the EVT and control groups. No treatment effect modification by baseline imaging features was noted for mortality at 90 days and parenchymal haematoma type 2. Among patients with ASPECTS 0–4, symptomatic intracranial haemorrhage was seen in ten (19%) of 52 patients in the EVT group versus three (5%) of 66 patients in the control group (adjusted cOR 3·94, 95% CI 0·94–16·49; $p_{interaction}$=0·025), and among patients with more than 33% involvement of middle cerebral artery territory, symptomatic intracranial haemorrhage was observed in 15 (14%) of 108 patients in the EVT group versus four (4%) of 113 patients in the control group (4·17, 1·30–13·44, $p_{interaction}$=0·012).

Interpretation EVT achieves better outcomes at 90 days than standard medical therapy across a broad range of baseline imaging categories, including infarcts affecting more than 33% of middle cerebral artery territory or ASPECTS less than 6, although in these patients the risk of symptomatic intracranial haemorrhage was higher in the EVT group than the control group. This analysis provides preliminary evidence for potential use of EVT in patients with large infarcts at baseline.

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Research in context

Evidence before this study

Randomised trials from the past 3 years have shown the efficacy of endovascular thrombectomy (EVT) in patients with acute ischaemic stroke and proximal anterior circulation occlusion. In February, 2016, the highly effective reperfusion evaluated in multiple endovascular stroke trials (HERMES) collaboration published a pooled analysis of individual patient-level data of the first five randomised trials of EVT. It confirmed the benefit of EVT across a wide range of clinical subgroups and reported on the effect of the Alberta Stroke Program Early CT Score (ASPECTS) and site of vessel occlusion as assessed by each individual trial. However, evidence regarding use of imaging in the selection of patients for EVT is scarce.

Added value of this study

To our knowledge, this is the first individual patient-level meta-analysis of imaging data obtained through single core laboratory analysis from all seven randomised endovascular stroke trials listed in PubMed (published between Jan 1, 2010, and Oct 31, 2017), which compared EVT with standard medical therapy in patients with acute ischaemic stroke and anterior circulation large-vessel occlusion. Trials requiring imaging to identify patients with anterior circulation ischaemic stroke and using second-generation neurothrombectomy devices in the EVT group were included. This unique dataset is unlikely to be replicated in the future, since randomised trials of thrombectomy for large-vessel occlusion stroke in the patient population studied by these trials are no longer considered ethically justifiable. This meta-analysis provides new evidence that patients with a broad range of baseline imaging characteristics, including those with large infarcts (ie, ASPECTS <6 or involvement of >33% of middle cerebral artery territory), poor collateral circulation, and any clot burden score, might benefit from EVT.

Implications of all the available evidence

Current guidelines by the American Heart Association recommend EVT for patients with an ASPECTS of 6 or more. This analysis provides evidence to support further investigation of the use of EVT for patients with large infarcts at baseline (ASPECTS as low as 3).

Introduction

Randomised clinical trials from the past 3 years have established the safety and efficacy of endovascular thrombectomy (EVT) in the treatment of patients with acute ischaemic stroke and proximal anterior circulation occlusion.[1–8] Because the clinical benefit observed in these trials was time dependent, the need for fast and efficient patient selection is well recognised.[9] Imaging is widely used to determine prognosis and to select patients for EVT.[10–12] After the results of five trials were reported in 2015, the new American Heart Association guidelines[13] recommended EVT as standard of care (level I, class A evidence) in patients with a baseline non-contrast Alberta Stroke Program Early CT Score (ASPECTS) between 6 and 10.

Imaging features are strong predictors of clinical outcome.[10] Large infarcts at baseline, large thrombi in proximal arteries, and poor collateral circulation identified with imaging are associated with overall lower likelihood of functional independence and increased risk of intracranial haemorrhage after reperfusion therapies.[14–19] However, evidence regarding whether these imaging features are useful for selecting patients for EVT is scarce. This patient-level meta-analysis by the highly effective reperfusion evaluated in multiple endovascular stroke trials (HERMES) collaboration aims to determine safety and efficacy of EVT compared with standard medical therapy, by baseline imaging features.

Methods

Search strategy and selection criteria

In this individual patient-level meta-analysis, we searched PubMed for randomised trials published between Jan 1, 2010, and Oct 31, 2017, which compared EVT predominantly done with stent retrievers with standard care in patients with anterior circulation ischaemic stroke. The PubMed search string was ((“randomized controlled trial”[Publication Type]) AND ((thrombectomy [Title/Abstract]) OR (clot retrieval [Title/Abstract]) OR intraarterial[Title/Abstract]) AND (stroke[Title/Abstract]) AND (“2010/01/01”[Date - Publication]: “2017/10/31”[Date - Publication])).

The HERMES collaboration pooled patient-level demographic, clinical, and imaging data, as well as functional and radiological outcomes from seven randomised trials: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE (appendix).[1–7] All of these trials required vessel imaging to identify patients with anterior circulation ischaemic stroke and used predominantly stent retrievers or second-generation neurothrombectomy devices in the EVT groups. All participants provided written informed consent according to each trial protocol (appendix), and each study was approved by the local ethics board. The methodological design for this patient-level pooling has been previously described.[8]

Data analysis

Differences in patient population, sampling frame, and operational definitions of intervention (EVT) and control were assessed before collating all data at a patient level (appendix). Baseline images included information available either on CT or on MRI. All imaging studies were de-identified at the HERMES central coordinating centre. The imaging datasets were then read by independent HERMES core laboratories for baseline CT or MRI, baseline CT angiography (CTA), MRI angiography (MRA), follow-up CT or MRI, and conventional

angiography. Readers were masked to all clinical information, except side of stroke.

