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Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data

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See Comment page 22

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Summary

Background CT perfusion (CTP) and diffusion or perfusion MRI might assist patient selection for endovascular thrombectomy. We aimed to establish whether imaging assessments of irreversibly injured ischaemic core and potentially salvageable penumbra volumes were associated with functional outcome and whether they interacted with the treatment effect of endovascular thrombectomy on functional outcome.

Methods In this systematic review and meta-analysis, the HERMES collaboration pooled patient-level data from all randomised controlled trials that compared endovascular thrombectomy (predominantly using stent retrievers) with standard medical therapy in patients with anterior circulation ischaemic stroke, published in PubMed from Jan 1, 2010, to May 31, 2017. The primary endpoint was functional outcome, assessed by the modified Rankin Scale (mRS) at 90 days after stroke. Ischaemic core was estimated, before treatment with either endovascular thrombectomy or standard medical therapy, by CTP as relative cerebral blood flow less than 30% of normal brain blood flow or by MRI as an apparent diffusion coefficient less than 620 μm²/s. Critically hypoperfused tissue was estimated as the volume of tissue with a CTP time to maximum longer than 6 s. Mismatch volume (ie, the estimated penumbral volume) was calculated as critically hypoperfused tissue volume minus ischaemic core volume. The association of ischaemic core and penumbral volumes with 90-day mRS score was analysed with multivariable logistic regression (functional independence, defined as mRS score 0–2) and ordinal logistic regression (functional improvement by at least one mRS category) in all patients and in a subset of those with more than 50% endovascular reperfusion, adjusted for baseline prognostic variables. The meta-analysis was prospectively designed by the HERMES executive committee, but not registered.

Findings We identified seven studies with 1764 patients, all of which were included in the meta-analysis. CTP was available and assessable for 591 (34%) patients and diffusion MRI for 309 (18%) patients. Functional independence was worse in patients who had CTP versus those who had diffusion MRI, after adjustment for ischaemic core volume (odds ratio [OR] 0·47 [95% CI 0·30–0·72], p=0·0007), so the imaging modalities were not pooled. Increasing ischaemic core volume was associated with reduced likelihood of functional independence (CTP OR 0·77 [0·69–0·86] per 10 mL, $p_{interaction}$=0·29; diffusion MRI OR 0·87 [0·81–0·94] per 10 mL, $p_{interaction}$=0·94). Mismatch volume, examined only in the CTP group because of the small numbers of patients who had perfusion MRI, was not associated with either functional independence or functional improvement. In patients with CTP with more than 50% endovascular reperfusion (n=186), age, ischaemic core volume, and imaging-to-reperfusion time were independently associated with functional improvement. Risk of bias between studies was generally low.

Interpretation Estimated ischaemic core volume was independently associated with functional independence and functional improvement but did not modify the treatment benefit of endovascular thrombectomy over standard medical therapy for improved functional outcome. Combining ischaemic core volume with age and expected imaging-to-reperfusion time will improve assessment of prognosis and might inform endovascular thrombectomy treatment decisions.

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Research in context

Evidence before this study

We did a systematic review of studies examining the prognostic effect of penumbral imaging parameters, including estimated irreversibly injured ischaemic core volume and mismatch volume (ie, estimated penumbral volume), published in any language in PubMed between Jan 1, 2010, and May 31, 2017, using the search terms "penumbral imaging" OR "mismatch" OR "ischaemic core" OR "diffusion" AND either "endovascular" OR "thrombectomy" OR "intra-arterial". The prospective, observational DEFUSE 2 study showed improved functional outcomes in patients with favourable mismatch profile (defined, in part, as an ischaemic core volume of <70 mL) who were reperfused versus those who were not reperfused but there was not a significant benefit of reperfusion in patients without the favourable penumbral mismatch profile. Two small retrospective studies suggested that reperfusion might benefit patients with large ischaemic core volumes defined as either more than 70 mL on diffusion MRI or extensive non-contrast CT hypodensity defined as Alberta Stroke Program Early CT Score 0–5. Subanalysis of patients with pretreatment CT perfusion in the MR CLEAN trial showed that an ischaemic core volume of more than 70 mL was associated with less favourable prognosis without loss of benefit from thrombectomy, with strength and precision of findings limited by sample size.

Added value of this study

This individual patient-level meta-analysis of 1764 patients quantifies the independent prognostic effect of ischaemic core volume on functional outcome. The risk of bias in component studies was low overall. A 10-mL increase in ischaemic core volume had a similar adverse effect on functional outcome as a 30-min delay in imaging-to-reperfusion time or a 5-year increase in age. However, the odds of improved functional outcome and absolute benefit (ie, number needed to treat to benefit) from treatment with thrombectomy were maintained in patients over a wide range of ischaemic core volumes.

Implications of all the available evidence

Patients should not be excluded from endovascular thrombectomy within 6 h of stroke onset purely on the basis of a large estimated ischaemic core. The patient's age and functional status, their views on disability outcomes (if known), and the expected time to achieve reperfusion should be considered alongside ischaemic core volume when estimating the attainable functional outcome and establishing the most appropriate treatment.

