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Title: Imaging features and safety and efficacy of endovascular stroke treatment: an individual patient data meta-analysis

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Abstract: Background

Evidence regarding the utility of imaging studies in selecting patients for endovascular thrombectomy (EVT) is limited. We aimed to investigate baseline-imaging features associated with efficacy and safe-ty of endovascular thrombectomy (EVT) in acute ischaemic stroke caused by anterior large vessel occlusion.

Methods

The HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration identified 7 randomized endovascular stroke trials listed in PubMed from 1/Jan/2010 to 31/October/2017 as comparing EVT to standard medical therapy. Only trials that required vessel imaging to identify patients with proximal anterior circulation ischemic stroke and used predominantly stent retrievers or second-generation neuro-thrombectomy devices in the EVT arm were included. The risk of bias was assessed using the Cochrane tool and was low except in the THRACE study that employed un-blinded assessment of 90-day outcome and MRI predominantly as the primary baseline imaging tool. Central, blinded readers rated baseline imaging for ischemic change using the Alberta Stroke Program Early Computed Tomography score (ASPECTS) or ischemic change involving > 1/3 of middle cerebral artery territory, thrombus volume, hyperdensity, and collateral status. Primary endpoint was the modified Rankin Scale (mRS) score at 90 days. Safety outcomes included symptomatic intracranial hemorrhage (sICH) , parenchymal

hematoma type 2 (PH2) within 5 days of randomization, and mortality within 90 days.
Primary analysis used mixed methods ordinal logistic regression adjusted for age, sex, NIHSS score at admission, intravenous alteplase and time from onset to randomization and interaction terms to test if imaging categorization at baseline modifies the relationship between treatment and outcome.

Findings
Among 1764 pooled patients, 871 were allocated to the EVT arm and 893 to control. The overall treatment effect favored EVT (adjusted common Odds Ratio for a shift towards better outcome on the mRS 2·00, 95% CI 1·69-2·38; p<0·0001). EVT achieves better 90 day outcomes than medical therapy alone across a broad range of baseline imaging categories including in patients with low AS-PECTS 0-4 (adjusted common Odds Ratio 2·15, 95% CI 1·06-4·37, interaction P= 0·054), > 1/3 MCA territory infarct (adjusted common Odds Ratio 1·70, 95% CI 1·04-2·78, interaction P= 0·262), poor collaterals (adjusted common Odds Ratio 1·49, 95% CI 0·86-2·55, interaction P= 0·296) and all levels of clot burden (interaction P= 0·050).
No treatment effect modification by baseline imaging features was noted for 90-day-mortality and PH2. Higher risk of sICH was seen in patients with ASPECTS 0-4 (19·2% versus 4·5%, adjusted common Odds Ratio 3·94, 95% CI 0·94-16·49, interaction P= 0·025) and with > 1/3 MCA territory infarct (13·9% versus 3·5%, adjusted common Odds Ratio 4·17, 95% CI 1·3-13·44, interaction P=0·012) when allocated EVT.

Interpretation
EVT achieves better 90-day outcomes than control across a broad range of baseline imaging catego-ries. This analysis provides evidentiary support to expand existing practice guidelines to provide EVT, in a qualified manner, even in patients with large infarcts at baseline.

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Imaging features and safety and efficacy of endovascular stroke treatment: an individual patient data meta-analysis

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SUMMARY

Background

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Methods

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Primary analysis used mixed methods ordinal logistic regression adjusted for age, sex, NIHSS score at admission, intravenous alteplase and time from onset to randomization and interaction terms to test if imaging categorization at baseline modifies the relationship between treatment and outcome.

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No treatment effect modification by baseline imaging features was noted for 90-day-mortality and PH2. Higher risk of sICH was seen in patients with ASPECTS 0-4 (19·2% versus 4·5%, adjusted common Odds Ratio 3·94, 95% CI 0·94–16·49, interaction P= 0·025) and with > 1/3 MCA territory infarct (13·9% versus 3·5%, adjusted common Odds Ratio 4·17, 95% CI 1·3–13·44, interaction P=0·012) when allocated EVT.

Interpretation

EVT achieves better 90-day outcomes than control across a broad range of baseline imaging categories. This analysis provides evidentiary support to expand existing practice guidelines to provide EVT, in a qualified manner, even in patients with large infarcts at baseline.

Funding Unrestricted grant from Medtronic.

Research in context

Evidence before the study:

Recent randomized trials have demonstrated the efficacy of endovascular thrombectomy (EVT). The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration published in Feb 2016 a pooled analysis of individual patient-level data of the first five randomized trials of endovascular thrombectomy. It confirmed benefit of endovascular thrombectomy across a wide range of clinical subgroups and reported on the effect of ASPECTS and site of vessel occlusion as assessed by each individual trial. However, evidence regarding utility of imaging in selecting patients for EVT is limited.

Added value of this study

This is the first individual level meta-analysis using imaging data obtained through single core lab analysis from all seven randomized endovascular stroke trials listed in PubMed (1/Jan/2010-31/October/2017) comparing EVT to standard medical therapy in patients with acute ischemic stroke and anterior circulation large vessel occlusion. Trials requiring imaging to identify patients with anterior circulation ischemic stroke and using second-generation neuro-thrombectomy devices in the EVT arm were included. It represents a unique dataset that is unlikely to ever be replicated in the future, as randomized 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 and substantial evidence that patients with a broad range of baseline imaging characteristics including those with larger infarcts, poor collaterals and any clot burden score benefit from endovascular thrombectomy (EVT).

Implications of all the available evidence

Current guidelines by the American Heart Association (AHA) recommend EVT in patients with ASPECTS>5. This analysis provides evidentiary support for expansion of existing practice guidelines to endorse, in a qualified manner, EVT even for patients with large infarcts at baseline (ASPECTS as low as 3).

INTRODUTION

Recent randomized clinical trials have established the efficacy and safety of endovascular thrombectomy (EVT) in the treatment of patients with acute ischemic stroke and proximal anterior circulation occlusion.[1-8] Because clinical benefit observed in these trials is time dependent, the need for fast and efficient patient selection is well recognized.[9] Imaging is widely used to determine prognosis and to select patients for EVT.[10-12] After the results of the five trials reported in 2015, the new AHA guidelines recommend EVT as standard of care (Level I, Class A evidence) in patients with baseline non-contrast CT ASPECTS 6-10.[13]

Imaging features are strong predictors of clinical outcome.[10] Large infarcts at baseline, large thrombus in proximal arteries and poor collateral circulation identified using imaging are overall associated with lower likelihood of functional dependence and increased risk after reperfusion therapies.[14-19] However, evidence regarding the utility of these imaging features in selecting patients for EVT is limited. This patient level meta-analysis of the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration aims to determine baseline-imaging features associated with efficacy and safety of EVT when compared to standard medical therapy.

METHODS

Study design and participants

We searched Pubmed for randomized trials published between 1 Jan 2010 and 31 October 2017 comparing endovascular thrombectomy performed using predominantly stent-retrievers with standard care in anterior circulation ischaemic stroke patients - Pubmed search string: (("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 (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration pooled patient level demographic, clinical and imaging data as well as functional and radiologic outcomes from 7 randomized trials: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE and PISTE (Supplement eFigure 1). All these trials required vessel imaging to identify patients with anterior circulation ischemic stroke and used predominantly stent retrievers or second-generation neuro-thrombectomy devices in the EVT arm. Data were assessed for quality and validity using PRISMA guidelines. Differences in patient population, sampling frame and operational definitions of intervention (EVT) and control were assessed before collating all data at a patient level (Supplement eTable 1). Risk of bias in the individual studies was assessed using the Cochrane handbook methodology and was low overall except in the THRACE study that used un-blinded assessment of 90-day outcome. In addition, in contrast to other studies, the THRACE study used MRI predominantly as the primary baseline imaging tool. This meta-analysis was prospectively designed by the HERMES executive committee but not registered. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. The methodological design for this patient level pooling has been previously described.[8]

Imaging variables

Baseline images included information available either on Computed Tomography (CT) or on Magnetic Resonance Imaging (MRI). All imaging studies were de-identified at the HERMES central coordinating center. The imaging datasets were then read by independent HERMES core labs for baseline CT/MRI, baseline CT Angiography (CTA), MRI Angiography (MRA), follow up CT or MR, and conventional angiography. Readers were blinded to all clinical information, except side of stroke.

Imaging in acute ischemic stroke is used to identify extent of early ischemic change and location and extent of thrombus. Pre-specified baseline imaging features of interest therefore were:

1. The Alberta Stroke Program Early CT Score (ASPECTS) defined on CT or MR Diffusion Weighted Imaging (MR-DWI). This widely used ordinal scale measures extent of ischemia in the middle cerebral artery (MCA) 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 > 30% of the respective region, and on CT if any signs of ischemia were visible on at least two consecutive cuts of the 10 standardized regions of the MCA territory. ASPECTS grading was evaluated independently by experts blinded to all clinical and imaging information except stroke side. Any disagreement was resolved by consensus. Trichotomized ASPECTS agreement between two raters (JB, LSR) assessed in 30 patients using weighted kappa was good (kappa 0.89, 95% CI 0.81 -0.99.
2. The > 1/3rd MCA rule defined on CT or MR-DWI as early ischemic change in > 1/3rd of the ischemic MCA territory.[21]
3. Thrombus location identified on CTA or MRA. Thrombus location was classified as that in the intracranial internal carotid artery (ICA), proximal M1 middle cerebral artery (MCA) segment, distal M1 MCA segment and M2 MCA segment. Tandem occlusion was defined as thrombus in extracranial ICA along with intracranial (ICA, M1-MCA, M2-MCA) thrombus.[22]
4. Collateral circulation distal to intracranial thrombus. Collateral circulation was evaluated on multi-phase CTA, single phase CTA or contrast-enhanced MRA and classified according to a previously published pre-specified collateral grade category (grade 0-1, poor; grade 2, intermediate; grade 3, good).[19]
5. Thrombus density on imaging identified using assessment of the hyperdense artery sign on CT 23 and thrombus volume on CTA, analyzed using the clot burden score (CBS).[24]

Data on number of patients assessed for each imaging variable at baseline and reasons for exclusion are described in Supplement eTable 2. Patients were excluded from further analyses if images were unavailable from primary trial or were of poor quality.

Outcomes

The primary endpoint was neurological functional disability scored on the modified Rankin Scale (mRS) 90 days after randomization with categories 5 (severe disability) and 6 (death) collapsed into a single category. Secondary efficacy outcomes were functional independence (mRS 0–2) at 90 days, excellent functional outcome (mRS 0–1) at 90 days and dramatic neurological improvement (defined as neurological improvement of ≥ 8 points in the NIHSS or a NIHSS 0-1 24 hours after stroke). Safety outcomes included intracranial hemorrhage defined as both symptomatic intracranial hemorrhage (sICH; defined by each trial), parenchymal hematoma type 2 (PH2; blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days of randomization, and mortality within 90 days.

Statistical analysis

All analyses were based on the "as randomized" population. Unless otherwise stated, all reported analyses were pre-specified in the Statistical Analysis Plan. (Supplementary Material) To account for between trial differences when pooling patient level data, mixed-effects modeling was used for all analyses, with fixed effects for parameters of interest and "trial" and the interaction term "trial*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 randomization) and multiplicative interaction terms to test if pre-specified baseline-imaging features modified the effect of treatment allocation on pre-defined outcomes. ASPECTS scores were trichotomized as 0-4, 5-7 and 8-10 for primary analysis. In addition, as pre-specified in the Statistical Analysis Plan, an attempt was made to analyze treatment effect across each ASPECTS

grade to identify an ASPECTS grade below which endovascular treatment may be considered futile or potentially harmful.[13] Sensitivity analyses were performed according to the primary imaging modality (CT or MRI) used at baseline. When missing (n= 21), the primary outcome was imputed as per methods pre-specified in each of the trials. All statistical analyses were performed using SAS v.9.2 (SAS Institute, Cary, North Carolina).

Data sharing
Anonymized Individual Participant Data (IPD) are already available in VISTA-endovascular, an open access registry (http://www.vista.gla.ac.uk)

Role of the funding source
An unrestricted grant was provided to the University of Calgary by Medtronic who had no role in study design, the collection, analysis or interpretation of data, the 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 the 1764 randomized participants, 871 patients assigned to endovascular thrombectomy (intervention population) and 893 assigned to standard medical treatment (control population). Pre-randomization brain imaging features were evaluated in 1388 patients on CT and in 364 patients on MRI. (Supplementary material Figure S2) Clinical characteristics and imaging features at baseline were balanced between the two treatment groups, but treatment with intravenous alteplase was more frequent in the control group (Table 1).

Treatment with EVT was associated with reduced disability at 90 days (adjusted common Odds Ratio for a shift in direction towards a better functional outcome on the mRS 2·00, 95% CI 1·69–2·38; p<0·0001). Figure 1 shows the effect of EVT vs. control on mRS at 90 days stratified by pre-specified baseline imaging features. Distribution of 90-day mRS by treatment group and baseline imaging features are shown in Supplement eFigures 3-8. A treatment effect favoring EVT over control was observed in a broad range of pre-specified imaging strata. (Figure 1) .The treatment effect favored EVT over standard treatment across all three ASPECTS (0-4, 5-7, 8-10) categories (interaction p value=0·054). Treatment effects favoring EVT over control were observed in both the CT and the MRI sub-groups. (Supplement eFigure 9). In analysis of treatment effect across each individual ASPECTS grade, since point estimates for treatment effect likely favored EVT for each individual ASPECTS grades except 0-2, an exploratory analyses informed by potential direction of treatment effect across each individual ASPECTS grade was attempted. In this analysis, statistically significant treatment effect favoring EVT were seen in patients with baseline ASPECTS 6-10 and 3-5. The point estimate of treatment effect (common odds ratio) was < 1 in the ASPECTS 0-2 group (n=37); however, no statistically significant interaction for treatment effect size was noted across the three exploratory ASPECTS categories (6-10, 3-5, 0-2) (interaction p value = 0.30) (Figure 2)

Table 2 summarizes results for secondary outcomes. A beneficial effect of EVT over control was seen across all imaging features for most pre-specified secondary outcomes. A statistically significant interaction between treatment effect and clot burden score was found for functional independence and dramatic neurological recovery at 24 hours (patients with more extensive thrombus at baseline likely benefit more with EVT); however, point estimates for treatment effect favored EVT across all strata.

In analysis of safety outcomes, no statistically significant difference was noted in 90-day-mortality (14·7% vs. 17·3%, p value = 0.15), sICH (3·8% vs. 3·5%, p value = 0.90) and PH2 (5·6% vs. 4·8%, p value = 0.52) between EVT and control group. No treatment effect modification by baseline

imaging features was noted for 90-day-mortality and PH2 (Figure 3 and Supplementary Material Figure S9). When considering intracranial hemorrhage, results were inconsistent.
EVT was associated with a higher risk of sICH in patients with low ASPECTS (0-4) (19·2% versus 4·5%, adjusted common Odds Ratio 3·94, 95% CI 0·94–16·49, interaction P= 0·025) and in patients with baseline early ischemic change in > 1/3 of the MCA territory (13·9% versus 3·5%, adjusted common Odds Ratio 4·17, 95% CI 1·3–13·44, interaction P=0·012) but not when the outcome was purely radiological using PH2. (Figure 3 and Supplement eFigure 10). No interaction was observed with thrombolysis or no thrombolysis in this group of patients. Among patients with ASPECTS 0-4, sICH was observed in 10/52 (19·2%) patients in the EVT group vs. 3/56 (4·5%) patients in the control group (p value = 0·016). Similarly, sICH was observed in 15/108 (13·9%) patients in the EVT group vs.4/113 (3·5%) patients in the control group among patients with baseline early ischemic change in > 1/3rd of the MCA territory (p value = 0·007 (Table 3).

DISCUSSION

Our patient level meta-analysis supports the benefit of EVT for acute ischemic stroke across a broad range of imaging sub-groups. Our results complement and add to previous work from the HERMES Collaboration that demonstrated benefit of EVT across a broad range of clinical subgroups.[8] Our analysis is larger than this previous work (7 trials instead of 5, 1764 patients instead of 1287), uses more rigorous imaging analysis (HERMES core lab uniform re-reading of all scans from all trials), and analyzes key imaging subgroups not previously analyzed. Our results suggest that the prevailing opinion of futility associated with EVT in patients with larger infarcts identified on baseline imaging may not be appropriate, at least among patients otherwise deemed eligible to participate in the component clinical trials of the collaboration. We show benefit with EVT over standard care even in patients with low baseline ASPECTS. Our findings are in line with recent CT perfusion based studies derived from the same cohort of patients, which were also not able to identify baseline ischemic core volumes associated with treatment futility.[25]

EVT is offered to patients with acute ischemic 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 modalities.[26] Thrombus in proximal intracranial arterial segments like in the ICA and M1 MCA 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. Unlike EVT therefore, intravenous alteplase is less likely to recanalize proximal thrombi early when compared to thrombi in distal arterial segments.[27] Moreover, patients with thrombi in proximal intracranial arterial segments are likely to have greater amount of brain tissue at risk than patients with more distal thrombi. .

Imaging is also used to identify extent of irreversibly injured brain tissue beyond target artery occlusion. Patients with large extent of irreversibly injured brain are less likely to have brain tissue that is salvageable with EVT.[10,14,16] Both ASPECTS and the 1/3rd MCA rule identify extent of probably irreversibly injured brain on CT or MRI.[20,23] Our analysis suggests relative treatment benefit with EVT across all ASPECTS categories and in patients with brain infarcts occupying > 1/3rd of the ischemic MCA territory. The effect size by ASPECTS categories is however graded, with larger effect sizes noted in patients with higher ASPECTS. Despite evidence of treatment benefit, the prognosis for patients with low ASPECTS remains poor with few achieving independent outcomes. We also note a statistically significant benefit with EVT even in patients with baseline ASPECTS 3-5, an ASPECTS category that until now may have been considered as indicative of treatment futility.[13] Faster and better reperfusion techniques available since the HERMES trials, may magnify potential benefit in these patients from EVT.[28] The number of patients with ASPECTS 0 (n=12), 1 (n=13), 2 (n=12) in our analyses was very few; this is also the only imaging sub-group where the point estimate for treatment effect does not favor EVT. Ongoing

clinical trials like TENSION and IN EXTRMEIS are likely to provide more evidentiary support for or against net benefit of thrombectomy in patients with large ischemic core at baseline.

Patients with good collateral circulation status beyond target arterial occlusion are more likely to have salvageable brain than patients with poorer collaterals.[29] CTA (or MRA) is often used to identify patients with poor collateral circulation. The technique therefore complements CT/MRI by identifying patients with large extent of irreversibly injured brain tissue. The ESCAPE trial used collateral circulation status to exclude patients with poor collaterals; other trials like SWIFT-PRIME and EXTEND-IA used CT Perfusion or MR Perfusion, techniques that 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 1/3rd MCA rule on CT/MRI, our analyses suggests benefit with EVT across all strata of collateral circulation status; however, patients with poor collaterals are less likely to benefit with EVT than those with better collaterals. Assessment of poor collateral circulation using dynamic angiographic techniques (rather than the single-phase CTA or MRA used in a majority of patients in our analyses) may help better identify patients unlikely to benefit with EVT.[30]

Finally, imaging is used to determine risk with treatment. Our analyses suggest that sICH rates are four times more common in patients with ASPECTS 0-4 and hypodensity in > 1/3rd of the ischemic MCA territory. This increase in sICH rates with EVT was not influenced 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 out of the seven HERMES trials used baseline imaging criteria to exclude patients likely to have large infarcts, we therefore 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 DWI MRI. Confirmatory randomized trials are in progress. No statistical adjustment for multiple comparisons was included. The central re-analysis of images in this study may not reflect the quality of on-site assessments. In clinical practice, patients are treated based on 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 analyzing the utility of baseline imaging in patients eligible for EVT, we found limited evidence of heterogeneity of treatment effect across imaging subgroups. Our analysis suggests that estimated treatment effect for EVT should be weighted in conjunction with other predictors of outcome when deciding whether or not to offer therapy to patients with large baseline infarcts.