Imaging in acute ischaemic stroke is used to identify extent of early ischaemic change and location and density of thrombi. We assessed the following five prespecified baseline imaging features. First, ASPECTS defined on CT or magnetic resonance diffusion-weighted imaging (MR-DWI)—a widely used ordinal scale that measures the extent of ischaemia in the middle cerebral artery territory (from score 0 in complete infarction to 10 for no infarction).[20] An ASPECTS region was considered as involved on DWI if the lesion occupied more than 30% of the respective region, and on CT if any signs of ischaemia were visible on at least two consecutive cuts of the ten standardised regions of the middle cerebral artery territory. ASPECTS categories were evaluated independently by experts masked to all clinical and imaging information except stroke side. Any disagreement was resolved by consensus. Trichotomised ASPECTS agreement between two raters (JB and LSR, since they read the majority of the scans) assessed in 30 patients with weighted κ was good (κ 0·89, 95% CI 0·81–0·99).

Second, infarcts were categorised as occupying more than or less than 33% of the middle cerebral artery territory, as determined on CT or MR-DWI, according to Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS)/CT Summit criteria.[21]

Third, thrombus location identified on CTA or MRA was classified as that in the intracranial internal carotid artery, proximal M1 middle cerebral artery segment, distal M1 segment, or M2 segment. Tandem occlusion was defined as a thrombus in the extracranial internal carotid artery along with an intracranial (internal carotid artery, M1 segment, and M2 segment) thrombus.[22]

Fourth, collateral circulation distal to an intracranial thrombus was evaluated on multiphase CTA, single-phase CTA, or contrast-enhanced MRA and classified according to a previously published prespecified collateral grade category (grade 0–1 was poor, grade 2 was intermediate, and grade 3 was good collateral circulation).[19]

Finally, thrombus density on imaging was assessed with the hyperdense artery sign on CT[23] and thrombus volume on CTA, analysed with the clot burden score.[24]

Data for number of patients assessed for each imaging variable at baseline and reasons for exclusion are described in the appendix. Patients were excluded from further analyses if images were unavailable from the primary trial or were of poor quality.

Anonymised individual participant data are available in VISTA, an open access registry.

The primary endpoint was neurological functional disability scored on the modified Rankin scale (mRS) 90 days after randomisation, with categories 5 (severe disability) and 6 (death) collapsed into a single category. Primary results are reported as adjusted treatment effects using common odds ratios (cORs) with 95% CIs (indicating the odds that the intervention would lead to improvement of 1 point on the mRS in a shift analysis). Secondary efficacy outcomes were functional independence (mRS 0–2) at 90 days, excellent functional outcome (mRS 0–1) at 90 days, and substantial neurological improvement (defined as neurological improvement of 8 or more points on the National Institute of Health Stroke Scale [NIHSS] or an NIHSS score of 0–1 24 h after stroke). Secondary results are reported as ORs with 95% CIs. Risk of bias in the individual studies was assessed with the Cochrane handbook methodology. Safety outcomes included intracranial haemorrhage defined as both symptomatic intracranial haemorrhage (defined by each trial) and parenchymal haematoma type 2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days of randomisation, and mortality within 90 days.

All analyses were based on the intention-to-treat population. Unless otherwise stated, all reported analyses were prespecified in the statistical analysis plan (appendix). To account for between-trial differences when pooling patient-level data, mixed-effects modelling was used for all analyses, with fixed effects for parameters of interest and "trial" and an interaction term between "trial" and

	Endovascular thrombectomy group (n=871)	Control group (n=893)
Age, years	67·4 (57·0–76·0)	67·8 (58·0–76·0)
Sex		
Female	412 (47%)	421/891 (47%)
Male	459/871 (53%)	470/891 (53%)
NIHSS	17 (14–20)	17 (13–21)
Onset to randomisation, min	181 (141–241)	184 (140–250)
Intravenous alteplase	763/871 (88%)	809/893 (91%)
ASPECTS	8 (7–9)	8 (7–9)
Clot burden score	4 (3–6)	4 (3–6)
>33% involvement of middle cerebral artery territory	114/860 (13%)	119/876 (14%)
Hyperdense vessel sign	356/687 (52%)	330/701 (47%)
Thrombus location		
Internal carotid artery	215/818 (26%)	227/828 (27%)
Proximal M1 segment of middle cerebral artery	315/818 (39%)	327/828 (39%)
Distal M1 segment of middle cerebral artery	221/818 (27%)	210/828 (25%)
M2 segment of middle cerebral artery	67/818 (8%)	64/828 (8%)
Collateral circulation grade		
0	6/639 (1%)	8/651 (1%)
1	91/639 (14%)	108/651 (17%)
2	283/639 (44%)	275/651 (42%)
3	259/639 (41%)	260/651 (40%)

Data are median (IQR), n (%), and n/N (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score.