Introduction

Endovascular thrombectomy substantially reduces disability in patients with ischaemic stroke due to large vessel occlusion.[1] The optimal selection of patients to identify all those who might benefit from this procedure is a key clinical question. A meta-analysis of individual-patient data on endovascular thrombectomy after large-vessel ischaemic stroke showed remarkable consistency in treatment effect across clinical subgroups, although age and clinical severity remained strongly prognostic[1] and treatment effect declined with delayed reperfusion.[2] Brain imaging is a key prognostic biomarker in stroke patients. The positive trials of endovascular thrombectomy at 0–6 h after ischaemic stroke onset have used different brain imaging selection criteria and the optimal approach to identifying patients who might benefit from thrombectomy using imaging has remained uncertain.[3–9]

Imaging selection for ischaemic stroke treatment aims to identify individual pathophysiology, rather than using traditional group-average time thresholds.[10] The presence of ischaemic penumbra (electrically non-functioning but metabolically viable brain tissue that is salvageable with rapid cerebral blood flow restoration) forms the rationale for reperfusion therapies. Patients have marked variation in collateral blood flow (via leptomeningeal anastomoses and other pathways) that maintains penumbra distal to an arterial occlusion.[11,12] Penumbral imaging with CT perfusion (CTP) or MRI, when processed in a reproducible manner using validated blood flow parameter thresholds, can estimate both the irreversibly injured ischaemic core and potentially salvageable ischaemic penumbra with reasonable accuracy in the individual patient.[13–16] The difference in volume between the critically hypoperfused tissue (or territory of the occluded artery) and the ischaemic core estimates the salvageable penumbra.

The DAWN[17] and DEFUSE 3[18] trials showed a benefit of endovascular thrombectomy beyond 6 h after stroke in patients with favourable penumbral patterns on CTP or MRI. However, the role of penumbral imaging selection within 6 h of stroke onset remains unclear. Patients with a large estimated ischaemic core (eg, ≥70 mL) are sometimes excluded from reperfusion therapies[4–7] and the positive trials of endovascular thrombectomy have used variable non-contrast CT, CT angiographic collaterals, CTP, and MRI criteria to select patients. Data characterising the clinical benefit of endovascular thrombectomy as ischaemic core volume increases are scarce. The DEFUSE 2 prospective cohort study showed benefit of endovascular reperfusion in patients with favourable perfusion and diffusion MRI (criteria included diffusion MRI lesion volume of <70 mL), while patients without the favourable imaging profile did not benefit.[12] By contrast, two retrospective observational studies suggested a benefit of reperfusion in patients with a diffusion MRI lesion volume of at least 70 mL[19] or Alberta Stroke Program Early CT Score (ASPECTS) less than 6, which indicates a large ischaemic core.[20] Furthermore, subanalysis of pretreatment CTP in 175 patients in MR

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CLEAN[21] found no interaction between ischaemic core volume and treatment effect.

We did a systematic review and meta-analysis of all randomised controlled trials of stent-retriever thrombectomy versus medical therapy within 6 h of stroke to assess the influence of ischaemic core volume and mismatch volume on functional outcome after thrombectomy.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we assessed endovascular thrombectomy predominantly performed with stent retrievers versus medical therapy in patients with anterior circulation ischaemic stroke, according to PRISMA guidelines. We searched PubMed for randomised controlled trials published in any language between Jan 1, 2010, and May 31, 2017, using the search string (("randomised controlled trial" [Publication Type]) AND ((thrombectomy[Title/Abstract]) OR (clot retrieval[Title/Abstract]) OR intraarterial[Title/Abstract]) AND (stroke[Title/Abstract])). Individual patient-level data from the identified seven randomised controlled trials (MR CLEAN,[3] EXTEND-IA,[4] ESCAPE,[5] SWIFT PRIME,[6] REVASCAT,[7] PISTE,[8] and THRACE[9]) were pooled by the Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) collaboration.[1] The study statistician (SB) extracted data for patients with CTP or diffusion MRI before treatment with either endovascular thrombectomy or standard medical therapy. BCVC finalised patient inclusion after masked review of imaging quality. Patients with corrupted data, absence of a perfusion abnormality within the image coverage, contrast bolus failure, or severe motion artefacts that precluded interpretation were excluded. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. The meta-analysis was prospectively designed by the HERMES executive committee, but not registered. The protocol is in the appendix.

Data analysis

An independent core laboratory (Los Angeles, CA, USA) collated imaging data, assigning a random HERMES ID for each patient to mask the assessors to the trial of origin. Individual CTP and diffusion MRI data were reprocessed using RAPID software (version 4.6) as used in EXTEND-IA[4] and SWIFT PRIME.[6] There were no duplicate data. All automated output was visually verified and artefacts removed by a stroke neurologist with extensive neuroimaging analysis experience, who was blinded to treatment allocation and all other imaging and clinical information. For CTP, irreversibly injured ischaemic core was defined as a relative cerebral blood flow of less than 30% of normal brain blood flow.[13] For diffusion MRI, ischaemic core was defined as an apparent diffusion coefficient of less than 620 μm²/s.[22] Volume of critically hypoperfused tissue (the penumbra and core combined) was estimated using CTP with a time to maximum (T_{max}) threshold of more than 6 s.[23] T_{max} relates to the time delay in tissue enhancement after a bolus of intravenous contrast. Mismatch volume (ie, estimated penumbral volume) was calculated as critically hypoperfused tissue volume minus ischaemic core volume. Mismatch ratio was calculated as critically hypoperfused tissue volume divided by ischaemic core volume. Mismatch status was defined as a mismatch ratio greater than 1·8 and a mismatch volume greater than 15 mL in the SWIFT PRIME trial[6] or as a mismatch ratio greater than 1·2 and a mismatch volume greater than 10 mL in the EXTEND-IA trial.[4] Perfusion MRI was available for only 33 patients, and thus mismatch volume was not assessed in these patients.

The primary outcome was functional outcome scored on the modified Rankin Scale (mRS) at 90 days after stroke reported as odds ratio (OR) with 95% CI. Regression analyses were adjusted for seven baseline prognostic variables as follows: age, sex, baseline clinical severity (National Institutes of Health Stroke Scale [NIHSS] score), time from stroke onset to randomisation, administration of intravenous alteplase, core lab-adjudicated non-contrast CT ASPECTS, and site of vessel occlusion. To account for between-trial variance, we used mixed-effects modelling with a random effect for trial incorporated in all regression models. The interaction between ischaemic core volume and treatment was tested by including the multiplicative volume-by-treatment term in regression models.

