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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

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 trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE and PISTE). The risk of bias and variability among studies was assessed to be low, using the Cochrane 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 functional endpoint was the modified Rankin Scale (mRS) score at 90 days.

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 2·00, 95% CI 1·69–2·38; p<0·0001) and limited heterogeneity of benefit was observed across all pre-specified imaging strata, including patients with low ASPECTS 0-4, > 1/3 MCA territory infarct, poor collaterals and all levels of clot burden. Higher risk of symptomatic intracranial hemorrhage (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. In sensitivity analysis to determine the optimal lower cut-point for baseline ASPECTS, patients with baseline ASPECTS as low as 3 showed benefit with EVT.

Interpretation

EVT achieves better 90 day outcomes than medical therapy alone across a broad range of baseline imaging categories including patients with large infarcts.

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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 two experts with more than 5 years of dedicated neuroradiology experience, blinded to all clinical and imaging information except stroke side. Any disagreement was resolved by consensus (inter-rater agreement Kappa 0·89, 95% CI 0·81 to 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) (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 (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, in post-hoc analysis, 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 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. In routine practice, extensive early ischemic change should prompt consideration of risk benefit balance in patients who do not conform to trial characteristics.

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, so confirmatory randomized trials may be necessary. The central re-analysis of images in the meta-analysis may not reflect the quality of on-site assessments. 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.

REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11-20.
2. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15(11):1138-1147.
3. Campbell BC, Mitchell PJ, Investigators E-I. Endovascular therapy for ischemic stroke. N Engl J Med. 2015;372(24):2365-2366.
4. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-1030.
5. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296-2306.
6. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(1):38-44.
7. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285-2295.
8. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723-1731.
9. Saver JL, Goyal M, van der Lugt A, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. JAMA. 2016;316(12):1279-1288.
10. Menon BK, Campbell BC, Levi C, Goyal M. Role of imaging in current acute ischemic stroke workflow for endovascular therapy. Stroke. 2015;46(6):1453-1461.
11. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378:11-21.
12. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378:708-718.
13. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46(10):3020-3035.
14. Hill MD, Demchuk AM, Tomsick TA, Palesch YY, Broderick JP. Using the baseline CT scan to select acute stroke patients for IV-IA therapy. AJNR Am J Neuroradiol. 2006;27(8):1612-1616.
15. Hussein HM, Georgiadis AL, Vazquez G, et al. Occurrence and predictors of futile recanalization following endovascular treatment among patients with acute ischemic stroke: a multicenter study. AJNR Am J Neuroradiol. 2010;31(3):454-458.
16. Yoo AJ, Berkhemer OA, Fransen PSS, et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). Lancet Neurol. 2016;15(7):685-694.
17. Menon BK, Qazi E, Nambiar V, et al. Differential Effect of Baseline Computed Tomographic Angiography Collaterals on Clinical Outcome in Patients Enrolled in the Interventional Management of Stroke III Trial. Stroke. 2015;46(5):1239-1244.
18. Nambiar V, Sohn SI, Almekhlafi MA, et al. CTA collateral status and response to recanalization in patients with acute ischemic stroke. AJNR Am J Neuroradiol. 2014;35(5):884-890.

19. Berkhemer OA, Jansen IG, Beumer D, et al. Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke. Stroke. 2016;47(3):768-776.
20. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355(9216):1670-1674.
21. Kalafut MA, Schriger DL, Saver JL, Starkman S. Detection of early CT signs of >1/3 middle cerebral artery infarctions : interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. Stroke. 2000;31(7):1667-1671.
22. Assis Z, Menon BK, Goyal M, et al. Acute ischemic stroke with tandem lesions: technical endovascular management and clinical outcomes from the ESCAPE trial. J Neurointerv Surg. 2017.
23. Schuierer G, Huk W. The unilateral hyperdense middle cerebral artery: an early CT-sign of embolism or thrombosis. Neuroradiology. 1988;30(2):120-122.
24. Puetz V, Dzialowski I, Hill MD, et al. Intracranial thrombus extent predicts clinical outcome, final infarct size and hemorrhagic transformation in ischemic stroke: the clot burden score. Int J Stroke. 2008;3(4):230-236.
25. Borst J, Berkhemer OA, Roos YB, et al. Value of Computed Tomographic Perfusion-Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment. Stroke. 2015;46(12):3375-3382.
26. Campbell BCV, Donnan GA, Lees KR, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol. 2015;14(8):846-854.
27. Mishra SM, Dykeman J, Sajobi TT, et al. Early reperfusion rates with IV tPA are determined by CTA clot characteristics. AJNR Am J Neuroradiol. 2014;35(12):2265-2272.
28. Lapergue B, Blanc R, Gory B, et al. Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial. JAMA. 2017;318(5):443-452.
29. Liebeskind DS. Collateral circulation. Stroke. 2003;34(9):2279-2284.
30. Menon BK, d'Esterre CD, Qazi EM, et al. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology. 2015;275(2):510-520.

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)	0.402	15.6 %	5.2%	4.05 (1.03-15.91)	0.623	31.9 %	18.3 %	2.18 (1.04-4.55)	0.145	11.2 %	2.9 %	3.47 (0.48 - 25.12)	0.975
Collateral grade 2 [n=552]	44.0 %	28.5 %	2.49 (1.68-3.69)		27.7 %	14.1 %	2.90 (1.80-4.69)		47.3 %	23.8 %	3.01 (2.07-4.39)		20.4 %	8.8 %	3.92 (2.20 - 6.99)	
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	
5-7	4.7% (11/233)	2.9% (7/240)	1.65 (0.63, 4.33)	0.344	0.063