Table 1: **Baseline clinical and imaging variables by treatment groups**

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See **Online** for appendix

For more on **VISTA** see http://www.virtualtrialsarchives.org/vista-endovascular/

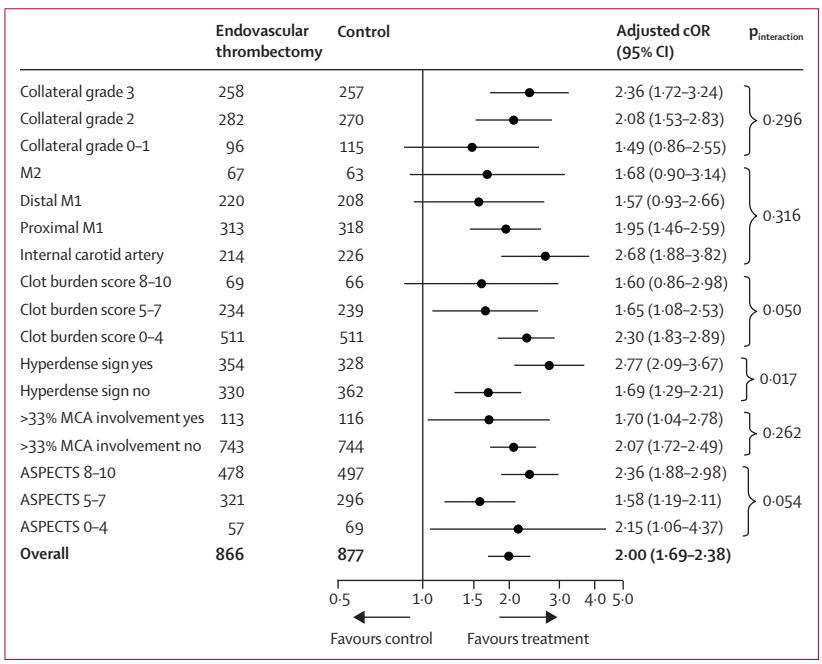

Figure 1: **Forest plot of endovascular treatment effect on primary outcome (modified Rankin Scale shift at 90 days), by baseline imaging variable categories**
cOR=common odds ratio. M1=M1 segment of MCA. M2=M2 segment of MCA. MCA=middle cerebral artery. ASPECTS=Alberta Stroke Program Early CT Score.

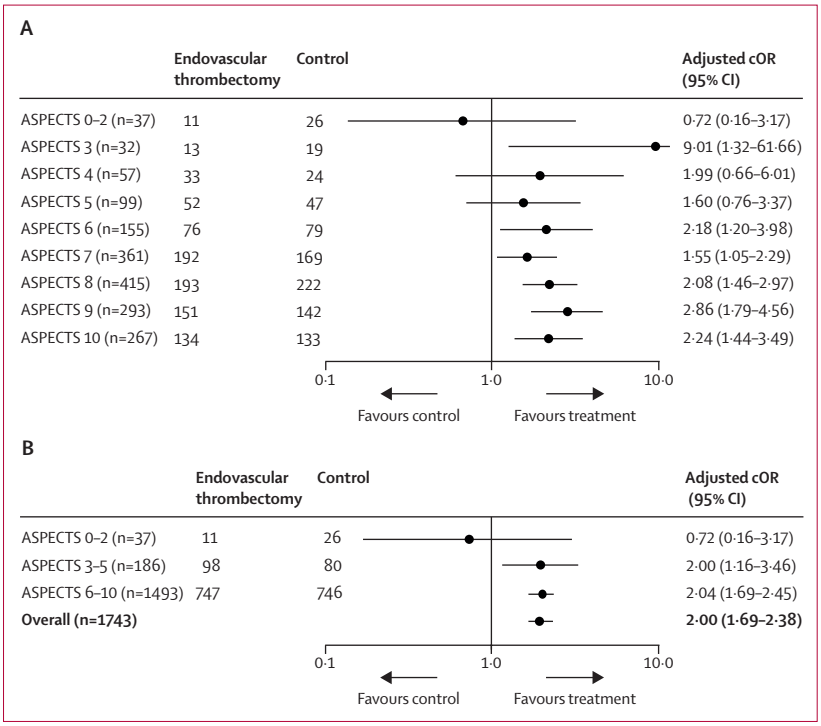

Figure 2: **Forest plot of endovascular treatment effect on primary outcome (modified Rankin Scale shift at 90 days), by ASPECTS**
(A) Endovascular treatment effect by individual baseline ASPECTS on primary outcome. There was no statistical evidence of heterogeneity across ASPECTS categories for the association between treatment and primary outcome. (B) Exploratory analysis informed by prespecified analyses of treatment effect by individual baseline ASPECTS and combines individual ASPECTS into categories (6–10 *vs* 3–5 and 0–2). ASPECTS=Alberta Stroke Program Early CT Score. cOR=common odds ratio.

"treatment" as random effects variables in all models.[8] Ordinal logistic regression models included fixed effects (age, sex, NIHSS score at admission, intravenous alteplase use, and time from onset to randomisation) and multiplicative interaction terms to test whether prespecified baseline imaging features modified the effect of treatment allocation on predefined outcomes. ASPECTS were trichotomised as 0–4, 5–7, and 8–10 for the primary analysis. Furthermore, as prespecified in the statistical analysis plan, an attempt was made to analyse treatment effect across each ASPECTS to identify an ASPECTS below which endovascular treatment might be considered futile or potentially harmful.[13] Sensitivity analyses were done according to the primary imaging modality (CT or MRI) used at baseline. Missing data (n=21) for the primary outcome were imputed as per methods prespecified in each of the trials. All statistical analyses were done with SAS, version 9.2. This meta-analysis was prospectively designed by the HERMES executive committee but not registered.