The effect of CTP versus MRI modality on the prognostic effect of ischaemic core volume was first tested in preliminary multivariable logistic regression for functional independence (defined as mRS 0–2) and ordinal logistic regression for functional improvement by at least one category for the six-level mRS, merging categories 5 (severe disability) and 6 (death) into a single category. Because imaging modality (CT or MRI) was a prognostic factor, these data were treated separately for all subsequent analyses.

Modelling of the effect of ischaemic core and mismatch volumes on functional outcome was done using mRS 0–2 (functional independence) and the utility-weighted mRS score, a patient-centred linear disability measure that converts each mRS score to a utility-weighted mRS score between 1 (perfect health) and 0 (death)[24] as follows: mRS 0=1, mRS 1=0·91, mRS 2=0·76, mRS 3=0·65, mRS 4=0·33, mRS 5=0, and mRS 6=0. Reduction in utility score can therefore be expressed as a percentage increase in disability. The treatment effect of endovascular thrombectomy versus medical therapy on functional outcome in the prespecified subgroups with ischaemic core volume less than 70 mL versus 70 mL or more was examined using binary logistic regression for functional independence and ordinal logistic regression for functional improvement by at least one mRS category in the six-level mRS. Symptomatic intracerebral haemorrhage was assessed as a safety outcome using the definitions applied in the original trials (appendix).

	CT perfusion		Diffusion MRI		All participants (n=1764)
	Endovascular thrombectomy group (n=289)	Standard therapy group (n=302)	Endovascular thrombectomy group (n=153)	Standard therapy group (n=156)	
Age, years	65·5 (13·7)	65·7 (13·0)	63·1 (13·1)	63·6 (14·0)	65·6 (13·5)
Sex					
Men	137 (47%)	168 (56%)	94 (61%)	73 (47%)	929 (53%)
Women	152 (53%)	134 (44%)	59 (39%)	83 (53%)	835 (47%)
NIHSS	17 (14–20)	17 (13–21)	18 (14–21)	17 (14–21)	17 (13–21)
ASPECTS	8 (7–9)	8 (7–9)	7 (6–8)	7 (5–8)	8 (7–9)
Site of arterial occlusion					
Internal carotid artery	79 (27%)	78 (26%)	25 (16%)	33 (21%)	442 (25%)
M1	171 (59%)	189 (63%)	112 (73%)	101 (65%)	1073 (61%)
M2	28 (10%)	24 (8%)	5 (3%)	8 (5%)	131 (7%)
Unknown	11 (4%)	11 (4%)	11 (7%)	14 (9%)	116 (7%)
Onset to emergency department, min	110 (57–183)	110 (54–197)	105 (75–139)	110 (80–159)	105 (60–180)
Emergency department to arterial access, min	103 (75–150)	NA	107 (85–140)	NA	115 (80–165)
Intravenous alteplase	248 (86%)	269 (89%)	145 (95%)	154 (99%)	1572 (89%)
Baseline ischaemic core volume, mL	10 (3–30)	9 (2·5–24)	18 (9–41)	23 (12–63)	NA
Baseline critical hypoperfusion volume, mL	122 (79–165)	123 (82–167)	NA	NA	NA

Data are mean (SD), median (IQR), or n (%). NIHSS is a standardised neurological examination for which the score ranges from normal (0) to death (42). ASPECTS reflects the extent of early ischaemic change on the CT brain: 10 is normal, 0 shows involvement of the entire middle cerebral artery territory. ASPECTS=Alberta Stroke Program Early CT Score. M1=first segment of middle cerebral artery (pre-bifurcation). M2=second segment of middle cerebral artery (from bifurcation to the circular sulcus of the insula in the Sylvian fissure). NA=not applicable. NIHSS=National Institutes of Health Stroke Scale.

Table 1: **Baseline clinical and imaging characteristics of patients receiving endovascular thrombectomy or standard medical therapy**

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See Online for appendix

The association between ischaemic core and mismatch volumes and the 90-day mRS score was examined by treatment status. The subgroup with more than 50% endovascular reperfusion (defined as post-procedure, core lab-adjudicated, modified Treatment in Cerebral Infarction 2b-3) was also examined.[25]

The number needed to treat to achieve mRS 0–1 (patients able to return to usual activities), 0–2 (all those with functional independence), 0–3 (also those requiring assistance with domestic activities) or at least a one-category improvement in mRS score (ie, functional improvement) with endovascular treatment versus standard medical therapy was calculated for a range of ischaemic core volumes, on the basis of model-derived adjusted treatment effects (absolute risk reduction). The number needed to treat was calculated as 1 over absolute risk reduction.

The effects of ischaemic core volume, time-to-treatment (onset-to-imaging and imaging-to-reperfusion time), and clinical prognostic variables (age, sex, NIHSS, and intravenous thrombolysis) on functional outcome were examined in the subgroup of patients with more than 50% endovascular reperfusion using multivariable logistic regression.

Qualitative assessment of between-trial differences, including patient eligibility and assessment of bias were done (appendix). Risk of bias was assessed using the Cochrane tool and was low overall, apart from the unmasked outcome assessment in THRACE.[9] Statistical analysis was done using SAS (version 9.4) and R (version 3.3).