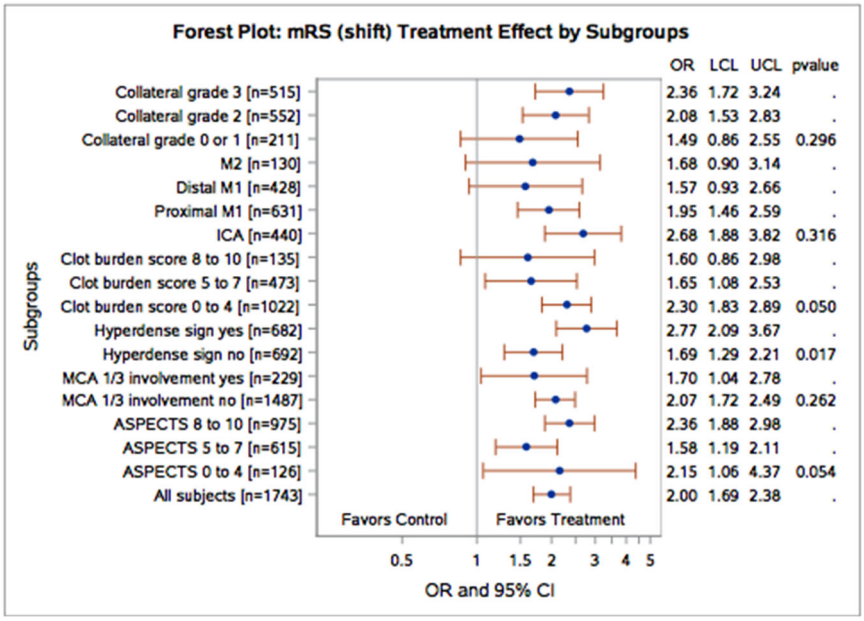
0-4	3.4% (17/503)	3.1% (16/513)	1.09 (0.54, 2.18)	0.861	
Occlusion location					
ICA	3.3% (7/210)	2.6% (6/227)	1.27 (0.42, 3.84)	0.781	0.154
Proximal M1	3.9% (12/307)	3.5% (11/318)	1.14 (0.49, 2.61)	0.834	
Distal M1	4.1% (9/218)	2.9% (6/207)	1.44 (0.50, 4.13)	0.603	
M2	0.0% (0/67)	7.8% (5/64)	0.00 (0.00, 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

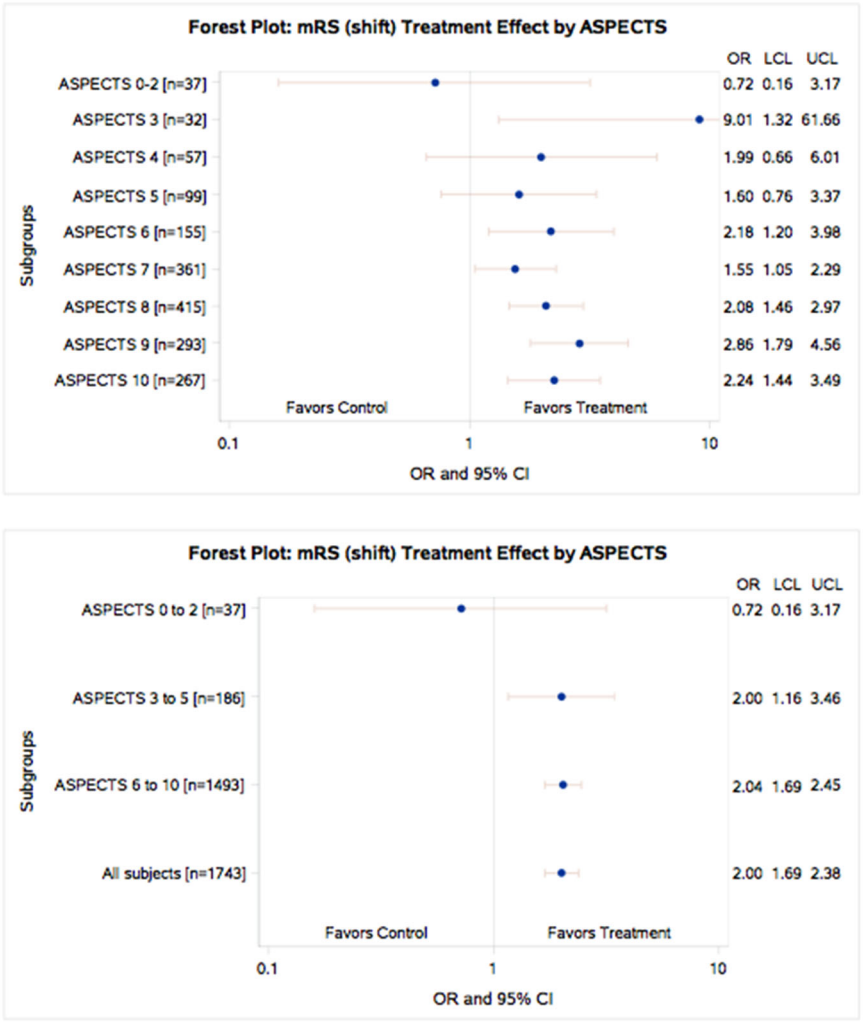
FIGURES

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



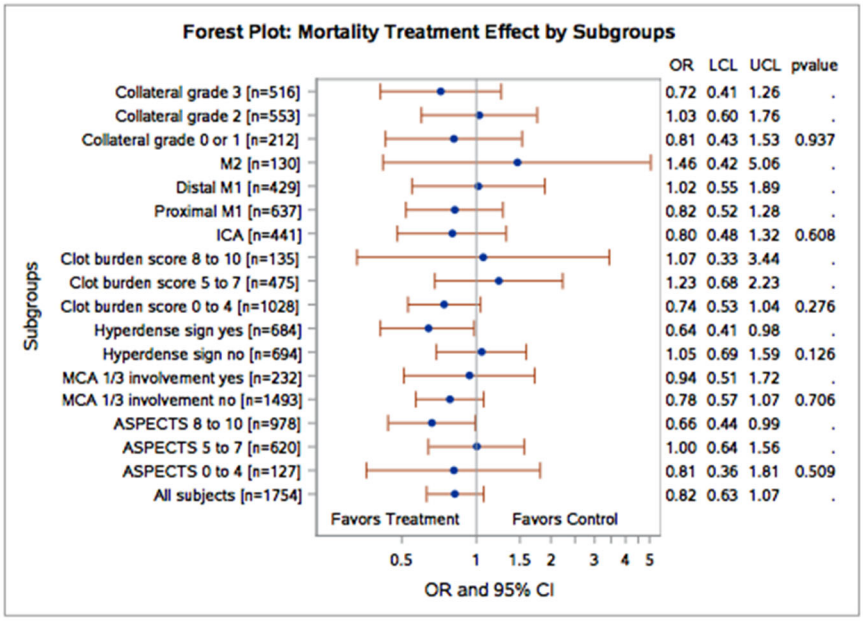
ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, Middle cerebral artery; M1, M1 segment of MCA; M2, M2 segment of MCA; mRS, modified Rankin Scale; OR, common Odds Ratio; LCL, lower confidence limit; UCL, upper confidence limit.