Contributors

LsR, BKM,AD, MG prepared the first draft of the report based on an analysis plan agreed by the HERMES Executive (BCVC, MG, DWJD, AMD, S Bracard, PW, AD, CBLM, FG, KWM, JLS, TJG, MDH, PJM) who also contributed to study interpretation. SB performed the statistical analyses. All authors participated in patient enrolment, data collection, critically reviewed the report and approved the final version. LsR, BKM contributed equally.

Declaration of interests

BKM reports in addition, has a patent "Methods of triaging patients with acute stroke" pending. AD reports grants from MEDTRONIC, outside the submitted work. CBLMM reports grants from CVON/Dutch Heart Foundation, grants from European Commission, grants from TWIN Foundation, grants from Stryker, outside the submitted work (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 National Health and Medical research Council, grants from Royal Australasian College of Physicians, grants from Royal Melbourne Hospital Foundation, from National Heart Foundation, from National Stroke Foundation of Australia, grants from Covidien (Medtronic), during the conduct of the study. JLS reports serving as an unpaid site investigator in multicenter trials sponsored by Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott, for which the University of California received payments on the basis of clinical trial contracts for the number of subjects enrolled; reports receiving contracted hourly payments and travel reimbursement from Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott, and stock options from Rapid Medical, for service on Trial Steering Committees, advising on rigorous trial design and conduct; and JLS is an employee of the University of California. The University of California has patent rights in retrieval devices for stroke. HM reports other from Nico.lab, outside the submitted work; GR reports personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Pfizer, personal fees from Daiichi Sankyo, outside the submitted work. DWJD reports grants from Dutch Heart Foundation, grants from AngioCare BV, grants from Medtronic/Covidien/EV3®, grants from MEDAC Gmbh/LAMEPRO, grants from Penumbra Inc., grants from Stryker, during the conduct of the MR CLEAN study. DY reports personal fees, non-financial support and other from Medtronic, personal fees from Neural Analytics, personal fees and other from Cerenovus, during the conduct of the study. SMDC reports personal fees and other from Boehringer Ingelheim, personal fees from Medtronic, outside the submitted work. GAD reports grants from National Health & Medical Research Council, other from Astra Zeneca, other from Boehringer Ingelheim, other from Bristol Meyers Squibb, other from Merck Sharpe Dohme, other from Pfizer, other from Servier, during the conduct of the study. AVDL reports grants from Dutch Heart Foundation , other from AngioCare BV, other from Covidien/EV3®, other from MEDAC Gmbh/LAMEPRO, other from Stryker® , other from Penumbra Inc, during the conduct of the study; grants from Stryker, grants from Penumbra Inc, grants from Medtronic, outside the submitted work. AMD reports reports personal fees from Medtronic, during the conduct of the study .AMC received funds from Stryker for consultations by OB. AMMB has owns stock in Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. GAF reports personal fees from Stryker, grants and personal fees from Medtronic, personal fees from Pfizer, personal fees from Bayer, personal fees from AstraZeneca, personal fees from Cerevast, outside the submitted work. KM reports grants from Medtronic, grants from Codman, during the conduct of the study. SB reports personal fees from University of Calgary, during the conduct of the study; personal fees from Medtronic, outside the submitted work. TJ reports other from Anaconda, other

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TABLES

Variables	Endovascular group (N=871)	Control group (N=893)
Age in years (Median, Range)	67.4 (23.1, 92.5)	67.8 (18.0, 96.7)
Female Sex (%)	47.3% (412/871)	47.3% (421/891)
NIHSS at baseline (Median, Range)	[17] (3, 30)	[17] (4, 38)
Onset to randomization in minutes (Median, Range)	[181] (49, 713)	[184] (37, 708)
Intravenous alteplase (%)	87.6% (763/871)	90.6% (809/893)
Baseline ASPECTS (Median, Range)	[8] (0, 10)	[8] (0, 10)
Clot burden score (Median, Range)	[4] (0, 9)	[4.0] (0, 10)
MCA > 1/3 involvement (%)	13.3% (114/860)	13.6% (119/876)
Hyperdense vessel sign (%)	51.8% (356/687)	47.1% (330/701)
Thrombus location (%)		
ICA	26.3% (215/818)	27.4% (227/828)
Proximal M1 MCA	38.5% (315/818)	39.5% (327/828)
Distal M1 MCA	27.0% (221/818)	25.4% (210/828)
M2 MCA	8.2% (67/818)	7.7% (64/828)
Collateral circulation grade (%)		
0	0.9% (6/639)	1.2% (8/651)
1	14.2% (91/639)	16.6% (108/651)
2	44.3% (283/639)	42.2% (275/651)
3	40.5% (259/639)	39.9% (260/651)

NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

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

	mRS 0-2				mRS 0-1				Dramatic neurological improvement at 24h*				NIHSS 0-2 at 24h			
	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value
Imaging Subgroups (CT OR MR IMAGIG MODALITY)																
All subjects [n=1743]	47.8%	30.6%	2.32 (1.87-2.87)	NA	29.3%	16.6%	2.29 (1.74-3.01)	NA	49.5%	23.8%	3.20 (2.59-3.96)	NA	20.0%	9.3%	2.91 (2.13-3.96)	NA
ASPECTS 0 to 4 [n=126]	24.6%	14.5%	2.72 (0.89-8.33)		15.8%	5.8%	9.10 (0.96-86.76)		31.4%	10.8%	4.62 (1.61-13.25)		2.0%	1.6%	0.05 (0.00-267)	
ASPECTS 5 to 7 [n=615]	43.6%	29.4%	2.07 (1.43-2.99)	0.308	22.7%	15.9%	1.61 (1.04-2.48)	0.251	43.8%	19.4%	3.34 (2.28-4.88)	0.516	13.8%	6.6%	2.68 (1.47-4.91)	0.557
ASPECTS 8 to 10 [n=975]	53.8%	34.0%	2.56 (1.93-3.40)		35.6%	18.9%	2.64 (1.89-3.68)		55.4%	28.7%	3.19 (2.42-4.20)		26%	12.0%	3.06 (2.12-4.42)	
ASPECTS 0 to 2 [n=37]	0.0%	11.5%	0.00 (0.00-5.81)		0.0%	0.0%	NA		10.0%	12.5%	0.63 (0.03-14.11)		0.0%	0.0%	NA	
ASPECTS 3 to 5 [n=186]	30.6%	15.6%	4.27 (1.62-11.25)	0.695	16.3%	8.9%	2.76 (0.86-8.86)	0.879	28.1%	8.2%	5.53 (2.06-14.84)	0.756	6.8%	3.6%	1.70 (0.32-9.15)	0.864
ASPECTS 6 to 10 [n=1493]	51.0%	33.4%	2.29 (1.83-2.88)		31.6%	18.4%	2.25 (1.69-2.99)		52.7%	26.4%	3.16 (2.53-3.95)		21.8%	10.4%	2.88 (2.09-3.95)	

MCA 1/3 involvement no [n=1487]	51.1%	32.9%	2.38 (1.89-2.98)	0.495	31.6%	18.3%	2.27 (1.70-3.03)	0.962	52.5%	26.3%	3.13 (2.50-3.91)	0.359	22.2%	10.4%	2.93 (2.14-4.02)	0.458
MCA 1/3 involvement yes [n=229]	27.4%	17.9%	2.23 (1.07-4.65)		15.0%	7.7%	3.16 (1.08-9.24)		29.1%	9.9%	4.74 (2.12-10.62)		3.9%	2.7%	0.08 (0.00-215)	
Hyperdense sign no [n=692]	45.7%	30.8%	1.95 (1.39-2.70)	0.034	28.0%	13.6%	2.40 (1.65 (3.50)	0.997	48.5%	22.9%	4.59 (1.65-12.23)	0.416	18.6%	8.8%	2.83 (1.71-4.70)	0.962
Hyperdense sign yes [n=682]	46.6%	23.8%	3.20 (2.26-4.53)		27.7%	14.0%	2.47 (1.70-3.60)		50.1%	22.3%	3.67 (2.58-5.20)		20.9%	9.1%	3.03 (1.83-5.02)	
Clot burden score 0 to 4 [n=1026]	41.5%	23.4%	2.84 (2.07-3.90)	0.038	24.4%	12.1%	2.69 (1.79-4.05)	0.244	47.7%	20.0%	3.61 (2.71-4.81)	0.082	16.9%	6.2%	4.14 (2.56-6.68)	0.042
Clot burden score 5 to 7 [n=475]	57.4%	45.4%	1.77 (1.19-2.64)		38.7%	25.8%	1.94 (1.17-3.19)		52.2%	33.6%	2.41 (1.59-3.64)		24.9%	16.5%	1.82 (1.11-2.96)	
Clot burden score 8 to 10 [n=135]	58.0%	40.9%	2.31 (1.06-5.04)		36.2%	22.7%	2.30 (0.72-7.30)		47.8%	21.9%	3.77 (1.64-8.64)		26.1%	9.4%	3.70 (1.21-11.30)	
ICA [n=440]	33.0%	15.5%	2.91 (1.79-4.73)	0.249	17.8%	8.4%	2.26 (1.23-4.15)	0.909	42.2%	15.1%	3.87 (2.41-6.21)	0.242	9.3%	3.7%	3.05 (1.23-7.60)	0.416

Proximal M1 [n=631]	47.0%	28.9%	2.63 (1.76-3.93)		27.8%	15.4%	2.42 (1.43-4.09)		51.1%	24.6%	3.18 (2.25-4.50)		21.9%	8.6%	3.81 (2.23-6.51)	
Distal M1 [n=428]	58.6%	48.1%	1.67 (1.10-2.54)		40.5%	26.4%	2.00 (1.16-3.43)		52.6%	34.6%	2.29 (1.46-3.59)		25.2%	17.2%	1.84 (1.09-3.12)	
M2 [n=130]	58.2%	39.7%	2.35 (1.07-5.14)		37.3%	20.6%	2.49 (0.80-7.75)		47.8%	18.0%	4.73 (2.00-11.21)		26.9%	8.2%	4.38 (1.39-13.82)	
Collateral grade 0 or 1 [n=211]	27.1%	13.9%	1.80 (0.69-4.71)		15.6%	5.2%	4.05 (1.03-15.91)		31.9%	18.3%	2.18 (1.04-4.55)		11.2%	2.9%	3.47 (0.48-25.12)	
Collateral grade 2 [n=552]	44.0%	28.5%	2.49 (1.68-3.69)	0.402	27.7%	14.1%	2.90 (1.80-4.69)	0.623	47.3%	23.8%	3.01 (2.07-4.39)	0.145	20.4%	8.8%	3.92 (2.20-6.99)	0.975
Collateral grade 3 [n=515]	55.4%	33.5%	2.63 (1.80-3.84)		33.3%	17.9%	2.25 (1.47-3.45)		56.3%	23.3%	4.30 (2.89-6.40)		21.9%	9.5%	2.95 (1.71-5.10)	

*defined as neurological improvement of ≥ 8 points in the NIHSS or a NIHSS 0-1 24 hours after stroke.

mRS, the modified Rankin Scale; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; CTA, Computed Tomography Angiography; MRA, Magnetic Resonance Angiography; NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

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

Subgroup	Endovascular group % (n/N)	Control group % (n/N)	Odds Ratio (95% CI)	p-value (subgroup)	p-value (interaction)
Baseline ASPECTS					
0-4	19.2% (10/52)	4.5% (3/66)	5.00 (1.30,19.25)	0.016	
5-7	3.8% (12/319)	3.7% (11/297)	1.02 (0.44, 2.34)	1	0.026
8-10	2.1% (10/473)	3.4% (17/498)	0.61 (0.28, 1.35)	0.245	
0-2	11.1% (1/9)	4.2% (1/24)	2.88 (0.16, 51.53)	0.477	
3-5	14.7% (14/95)	3.4% (3/87)	4.84 (1.27, 27.03)	0.010	0.008
6-10	2.3% (17/740)	3.6% (27/750)	0.63 (0.32, 1.21)	0.168	
MCA > 1/3 involvement					
No	2.3% (17/736)	3.6% (27/748)	0.63 (0.34, 1.17)	0.168	0.002
Yes	13.9% (15/108)	3.5% (4/113)	4.40 (1.41, 13.70)	0.007	
Hyperdense sign					
No	3.3% (12/360)	3.5% (14/401)	0.95 (0.43, 2.09)	1	0.865
Yes	4.5% (16/353)	5.2% (17/328)	0.87 (0.43, 1.75)	0.724	
Clot burden score					

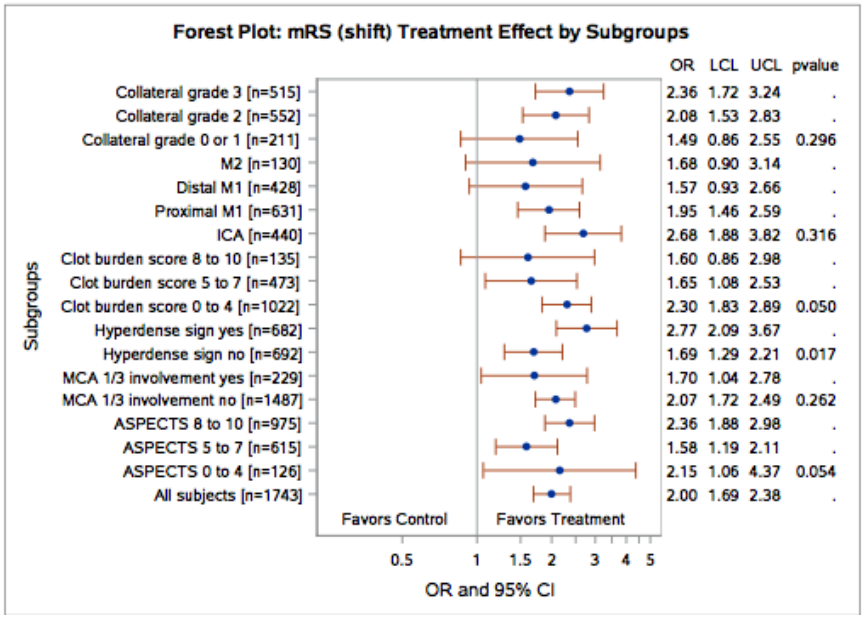
8-10	0.0% (0/69)	7.5% (5/67)	0.00 (0.00, 0.95)	0.027	0.063
5-7	4.7% (11/233)	2.9% (7/240)	1.65 (0.63, 4.33)	0.344	
0-4	3.4% (17/503)	3.1% (16/513)	1.09 (0.54, 2.18)	0.861	
Occlusion location					
ICA	3.3% (7/210)	2.6% (6/227)	1.27 (0.42, 3.84)	0.781	0.154
Proximal M1	3.9% (12/307)	3.5% (11/318)	1.14 (0.49, 2.61)	0.834	
Distal M1	4.1% (9/218)	2.9% (6/207)	1.44 (0.50, 4.13)	0.603	
M2	0.0% (0/67)	7.8% (5/64)	0.00 (0.00, 0.96)	0.026	
Collateral grade					
3	3.1% (8/259)	2.7% (7/259)	1.15 (0.41, 3.21)	1	0.443
2	3.2% (9/281)	2.9% (8/275)	1.10 (0.42, 2.91)	1	
0-1	5.3% (5/94)	10.5% (12/114)	0.48 (0.16, 1.41)	0.209	

ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

Table 3: Symptomatic intracerebral hemorrhage (sICH) rate by treatment and baseline imaging variable categories

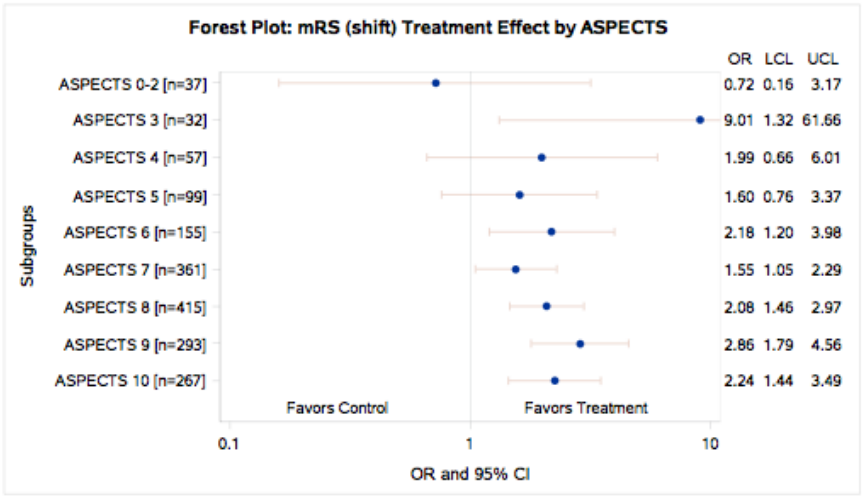
FIGURES

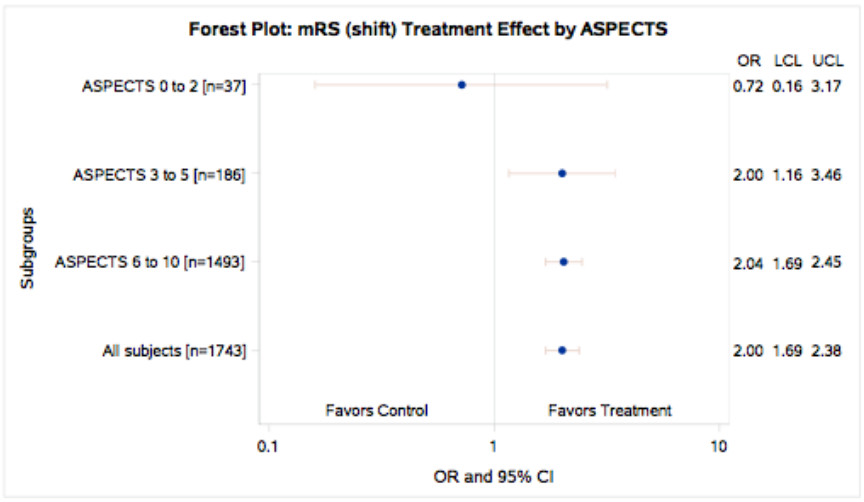
Figure 1. Endovascular treatment effect by baseline imaging variable categories on primary outcome (mRS shift at 90 days)



ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, Middle cerebral artery; M1, M1 segment of MCA; M2, M2 segment of MCA; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

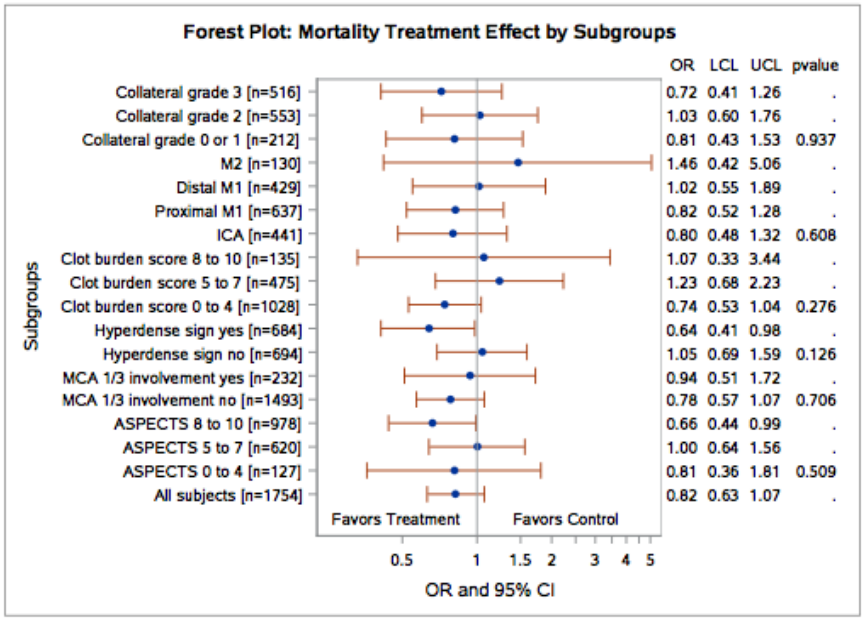
Figure 2. Panel A shows endovascular treatment effect by individual baseline ASPECTS grades on primary outcome (mRS shift at 90 days). There was no statistical evidence of heterogeneity across ASPECTS categories for the relationship between treatment and primary outcome. Panel B shows exploratory analysis informed by pre-specified analyses of treatment effect by individual baseline ASPECTS grades and combines individual ASPECTS grades into categories (6-10 vs. 3-5 and 0-2).