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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

Seven studies were identified in PubMed, and all were included in the systematic review and meta-analysis (appendix). Of 1764 patients included in the seven randomised controlled trials, penumbral imaging was performed and assessable in 900 (51%). CTP was obtained in 625 (35%) of the 1764 patients, and 34 of these patients were excluded (11 severe motion artefacts, seven no lesion within coverage, two contrast bolus failure, and 14 because of data corruption during transfer from site). Of the 591 patients with CTP who were included in the analysis, 289 (49%) were randomly assigned to the endovascular thrombectomy group and 302 (51%) to the standard medical therapy (control) group. Median CTP-estimated ischaemic core volume was 10 mL (IQR 3–28 mL; appendix). Diffusion MRI was obtained in 309 (18%) of the 1764 patients, of whom 153 (50%) were randomly assigned to endovascular thrombectomy and 156 (50%) were assigned to the control group. Median diffusion

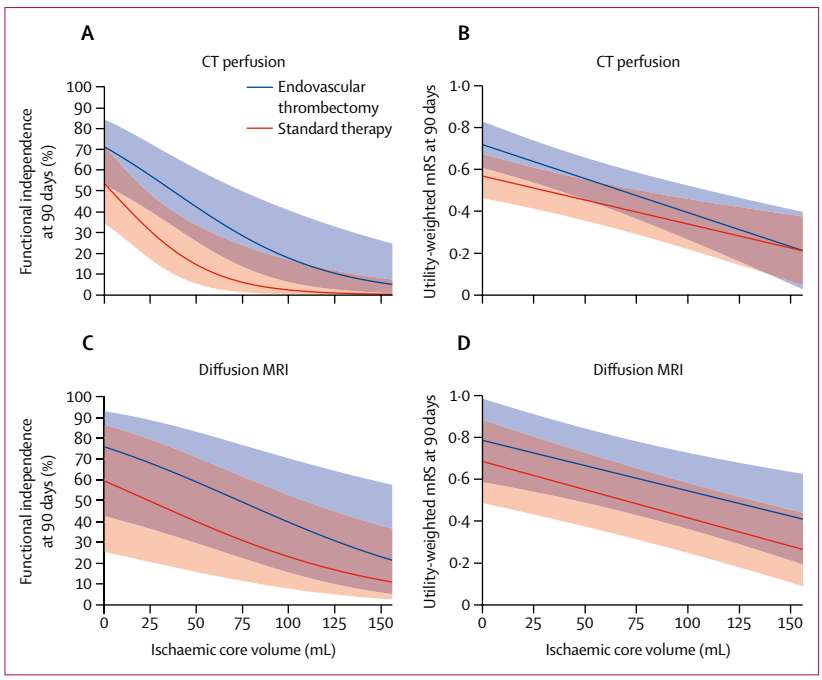

Figure 1: **Association of ischaemic core volume with functional outcome**
Ischaemic core volume estimated by CT perfusion versus (A) functional independence and (B) disability (utility scores derived from mRS). Ischaemic core volume estimated by diffusion MRI versus (C) functional independence and (D) disability. Solid line shows point estimates and shaded regions show 95% CIs. Models are adjusted for age, sex, baseline clinical severity (National Institutes of Health Stroke Scale score), time from stroke onset to randomisation, administration of intravenous alteplase, core lab-adjudicated non-contrast CT Alberta Stroke Program Early CT Score, and site of vessel occlusion, with a random effect for trial. mRS=modified Rankin Scale.

MRI-estimated ischaemic core volume was 21 mL (IQR 10–52 mL; appendix). Imaging was done within 6 h of stroke onset in 887 (99%) of 900 patients. The 13 patients who were scanned more than 6 h after onset were kept in the analysis because of the low influence of time to imaging on functional outcomes in the DAWN and DEFUSE 3 trials.[17,18] Baseline characteristics were similar between patients treated with endovascular thrombectomy or standard medical therapy in both the CTP and diffusion MRI subgroups (table 1).

Ischaemic core volume per 10 mL increase was associated with reduced functional independence in the preliminary multivariable logistic regression analysis (OR 0·85 [95% CI 0·80–0·90], p<0·0001) and less functional improvement in ordinal logistic regression analysis of mRS score (common OR [cOR] 0·86 [0·83–0·89], p<0·0001) after adjustment for the seven prespecified covariates. When comparing imaging modalities (CTP and diffusion MRI), CTP was independently associated with a reduced proportion of patients with functional independence (OR 0·47 [0·30–0·72], p=0·0007) and less functional improvement (cOR 0·51 [0·36–0·72], p=0·0001) than diffusion MRI. There was no interaction between imaging modality and treatment effect (p=0·86), indicating that the relative effect on functional outcome per 10 mL increase in ischaemic core was consistent between modalities. Given these differences in predicted functional outcome modelled on ischaemic core volume between the diffusion MRI and CTP groups, these data were not pooled for subsequent analyses. Large ischaemic core volume estimated using CTP was associated with lower probability of functional independence in endovascular (OR 0·79 [95% CI 0·69–0·90]) and control patients (OR 0·71 [95% CI 0·56–0·90]) per 10 mL increase in volume in the seven-covariate-adjusted model. Benefit from thrombectomy was not modified by ischaemic core volume (core–treatment interaction p=0·29; figure 1A). When ASPECTS (which was correlated with ischaemic core volume but not independently associated with functional independence; appendix) was omitted from the model, the core–treatment interaction remained non-significant (p=0·26). In a multivariable logistic regression model including both endovascular and control patients, a 10 mL increase in ischaemic core volume was associated with reduced functional independence (OR 0·77 [95% CI 0·69–0·86]) with the other significant covariates being age, baseline NIHSS, endovascular treatment, onset-to-randomisation time, and site of vessel occlusion, but not ASPECTS (appendix). Ischaemic core volume was also independently associated with functional independence in the subgroup of endovascular patients with more than 50% reperfusion (n=186; OR 0·83 [95% CI 0·71–0·97] per 10 mL increase in ischaemic core volume). At 100 mL ischaemic core volume, the absolute increase in functional independence was 25·4% (95% CI 0·8–49·9) in the endovascular versus the control patients.