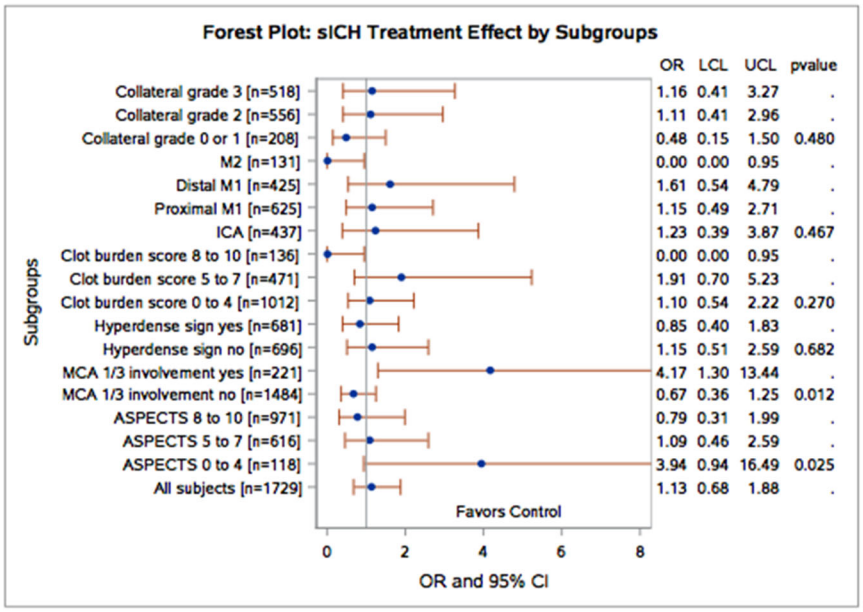
Figure 2. Panel A shows endovascular treatment effect by individual baseline ASPECTS grades on primary outcome (mRS shift at 90 days). There was no statistical evidence of heterogeneity across ASPECTS categories for the relationship between treatment and primary outcome. Panel B shows exploratory analysis 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.

SUPPLEMENTARY MATERIAL

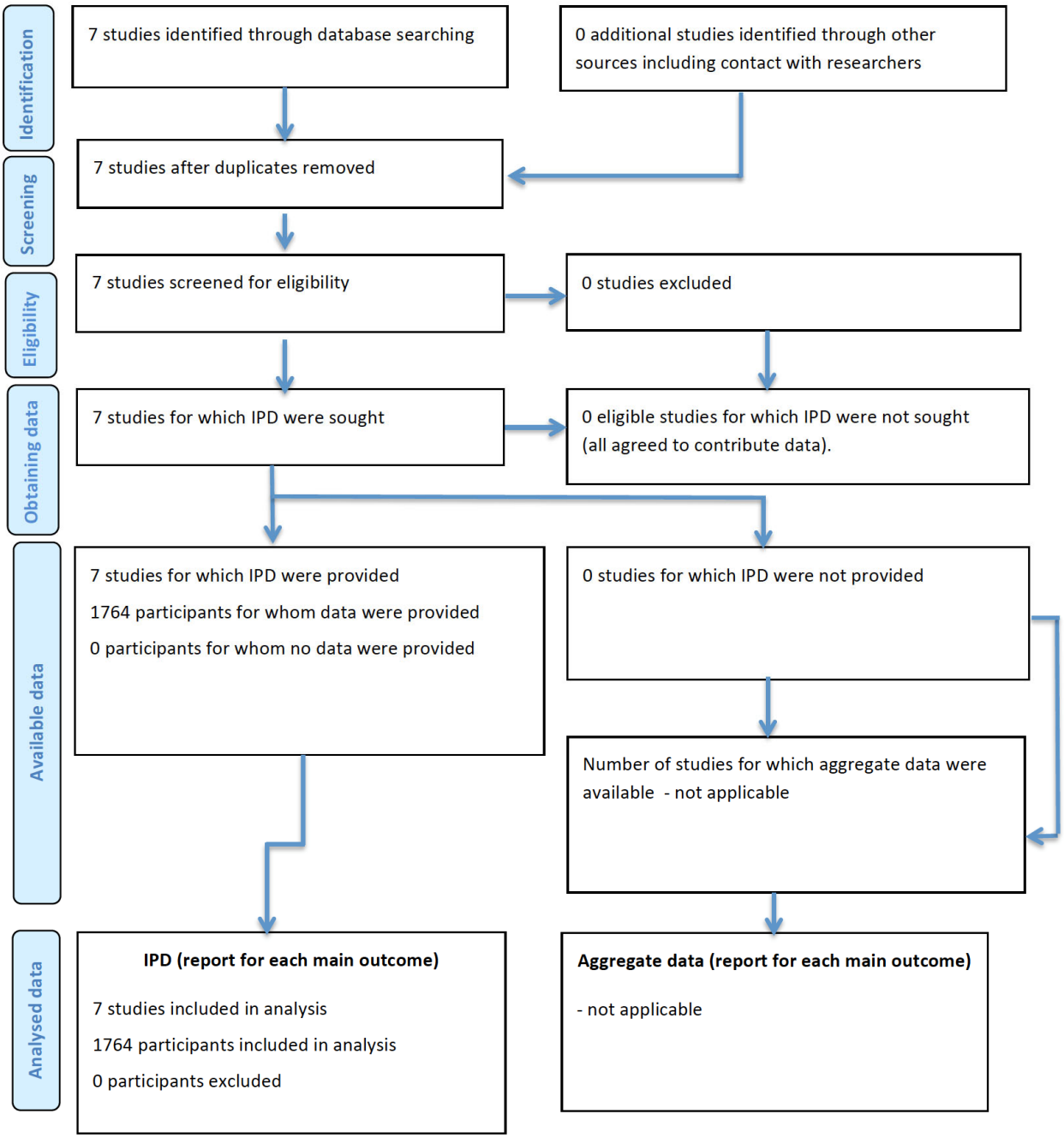
Imaging predictors of treatment effects and clinical outcome in acute large vessel stroke: meta-analysis of the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES)