Role of the funding source

An unrestricted grant was provided to the University of Calgary (Calgary, AB, Canada) by Medtronic. The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We obtained data from 1764 randomised participants, of whom 871 were assigned to receive EVT and 893 to receive standard medical treatment (control group). Pre-randomisation brain imaging features were evaluated in 1388 patients on CT and in 364 patients on MRI (appendix). Clinical characteristics and imaging features at baseline were balanced between the two treatment groups, but treatment with intravenous alteplase was more common in the control group (table 1). Risk of bias was low except in the THRACE study,[2] which used unblinded assessment of outcomes 90 days after randomisation and MRI predominantly as the primary baseline imaging tool.

Treatment with EVT was associated with reduced disability at 90 days (adjusted cOR for a shift in direction towards a better functional outcome on the mRS 2·00, 95% CI 1·69–2·38; $p_{interaction}$<0·0001; figure 1). Distribution of 90-day mRS by treatment group and baseline imaging features are shown in the appendix. A treatment effect favouring EVT over control was observed in a broad range of prespecified imaging strata (figure 1). The treatment effect favoured EVT over standard treatment across all three categories of ASPECTS (0–4, 5–7, and 8–10; $p_{interaction}$=0·054; figure 1). Treatment effects favouring EVT over control were observed in both the CT and the MRI subgroups (appendix). An exploratory analysis was

	Modified Rankin Scale 0–2 at 90 days				Modified Rankin Scale 0–1 at 90 days				Substantial neurological improvement at 24 h*				NIHSS 0–2 at 24 h			
	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value
All participants (n=1743)	414/866 (48%)	268/877 (31%)	2·32 (1·87–2·87)	NA	254/866 (29%)	146/877 (17%)	2·29 (1·74–3·01)	NA	416/841 (49%)	204/857 (24%)	3·20 (2·59–3·96)	NA	167/835 (20%)	79/853 (9%)	2·91 (2·13–3·96)	NA
ASPECTS 0–4, 5–7, and 8–10	..	..	..	0·308	..	..	..	0·251	..	..	..	0·516	..	..	..	0·557
0–4 (n=126)	14/57 (25%)	10/69 (14%)	2·72 (0·89–8·33)	..	9/57 (16%)	4/69 (6%)	9·10 (0·96–86·76)	..	16/51 (31%)	7/65 (11%)	4·62 (1·61–13·25)	..	1/50 (2%)	1/64 (2%)	0·05 (0·00–266·93)	..
5–7 (n=615)	140/321 (44%)	87/296 (29%)	2·07 (1·43–2·99)	..	73/321 (23%)	47/296 (16%)	1·61 (1·04–2·48)	..	137/313 (44%)	56/288 (19%)	3·34 (2·28–4·88)	..	43/312 (14%)	19/287 (7%)	2·68 (1·47–4·91)	..
8–10 (n=975)	257/478 (54%)	169/497 (34%)	2·56 (1·93–3·40)	..	170/478 (36%)	94/497 (19%)	2·64 (1·89–3·68)	..	260/469 (55%)	141/492 (29%)	3·19 (2·42–4·20)	..	121/465 (26%)	59/490 (12%)	3·06 (2·12–4·42)	..
ASPECTS 0–2, 3–5, and 6–10	..	..	..	0·695	..	..	..	0·879	..	..	..	0·756	..	..	..	0·864
0–2 (n=37)	0/11 (0%)	3/26 (12%)	0·00 (0·00–5·81)	..	0/11 (0%)	0/26 (0%)	NA	..	1/10 (10%)	3/24 (13%)	0·63 (0·03–14·11)	..	0/10 (0%)	0/24 (0%)	NA	..
3–5 (n=186)	30/98 (31%)	14/90 (16%)	4·27 (1·62–11·25)	..	16/98 (16%)	8/90 (9%)	2·76 (0·86–8·86)	..	25/89 (28%)	7/85 (8%)	5·53 (2·06–14·84)	..	6/88 (7%)	3/84 (4%)	1·70 (0·32–9·15)	..
6–10 (n=1493)	381/747 (51%)	249/746 (33%)	2·29 (1·83–2·88)	..	236/747 (32%)	137/746 (18%)	2·25 (1·69–2·99)	..	387/734 (53%)	194/736 (26%)	3·16 (2·53–3·95)	..	159/729 (22%)	76/733 (10%)	2·88 (2·09–3·95)	..
>33% involvement of middle cerebral artery territory	..	..	..	0·495	..	..	..	0·962	..	..	..	0·359	..	..	..	0·458
No (n=1487)	380/743 (51%)	245/744 (33%)	2·38 (1·89–2·98)	..	235/743 (32%)	136/744 (18%)	2·27 (1·70–3·03)	..	383/730 (52%)	193/734 (26%)	3·13 (2·50–3·91)	..	161/725 (22%)	76/731 (10%)	2·93 (2·14–4·02)	..
Yes (n=229)	31/113 (27%)	21/116 (18%)	2·23 (1·07–4·65)	..	17/113 (15%)	9/116 (8%)	3·16 (1·08–9·24)	..	30/103 (29%)	11/111 (10%)	4·74 (2·12–10·62)	..	4/102 (4%)	3/110 (3%)	0·08 (0·00–215·24)	..
Hyperdense sign	..	..	..	0·034	..	..	..	0·997	..	..	..	0·416	..	..	..	0·962
No (n=692)	151/330 (46%)	112/362 (31%)	1·95 (1·39–2·70)	..	93/330 (28%)	50/362 (14%)	2·40 (1·65–3·50)	..	158/326 (48%)	82/359 (23%)	4·59 (1·65–12·23)	..	60/324 (19%)	32/357 (9%)	2·83 (1·71–4·70)	..
Yes (n=682)	165/354 (47%)	78/328 (24%)	3·20 (2·26–4·53)	..	98/354 (28%)	46/328 (14%)	2·47 (1·70–3·60)	..	171/341 (50%)	71/318 (22%)	3·67 (2·58–5·20)	..	71/339 (21%)	29/318 (9%)	3·03 (1·83–5·02)	..