Large CTP-estimated ischaemic core volume was also associated with worse disability outcome using utility-weighted mRS score. Utility was reduced by 3% (95% CI 1–4) per 10 mL increase in ischaemic core volume for endovascular patients and reduced by 2% (95% CI 1–3) for control patients. Although prognostically important, ischaemic core volume did not modify the benefit from thrombectomy (core–treatment interaction p=0·23, or p=0·51 when ASPECTS was omitted; figure 1B). In endovascular-treated patients with more than 50% reperfusion, utility was reduced by 3% (95% CI 1–5) per 10 mL increase in ischaemic core volume (appendix). In the ordinal logistic regression model including both endovascular and control CTP patients, increase in ischaemic core volume was associated with reduced functional improvement, with a cOR of 0·85 (95% CI 0·81–0·91) per 10 mL increase. Other significant covariates were age, baseline NIHSS, endovascular treatment, and site of vessel occlusion (appendix).

In the preplanned subgroup analysis of patients with ischaemic core volume of at least 70 mL using CTP (n=50, median ischaemic core volume 100 mL [IQR 82–144 mL]), two (8%) of 25 endovascular and none of 25 control patients achieved functional independence (OR infinite; figure 2A). Endovascular patients had greater functional improvement in unadjusted ordinal logistic regression analysis of the mRS score, with a cOR of

3·1 (95% CI 1·0–9·4). However, despite similar age in both treatment groups, NIHSS was higher in the control group (median NIHSS of 22 [IQR 18–26]) than in the endovascular group (median NIHSS of 18 [16–21], p=0·005) and the ischaemic core volume was numerically larger in controls (median 110 mL [86–137] and ASPECTS 5 [4–7]) than in the endovascular patients (median 85 mL [74–108], p=0·12 and ASPECTS 8 [6–9], p=0·001). There was insufficient sample size in the 70 mL or greater subgroup (n=50) to include all seven covariates, but adjustments for age and NIHSS resulted in a cOR of 1·8 (95% CI 0·3–12·5; p=0·53). In the 70 mL or greater subgroup, numbers of patients with symptomatic intracerebral haemorrhage were not different between endovascular patients (none of 25 patients) and control patients (three [12%] of 25 patients; p=0·24; appendix).

Diffusion MRI lesion volume was independently associated with functional independence in endovascular (OR 0·88 [95% CI 0·78–0·97]) and control (OR 0·87 [0·79–0·96]) patients, per 10 mL increase in ischaemic core volume (figure 1C; appendix) but did not significantly interact with thrombectomy treatment effect (p=0·94). In a multivariable logistic regression model including both endovascular and control patients, a 10-mL increase in ischaemic core volume was associated with reduced functional independence (OR 0·87 [95% CI 0·81–0·94]), and other significant covariates were age, baseline NIHSS, and endovascular treatment, but not ASPECTS (appendix). Increasing diffusion MRI lesion volume was independently associated with a reduction in utility score in endovascular (2%; 95% CI 1–3) and control patients (2%; 1–3) per 10 mL increase in volume ($p_{interaction}$=0·58; figure 1D). The relationship between ischaemic core volume and functional outcomes in endovascular patients with greater than 50% reperfusion was similar to that observed in the CTP reperfusion subgroup (appendix). Patients with at least 70 mL diffusion MRI lesion volume (n=59) achieved functional independence in seven (30%) of 23 endovascular patients versus seven (20%) of 36 control patients (OR 1·8 [95% CI 0·5–6·3] and cOR 2·1 [95% CI 0·8–5·6], both unadjusted; figure 2B). In patients with a diffusion MRI volume of at least 70 mL, symptomatic intracerebral haemorrhage occurred in a similar number of patients between the two treatment groups (appendix).

In multivariable logistic regression analysis of the CTP-imaged, endovascular-treated patients who achieved more than 50% reperfusion (n=186), age, imaging-to-reperfusion time, and ischaemic core volume were associated with both functional improvement and functional independence (table 2). We also assessed the effect of age and imaging-to-reperfusion time on functional outcomes for a given CTP-estimated ischaemic core volume in patients with more than 50% endovascular reperfusion (figure 3; appendix). Patients with a small (10 mL) ischaemic core volume often achieved functional independence (mRS 0–2) despite advanced age or extended delays between imaging and reperfusion. By contrast, most patients with a large (75 mL) or very large (125 mL) ischaemic core volume did not achieve functional independence unless reperfusion was achieved soon after imaging (figure 3A). However, mild disability (mRS 0–3) was often achievable even for older patients with a large