*The HERMES collaborative group**

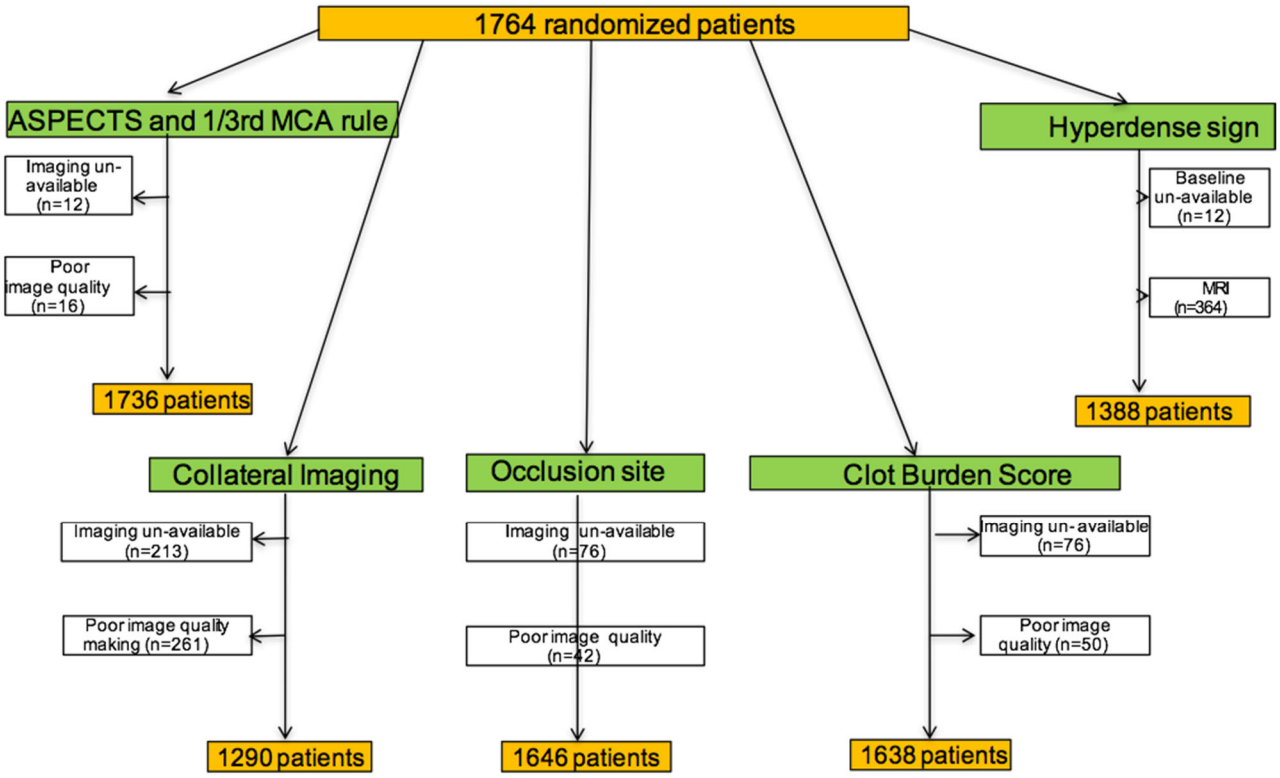
I. TABLE OF CONTENT

II. FIGURES

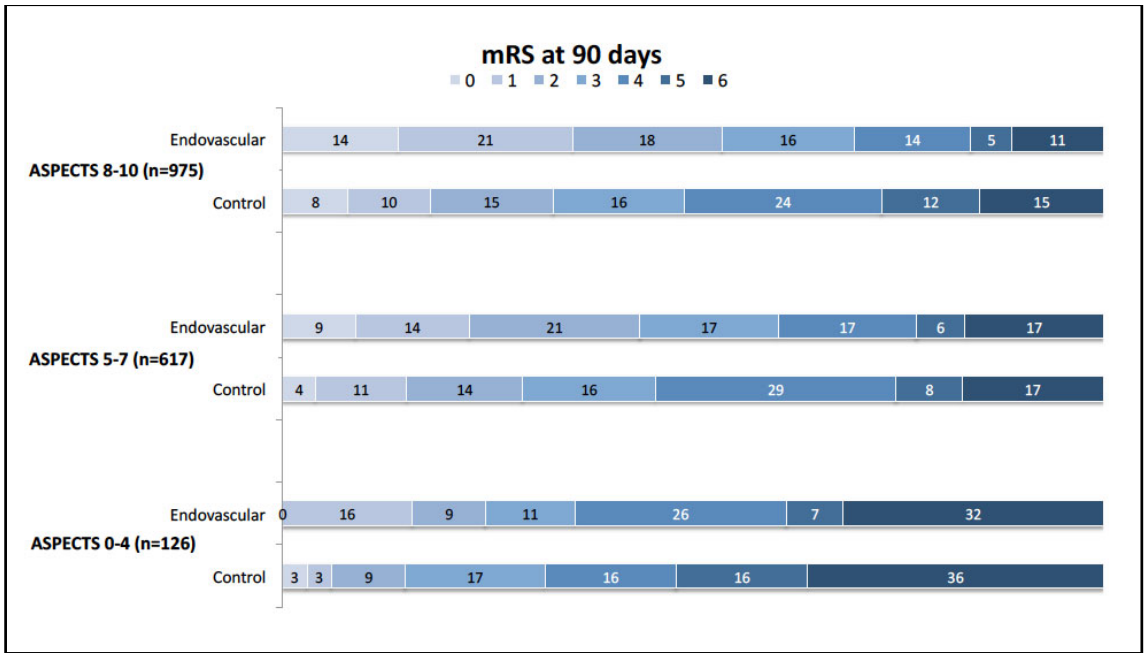
eFigure 1: PRISMA IPD flow diagram illustrating study selection.