(Table 2 continues on next page)

	Modified Rankin Scale 0–2 at 90 days				Modified Rankin Scale 0–1 at 90 days				Substantial neurological improvement at 24 h*				NIHSS 0–2 at 24 h			
	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value
(Continued from previous page)																
Clot burden score	..	..	..	0·038	..	..	..	0·244	..	..	..	0·082	..	..	..	0·042
0–4 (n=1026)	212/511 (41%)	118/511 (23%)	2·84 (2·07–3·90)	..	123/511 (24%)	61/511 (12%)	2·69 (1·79–4·05)	..	236/495 (47%)	100/501 (20%)	3·61 (2·71–4·81)	..	82/490 (17%)	31/499 (6%)	4·14 (2·56–6·68)	..
5–7 (n=475)	134/234 (57%)	108/239 (45%)	1·77 (1·19–2·64)	..	91/234 (39%)	61/239 (26%)	1·94 (1·17–3·19)	..	120/229 (52%)	80/237 (34%)	2·41 (1·59–3·64)	..	57/228 (25%)	39/236 (17%)	1·82 (1·11–2·96)	..
8–10 (n=135)	40/69 (58%)	27/66 (41%)	2·31 (1·06–5·04)	..	25/69 (36%)	15/66 (23%)	2·30 (0·72–7·30)	..	33/69 (48%)	14/64 (22%)	3·77 (1·64–8·64)	..	18/69 (26%)	6/64 (9%)	3·70 (1·21–11·30)	..
Occlusion location	..	..	..	0·249	..	..	..	0·909	..	..	..	0·242	..	..	..	0·416
Internal carotid artery (n=440)	71/214 (33%)	35/226 (15%)	2·91 (1·79–4·73)	..	38/214 (18%)	19/226 (8%)	2·26 (1·23–4·15)	..	87/206 (42%)	33/218 (15%)	3·87 (2·41–6·21)	..	19/205 (9%)	8/218 (4%)	3·05 (1·23–7·60)	..
Proximal M1 segment of middle cerebral artery (n=631)	147/313 (47%)	92/318 (29%)	2·63 (1·76–3·93)	..	87/313 (28%)	49/318 (15%)	2·42 (1·43–4·09)	..	156/305 (51%)	78/317 (25%)	3·18 (2·25–4·50)	..	66/301 (22%)	27/315 (9%)	3·81 (2·23–6·51)	..
Distal M1 segment of middle cerebral artery (n=428)	129/220 (59%)	100/208 (48%)	1·67 (1·10–2·54)	..	89/220 (40%)	55/208 (26%)	2·00 (1·16–3·43)	..	113/215 (53%)	71/205 (35%)	2·29 (1·46–3·59)	..	54/214 (25%)	35/204 (17%)	1·84 (1·09–3·12)	..
M2 segment of middle cerebral artery (n=130)	39/67 (58%)	25/63 (40%)	2·35 (1·07–5·14)	..	25/67 (37%)	13/63 (21%)	2·49 (0·80–7·75)	..	32/67 (48%)	11/61 (18%)	4·73 (2·00–11·21)	..	18/67 (27%)	5/61 (8%)	4·38 (1·39–13·82)	..
Collateral grade	..	..	..	0·402	..	..	..	0·623	..	..	..	0·145	..	..	..	0·975
0–1 (n=211)	26/96 (27%)	16/115 (14%)	1·80 (0·69–4·71)	..	15/96 (16%)	6/115 (5%)	4·05 (1·03–15·91)	..	29/91 (32%)	19/104 (18%)	2·18 (1·04–4·55)	..	10/89 (11%)	3/103 (3%)	3·47 (0·48–25·12)	..
2 (n=552)	124/282 (44%)	77/270 (29%)	2·49 (1·68–3·69)	..	78/282 (28%)	38/270 (14%)	2·90 (1·80–4·69)	..	131/277 (47%)	65/273 (24%)	3·01 (2·07–4·39)	..	56/275 (20%)	24/273 (9%)	3·92 (2·20–6·99)	..
3 (n=515)	143/258 (55%)	86/257 (33%)	2·63 (1·80–3·84)	..	86/258 (33%)	46/257 (18%)	2·25 (1·47–3·45)	..	144/256 (56%)	59/253 (23%)	4·30 (2·89–6·40)	..	56/256 (22%)	24/253 (9%)	2·95 (1·71–5·10)	..

Data are n/N (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. NA=not applicable. *Defined as neurological improvement of ≥8 points in the NIHSS or a NIHSS 0–1 24 h after stroke.

Table 2: **Endovascular treatment effect on secondary outcomes by baseline imaging variable categories**

done that combined individual ASPECTS into categories (6–10 *vs* 3–5 and 0–2), informed by prespecified analyses of treatment effect by individual baseline ASPECTS and by potential direction of treatment effect across each individual ASPECTS that suggested that point estimates for treatment effect probably favoured EVT for each individual ASPECTS category except 0–2. In this analysis, significant treatment effects favouring EVT were seen in patients with baseline ASPECTS 6–10 and 3–5. The point estimate of treatment effect (cOR) was less than 1 in the ASPECTS 0–2 group (n=37); however, no significant interaction for treatment effect size was noted across the three exploratory ASPECTS categories (6–10, 3–5, and 0–2; $p_{interaction}$=0·30; figure 2).