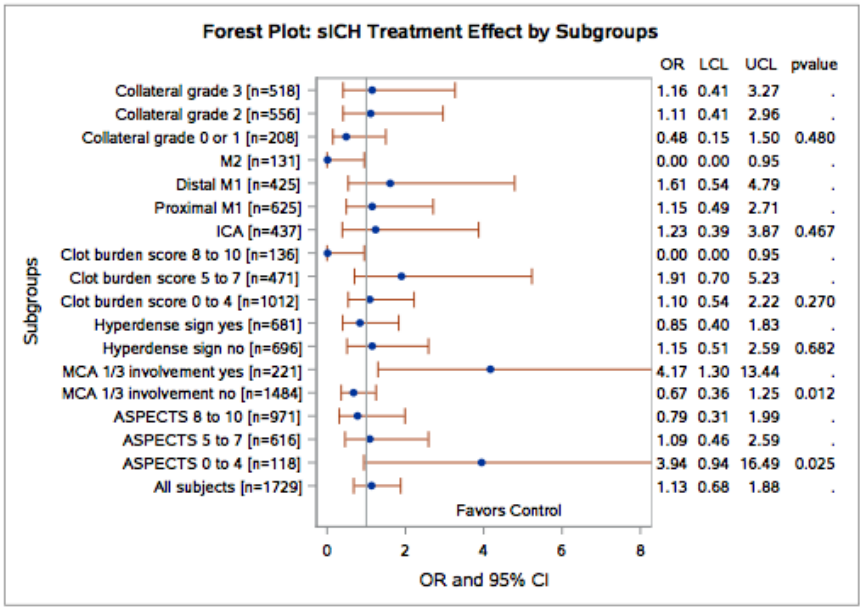




ASPECTS, Alberta Stroke Program Early CT score; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

Figure 3: Endovascular treatment effect by baseline imaging variable categories on safety outcomes, namely, mortality at 90 days and symptomatic ICH incidence.





ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, Middle cerebral artery; M1, M1 segment of MCA; M2, M2 segment of MCA; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

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Imaging features and safety and efficacy of endovascular stroke treatment: an individual patient data meta-analysis

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SUMMARY

Background

Evidence regarding the utility of imaging studies in selecting patients for endovascular thrombectomy (EVT) is limited. We aimed to investigate baseline-imaging features associated with efficacy and safety of endovascular thrombectomy (EVT) in acute ischaemic stroke caused by anterior large vessel occlusion.

Methods

The HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration identified 7 randomized endovascular stroke trials listed in PubMed from 1/Jan/2010 to 31/October/2017 as comparing EVT to standard medical therapy. Only trials that required vessel imaging to identify patients with proximal anterior circulation ischemic stroke and used predominantly stent retrievers or second-generation neuro-thrombectomy devices in the EVT arm were included. The risk of bias was assessed using the Cochrane tool and was low except in the THRACE study that employed un-blinded assessment of 90-day outcome and MRI predominantly as the primary baseline imaging tool. Central, blinded readers rated baseline imaging for ischemic change using the Alberta Stroke Program Early Computed Tomography score (ASPECTS) or ischemic change involving > 1/3 of middle cerebral artery territory, thrombus volume, hyperdensity, and collateral status. Primary endpoint was the modified Rankin Scale (mRS) score at 90 days. Safety outcomes included symptomatic intracranial hemorrhage (sICH), parenchymal hematoma type 2 (PH2) within 5 days of randomization, and mortality within 90 days.
Primary analysis used mixed methods ordinal logistic regression adjusted for age, sex, NIHSS score at admission, intravenous alteplase and time from onset to randomization and interaction terms to test if imaging categorization at baseline modifies the relationship between treatment and outcome.

Findings

Among 1764 pooled patients, 871 were allocated to the EVT arm and 893 to control. The overall treatment effect favored EVT (adjusted common Odds Ratio for a shift towards better outcome on the mRS 2·00, 95% CI 1·69–2·38; p<0·0001). EVT achieves better 90 day outcomes than medical therapy alone across a broad range of baseline imaging categories including in patients with low ASPECTS 0-4 (adjusted common Odds Ratio 2·15, 95% CI 1·06–4·37, interaction P= 0·054), > 1/3 MCA territory infarct (adjusted common Odds Ratio 1·70, 95% CI 1·04–2·78, interaction P= 0·262), poor collaterals (adjusted common Odds Ratio 1·49, 95% CI 0·86–2·55, interaction P= 0·296) and all levels of clot burden (interaction P= 0·050).
No treatment effect modification by baseline imaging features was noted for 90-day-mortality and PH2. Higher risk of sICH was seen in patients with ASPECTS 0-4 (19·2% versus 4·5%, adjusted common Odds Ratio 3·94, 95% CI 0·94–16·49, interaction P= 0·025) and with > 1/3 MCA territory infarct (13·9% versus 3·5%, adjusted common Odds Ratio 4·17, 95% CI 1·3–13·44, interaction P=0·012) when allocated EVT.

Interpretation

EVT achieves better 90-day outcomes than control across a broad range of baseline imaging categories. This analysis provides evidentiary support to expand existing practice guidelines to provide EVT, in a qualified manner, even in patients with large infarcts at baseline.

Funding Unrestricted grant from Medtronic.

Research in context

Evidence before the study:

Recent randomized trials have demonstrated the efficacy of endovascular thrombectomy (EVT). The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration published in Feb 2016 a pooled analysis of individual patient-level data of the first five randomized trials of endovascular thrombectomy. It confirmed benefit of endovascular thrombectomy across a wide range of clinical subgroups and reported on the effect of ASPECTS and site of vessel occlusion as assessed by each individual trial. However, evidence regarding utility of imaging in selecting patients for EVT is limited.

Added value of this study

This is the first individual level meta-analysis using imaging data obtained through single core lab analysis from all seven randomized endovascular stroke trials listed in PubMed (1/Jan/2010-31/October/2017) comparing EVT to standard medical therapy in patients with acute ischemic stroke and anterior circulation large vessel occlusion. Trials requiring imaging to identify patients with anterior circulation ischemic stroke and using second-generation neuro-thrombectomy devices in the EVT arm were included. It represents a unique dataset that is unlikely to ever be replicated in the future, as randomized 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 and substantial evidence that patients with a broad range of baseline imaging characteristics including those with larger infarcts, poor collaterals and any clot burden score benefit from endovascular thrombectomy (EVT).

Implications of all the available evidence

Current guidelines by the American Heart Association (AHA) recommend EVT in patients with ASPECTS>5. This analysis provides evidentiary support for expansion of existing practice guidelines to endorse, in a qualified manner, EVT even for patients with large infarcts at baseline (ASPECTS as low as 3).

INTRODUTION

Recent randomized clinical trials have established the efficacy and safety of endovascular thrombectomy (EVT) in the treatment of patients with acute ischemic stroke and proximal anterior circulation occlusion.[1-8] Because clinical benefit observed in these trials is time dependent, the need for fast and efficient patient selection is well recognized.[9] Imaging is widely used to determine prognosis and to select patients for EVT.[10-12] After the results of the five trials reported in 2015, the new AHA guidelines recommend EVT as standard of care (Level I, Class A evidence) in patients with baseline non-contrast CT ASPECTS 6-10.[13]

Imaging features are strong predictors of clinical outcome.[10] Large infarcts at baseline, large thrombus in proximal arteries and poor collateral circulation identified using imaging are overall associated with lower likelihood of functional dependence and increased risk after reperfusion therapies.[14-19] However, evidence regarding the utility of these imaging features in selecting patients for EVT is limited. This patient level meta-analysis of the HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration aims to determine baseline-imaging features associated with efficacy and safety of EVT when compared to standard medical therapy.

METHODS

Study design and participants

We searched Pubmed for randomized trials published between 1 Jan 2010 and 31 October 2017 comparing endovascular thrombectomy performed using predominantly stent-retrievers with standard care in anterior circulation ischaemic stroke patients - Pubmed search string: (("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 (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) Collaboration pooled patient level demographic, clinical and imaging data as well as functional and radiologic outcomes from 7 randomized trials: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE and PISTE (Supplement eFigure 1). All these trials required vessel imaging to identify patients with anterior circulation ischemic stroke and used predominantly stent retrievers or second-generation neuro-thrombectomy devices in the EVT arm. Data were assessed for quality and validity using PRISMA guidelines. Differences in patient population, sampling frame and operational definitions of intervention (EVT) and control were assessed before collating all data at a patient level (Supplement eTable 1). Risk of bias in the individual studies was assessed using the Cochrane handbook methodology and was low overall except in the THRACE study that used un-blinded assessment of 90-day outcome. In addition, in contrast to other studies, the THRACE study used MRI predominantly as the primary baseline imaging tool. This meta-analysis was prospectively designed by the HERMES executive committee but not registered. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. The methodological design for this patient level pooling has been previously described.[8]

Imaging variables

Baseline images included information available either on Computed Tomography (CT) or on Magnetic Resonance Imaging (MRI). All imaging studies were de-identified at the HERMES central coordinating center. The imaging datasets were then read by independent HERMES core labs for baseline CT/MRI, baseline CT Angiography (CTA), MRI Angiography (MRA), follow up CT or MR, and conventional angiography. Readers were blinded to all clinical information, except side of stroke.

Imaging in acute ischemic stroke is used to identify extent of early ischemic change and location and extent of thrombus. Pre-specified baseline imaging features of interest therefore were:

1. The Alberta Stroke Program Early CT Score (ASPECTS) defined on CT or MR Diffusion Weighted Imaging (MR-DWI). This widely used ordinal scale measures extent of ischemia in the middle cerebral artery (MCA) 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 > 30% of the respective region, and on CT if any signs of ischemia were visible on at least two consecutive cuts of the 10 standardized regions of the MCA territory. ASPECTS grading was evaluated independently by experts blinded to all clinical and imaging information except stroke side. Any disagreement was resolved by consensus. Trichotomized ASPECTS agreement between two raters (JB, LSR) assessed in 30 patients using weighted kappa was good (kappa 0.89, 95% CI 0.81 -0.99.
2. The > 1/3rd MCA rule defined on CT or MR-DWI as early ischemic change in > 1/3rd of the ischemic MCA territory.[21]
3. Thrombus location identified on CTA or MRA. Thrombus location was classified as that in the intracranial internal carotid artery (ICA), proximal M1 middle cerebral artery (MCA) segment, distal M1 MCA segment and M2 MCA segment. Tandem occlusion was defined as thrombus in extracranial ICA along with intracranial (ICA, M1-MCA, M2-MCA) thrombus.[22]
4. Collateral circulation distal to intracranial thrombus. Collateral circulation was evaluated on multi-phase CTA, single phase CTA or contrast-enhanced MRA and classified according to a previously published pre-specified collateral grade category (grade 0-1, poor; grade 2, intermediate; grade 3, good).[19]
5. Thrombus density on imaging identified using assessment of the hyperdense artery sign on CT 23 and thrombus volume on CTA, analyzed using the clot burden score (CBS).[24]

Data on number of patients assessed for each imaging variable at baseline and reasons for exclusion are described in Supplement eTable 2. Patients were excluded from further analyses if images were unavailable from primary trial or were of poor quality.

Outcomes

The primary endpoint was neurological functional disability scored on the modified Rankin Scale (mRS) 90 days after randomization with categories 5 (severe disability) and 6 (death) collapsed into a single category. Secondary efficacy outcomes were functional independence (mRS 0–2) at 90 days, excellent functional outcome (mRS 0–1) at 90 days and dramatic neurological improvement (defined as neurological improvement of ≥ 8 points in the NIHSS or a NIHSS 0-1 24 hours after stroke). Safety outcomes included intracranial hemorrhage defined as both symptomatic intracranial hemorrhage (sICH; defined by each trial), parenchymal hematoma type 2 (PH2; blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days of randomization, and mortality within 90 days.

Statistical analysis

All analyses were based on the "as randomized" population. Unless otherwise stated, all reported analyses were pre-specified in the Statistical Analysis Plan. (Supplementary Material) To account for between trial differences when pooling patient level data, mixed-effects modeling was used for all analyses, with fixed effects for parameters of interest and "trial" and the interaction term "trial*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 randomization) and multiplicative interaction terms to test if pre-specified baseline-imaging features modified the effect of treatment allocation on pre-defined outcomes. ASPECTS scores were trichotomized as 0-4, 5-7 and 8-10 for primary analysis. In addition, as pre-specified in the Statistical Analysis Plan, an attempt was made to analyze treatment effect across each ASPECTS

grade to identify an ASPECTS grade below which endovascular treatment may be considered futile or potentially harmful.[13] Sensitivity analyses were performed according to the primary imaging modality (CT or MRI) used at baseline. When missing (n= 21), the primary outcome was imputed as per methods pre-specified in each of the trials. All statistical analyses were performed using SAS v.9.2 (SAS Institute, Cary, North Carolina).

Data sharing
Anonymized Individual Participant Data (IPD) are already available in VISTA-endovascular, an open access registry (http://www.vista.gla.ac.uk)

Role of the funding source
An unrestricted grant was provided to the University of Calgary by Medtronic who had no role in study design, the collection, analysis or interpretation of data, the 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 the 1764 randomized participants, 871 patients assigned to endovascular thrombectomy (intervention population) and 893 assigned to standard medical treatment (control population). Pre-randomization brain imaging features were evaluated in 1388 patients on CT and in 364 patients on MRI. (Supplementary material Figure S2) Clinical characteristics and imaging features at baseline were balanced between the two treatment groups, but treatment with intravenous alteplase was more frequent in the control group (Table 1).

Treatment with EVT was associated with reduced disability at 90 days (adjusted common Odds Ratio for a shift in direction towards a better functional outcome on the mRS 2·00, 95% CI 1·69–2·38; p<0·0001). Figure 1 shows the effect of EVT vs. control on mRS at 90 days stratified by pre-specified baseline imaging features. Distribution of 90-day mRS by treatment group and baseline imaging features are shown in Supplement eFigures 3-8. A treatment effect favoring EVT over control was observed in a broad range of pre-specified imaging strata. (Figure 1) .The treatment effect favored EVT over standard treatment across all three ASPECTS (0-4, 5-7, 8-10) categories (interaction p value=0·054). Treatment effects favoring EVT over control were observed in both the CT and the MRI sub-groups. (Supplement eFigure 9). In analysis of treatment effect across each individual ASPECTS grade, since point estimates for treatment effect likely favored EVT for each individual ASPECTS grades except 0-2, an exploratory analyses informed by potential direction of treatment effect across each individual ASPECTS grade was attempted. In this analysis, statistically significant treatment effect favoring EVT were seen in patients with baseline ASPECTS 6-10 and 3-5. The point estimate of treatment effect (common odds ratio) was < 1 in the ASPECTS 0-2 group (n=37); however, no statistically significant interaction for treatment effect size was noted across the three exploratory ASPECTS categories (6-10, 3-5, 0-2) (interaction p value = 0.30) (Figure 2)

Table 2 summarizes results for secondary outcomes. A beneficial effect of EVT over control was seen across all imaging features for most pre-specified secondary outcomes. A statistically significant interaction between treatment effect and clot burden score was found for functional independence and dramatic neurological recovery at 24 hours (patients with more extensive thrombus at baseline likely benefit more with EVT); however, point estimates for treatment effect favored EVT across all strata.

In analysis of safety outcomes, no statistically significant difference was noted in 90-day-mortality (14·7% vs. 17·3%, p value = 0.15), sICH (3·8% vs. 3·5%, p value = 0.90) and PH2 (5·6% vs. 4·8%, p value = 0.52) between EVT and control group. No treatment effect modification by baseline

imaging features was noted for 90-day-mortality and PH2 (Figure 3 and Supplementary Material Figure S9). When considering intracranial hemorrhage, results were inconsistent.
EVT was associated with a higher risk of sICH in patients with low ASPECTS (0-4) (19·2% versus 4·5%, adjusted common Odds Ratio 3·94, 95% CI 0·94–16·49, interaction P= 0·025) and in patients with baseline early ischemic change in > 1/3 of the MCA territory (13·9% versus 3·5%, adjusted common Odds Ratio 4·17, 95% CI 1·3–13·44, interaction P=0·012) but not when the outcome was purely radiological using PH2. (Figure 3 and Supplement eFigure 10). No interaction was observed with thrombolysis or no thrombolysis in this group of patients. Among patients with ASPECTS 0-4, sICH was observed in 10/52 (19·2%) patients in the EVT group vs. 3/56 (4·5%) patients in the control group (p value = 0·016). Similarly, sICH was observed in 15/108 (13·9%) patients in the EVT group vs.4/113 (3·5%) patients in the control group among patients with baseline early ischemic change in > 1/3rd of the MCA territory (p value = 0·007 (Table 3).

DISCUSSION

Our patient level meta-analysis supports the benefit of EVT for acute ischemic stroke across a broad range of imaging sub-groups. Our results complement and add to previous work from the HERMES Collaboration that demonstrated benefit of EVT across a broad range of clinical subgroups.[8] Our analysis is larger than this previous work (7 trials instead of 5, 1764 patients instead of 1287), uses more rigorous imaging analysis (HERMES core lab uniform re-reading of all scans from all trials), and analyzes key imaging subgroups not previously analyzed. Our results suggest that the prevailing opinion of futility associated with EVT in patients with larger infarcts identified on baseline imaging may not be appropriate, at least among patients otherwise deemed eligible to participate in the component clinical trials of the collaboration. We show benefit with EVT over standard care even in patients with low baseline ASPECTS. Our findings are in line with recent CT perfusion based studies derived from the same cohort of patients, which were also not able to identify baseline ischemic core volumes associated with treatment futility.[25]

EVT is offered to patients with acute ischemic 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 modalities.[26] Thrombus in proximal intracranial arterial segments like in the ICA and M1 MCA 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. Unlike EVT therefore, intravenous alteplase is less likely to recanalize proximal thrombi early when compared to thrombi in distal arterial segments.[27] Moreover, patients with thrombi in proximal intracranial arterial segments are likely to have greater amount of brain tissue at risk than patients with more distal thrombi. .