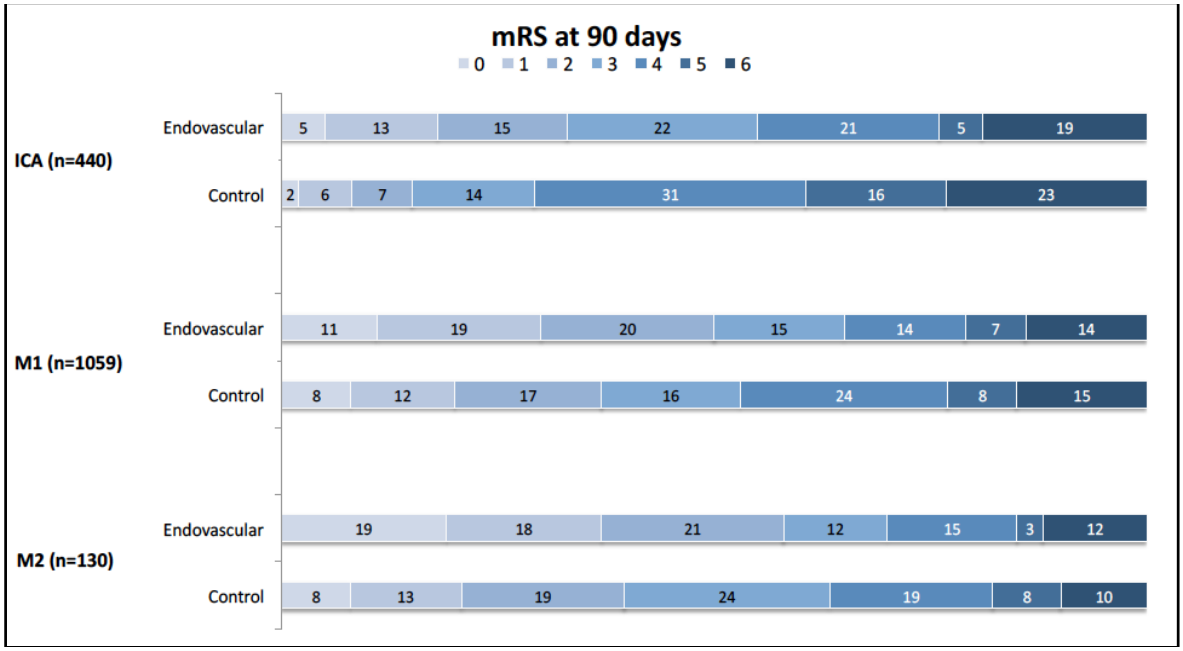
eFigure 2: Flow chart describing number of patients assessed for imaging variable at baseline and reasons for exclusion. Missing patients were not included in the different analysis of each imaging variable.



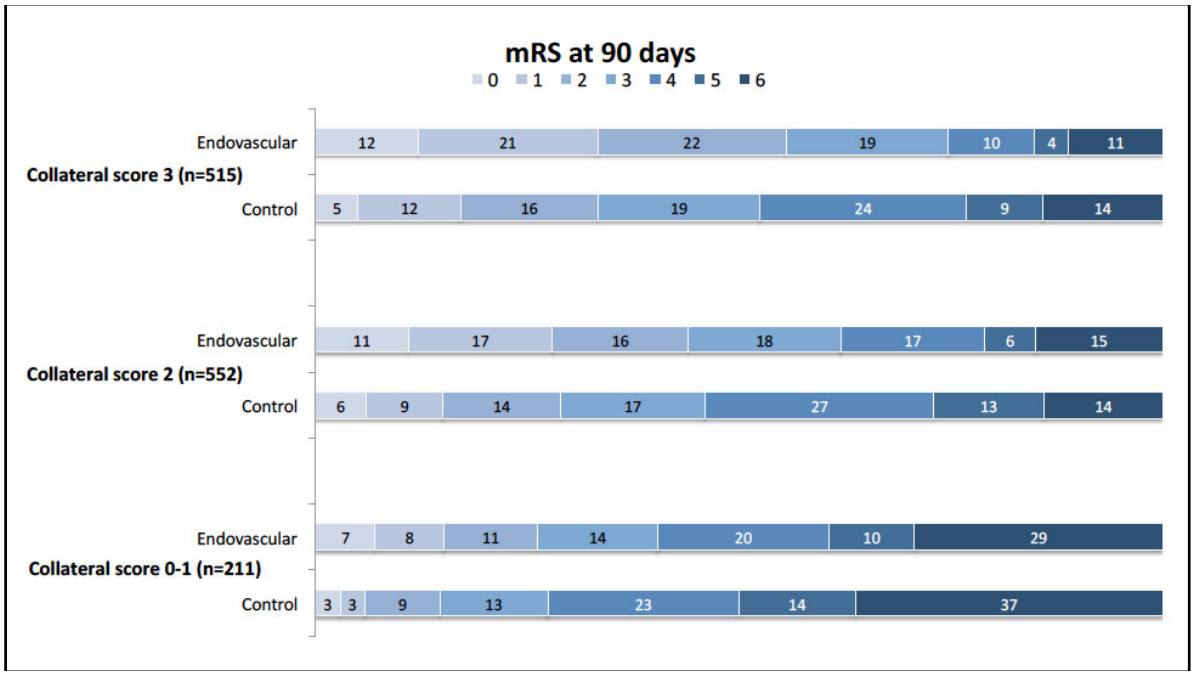
eFigure 3: Distribution of modified Rankin Scale at 90 days stratified by ASPECTS categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