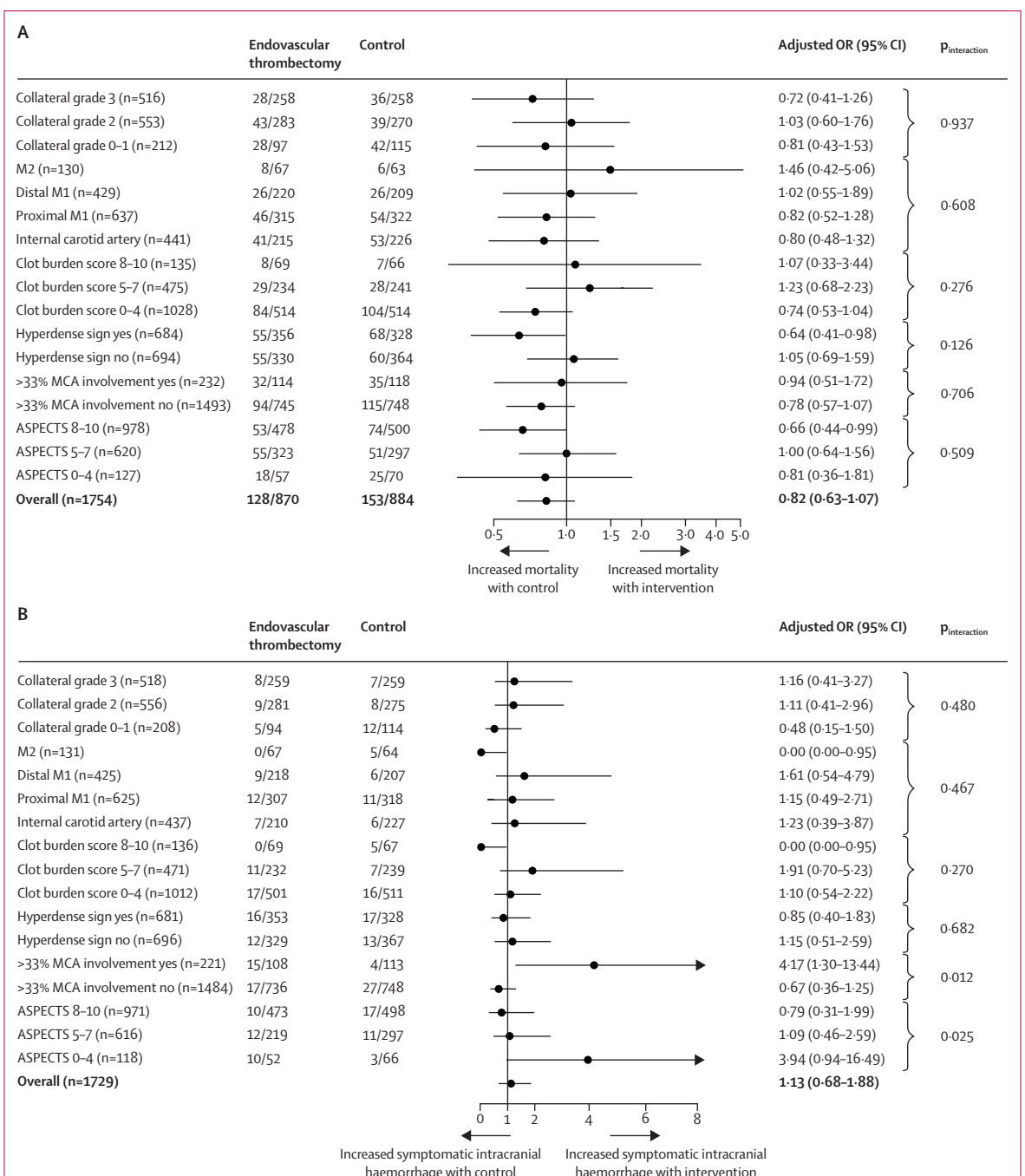

***Figure 3*: Forest plot of endovascular treatment effect on safety outcomes (mortality at 90 days and symptomatic intracranial haemorrhage incidence), by baseline imaging variable categories**

OR=odds ratio. M1=M1 segment of MCA. M2=M2 segment of MCA. MCA=middle cerebral artery. ASPECTS=Alberta Stroke Program Early CT Score.