Imaging is also used to identify extent of irreversibly injured brain tissue beyond target artery occlusion. Patients with large extent of irreversibly injured brain are less likely to have brain tissue that is salvageable with EVT.[10,14,16] Both ASPECTS and the 1/3rd MCA rule identify extent of probably irreversibly injured brain on CT or MRI.[20,23] Our analysis suggests relative treatment benefit with EVT across all ASPECTS categories and in patients with brain infarcts occupying > 1/3rd of the ischemic MCA territory. The effect size by ASPECTS categories is however graded, with larger effect sizes noted in patients with higher ASPECTS. Despite evidence of treatment benefit, the prognosis for patients with low ASPECTS remains poor with few achieving independent outcomes. We also note a statistically significant benefit with EVT even in patients with baseline ASPECTS 3-5, an ASPECTS category that until now may have been considered as indicative of treatment futility.[13] Faster and better reperfusion techniques available since the HERMES trials, may magnify potential benefit in these patients from EVT.[28] The number of patients with ASPECTS 0 (n=12), 1 (n=13), 2 (n=12) in our analyses was very few; this is also the only imaging sub-group where the point estimate for treatment effect does not favor EVT. Ongoing

clinical trials like TENSION and IN EXTRMEIS are likely to provide more evidentiary support for or against net benefit of thrombectomy in patients with large ischemic core at baseline.

Patients with good collateral circulation status beyond target arterial occlusion are more likely to have salvageable brain than patients with poorer collaterals.[29] CTA (or MRA) is often used to identify patients with poor collateral circulation. The technique therefore complements CT/MRI by identifying patients with large extent of irreversibly injured brain tissue. The ESCAPE trial used collateral circulation status to exclude patients with poor collaterals; other trials like SWIFT-PRIME and EXTEND-IA used CT Perfusion or MR Perfusion, techniques that 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 1/3rd MCA rule on CT/MRI, our analyses suggests benefit with EVT across all strata of collateral circulation status; however, patients with poor collaterals are less likely to benefit with EVT than those with better collaterals. Assessment of poor collateral circulation using dynamic angiographic techniques (rather than the single-phase CTA or MRA used in a majority of patients in our analyses) may help better identify patients unlikely to benefit with EVT.[30]

Finally, imaging is used to determine risk with treatment. Our analyses suggest that sICH rates are four times more common in patients with ASPECTS 0-4 and hypodensity in > 1/3rd of the ischemic MCA territory. This increase in sICH rates with EVT was not influenced 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 out of the seven HERMES trials used baseline imaging criteria to exclude patients likely to have large infarcts, we therefore 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 DWI MRI. Confirmatory randomized trials are in progress. No statistical adjustment for multiple comparisons was included. The central re-analysis of images in this study may not reflect the quality of on-site assessments. In clinical practice, patients are treated based on 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 analyzing the utility of baseline imaging in patients eligible for EVT, we found limited evidence of heterogeneity of treatment effect across imaging subgroups. Our analysis suggests that estimated treatment effect for EVT should be weighted in conjunction with other predictors of outcome when deciding whether or not to offer therapy to patients with large baseline infarcts.

Contributors

LsR, BKM, AD, MG prepared the first draft of the report based on an analysis plan agreed by the HERMES Executive (BCVC, MG, DWJD, AMD, S Bracard, PW, AD, CBLM, FG, KWM, JLS, TJG, MDH, PJM) who also contributed to study interpretation. SB performed the statistical analyses. All authors participated in patient enrolment, data collection, critically reviewed the report and approved the final version. LsR, BKM contributed equally.

Declaration of interests

BKM reports in addition, has a patent "Methods of triaging patients with acute stroke" pending. AD reports grants from MEDTRONIC, outside the submitted work. CBLMM reports grants from CVON/Dutch Heart Foundation, grants from European Commission, grants from TWIN Foundation, grants from Stryker, outside the submitted work (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 National Health and Medical research Council, grants from Royal Australasian College of Physicians, grants from Royal Melbourne Hospital Foundation, from National Heart Foundation, from National Stroke Foundation of Australia, grants from Covidien (Medtronic), during the conduct of the study. JLS reports serving as an unpaid site investigator in multicenter trials sponsored by Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott, for which the University of California received payments on the basis of clinical trial contracts for the number of subjects enrolled; reports receiving contracted hourly payments and travel reimbursement from Covidien, Medtronic/Abbott, Stryker, and Neuravi/Abbott, and stock options from Rapid Medical, for service on Trial Steering Committees, advising on rigorous trial design and conduct; and JLS is an employee of the University of California. The University of California has patent rights in retrieval devices for stroke. HM reports other from Nico.lab, outside the submitted work; GR reports personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Pfizer, personal fees from Daiichi Sankyo, outside the submitted work. DWJD reports grants from Dutch Heart Foundation, grants from AngioCare BV, grants from Medtronic/Covidien/EV3®, grants from MEDAC Gmbh/LAMEPRO, grants from Penumbra Inc., grants from Stryker, during the conduct of the MR CLEAN study. DY reports personal fees, non-financial support and other from Medtronic, personal fees from Neural Analytics, personal fees and other from Cerenovus, during the conduct of the study. SMDC reports personal fees and other from Boehringer Ingelheim, personal fees from Medtronic, outside the submitted work. GAD reports grants from National Health & Medical Research Council, other from Astra Zeneca, other from Boehringer Ingelheim, other from Bristol Meyers Squibb, other from Merck Sharpe Dohme, other from Pfizer, other from Servier, during the conduct of the study. AVDL reports grants from Dutch Heart Foundation , other from AngioCare BV, other from Covidien/EV3®, other from MEDAC Gmbh/LAMEPRO, other from Stryker® , other from Penumbra Inc, during the conduct of the study; grants from Stryker, grants from Penumbra Inc, grants from Medtronic, outside the submitted work. AMD reports reports personal fees from Medtronic, during the conduct of the study .AMC received funds from Stryker for consultations by OB. AMMB has owns stock in Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. GAF reports personal fees from Stryker, grants and personal fees from Medtronic, personal fees from Pfizer, personal fees from Bayer, personal fees from AstraZeneca, personal fees from Cerevast, outside the submitted work. KM reports grants from Medtronic, grants from Codman, during the conduct of the study. SB reports personal fees from University of Calgary, during the conduct of the study; personal fees from Medtronic, outside the submitted work. TJ reports other from Anaconda, other from Silk Road, other from Route

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TABLES

Variables	Endovascular group (N=871)	Control group (N=893)
Age in years (Median, Range)	67.4 (23.1, 92.5)	67.8 (18.0, 96.7)
Female Sex (%)	47.3% (412/871)	47.3% (421/891)
NIHSS at baseline (Median, Range)	[17] (3, 30)	[17] (4, 38)
Onset to randomization in minutes (Median, Range)	[181] (49, 713)	[184] (37, 708)
Intravenous alteplase (%)	87.6% (763/871)	90.6% (809/893)
Baseline ASPECTS (Median, Range)	[8] (0, 10)	[8] (0, 10)
Clot burden score (Median, Range)	[4] (0, 9)	[4.0] (0, 10)
MCA > 1/3 involvement (%)	13.3% (114/860)	13.6% (119/876)
Hyperdense vessel sign (%)	51.8% (356/687)	47.1% (330/701)
Thrombus location (%)		
ICA	26.3% (215/818)	27.4% (227/828)
Proximal M1 MCA	38.5% (315/818)	39.5% (327/828)
Distal M1 MCA	27.0% (221/818)	25.4% (210/828)
M2 MCA	8.2% (67/818)	7.7% (64/828)
Collateral circulation grade (%)		
0	0.9% (6/639)	1.2% (8/651)
1	14.2% (91/639)	16.6% (108/651)
2	44.3% (283/639)	42.2% (275/651)
3	40.5% (259/639)	39.9% (260/651)

NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

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

	mRS 0-2				mRS 0-1				Dramatic neurological improvement at 24h*				NIHSS 0-2 at 24h			
	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value	EVT (%)	Control (%)	OR (95% CI)	p-value
Imaging Subgroups (CT OR MR IMAGIG MODALITY)																
All subjects [n=1743]	47.8%	30.6%	2.32 (1.87-2.87)	NA	29.3%	16.6%	2.29 (1.74-3.01)	NA	49.5%	23.8%	3.20 (2.59-3.96)	NA	20.0%	9.3%	2.91 (2.13-3.96)	NA
ASPECTS 0 to 4 [n=126]	24.6%	14.5%	2.72 (0.89-8.33)		15.8%	5.8%	9.10 (0.96-86.76)		31.4%	10.8%	4.62 (1.61-13.25)		2.0%	1.6%	0.05 (0.00-267)	
ASPECTS 5 to 7 [n=615]	43.6%	29.4%	2.07 (1.43-2.99)	0.308	22.7%	15.9%	1.61 (1.04-2.48)	0.251	43.8%	19.4%	3.34 (2.28-4.88)	0.516	13.8%	6.6%	2.68 (1.47-4.91)	0.557
ASPECTS 8 to 10 [n=975]	53.8%	34.0%	2.56 (1.93-3.40)		35.6%	18.9%	2.64 (1.89-3.68)		55.4%	28.7%	3.19 (2.42-4.20)		26%	12.0%	3.06 (2.12-4.42)	
ASPECTS 0 to 2 [n=37]	0.0%	11.5%	0.00 (0.00-5.81)		0.0%	0.0%	NA		10.0%	12.5%	0.63 (0.03-14.11)		0.0%	0.0%	NA	
ASPECTS 3 to 5 [n=186]	30.6%	15.6%	4.27 (1.62-11.25)	0.695	16.3%	8.9%	2.76 (0.86-8.86)	0.879	28.1%	8.2%	5.53 (2.06-14.84)	0.756	6.8%	3.6%	1.70 (0.32-9.15)	0.864
ASPECTS 6 to 10 [n=1493]	51.0%	33.4%	2.29 (1.83-2.88)		31.6%	18.4%	2.25 (1.69-2.99)		52.7%	26.4%	3.16 (2.53-3.95)		21.8%	10.4%	2.88 (2.09-3.95)	

MCA 1/3 involvement no [n=1487]	51.1%	32.9%	2.38 (1.89-2.98)	0.495	31.6%	18.3%	2.27 (1.70-3.03)	0.962	52.5%	26.3%	3.13 (2.50-3.91)	0.359	22.2%	10.4%	2.93 (2.14-4.02)	0.458
MCA 1/3 involvement yes [n=229]	27.4%	17.9%	2.23 (1.07-4.65)		15.0%	7.7%	3.16 (1.08-9.24)		29.1%	9.9%	4.74 (2.12-10.62)		3.9%	2.7%	0.08 (0.00-215)	
Hyperdense sign no [n=692]	45.7%	30.8%	1.95 (1.39-2.70)	0.034	28.0%	13.6%	2.40 (1.65 (3.50)	0.997	48.5%	22.9%	4.59 (1.65-12.23)	0.416	18.6%	8.8%	2.83 (1.71-4.70)	0.962
Hyperdense sign yes [n=682]	46.6%	23.8%	3.20 (2.26-4.53)		27.7%	14.0%	2.47 (1.70-3.60)		50.1%	22.3%	3.67 (2.58-5.20)		20.9%	9.1%	3.03 (1.83-5.02)	
Clot burden score 0 to 4 [n=1026]	41.5%	23.4%	2.84 (2.07-3.90)	0.038	24.4%	12.1%	2.69 (1.79-4.05)	0.244	47.7%	20.0%	3.61 (2.71-4.81)	0.082	16.9%	6.2%	4.14 (2.56-6.68)	0.042
Clot burden score 5 to 7 [n=475]	57.4%	45.4%	1.77 (1.19-2.64)		38.7%	25.8%	1.94 (1.17-3.19)		52.2%	33.6%	2.41 (1.59-3.64)		24.9%	16.5%	1.82 (1.11-2.96)	
Clot burden score 8 to 10 [n=135]	58.0%	40.9%	2.31 (1.06-5.04)		36.2%	22.7%	2.30 (0.72-7.30)		47.8%	21.9%	3.77 (1.64-8.64)		26.1%	9.4%	3.70 (1.21-11.30)	
ICA [n=440]	33.0%	15.5%	2.91 (1.79-4.73)	0.249	17.8%	8.4%	2.26 (1.23-4.15)	0.909	42.2%	15.1%	3.87 (2.41-6.21)	0.242	9.3%	3.7%	3.05 (1.23-7.60)	0.416

Proximal M1 [n=631]	47.0%	28.9%	2.63 (1.76-3.93)		27.8%	15.4%	2.42 (1.43-4.09)		51.1%	24.6%	3.18 (2.25-4.50)		21.9%	8.6%	3.81 (2.23-6.51)	
Distal M1 [n=428]	58.6%	48.1%	1.67 (1.10-2.54)		40.5%	26.4%	2.00 (1.16-3.43)		52.6%	34.6%	2.29 (1.46-3.59)		25.2%	17.2%	1.84 (1.09-3.12)	
M2 [n=130]	58.2%	39.7%	2.35 (1.07-5.14)		37.3%	20.6%	2.49 (0.80-7.75)		47.8%	18.0%	4.73 (2.00-11.21)		26.9%	8.2%	4.38 (1.39-13.82)	
Collateral grade 0 or 1 [n=211]	27.1%	13.9%	1.80 (0.69-4.71)		15.6%	5.2%	4.05 (1.03-15.91)		31.9%	18.3%	2.18 (1.04-4.55)		11.2%	2.9%	3.47 (0.48-25.12)	
Collateral grade 2 [n=552]	44.0%	28.5%	2.49 (1.68-3.69)	0.402	27.7%	14.1%	2.90 (1.80-4.69)	0.623	47.3%	23.8%	3.01 (2.07-4.39)	0.145	20.4%	8.8%	3.92 (2.20-6.99)	0.975
Collateral grade 3 [n=515]	55.4%	33.5%	2.63 (1.80-3.84)		33.3%	17.9%	2.25 (1.47-3.45)		56.3%	23.3%	4.30 (2.89-6.40)		21.9%	9.5%	2.95 (1.71-5.10)	

*defined as neurological improvement of ≥ 8 points in the NIHSS or a NIHSS 0-1 24 hours after stroke.

mRS, the modified Rankin Scale; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; CTA, Computed Tomography Angiography; MRA, Magnetic Resonance Angiography; NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

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

Subgroup	Endovascular group % (n/N)	Control group % (n/N)	Odds Ratio (95% CI)	p-value (subgroup)	p-value (interaction)
Baseline ASPECTS					
0-4	19.2% (10/52)	4.5% (3/66)	5.00 (1.30,19.25)	0.016	
5-7	3.8% (12/319)	3.7% (11/297)	1.02 (0.44, 2.34)	1	0.026
8-10	2.1% (10/473)	3.4% (17/498)	0.61 (0.28, 1.35)	0.245	
0-2	11.1% (1/9)	4.2% (1/24)	2.88 (0.16, 51.53)	0.477	
3-5	14.7% (14/95)	3.4% (3/87)	4.84 (1.27, 27.03)	0.010	0.008
6-10	2.3% (17/740)	3.6% (27/750)	0.63 (0.32, 1.21)	0.168	
MCA > 1/3 involvement					
No	2.3% (17/736)	3.6% (27/748)	0.63 (0.34, 1.17)	0.168	0.002
Yes	13.9% (15/108)	3.5% (4/113)	4.40 (1.41, 13.70)	0.007	
Hyperdense sign					
No	3.3% (12/360)	3.5% (14/401)	0.95 (0.43, 2.09)	1	0.865
Yes	4.5% (16/353)	5.2% (17/328)	0.87 (0.43, 1.75)	0.724	
Clot burden score					

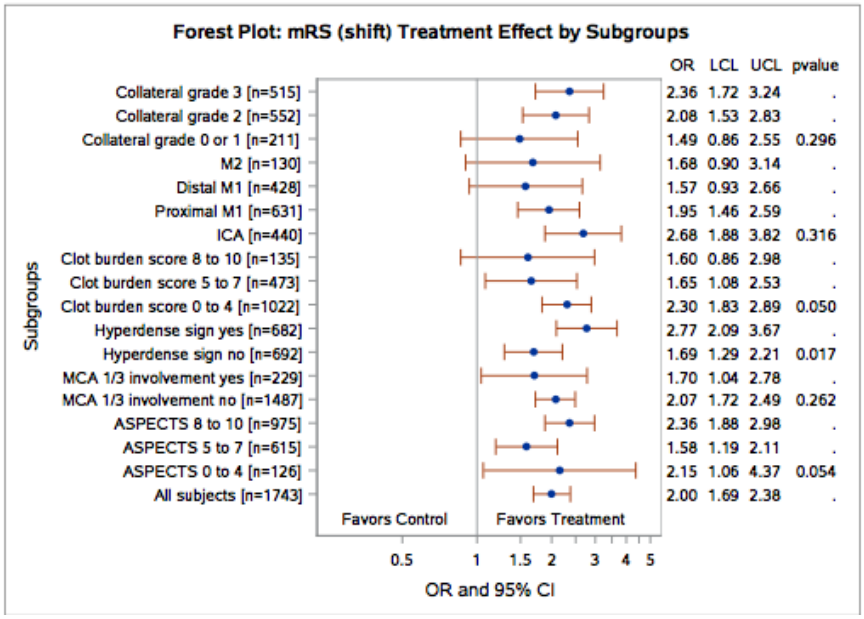
8-10	0.0% (0/69)	7.5% (5/67)	0.00 (0.00, 0.95)	0.027	0.063
5-7	4.7% (11/233)	2.9% (7/240)	1.65 (0.63, 4.33)	0.344	
0-4	3.4% (17/503)	3.1% (16/513)	1.09 (0.54, 2.18)	0.861	
Occlusion location					
ICA	3.3% (7/210)	2.6% (6/227)	1.27 (0.42, 3.84)	0.781	0.154
Proximal M1	3.9% (12/307)	3.5% (11/318)	1.14 (0.49, 2.61)	0.834	
Distal M1	4.1% (9/218)	2.9% (6/207)	1.44 (0.50, 4.13)	0.603	
M2	0.0% (0/67)	7.8% (5/64)	0.00 (0.00, 0.96)	0.026	
Collateral grade					
3	3.1% (8/259)	2.7% (7/259)	1.15 (0.41, 3.21)	1	0.443
2	3.2% (9/281)	2.9% (8/275)	1.10 (0.42, 2.91)	1	
0-1	5.3% (5/94)	10.5% (12/114)	0.48 (0.16, 1.41)	0.209	

ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Cerebral Artery; MCA, Middle Cerebral Artery.