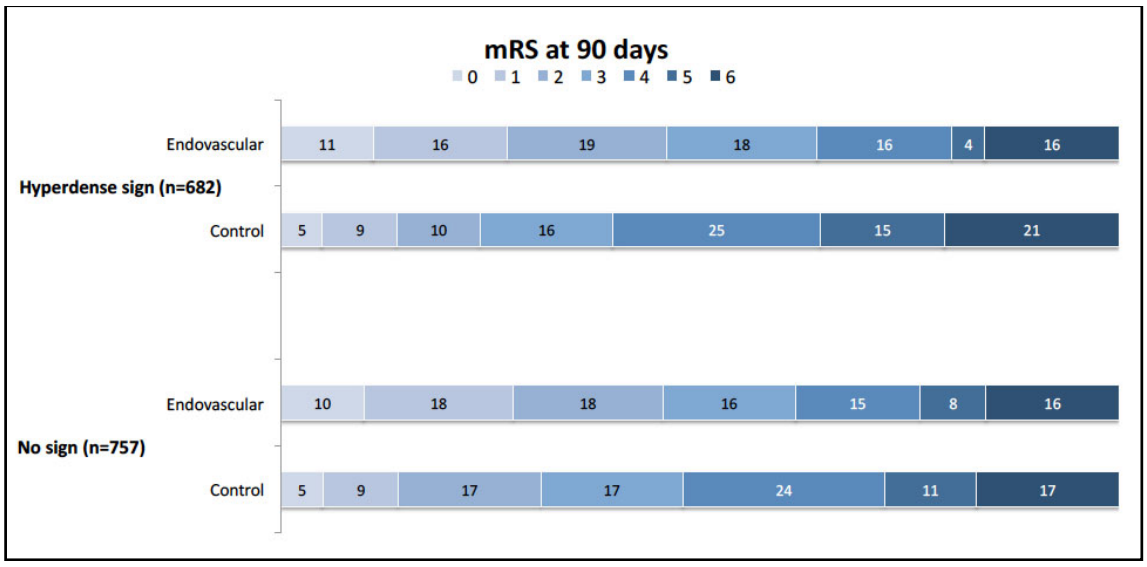
eFigure 4: Distribution of modified Rankin Scale at 90 days stratified by thrombus location in the endovascular and control groups (numbers within the horizontal bars represent percentages).



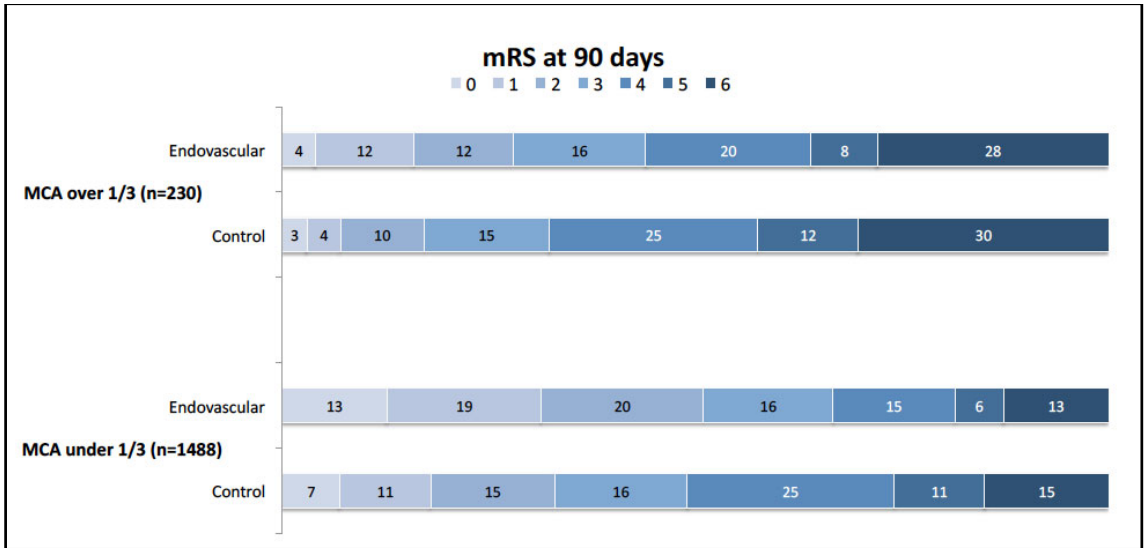
eFigure 5: Distribution of modified Rankin Scale at 90 days stratified by collateral circulation score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