	Endovascular thrombectomy group	Control group	Unadjusted odds ratio (95% CI)	Unadjusted p value	Unadjusted $p_{interaction}$ value
Baseline ASPECTS 0–4, 5–7, and 8–10	..	..	..	..	0·026
0–4	10/52 (19%)	3/66 (5%)	5·00 (1·30–19·25)	0·016	..
5–7	12/319 (4%)	11/297 (4%)	1·02 (0·44–2·34)	1	..
8–10	10/473 (2%)	17/498 (3%)	0·61 (0·28–1·35)	0·245	..
Baseline ASPECTS 0–2, 3–5, and 6–10	..	..	..	..	0·0084
0–2	1/9 (11%)	1/24 (4%)	2·88 (0·16–51·53)	0·477	..
3–5	14/95 (15%)	3/87 (3%)	4·84 (1·27–27·03)	0·010	..
6–10	17/740 (2%)	27/750 (4%)	0·63 (0·32–1·21)	0·168	..
>33% involvement of middle cerebral artery territory	..	..	..	..	0·0019
No	17/736 (2%)	27/748 (4%)	0·63 (0·34, 1·17)	0·168	..
Yes	15/108 (14%)	4/113 (4%)	4·40 (1·41–13·70)	0·0075	..
Hyperdense sign	..	..	..	..	0·865
No	12/360 (3%)	14/401 (4%)	0·95 (0·43–2·09)	1	..
Yes	16/353 (5%)	17/328 (5%)	0·87 (0·43–1·75)	0·724	..
Clot burden score	..	..	..	..	0·063
8–10	0/69 (0)	5/67 (8%)	0·00 (0·00–0·95)	0·027	..
5–7	11/233 (5%)	7/240 (3%)	1·65 (0·63–4·33)	0·344	..
0–4	17/503 (3%)	16/513 (3%)	1·09 (0·54–2·18)	0·861	..
Occlusion location	..	..	..	..	0·154
Internal carotid artery	7/210 (3%)	6/227 (3%)	1·27 (0·42–3·84)	0·781	..
Proximal M1 segment of middle cerebral artery	12/307 (4%)	11/318 (4%)	1·14 (0·49–2·61)	0·834	..
Distal M1 segment of middle cerebral artery	9/218 (4%)	6/207 (3%)	1·44 (0·50–4·13)	0·603	..
M2 segment of middle cerebral artery	0/67 (0)	5/64 (8%)	0·00 (0·00–0·96)	0·026	..
Collateral grade	..	..	..	..	0·443
3	8/259 (3%)	7/259 (3%)	1·15 (0·41–3·21)	1	..
2	9/281 (3%)	8/275 (3%)	1·10 (0·42–2·91)	1	..
0–1	5/94 (5%)	12/114 (11%)	0·48 (0·16–1·41)	0·209	..

Data are n/N (%). ASPECTS=Alberta Stroke Program Early CT Score.

***Table 3*: Symptomatic intracranial haemorrhage by treatment and baseline imaging variable categories**

A beneficial effect of EVT over control was seen across all imaging features for most prespecified secondary outcomes (table 2). A significant interaction between treatment effect and clot burden score was found for functional independence and substantial neurological recovery at 24 h (patients with more extensive thrombus at baseline probably benefit more with EVT); however, point estimates for treatment effect favoured EVT across all strata.

In the analysis of safety outcomes, mortality at 90 days (14·7% *vs* 17·3%, p=0·15), symptomatic intracranial haemorrhage (3·8% *vs* 3·5%, p=0·90), and parenchymal haematoma type 2 (5·6% *vs* 4·8%, p=0·52) did not differ between the EVT and control groups. We noted no treatment effect modification by baseline imaging features for mortality at 90 days (figure 3A) and parenchymal haematoma type 2 (appendix). When considering intracranial haemorrhage, results were inconsistent. EVT was associated with a higher risk of symptomatic intracranial haemorrhage in the ASPECTS 0–4 subgroup than in other ASPECTS subgroups (adjusted cOR 3·94, 95% CI 0·94–16·49; $p_{interaction}$=0·025; figure 3B) and in patients with baseline early ischaemic change in more than 33% of middle cerebral artery territory than in those without (4·17, 1·30–13·44; $p_{interaction}$=0·012; figure 3B), but not when the outcome was purely radiological using parenchymal haematoma type 2 (appendix). Among patients with ASPECTS 0–4, symptomatic intracranial haemorrhage was observed in ten (19%) of 52 patients in the EVT group versus three (5%) of 66 in the control group (unadjusted p=0·016; table 3). Similarly, symptomatic intracranial haemorrhage was observed in 15 (14%) of 108 patients in the EVT group versus four (4%) of 113 patients in the control group among patients with baseline early ischaemic change in more than 33% of middle cerebral artery territory (unadjusted p=0·0075; table 3).

Discussion

Our patient-level meta-analysis lends support to a benefit of EVT for acute ischaemic stroke across a broad range of imaging subgroups. Our results add to previous work from the HERMES collaboration that showed benefit of EVT across a broad range of clinical subgroups.[8] Our analysis is larger than this previous work (seven trials instead of five and 1764 patients instead of 1287), uses more rigorous imaging analysis (HERMES core laboratory uniform rereading of all scans from all trials), and analyses key imaging subgroups not previously assessed. Our results suggest that EVT might not be futile in patients with large (ASPECTS <6 or more than 33% involvement of middle cerebral artery territory) infarcts identified on baseline imaging, at least among patients otherwise deemed eligible to participate in the component clinical trials of the collaboration. Our findings are in line with CT perfusion-based studies derived from the same cohort of patients, which were also not able to identify baseline ischaemic core volumes associated with treatment futility.[25]

EVT is offered to patients with acute ischaemic stroke when there is a target artery occlusion and what is presumed to be salvageable brain beyond that occlusion, based on interpretation of various imaging methods.[26] Thrombus in proximal intracranial arterial segments such as in the internal carotid artery and M1 segment of the middle cerebral artery are more easily reached by current EVT than thrombus in more distal arterial segments.[10] Proximal intracranial arterial segment thrombi are also larger in volume (greater clot burden) than more distal thrombi. Therefore, unlike EVT, intravenous alteplase is less likely to recanalise proximal thrombi early than thrombi in distal arterial segments.[27] Moreover, patients with thrombi in proximal intracranial

arterial segments are likely to have a greater amount of brain tissue at risk than patients with more distal thrombi.