Table 3: Symptomatic intracerebral hemorrhage (sICH) rate by treatment and baseline imaging variable categories

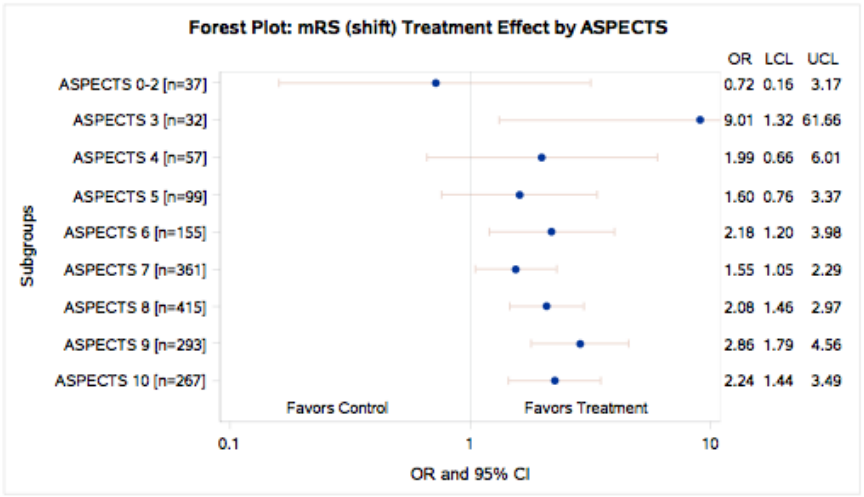
FIGURES

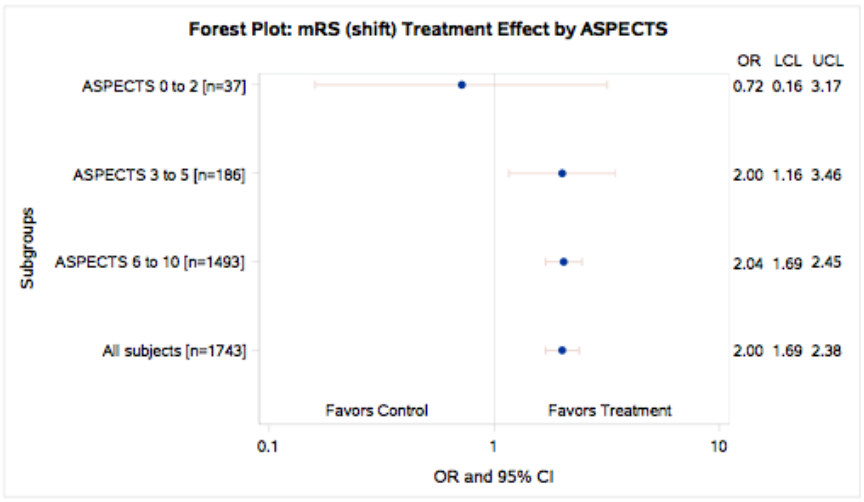
Figure 1. Endovascular treatment effect by baseline imaging variable categories on primary outcome (mRS shift at 90 days)



ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, Middle cerebral artery; M1, M1 segment of MCA; M2, M2 segment of MCA; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

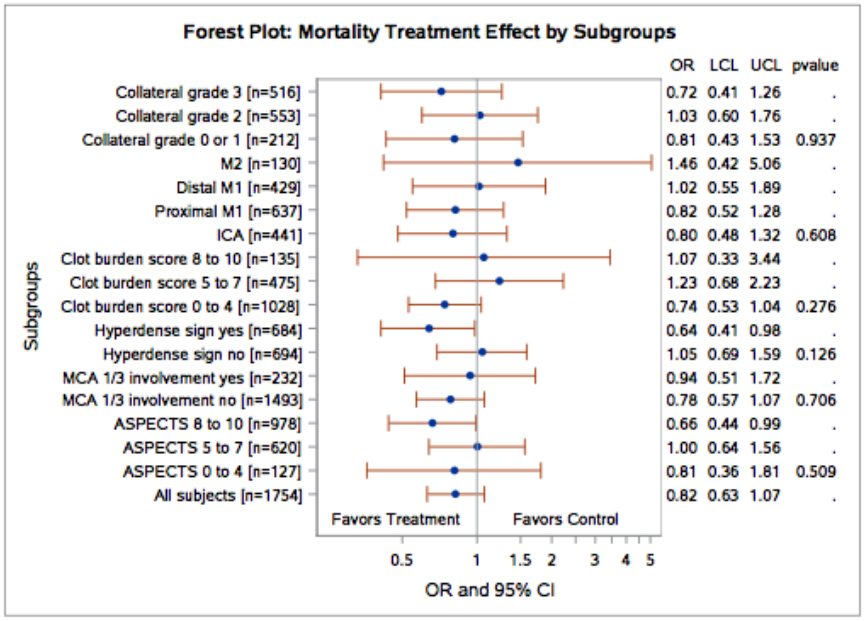
Figure 2. Panel A shows endovascular treatment effect by individual baseline ASPECTS grades on primary outcome (mRS shift at 90 days). There was no statistical evidence of heterogeneity across ASPECTS categories for the relationship between treatment and primary outcome. Panel B shows exploratory analysis informed by pre-specified analyses of treatment effect by individual baseline ASPECTS grades and combines individual ASPECTS grades into categories (6-10 vs. 3-5 and 0-2).

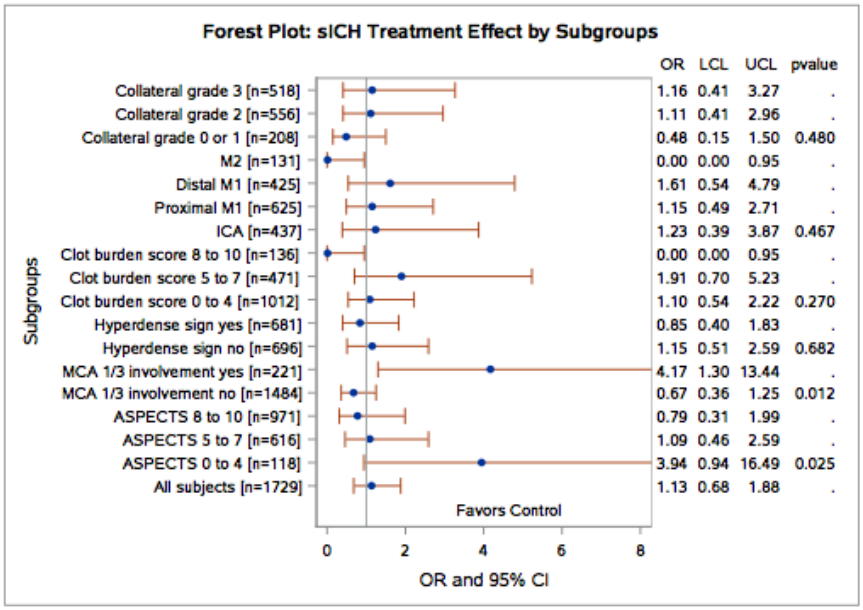




ASPECTS, Alberta Stroke Program Early CT score; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

Figure 3: Endovascular treatment effect by baseline imaging variable categories on safety outcomes, namely, mortality at 90 days and symptomatic ICH incidence.





ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, Middle cerebral artery; M1, M1 segment of MCA; M2, M2 segment of MCA; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

Figure 1

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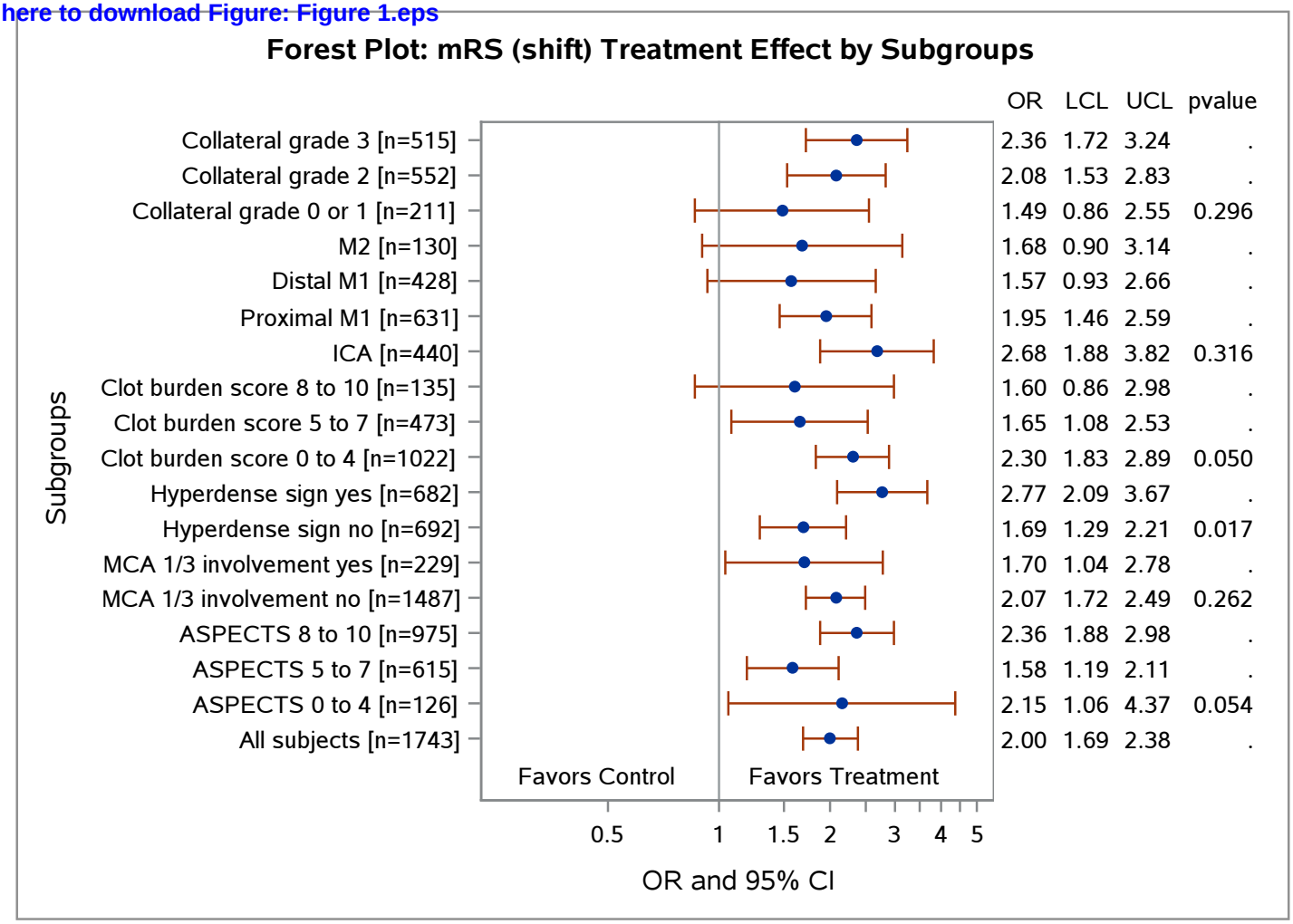

Figure 2a

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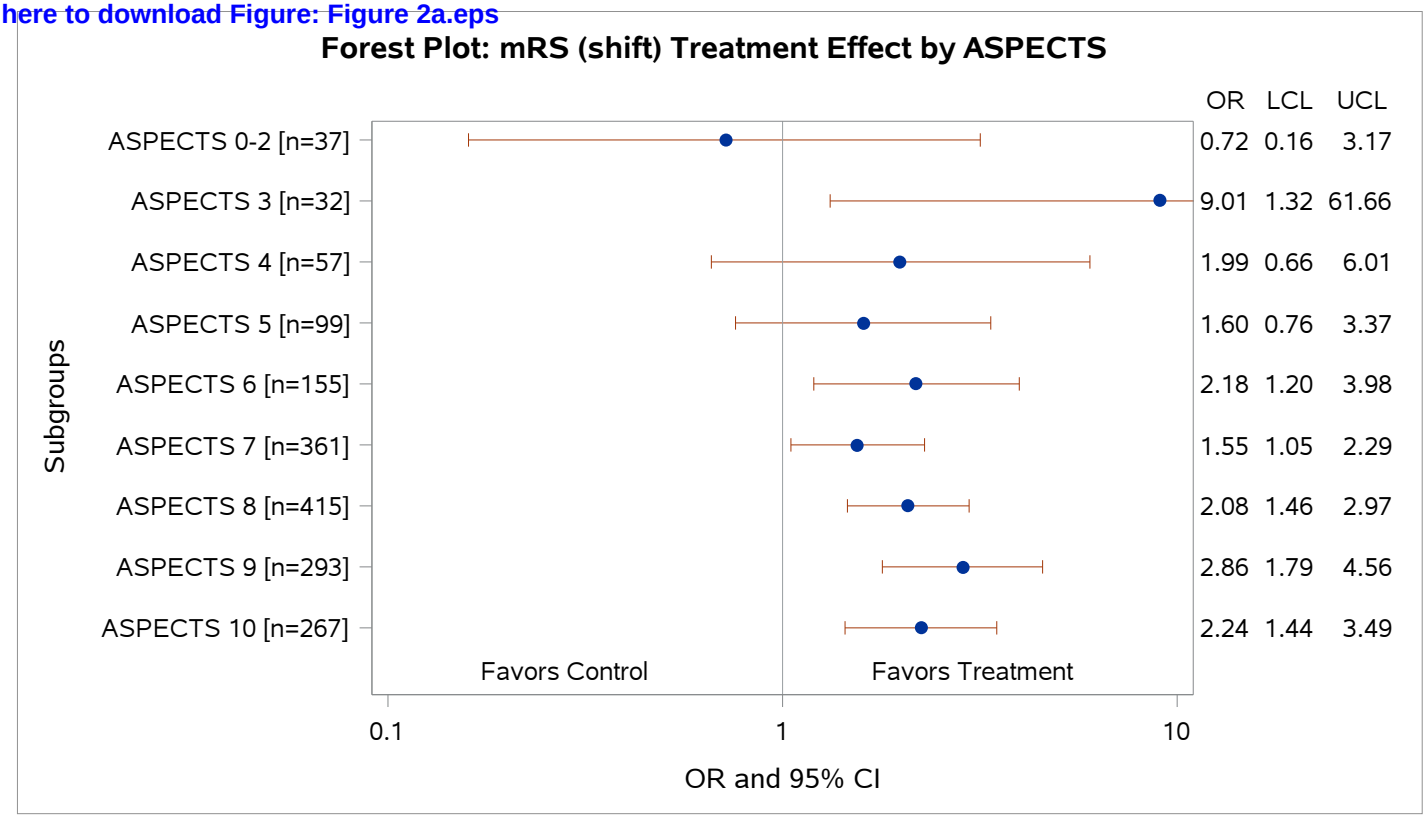

Figure 2b

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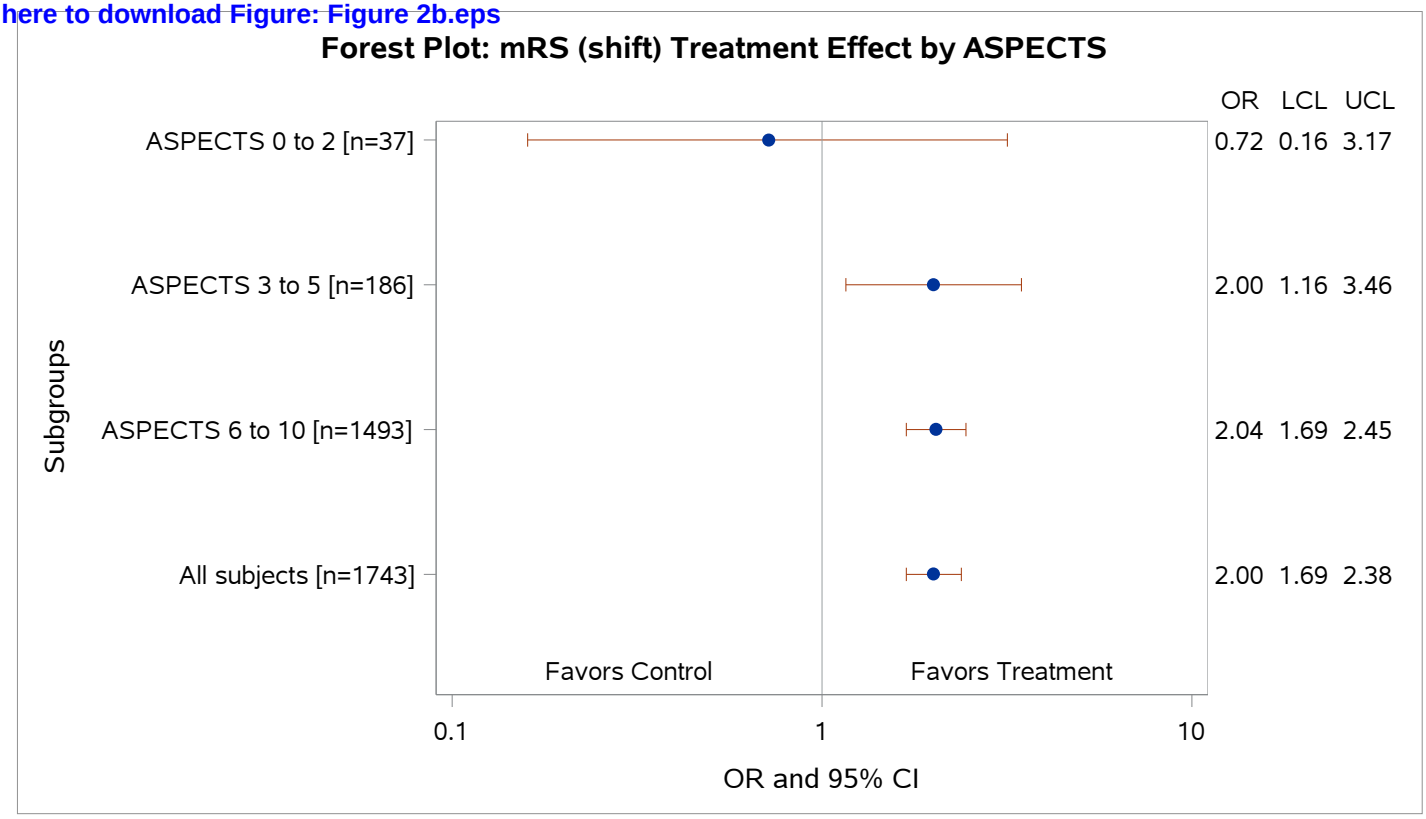