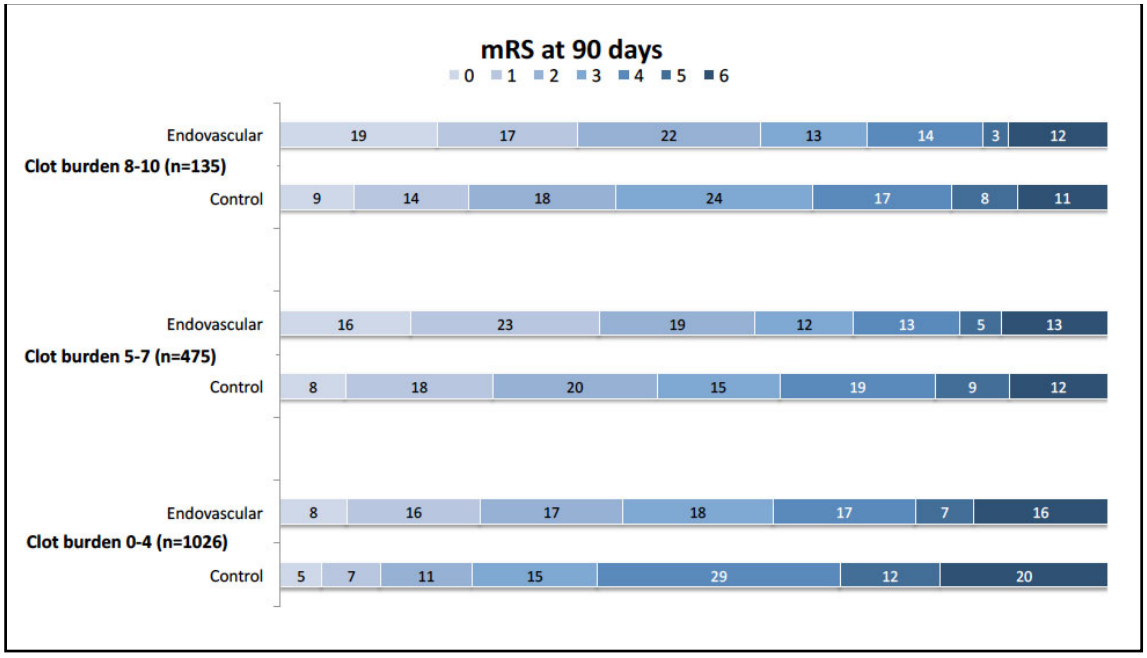
eFigure 6: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of hyperdense sign on CT in the endovascular and control groups (numbers within the horizontal bars represent percentages).



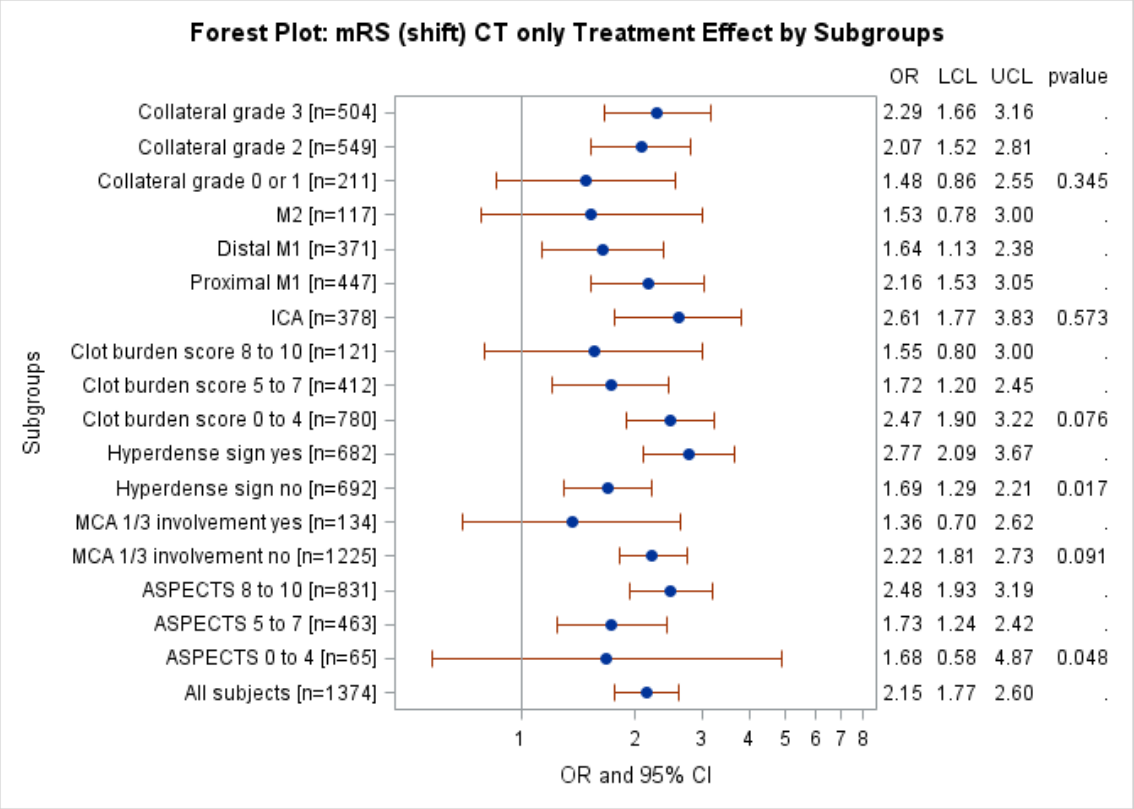
eFigure 7: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of early ischemic changes in 1/3rd of MCA territory in the endovascular and control groups (numbers within the horizontal bars represent percentages).