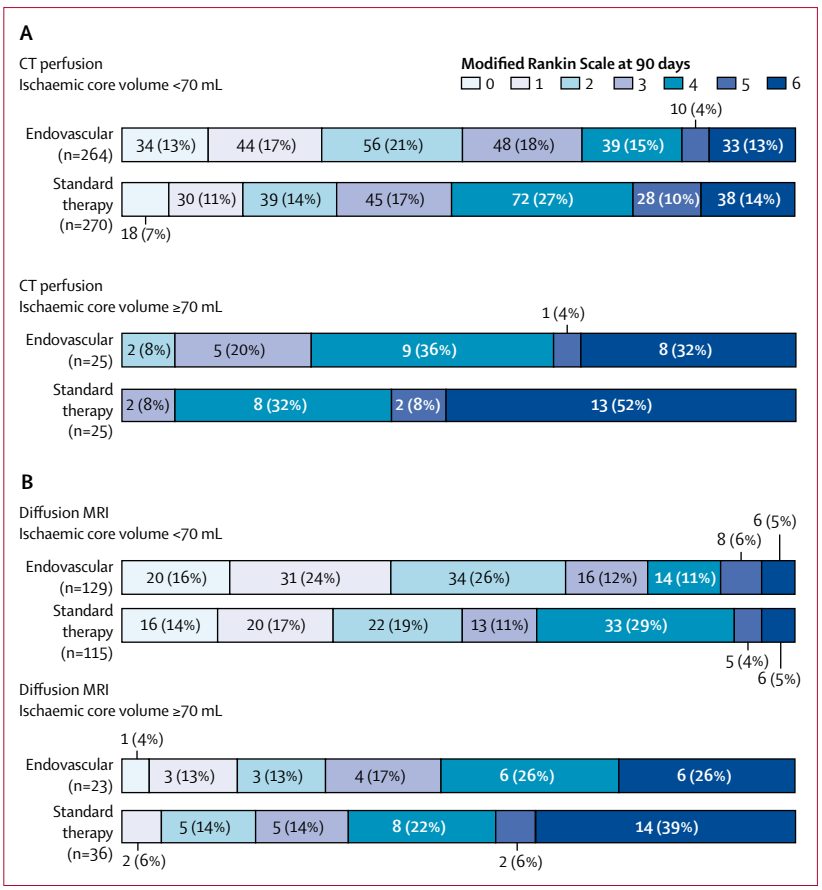

Figure 2: **Functional outcome at day 90 stratified by ischaemic core volume**
(A) Ischaemic core volume estimated by CT perfusion <70 mL (upper panel) and ≥70 mL (lower panel). (B) Ischaemic core volume estimated by diffusion MRI <70 mL (upper panel) and ≥70 mL (lower panel). Numbers and percentages show patients with modified Rankin Scale scores 0–6 in each category. Endovascular=endovascular thrombectomy.

	Functional improvement (by at least one mRS category)		Functional independence (mRS 0–2)	
	cOR (95% CI)	p value	OR (95% CI)	p value
Age (per 5 years)	0·83 (0·72–0·94)	0·005	0·81 (0·69–0·96)	0·02
NIHSS (per 5 points)	0·83 (0·60–1·14)	0·25	0·59 (0·41–0·87)	0·008
Women (*vs* men)	0·54 (0·31–0·96)	0·04	0·80 (0·41–1·56)	0·52
Alteplase delivered (*vs* not)	0·75 (0·31–1·76)	0·50	0·84 (0·30–2·34)	0·75
Onset to imaging (per 30 min)	0·92 (0·84–1·00)	0·06	0·89 (0·80–0·99)	0·04
Imaging to reperfusion (per 30 min)	0·79 (0·66–0·95)	0·01	0·74 (0·57–0·96)	0·02
Ischaemic core volume (per 10 mL)	0·82 (0·73–0·92)	0·001	0·77 (0·67–0·90)	0·001

cOR=common odds ratio. mRS=modifed Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio.

Table 2: **Functional outcome in 186 patients with CT perfusion who achieved more than 50% endovascular reperfusion**

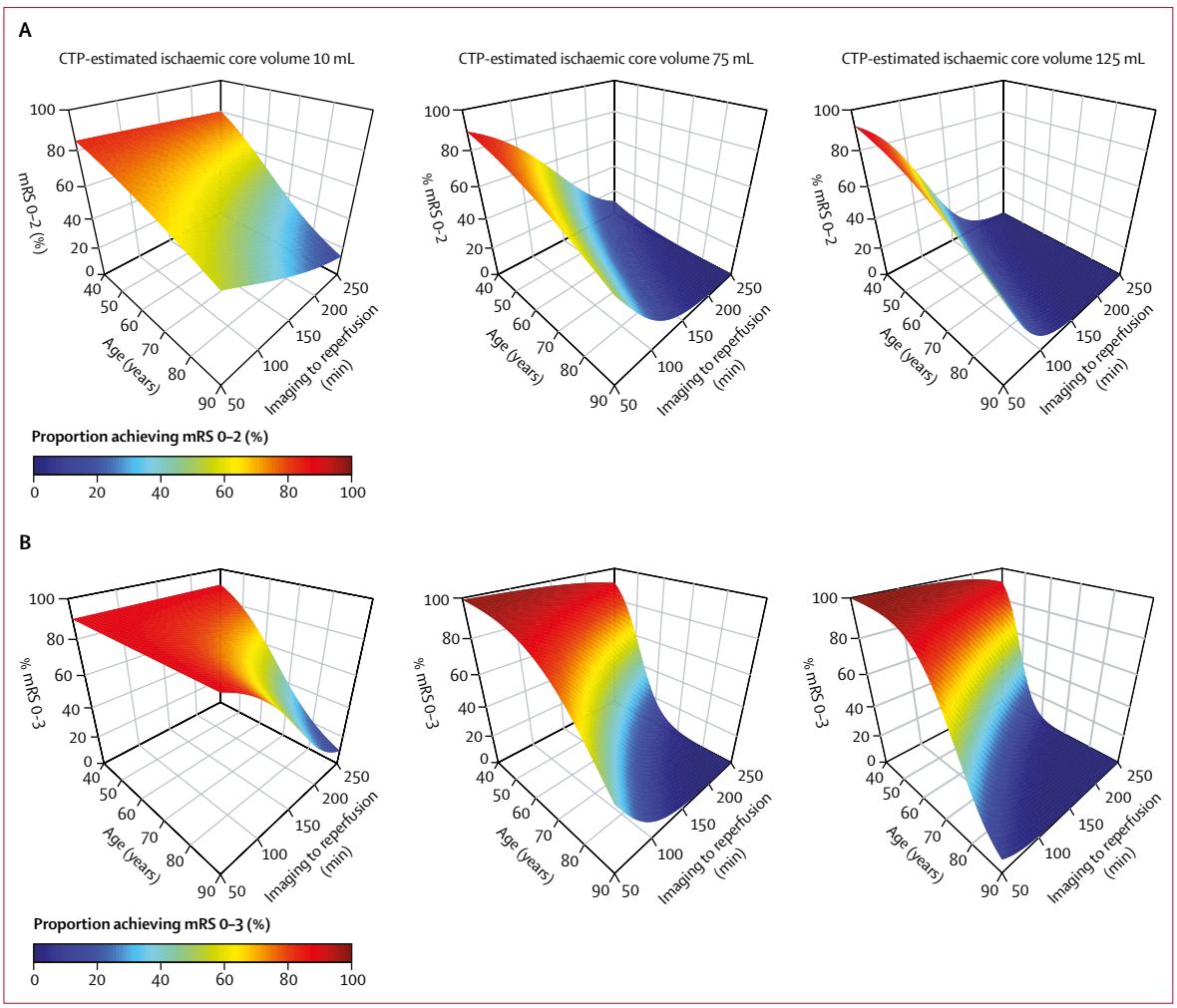

Figure 3: **Effect of ischaemic core volume estimated by CT perfusion, age, and imaging-to-reperfusion time on functional outcome in the 186 patients with more than 50% endovascular reperfusion**

90-day functional outcome dichotomised at mRS 0–2 (functional independence; A) and mRS 0–3 (B). mRS=modified Rankin Scale.

ischaemic core when rapid reperfusion was possible (figure 3B).