Figure 3a

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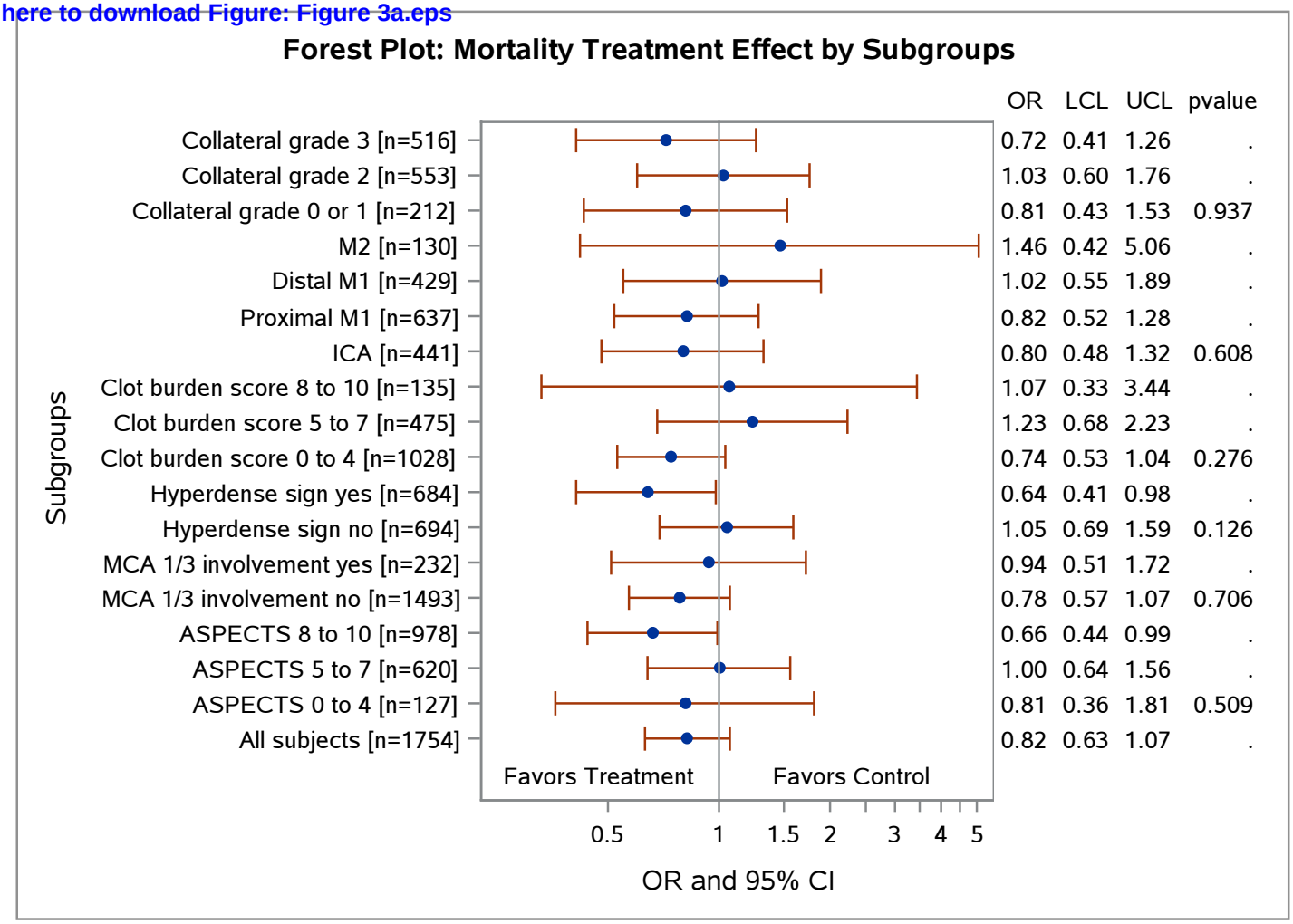

Figure 3b

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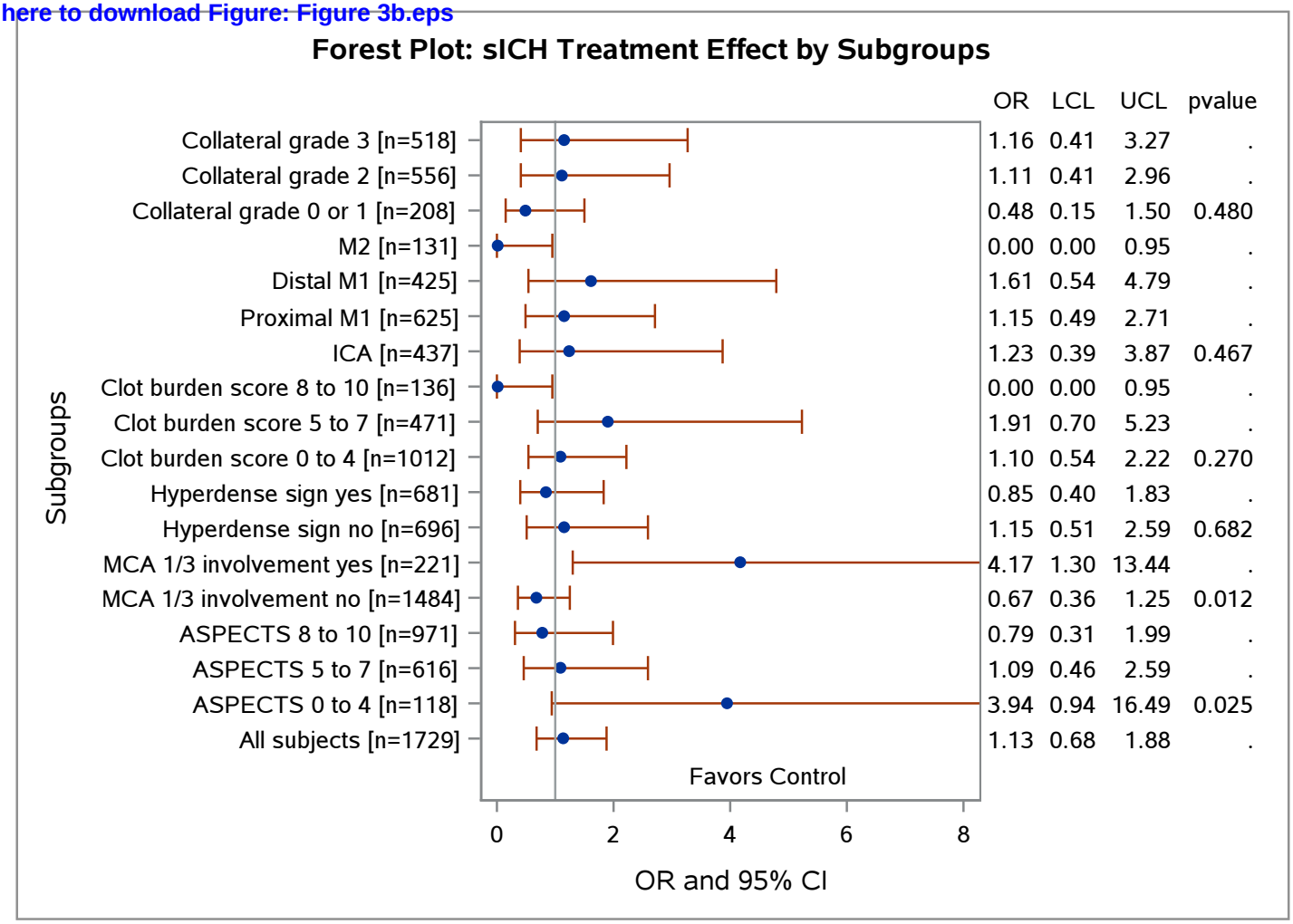

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E	Huerga
S	Gelabert
P	Coscojuela
A	Tomasello
D	Rodriguez
E	Santamarina
O	Maisterra
S	Boned
L	Seró
A	Rovira
CA	Molina
M	Millán
L	Muñoz

N	Pérez de la Ossa
M	Gomis
L	Dorado
E	López-Cancio
E	Palomeras
J	Munuera
P	García Bermejo
S	Remollo
C	Castaño
R	García-Sort
P	Cuadras

P	Puyalto
M	Hernández-Pérez
M	Jiménez
A	Martínez-Piñeiro
G	Lucente
A	Dávalos
A	Chamorro
X	Urra
V	Obach
A	Cervera
S	Amaro
L	Llull
J	Codas

M	Balasa
J	Navarro
H	Ariño
A	Aceituno
S	Rudilosso
A	Renu
JM	Macho
L	San Roman
J	Blasco
A	López
N	Macías
P	Cardona
H	Quesada
F	Rubio
L	Cano
B	Lara
MA	de Miquel
L	Aja
J	Serena
E	Cobo
Gregory W	Albers
Kennedy R	Lees
J	Arenillas
R	Roberts
P	Minhas
F	Al-Ajlan

M	Salluzzi
L	Zimmel
S	Patel
M	Eesa
J	Martí-Fàbregas
B	Jankowitz
J	Serena
M	Salvat-Plana
E	López-Cancio
S	Bracard
Xavier	Ducrocq
René	Anxionnat
Pierre-Alexandre	Baillot
Charlotte	Barbier
Anne-Laure	Derelle
Jean-Christophe	Lacour
Sébastien	Richard
Yves	Samson
Nader	Sourour
Flore	Baronnet-Chauvet
Frédéric	Clarencon
Sophie	Crozier
Sandrine	Deltour
Federico	Di Maria
Raphael	Le Bouc
Anne	Leger

Gurkan	Mutlu
Charlotte	Rosso
Zoltan	Szatmary
Marion	Yger
Chiara	Zavanone
Serge	Bakchine
Laurent	Pierot
Nathalie	Caucheteux
Laurent	Estrade
Krzysztof	Kadziolka
Alexandre	Leautaud
Céline	Renkes
Isabelle	Serre
Hubert	Desal
Benoît	Guillon
Claire	Boutoleau-Bretonniere
Benjamin	Daumas-Duport
Solène	De Gaalon
Pascal	Derkinderen
Sarah	Evain
Fanny	Herisson
David-Axel	Laplaud
Thibaud	Lebouvier
Alina	Lintia-Gaultier
Hélène	Pouclet-Courtemanche
Tiphaine	Rouaud

Violaine	Rouaud Jaffrenou
Aurélia	Schunck
Mathieu	Sevin-Allouet
Frederique	Toulgoat
Sandrine	Wiertlewski
Jean-Yves	Gauvrit
Thomas	Ronziere
Vincent	Cahagne
Jean-Christophe	Ferre
Jean-François	Pinel
Hélène	Raoult
Jean-Louis	Mas
Jean-François	Meder
Amen-Adam	Al Najjar-Carpentier
Julia	Birchenall
Eric	Bodiguel
David	Calvet
Valérie	Domigo
Sylvie	Godon-Hardy
Vincent	Guiraud
Catherine	Lamy
Loubna	Majhadi
Ludovic	Morin
Olivier	Naggara
Denis	Trystram
Guillaume	Turc

Jérôme	Berge
Igor	Sibon
Patrice	Menegon
Xavier	Barreau
François	Rouanet
Sabrina	Debruxelles
Annabelle	Kazadi
Pauline	Renou
Olivier	Fleury
Anne	Pasco-Papon
Frédéric	Dubas
Jildaz	Caroff
Sophie	Godard Ducceschi
Marie-Aurélie	Hamon
Alderic	Lecluse
Guillaume	Marc
Maurice	Giroud
Frédéric	Ricolfi
Yannick	Bejot
Adrien	Chavent
Arnaud	Gentil
Apolline	Kazemi
Guy-Victor	Osseby
Charlotte	Voguet
Marie-Hélène	Mahagne
Jacques	Sedat

Yves	Chau
Laurent	Suissa
Sylvain	Lachaud
Emmanuel	Houdart
Christian	Stapf
Frédérique	Buffon Porcher
Hugues	Chabriat
Pierre	Guedin
Dominique	Herve
Eric	Jouvent
Jérôme	Mawet
Jean-Pierre	Saint-Maurice
Hans-Martin	Schneble
Francis	Turjman
Norbert	Nighoghossian
Nadia-Nawel	Berhoune
Françoise	Bouhour
Tae-Hee	Cho
Laurent	Derex
Sandra	Felix
Hélène	Gervais-Bernard
Benjamin	Gory
Luis	Manera
Laura	Mechtouff
Thomas	Ritzenthaler
Roberto	Riva

Fabrizio	Salaris Silvio
Caroline	Tilikete
Raphael	Blanc
Michaël	Obadia
Mario Bruno	Bartolini
Antoine	Gueguen
Michel	Piotin
Silvia	Pistocchi
Hocine	Redjem
Jacques	Drouineau
Jean-Philippe	Neau
Gaelle	Godeneche
Matthias	Lamy
Emilia	Marsac
Stephane	Velasco
Pierre	Clavelou
Emmanuel	Chabert
Nathalie	Bourgois
Catherine	Cornut-Chauvinc
Anna	Ferrier
Jean	Gabrillargues
Betty	Jean
Anna-Raquel	Marques
Nicolas	Vitello
Olivier	Detante
Marianne	Barbieux

Kamel	Boubagra
Isabelle	Favre Wiki
Katia	Garambois
Florence	Tahon
Vasdev	Ashok
Charlotte	Voguet
Oguzhan	Coskun
Pierre	Guedin
Georges	Rodesch
Bertrand	Lapergue
Frédéric	Bourdain
Serge	Evrard
Philippe	Graveleau
Jean Pierre	Decroix
Adrien	Wang
François	Sellal
Guido	Ahle
Gabriela	Carelli
Marie-Hélène	Dugay
Claude	Gaultier
Ariel Pablo	Lebedinsky
Lavinia	Lita
Raul Mariano	Musacchio
Catherine	Renglewicz-Destuynder
Alain	Tournade
Françis	Vuillemet

Francisco Macian	Montoro
Charbel	Mounayer
Frederic	Faugeras
Laetitia	Gimenez
Catherine	Labach
Géraldine	Lautrette
Christian	Denier
Guillaume	Saliou
Olivier	Chassin
Claire	Dussaule
Elsa	Melki
Augustin	Ozanne
Francesco	Puccinelli
Marina	Sachet
Mariana	Sarov
Jean-François	Bonneville
Thierry	Moulin
Alessandra	Biondi
Elisabeth	De Bustos Medeiros
Fabrice	Vuillier
Patrick	Courtheoux
Fausto	Viader
Marion	Apoil-Brissard
Mathieu	Bataille
Anne-Laure	Bonnet
Julien	Cogez

Apolline	Kazemi
Emmanuel	Touze
Xavier	Leclerc
Didier	Leys
Mohamed	Aggour
Pierre	Aguettaz
Marie	Bodenant
Charlotte	Cordonnier
Dominique	Deplanque
Marie	Girot
Hilde	Henon
Erwah	Kalsoum
Christian	Lucas
Jean-Pierre	Pruvo
Paolo	Zuniga
Alain	Bonafé
Caroline	Arquizan
Vincent	Costalat
Paolo	Machi
Isabelle	Mourand
Carlos	Riquelme
Pierre	Bounolleau
Charles	Arteaga
Anthony	Faivre
Marc	Bintner
Patrice	Tournebize

Cyril	Charlin
Françoise	Darcel
Pascale	Gauthier-Lasalarie
Marcia	Jeremenko
Servane	Mouton
Jean-Baptiste	Zerlauth
Chantal	Lamy
Deramond	Hervé
Hosseini	Hassan
André	Gaston
Francis-Guy	Barral
Pierre	Garnier
Rémy	Beaujeux
Valérie	Wolff
Denis	Herbreteau
Séverine	Debiais
Alicia	Murray
Gary	Ford
Keith W	Muir
Philip	White
Martin M	Brown
Andy	Clifton
Janet	Freeman
Ian	Ford
Hugh	Markus
Joanna	Wardlaw

Kennedy R	Lees
Andy	Molyneux
Thompson	Robinson
Steff	Lewis
John	Norrie
Fergus	Robertson
Richard	Perry
Anand	Dixit
Geoffrey	Cloud
Andrew	Clifton
Jeremy	Madigan
Christine	Roffe
Sanjeev	Nayak
Kyriakos	Lobotesis
Craig	Smith
Amit	Herwadkar
Naga	Kandasamy
Tony	Goddard
John	Bamford
Ganesh	Subramanian
Rob	Lenthall
Edward	Littleton
Sal	Lamin
Kelley	Storey
Rita	Ghatala
Azra	Banaras

John	Aeron-Thomas
Bath	Hazel
Holly	Maguire
Emelda	Veraque
Louise	Harrison
Rekha	Keshvara
James	Cunningham

Manuscript reference number: THELANCETNEUROLOGY-D-18-00326.

SUPPLEMENTARY MATERIAL

Imaging predictors of treatment effects and clinical outcome in acute large vessel stroke: meta-analysis of the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES)