Imaging is also used to identify the extent of irreversibly injured brain tissue beyond target artery occlusion. Patients with a large extent of irreversible brain injury are less likely to have brain tissue that is salvageable with EVT.[10,14,16] Both ASPECTS and the 33% of the middle cerebral artery rule inform the extent of probable irreversible brain injury on CT or MRI.[20,23] Our analysis suggested relative treatment benefit with EVT across all ASPECTS categories and in patients with brain infarcts occupying more than 33% of the ischaemic middle cerebral artery territory. The effect size by ASPECTS categories was, however, graded, with larger effect sizes noted in patients with higher ASPECTS. Despite evidence of treatment benefit, the prognosis for patients with a low ASPECTS remains poor, with few achieving independent outcomes. We also noted a significant benefit with EVT even in patients with baseline ASPECTS 3–5, an ASPECTS category that until now might have been considered as indicative of treatment futility.[13] Faster and better reperfusion techniques available since the HERMES trials could magnify potential benefit from EVT in these patients.[28] The number of patients with ASPECTS 0 (n=12), 1 (n=13), and 2 (n=12) in our analyses was very small; this imaging subgroup was the only one for which the point estimate for treatment effect did not favour EVT. Ongoing clinical trials, such as TENSION (NCT03094715) and IN EXTREMIS, are likely to provide more evidentiary support for or against the net benefit of thrombectomy in patients with ASPECTS less than 6 and with a large ischaemic core at baseline.

Patients with good collateral circulation status beyond target arterial occlusion are more likely to have salvageable brain tissue than are patients with poorer collaterals.[29] CTA (or MRA) is often used to identify patients with poor collateral circulation. The technique therefore complements CT and MRI by identifying patients with a large extent of irreversibly injured brain tissue. The ESCAPE trial[4] used collateral circulation status to exclude patients with poor collaterals; other trials such as SWIFT PRIME[7] and EXTEND-IA[3] used CT perfusion or MR perfusion. These techniques are based on the same principle of blood flow imaging that collateral assessments are based on for selecting patients for those trials.[3,4,7] Like ASPECTS and the 33% middle cerebral artery rule on CT and MRI, our analyses suggest benefit with EVT across all strata of collateral circulation status; however, patients with poor collaterals are less likely to benefit from EVT than those with better collaterals. Assessment of poor collateral circulation with dynamic angiographic techniques (rather than the single-phase CTA or MRA used in most patients in our analyses) could help to better identify patients who are unlikely to benefit with EVT.[30]

Finally, imaging is used to determine risk with treatment. Our analyses suggest that symptomatic intracranial haemorrhage is four times more common in patients with ASPECTS 0–4 and hypodensity where more than 33% of the ischaemic middle cerebral artery territory is involved. This increase in symptomatic intracranial haemorrhage with EVT was not affected by age, baseline stroke severity, or intravenous alteplase use. A net beneficial effect of EVT was, however, still seen in these patients.

Our study has limitations. Since five of the seven HERMES trials used baseline imaging criteria to exclude patients who were likely to have large infarcts, we had relatively few patients with such imaging signatures in our analyses. Our results are reasonably consistent across both CT and MRI, and the sensitivity analyses suggest similar effects but could not confirm a significant benefit of thrombectomy in patients with largest baseline infarcts when assessed separately by either CT or MR-DWI. Confirmatory randomised trials are in progress (TENSION and IN EXTREMIS) in patients with ASPECTS less than 6. No statistical adjustment for multiple comparisons was included. The central re-analysis of images in this study might not reflect the quality of on-site assessments. In clinical practice, patients are treated on the basis of investigator reads, not expert consensus reads. There was heterogeneity in the use of imaging tools, techniques, and scanners in our study.[10] This heterogeneity is, however, reflective of real-world practice.

In summary, in the first individual patient-level meta-analysis analysing the usefulness of baseline imaging in patients eligible for EVT, we found limited evidence of heterogeneity of treatment effect across imaging subgroups. Our analysis provides some evidence to suggest that the estimated treatment effect for EVT should be weighted in conjunction with other predictors of outcome when deciding whether to offer therapy to patients with large baseline infarcts.

Contributors

LSR, BKM, AD, and MG prepared the first draft of the report on the basis of an analysis plan agreed by the HERMES executive committee (BCVC, MG, DWJD, AD, SB, PW, AMD, CBLMM, FG, KWM, JLS, TJ, MDH, and PJM), who also contributed to study interpretation. SB did the statistical analyses. All authors participated in patient enrolment and data collection, and critically reviewed the report and approved the final version. LSR and BKM contributed equally.

Declaration of interests

BKM has a patent pending related to methods of triaging patients with acute stroke. AD reports grants from Medtronic. CBLMM reports grants from CVON/Dutch Heart Foundation, the European Commission, the TWIN Foundation, and Stryker (all paid to institution), and owns stock in Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. BCVC reports grants from the Australian National Health and Medical Research Council, Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, National Heart Foundation of Australia, National Stroke Foundation of Australia, and Covidien (Medtronic). JLS reports serving as an unpaid site investigator in multicentre trials sponsored by Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott, for which the University of California, Los Angeles, received payments on the basis of clinical trial contracts for the number of participants enrolled; receiving contracted hourly payments and travel reimbursement from Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott; and receiving stock options from Rapid Medical for service on trial steering committees and advising on rigorous trial design and conduct. The University of California, Los Angeles, has patent rights in retrieval devices for stroke. HM is founder of and holds shares in Nico.

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