CTP mismatch volume was assessable in 583 (99%) of 591 patients (eight had motion artefacts preventing measurement of T_{max}). The median CTP mismatch volume was 96 mL (IQR 64–138 mL); a mismatch of 0–10 mL was present in five (1%) of 583 patients, 10–60 mL in 125 (21%) patients, and 60 mL or more in 453 (78%) patients. The median CTP mismatch ratio was 9·4 (IQR 3·6–33·7). Of the 583 patients, 556 (95%) met the mismatch ratio threshold of more than 1·8 as initially applied in SWIFT PRIME[6] and 580 (99%) met the threshold of more than 1·2 as applied in EXTEND-IA.[4] CTP mismatch volume was correlated with ischaemic core volume (ρ=0·13; p=0·002). In univariable analysis, CTP mismatch volume was associated with functional improvement (cOR per 10 mL 0·96 [95% CI 0·93 to 0·99], p=0·009) and utility-weighted mRS (β per 10 mL –0·007 [–0·011 to –0·002], p=0·001) but not functional independence (OR per 10 mL 0·97 [0·93–1·00], p=0·08). When ischaemic core volume was included in the model, CTP mismatch volume was not associated with either outcome (utility-weighted mRS β per 10 mL –0·001 [95% CI –0·006 to 0·004], p=0·60; functional independence OR per 10 mL 1·01 [0·97–1·05], p=0·65).

Using SWIFT PRIME mismatch criteria,[6] 34 (6%) of 583 patients (14 in the endovascular group and 20 in the control group) had no CTP mismatch. These patients had no functional improvement from endovascular treatment (cOR 0·87 [95% CI 0·20–3·81], p=0·85) in a model adjusted for ischaemic core volume. Ischaemic core volume remained prognostic in this group (cOR 0·78 [0·67–0·90], p=0·002). The interaction between CTP mismatch status (as per SWIFT PRIME criteria) and endovascular treatment effect was not significant (p=0·15), although power was limited by the small number of patients not meeting criteria for mismatch. The included trials were of high quality, and

in both CTP and MRI analyses, risk of bias was assessed to be low overall, apart from the unblinded outcome assessment in THRACE (which did not contribute to the CTP analyses).[9]

Increasing CTP-estimated ischaemic core volume was not associated with a significant reduction in absolute treatment effect or increased number needed to treat, assessed using common dichotomies and ordinal logistic regression analysis of mRS (figure 4). Notably, the lower boundary of the 95% CI for treatment effect on functional improvement remained more than 0 for ischaemic core volumes up to 150 mL. The number needed to treat point estimate remained less than ten for most functional outcomes and less than five for functional improvement in patients with ischaemic core volumes up to about 125 mL, noting wide CIs. Absolute risk reduction by diffusion MRI lesion volume and number needed to treat is in the appendix.

Discussion

Large estimated ischaemic core volume was independently associated with worse functional outcome in patients treated with endovascular thrombectomy and in those who received standard medical therapy. Every 10 mL increase in pretreatment ischaemic core volume reduced the odds of favourable functional outcomes by 20–30%. However, large ischaemic core volume did not prevent benefit of endovascular thrombectomy compared with standard medical therapy in patients who otherwise met eligibility for these trials. At every ischaemic core volume level, favourable functional outcomes were more likely with thrombectomy than with medical therapy alone. Favourable functional outcomes among thrombectomy patients were associated with age, ischaemic core volume (reflecting accumulated injury before imaging) and time from imaging to reperfusion (reflecting additional injury before reperfusion). This combination of prognostic factors might inform more individualised decision making in patients with large ischaemic core volumes. CTP mismatch volume was not associated with functional outcomes independent of ischaemic core volume and did not interact with treatment effect. However, the few patients with no CTP mismatch by SWIFT PRIME[6] criteria had no benefit from endovascular thrombectomy.

The early time window and imaging selection approaches used in many of the included trials resulted in a modest number of patients with large ischaemic core volumes, even in this large pooled dataset, and thus the power to probe for treatment effect modification by ischaemic core volume was constrained. Moreover, similar ORs (and hence absence of statistical interaction) can mask substantial differences in absolute treatment effect, which might be clinically relevant. Notably, the absolute benefit and number needed to treat point estimates for different functional outcomes across a wide range of ischaemic core volumes remained clinically meaningful.