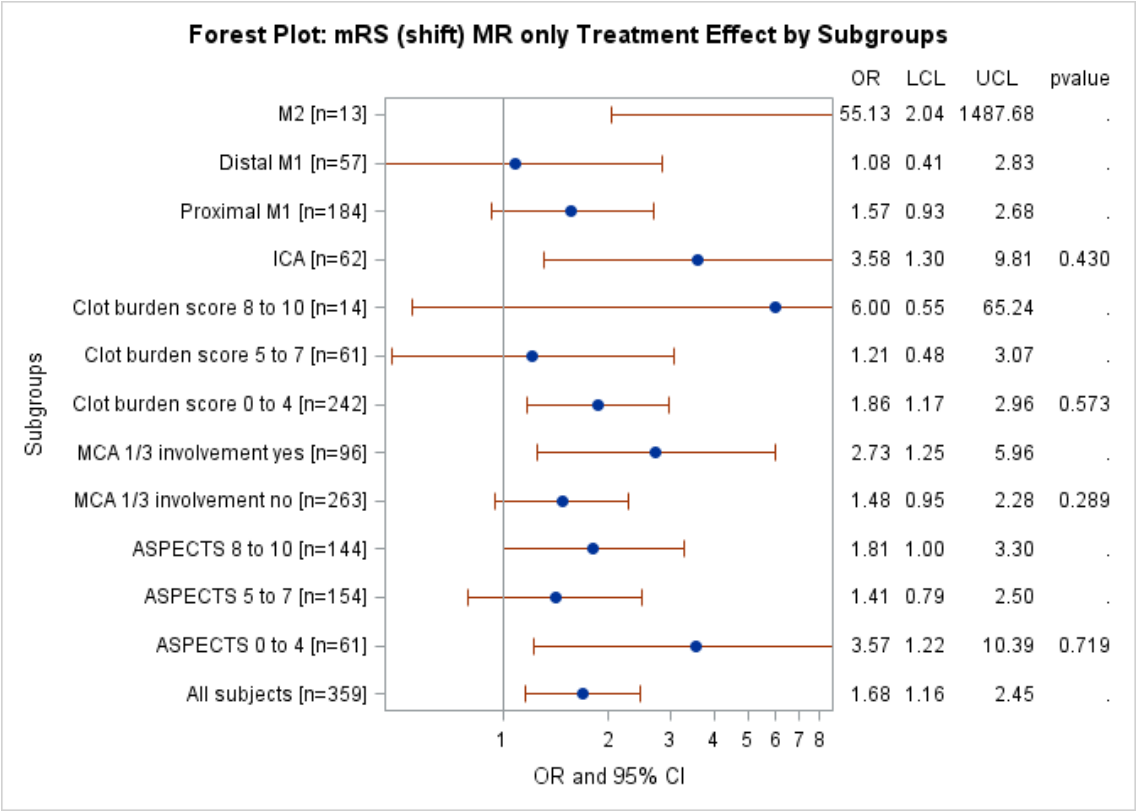


eFigure 8: Distribution of modified Rankin Scale at 90 days stratified by clot burden score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).

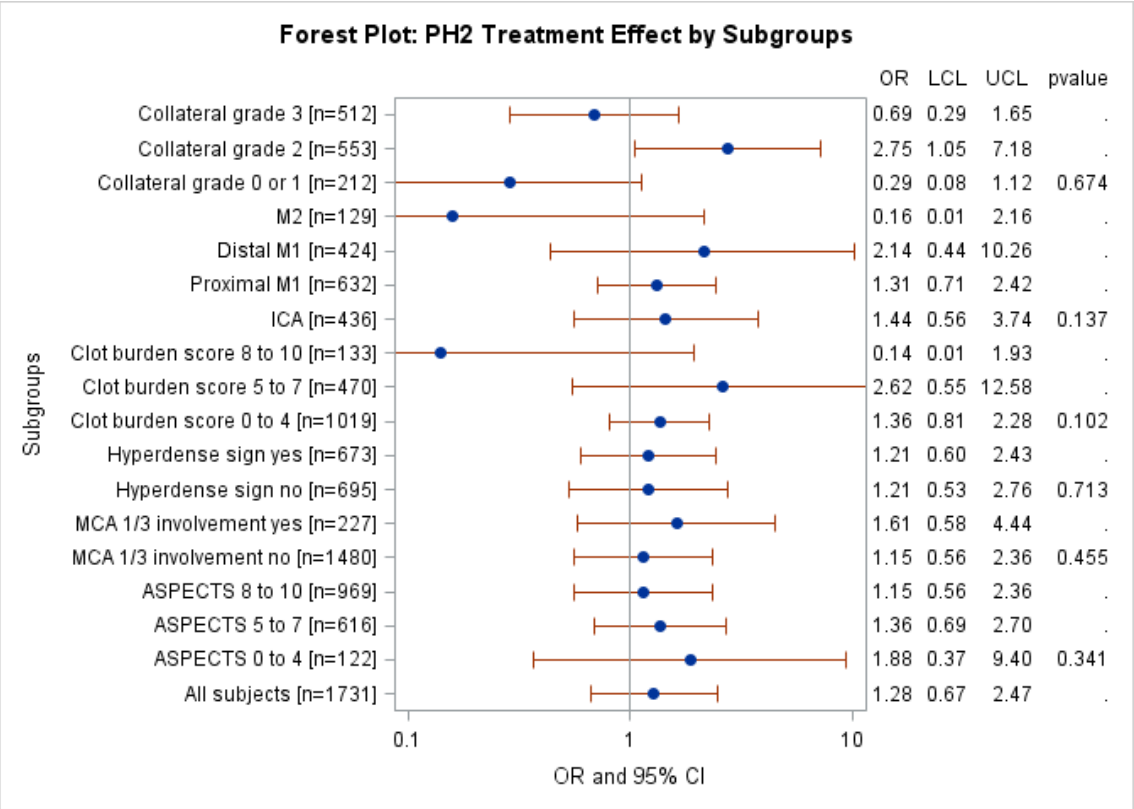


eFigure 9: Endovascular treatment effect by baseline imaging variable categories on primary outcome (mRS at 90 days) stratified by imaging modality (CT vs. MRI). Treatment effect is assessed through the common odds ratio for mRS shift.





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**	**RE**
			Population		
Continent	Europe	North America, Europe, East Asia	Oceania	North America and Europe	Eu

Country	Netherlands	Multiple	Australia and New Zealand	Multiple	Sp
			Sampling Frame		
Imaging Criteria					
Modality	NCCT/CTA	NCCT/CTA *CTP optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA/CTP *MRI optional	NC tio
Occlusion Site	ICA M1 M2	ICA M1	ICA M1 M2	ICA M1	IC
Ischaemic Core Definition	Not used	ASPECTS 6-10 Good Collaterals	CTP mismatch and ischemic core <70mL	CTP and NCCT ASPECTS criteria (modified protocol)	AS
Clinical Criteria					
Age (years)	≥18	≥18	≥18	18-85 (later amended to 18-80)	18- all PE
Baseline Stroke Severity	NIHSS ≥2	NIHSS ≥6	No limit	NIHSS 8-29	NI
Time to randomization	6 hours	12 hours	6 hours	6 hours	8 h
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	PH inc
			Control Group		
	Standard care	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients	Sta
			Intervention Group		
Wait for response to IV alteplase	No	No	No	No	Ye
Pre-specified time metrics	No	Yes	No	Yes	Ye
Type of Devices	Any	Any	Solitaire	Solitaire	So

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.