*The HERMES collaborative group**

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II. FIGURES

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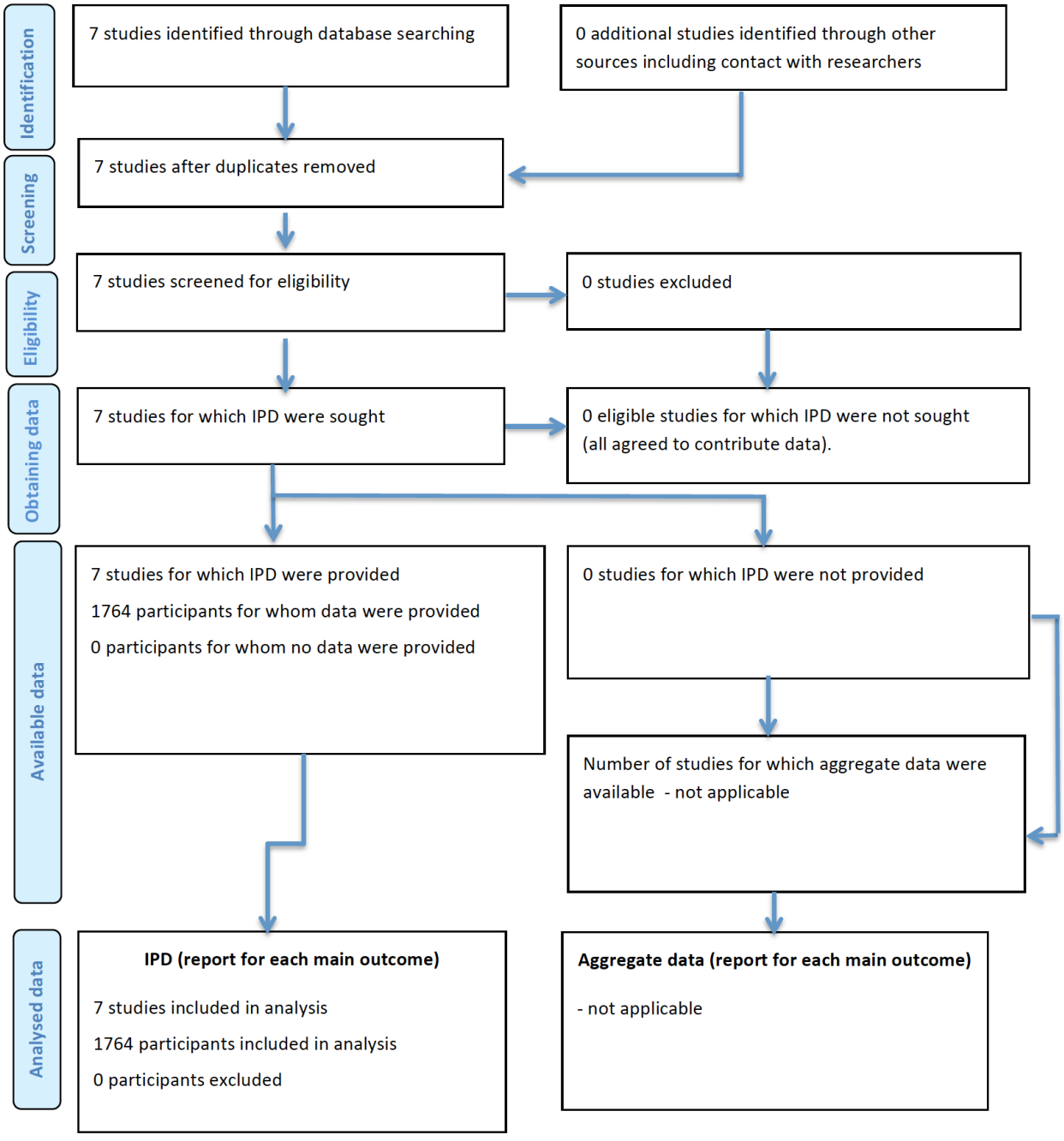
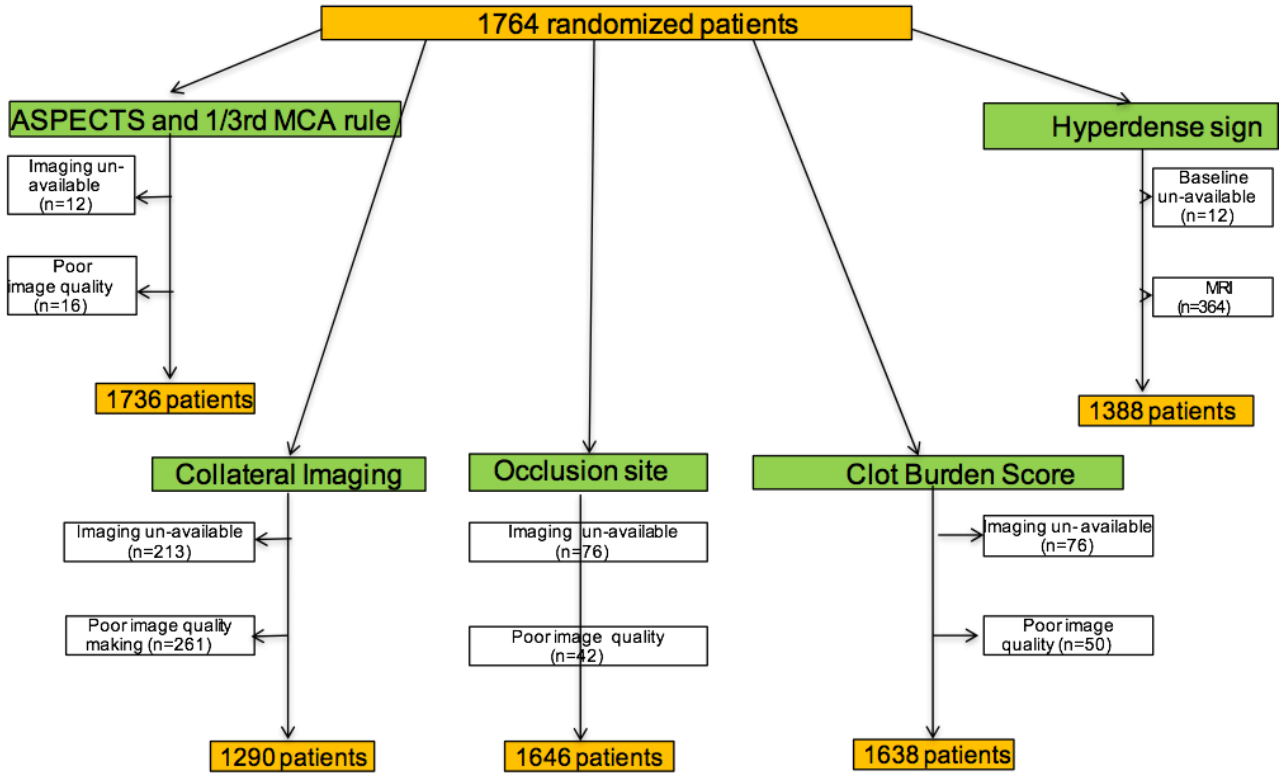
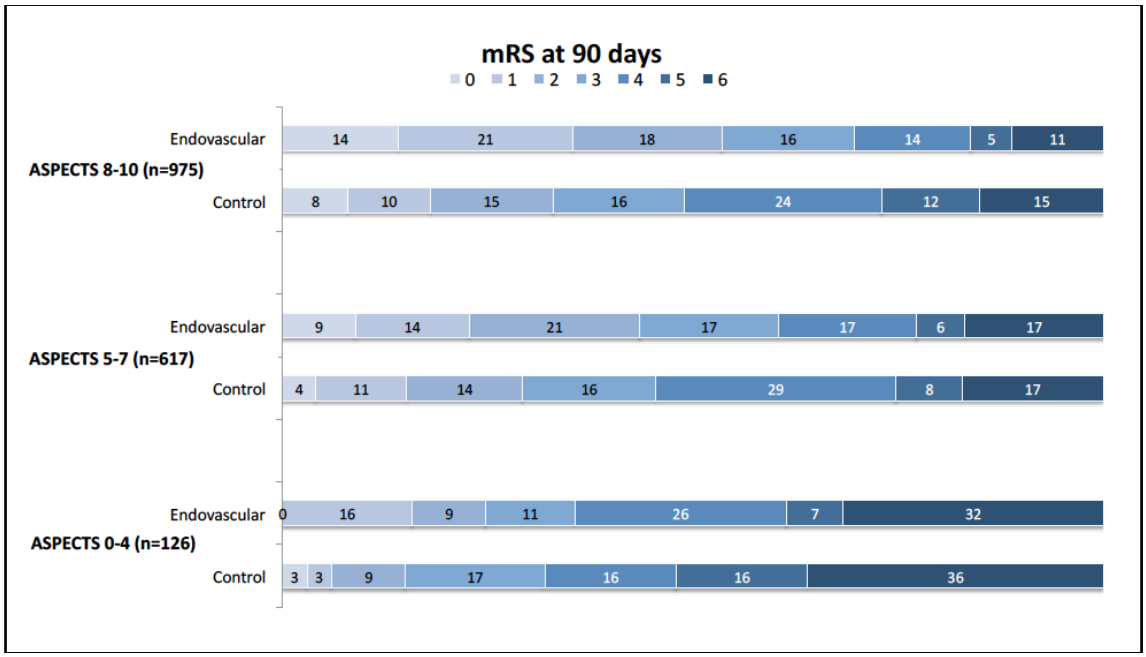


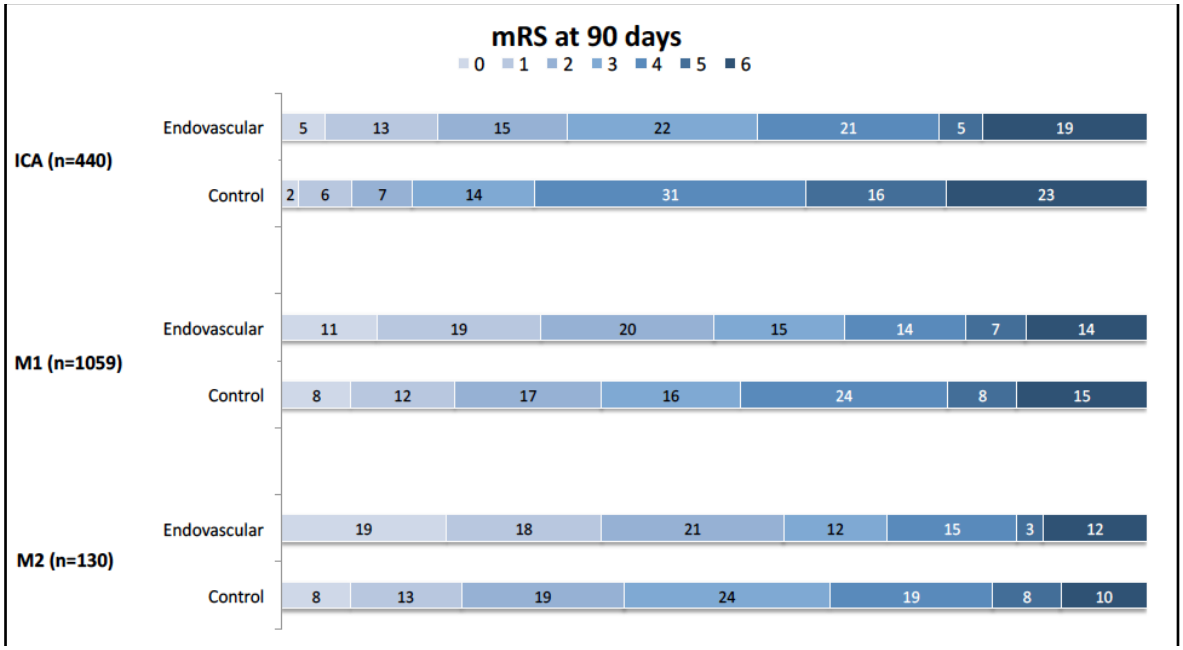
eFigure 2: Flow chart describing number of patients assessed for imaging variable at baseline and reasons for exclusion. Missing patients were not included in the different analysis of each imaging variable.



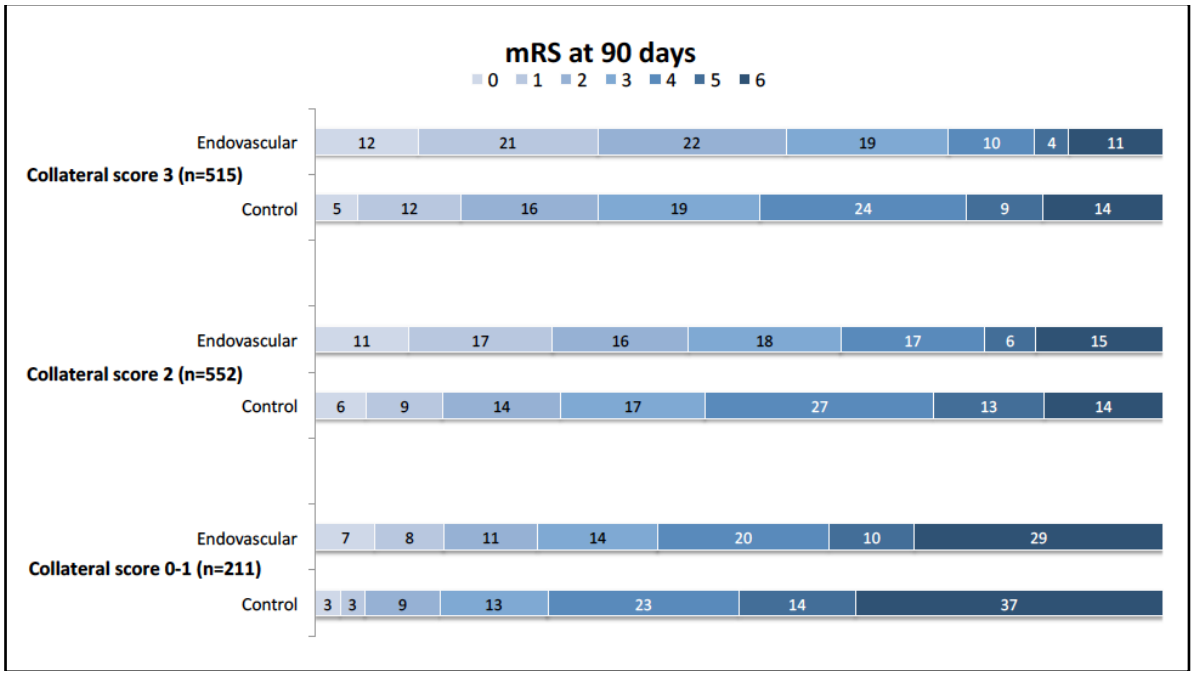
eFigure 3: Distribution of modified Rankin Scale at 90 days stratified by ASPECTS categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



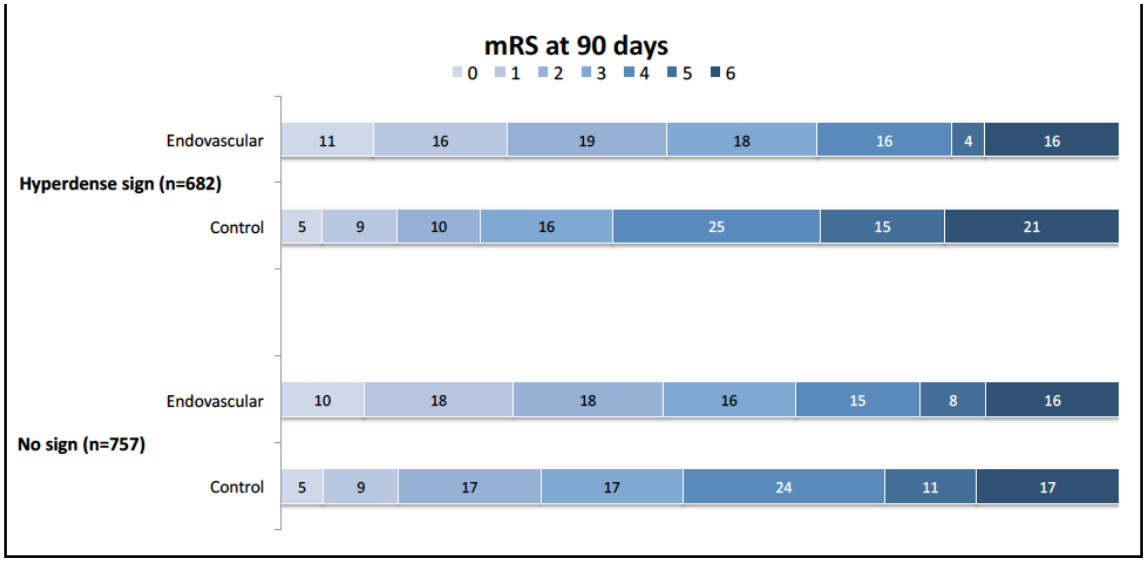
eFigure 4: Distribution of modified Rankin Scale at 90 days stratified by thrombus location in the endovascular and control groups (numbers within the horizontal bars represent percentages).



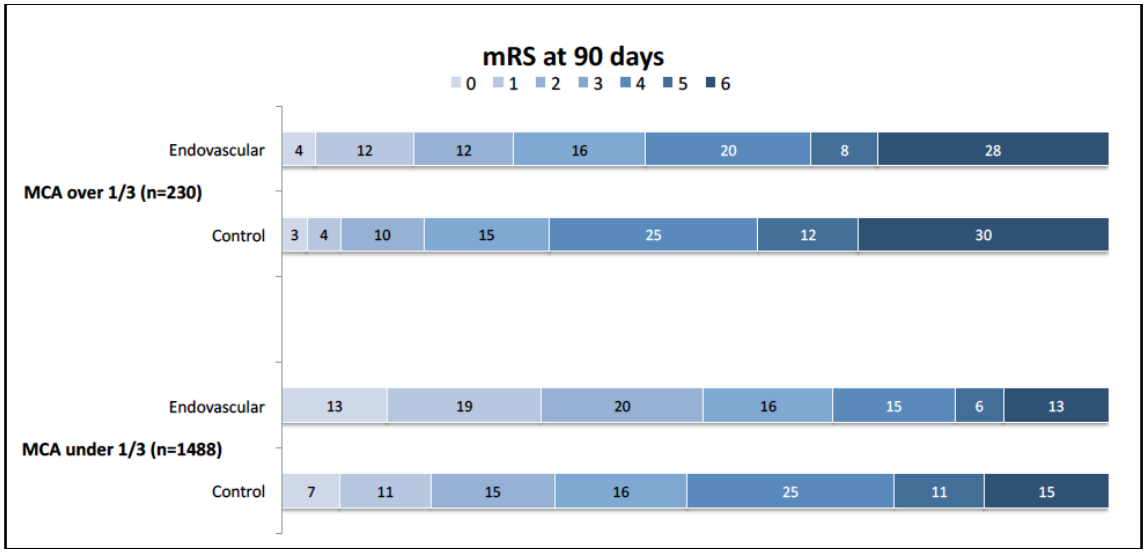
eFigure 5: Distribution of modified Rankin Scale at 90 days stratified by collateral circulation score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



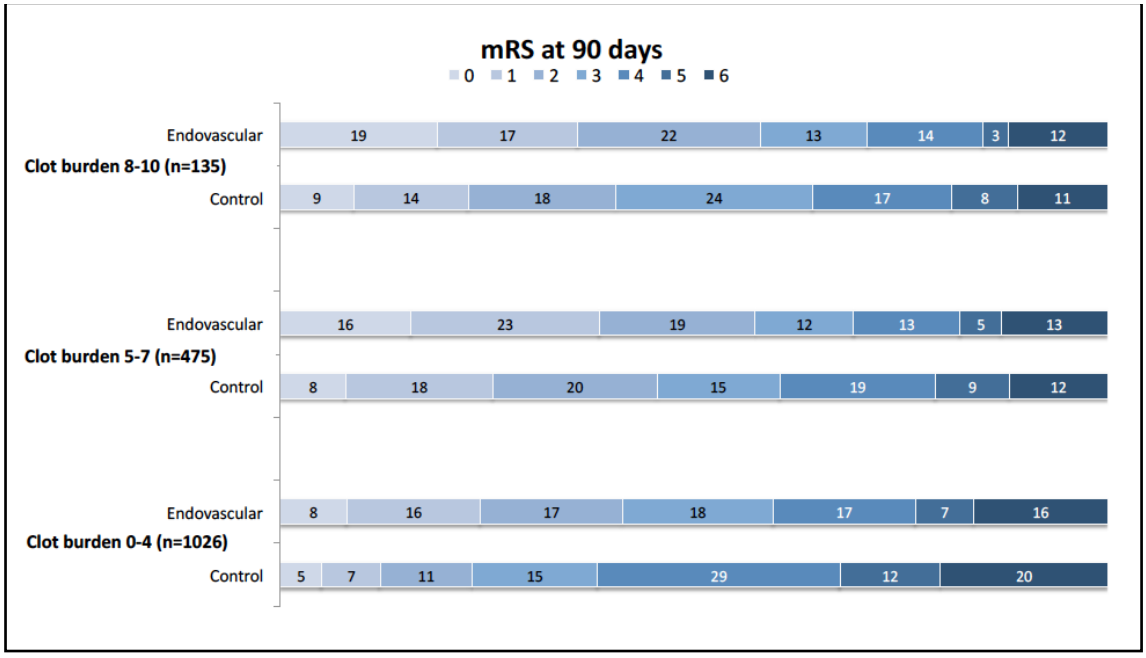
eFigure 6: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of hyperdense sign on CT in the endovascular and control groups (numbers within the horizontal bars represent percentages).



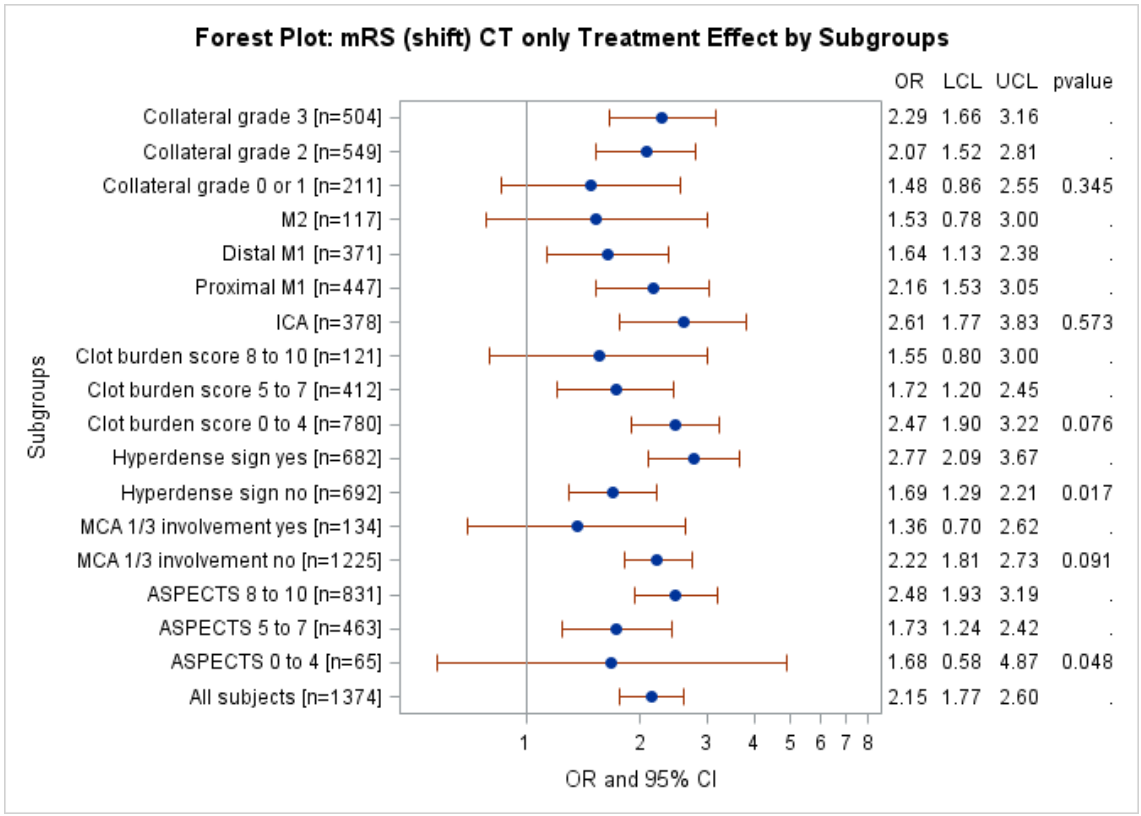
eFigure 7: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of early ischemic changes in 1/3rd of MCA territory in the endovascular and control groups (numbers within the horizontal bars represent percentages).

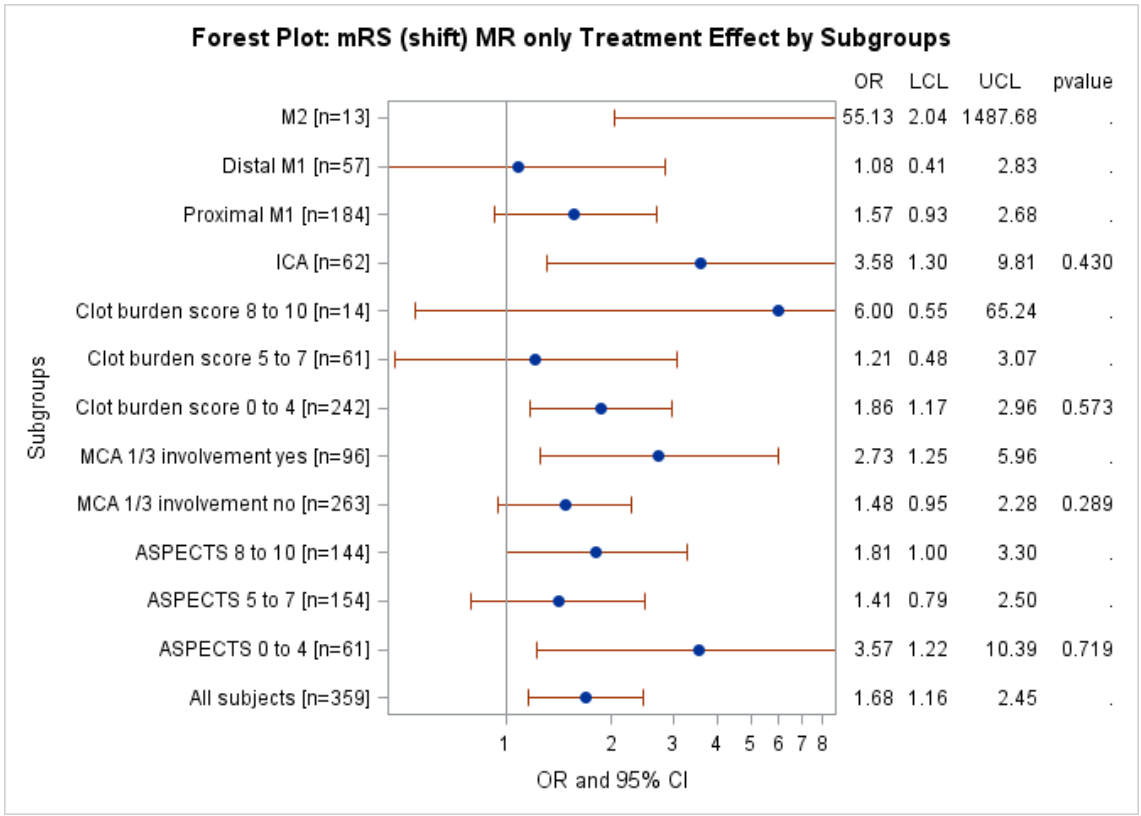


eFigure 8: Distribution of modified Rankin Scale at 90 days stratified by clot burden score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).

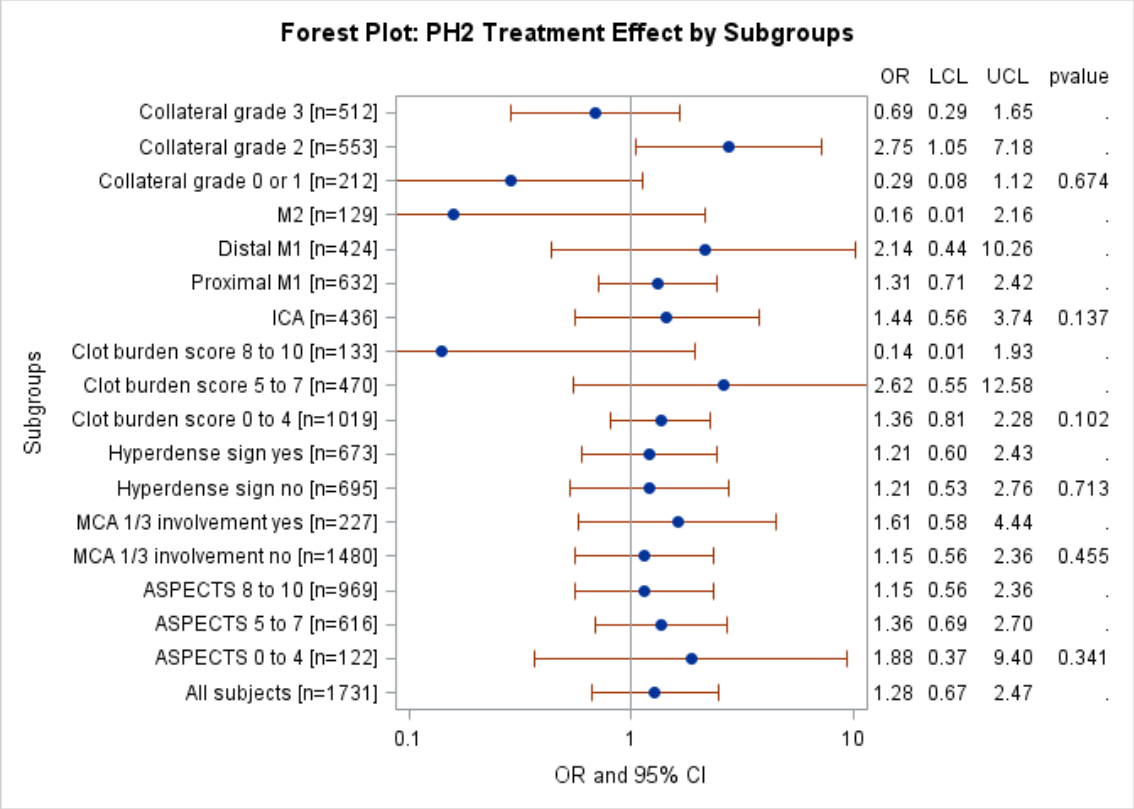


eFigure 9: Endovascular treatment effect by baseline imaging variable categories on primary outcome (mRS at 90 days) stratified by imaging modality (CT vs. MRI). Treatment effect is assessed through the common odds ratio for mRS shift.





eFigure 10: Endovascular treatment effect by baseline imaging variable categories on imaging safety outcome, namely, Parenchymal Hemorrhage Type 2. Treatment effect is assessed through the common odds ratio for mRS shift.



I. TABLES

eTable 1: Qualitative assessment of between-trial differences in population, sampling frame and operational definitions of treatment groups.

	MR CLEAN	ESCAPE	EXTEND IA	SWIFT PRIME	REVASCAT	THRACE	PISTE
Population							
Continent	Europe	North America, Europe, East Asia	Oceania	North America and Europe	Europe	Europe	Europe
Country	Netherlands	Multiple	Australia and New Zealand	Multiple	Spain	France	United Kingdom
Sampling Frame							
Imaging Criteria							
Modality	NCCT/CTA	NCCT/CTA *CTP optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA *CTP optional	MRI or NCCT/CTA	NCCT/CTA
Occlusion Site	ICA M1 M2	ICA M1	ICA M1 M2	ICA M1	ICA M1	ICA M1	ICA M1
Ischaemic Core Definition	Not used	ASPECTS 6-10 Good Collaterals	CTP mismatch and ischemic core <70mL	CTP and NCCT ASPECTS criteria (modified protocol)	ASPECTS 6-10	Not used	ASPECTS 6-10
Clinical Criteria							
Age (years)	≥18	≥18	≥18	18-85 (later amended to 18-80)	18-80 (later amended to allow 81-85 if ASPECTS>8)	18-80	≥18
Baseline Stroke Severity	NIHSS ≥2	NIHSS ≥6	No limit	NIHSS 8-29	NIHSS ≥6	NIHSS 10-25	NIHSS ≥6
Time to randomization	6 hours	12 hours	6 hours	6 hours	8 hours	5 hours	6 hours
Definition of sICH	Any ICH and ≥4-point increase NIHSS	Any ICH judged to cause ≥2-point increase NIHSS	PH2/SAH + ≥4-point increase NIHSS	Any PH/SAH/IVH + ≥4-point increase NIHSS	PH2 + ≥4 point increase NIHSS	Any ICH and ≥4-point increase NIHSS	PH2 + ≥4 point increase NIHSS
Control Group							
	Standard care	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients
Intervention Group							
Wait for response to IV alteplase	No	No	No	No	Yes	No	No
Pre-specified time metrics	No	Yes	No	Yes	Yes	No	No

Type of Devices	Any	Any	Solitaire	Solitaire	Solitaire	Any	Any

NCCT, Non contrast CT; CTA, CT angiography; CTP, CT Perfusion; MRI, Magnetic Resonance Imaging; ICA, Internal Carotid Artery; MCA, Middle Cerebral Artery; ASPECTS, Alberta Stroke Program Early CT Score; PH, Parenchymal Hemorrhage; SAH, Subarachnoid hemorrhage; IVH, Intra-ventricular Hemorrhage; NIHSS, National Institute of Health Stroke Scale; IV, intravenous.

eTable 2: Endovascular treatment effect in patients with large ischemic core at baseline defined post-hoc using different ASPECTS scores on CT and/or MRI.

Large extent of early ischemic change at baseline*	**common Odds Ratio**	**95% Confidence Interval**	**p-value**
ASPECTS 0 to 4 [n=126]	2.15	1.06 - 4.37	0.036
ASPECTS 0 to 4 CT or 0 to 3 MR [n=105]	1.9	0.86 - 4.2	0.12
ASPECTS 0 to 4 CT or 0 to 2 MR [n=89]	1.38	0.58 - 3.29	0.47
ASPECTS 0 to 4 CT only [n=65]	1.68	0.58 - 4.87	0.34

*Post-hoc definitions of large early ischemic change extent combining using different ASPECTS cut-points for CT and MRI. Statistical significance is only obtained once all CT/MR data are used for ASPECTS 0-4. Since most MRI data are from one study (THRACE), we are not confident that one can reliably distinguish MRI specific effect from a trial specific effect, especially among subgroups of this size.

eTable 3: sICH numbers in patients who underwent EVT stratified by reperfusion status (mTICI>=2b or not) and ASPECTS categories 0-4.

mTICI<2b				**mTICI>=2b**			
ASPECTS	**sICH**			**ASPECTS**	**sICH**		
	No	**Yes**	**Total**		**No**	**Yes**	**Total**
0	1	0	1	**0**	0	1	1
1	1	0	1	**1**	0	0	0
2	2	0	2	**2**	3	0	3
3	7	2	9	**3**	2	0	2
4	1	4	5	**4**	21	2	23
Total	12	6	18	**Total**	26	3	29

IV. STATISTICAL ANALYSIS PLAN

A) Objective

Endovascular treatment of acute stroke has been proven in randomized controlled trials as the standard of care for patients with proximal anterior circulation occlusions. This new evidence in the treatment of acute large vessel ischemic stroke has created a need for effective and rapid selection of stroke patients who will most benefit from endovascular stroke therapy.

Imaging features have been proven to play a role in clinical outcome. We want to take advantage of the data accumulated through the different clinical trials to study if there are chances to improve the imaging protocol to adequately select patients that will benefit endovascular treatment.

From the Hermes (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials) neuroimaging studies of all patients in the MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA, PISTE and THRACE trials, we propose to determine whether imaging features at baseline that measure extent of parenchymal involvement, thrombus and collaterals are associated with response to endovascular treatment. We also seek to extend safety information by looking for subgroups of patients (identified using imaging) who may a higher risk of complications from endovascular therapy.

B) Imaging variables

Parenchymal Imaging

a) ASPECTS on non-contrast CT read blinded to other baseline imaging modalities.

We will attempt analysis based on pre-specified ASPECTS categories, namely, 8-10, 5-7 and 0-4. If sample size is sufficient across all ASPECTS grades, we will also attempt analysis by each ASPECTS grade i.e. 0,1,2,3,4,5,6,7,8,9,10 to identify an ASPECTS cut-point that suggests to futility of endovascular treatment. The majority of baseline imaging in the HERMES data is non-contrast CT. When MRI is the baseline imaging modality, ASPECTS will be defined on baseline DWI. A region will be considered as involved if DWI lesion affects > 30% of the ASPECTS region.

b) Extent of early ischemic change in the MCA territory dichotomized as > or < 33% MCA territory.

Thrombus Imaging

a) Location and nature of baseline thrombus on CTA (or if CTA not available on MRA).

We will attempt analysis based on pre-specified baseline occlusion categories i.e. (ICA, proximal M1 MCA, distal M1 MCA, M2 MCA and beyond). M1 MCA segment is defined as the first branch of the intracranial ICA which courses horizontally from its branching point off the ICA through the sphenoidal section of the Sylvian fissure up to the first bifurcation distal to the origin of the lenticulostriate arteries in the distal aspect of the sphenoidal Sylvian fissure. The M2 MCA segment was defined as distal to the MCA bifurcation and into the operculo-insular segment of the Sylvian fissure. Tandem occlusion was defined by CTA/MRA as occlusion of extracranial ICA with intracranial (ICA, M1-MCA, M2-MCA).

b) Hyperdense artery sign presence, location and extent on non-contrast CT. Differential outcomes will be reported by above categories.

c) Clot burden score (CBS) on CTA (or if CTA unavailable, on MRA). The CBS is a scoring system to define the extent of thrombus found in the proximal anterior circulation by location and is scored on a scale of 0–10. The thrombus can be partially or completely occlusive. A score of 10 is normal, implying clot absence. A score of 0 implies complete multi-segment vessel occlusion.

Collateral Circulation Imaging

Collateral imaging is best done on multi-phase CTA or if not available, on appropriately phase weighted single-phase CTA. Analysis of collateral status and its relationship to final outcomes by treatment arm will be reported for pre-specified collateral grade categories: Grade 0-1 poor, grade 2: intermediate and grade 3: good as well as in a granular manner for each category.

C) Primary Outcome

The modified Rankin Scale (mRS) at 3 months from onset.

D) Secondary Outcomes

Secondary efficacy outcomes were functional independence (mRS 0–2) at 90 days, excellent functional outcome (mRS 0–1) at 90 days, dramatic neurological improvement (defined as neurological improvement of ≥ 8 points in the NIHSS or a NIHSS 0-1 24 hours after stroke) and patients in the endovascular group with complete arterial recanalization [defined as a modified Thrombolysis In Cerebral Infarction (mTICI) score 2b or 3]. Safety outcomes included the symptomatic intracranial hemorrhage (sICH; defined by each trial), parenchymal hematoma type 2 (PH2; blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days of randomization, and mortality within 90 days.

E) Primary Analyses

All analyses will be based on the "as randomized" population. To account for between trial differences when pooling patient level data, mixed-effects modeling will be used for all analyses, with fixed effects for parameters of interest and "trial" and the interaction term "trial*treatment" as random effects variables in all models. Regression models will include fixed effects (age, sex, NIHSS score at admission, intravenous alteplase use and time from onset to randomization) and multiplicative interaction terms to test if pre-specified baseline-imaging features modified the effect of treatment allocation on pre-defined outcomes. The primary analyses will try to ascertain if baseline imaging categorization modifies the effect of treatment on mRS at 90 days when adjusted for pre-specified co-variates. Primary analysis will use ordinal logistic regression adjusted for age, sex, NIHSS score at admission, intravenous alteplase (yes/no) and time from onset to randomization. It will include interaction terms testing if imaging categorization at baseline (parenchymal imaging, thrombus imaging and collateral imaging independently) modifies the relationship between treatment and outcome. If statistically significant interaction is noted, category specific effects will be reported (in text and using figures).

F) Secondary Analysis

Depending on the nature and distribution of secondary outcomes specified above, secondary analyses will use appropriate regression techniques adjusted for age, sex, NIHSS score at admission, intravenous alteplase (yes/no) and time from onset to randomization to analyze if the above-defined imaging categories modify the effect of treatment on outcome. Multiplicative interaction terms will be used to test for these statistical interactions. If statistically significant interaction is noted, category specific effects will be reported (in text and using figures). For primary and secondary analyses, forest plots with each imaging category specific effect including interaction p value will be reported.

Sensitivity analyses as above will be performed for patients imaged using CT vs. MRI.

Manuscript reference number: THELANCETNEUROLOGY-D-18-00326.

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	3
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	

Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	4
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	Previous SAP is stated in page 6 and included as an appendix
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	5
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	5
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5

Study selection processes	9	State the process for determining which studies were eligible for inclusion.	5 and e figure 1 in the supplement
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	5 and e figure 1 in the supplement
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	Not applicable
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	5 and e figure 1 in the supplement
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	6-7 and e figure 1 in the supplement
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	Page 6: Risk of bias in the individual studies was assessed using the Cochrane handbook methodology
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	6-7

Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	6-7 and STATISTICAL ANALYSIS PLAN in the supplement page 11
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	6-7 and STATISTICAL ANALYSIS PLAN in the supplement page 11
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	6-7 and STATISTICAL ANALYSIS PLAN in the supplement page 14
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	6-7 and STATISTICAL ANALYSIS PLAN in the supplement page 11

Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	6 and e figure 1 in the supplement
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	6 and Table1
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	6 and e figure 1 in the supplement
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	6
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	N/A

Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	6-7 , Figure 1, Figure 2, Table 2, Figure 3, Table 3, Supplement eFigure 9, Supplement eFigure 10.
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	7-8
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	9
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	8-9
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	8-9

Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	8-9
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	8-9
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	7

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

***Reply to Reviewers Comments**

Response to Review Manuscript reference number: THELANCETNEUROLOGY-D-18-00326R3

Editorial points:

Editorial points to be addressed:

1. Please provide the missing signatures for the following authors:

Maria Hernandez Perez
Antoni Davalos
Charles Majoie
Jeffrey Saver
Demetrius Lopes
Carlos Molina
Vivek Reddy
Alim Mitha
Erik Cobo
Gary Ford

RESPONSE: We have provided them excepting Dr Reddy´s who has been excluded as an author by not contributing with his signature for this article

2. Please include a statement of authors' contributions and a statement on authors' declarations of interests in your revised manuscript. Please note, these statements should match the information provided on the submitted forms

RESPONSE: We have included statement of authors' contributions and a statement on authors' declarations of interests in the manuscript

3. Please amend your abstract to include the primary safety outcome.

RESPONSE: We have made changes as suggested