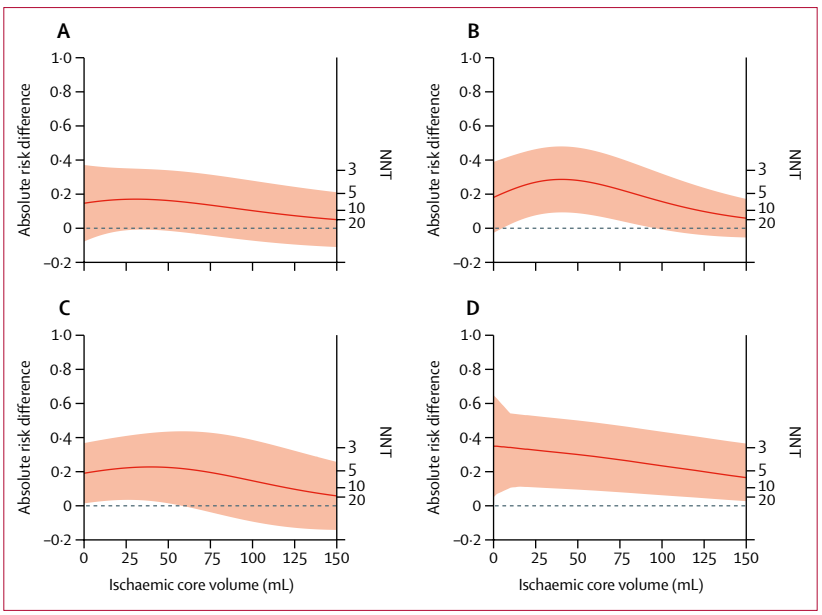

Figure 4: **Treatment effect of endovascular thrombectomy versus medical therapy by ischaemic core volume estimated by CT perfusion**
(A) Excellent functional outcome (mRS 0–1). (B) Functional independence (mRS 0–2). (C) mRS 0–3. (D) Functional improvement by at least one mRS category (n=591). Solid lines show point estimates and shaded regions show 95% CI. Models adjusted for age, sex, baseline clinical severity (National Institutes of Health Stroke Scale score), time from stroke onset to randomisation, administration of intravenous alteplase, core lab-adjudicated non-contrast CT Alberta Stroke Program Early CT Score, and site of vessel occlusion, with a random effect for trial. NNT=number needed to treat. mRS=modified Rankin Scale.

In ordinal logistic regression analysis of the mRS score, confidence intervals indicated that a clinically significant benefit of at least one-point improvement was maintained up to approximately 150 mL of ischaemic core volume as estimated by CTP or diffusion MRI. Additionally, treatment of patients with large ischaemic core volumes did not appear to cause harm because symptomatic intracerebral haemorrhage was not increased in those patients.

In patients with more than 50% endovascular reperfusion, the key prognostic variables were age, ischaemic core volume, and imaging-to-reperfusion delay. When CTP ischaemic core volume was included in the multivariable logistic regression model, it was strongly related to functional outcome, ASPECTS was no longer associated with outcome, and the effect of stroke onset-to-imaging time on functional improvement became non-significant. This reflects the benefits of directly assessing the extent of ischaemic injury that can be highly variable between patients, despite similar time elapsed from stroke onset. The impact of a 10-mL increase in ischaemic core volume was approximately equivalent to a 30-min delay in imaging to reperfusion or a 5-year increase in age. Chronological age is not an ideal selection criterion and physiological robustness and functional reserve might be more valid in clinical practice, albeit harder to quantify objectively. Our data illustrate the principle that weighing patient functional status, the estimated volume of

irreversible injury at the time of imaging (ie, ischaemic core volume), and the expected time to achieve reperfusion (particularly when transfer to another hospital might be required) can improve patient selection for endovascular thrombectomy. The importance of faster workflow to reduce treatment delay is particularly evident for patients with a large ischaemic core.

There has been debate about the relative merits of CTP versus MRI as initial imaging strategy and, indeed, whether either is useful for endovascular thrombectomy selection within 6 h of stroke onset.[24] By contrast, penumbral imaging is central to selecting patients who benefit from thrombectomy beyond 6 h.[17,18] However, our data show a strong relationship between ischaemic core volume and functional outcome that substantially improves estimation of prognosis versus non-contrast CT and clinical variables. The absolute probability of meaningful improvement in a patient with a large ischaemic core volume, in addition to poor clinical prognostic factors, might be sufficiently low that thrombectomy might be regarded as futile, even within 6 h of stroke onset.

Notably, CTP and diffusion MRI ischaemic core volume versus functional outcome curves were offset (diffusion MRI was associated with better outcome at any estimated ischaemic core volume). However, the absence of statistical interaction indicated that the prognostic influence per mL increase in ischaemic core was similar. It remains unclear whether this imaging modality difference occurred because of underestimation of infarct volume by CTP, overestimation by diffusion MRI, a trial-specific effect (with most diffusion MRI data coming from a single trial), or some combination of these factors. Regardless, no evidence was found for a difference in prognostic accuracy between diffusion MRI and CTP.

Study limitations include that CTP was not required in all trials and therefore, imaging acquisition protocols varied. Overestimation of the actual ischaemic core volume could potentially explain good functional outcomes in some patients with a large ischaemic core volume. However, analyses using follow-up infarct volume in the HERMES dataset,[26] SWIFT PRIME,[27] and EXTEND-IA[2] showed that substantial overestimation of the ischaemic core volume using CTP processed with RAPID software was rare. RAPID has been used in multiple trials and its accuracy is well described.[12,27–29] Results using other software packages vary substantially[30] and our findings might not apply. Most diffusion MRI data came from one trial (THRACE[9]). Although all analyses were adjusted by trial, some residual trial effect might have persisted in the diffusion MRI data. The multivariable model for favourable functional outcome among CTP-imaged patients with more than 50% reperfusion was assessed in 186 patients. Collection of large patient datasets with baseline CTP and diffusion MRI, successful reperfusion, and 90-day functional outcomes is desirable to validate and improve precision of the prognostic model.

In conclusion, our individual patient-level meta-analysis showed the potential for clinically meaningful benefit of endovascular thrombectomy in patients with large baseline ischaemic core when treated within 6 h of stroke onset. This benefit was particularly evident in younger patients with fast imaging-to-reperfusion times. Patients should therefore not be excluded from therapy solely based on a large ischaemic core volume. Clinical judgement is required based on the individual patient's overall health status, location of the core relative to critical brain regions, the time to expected reperfusion and, where known, the patient's attitudes to different potential disability states. Further study of the risk and benefit of endovascular reperfusion in patients with a large ischaemic core volume at initial imaging is crucial to ensure that thrombectomy is available to the broadest possible range of appropriate patients with large-vessel ischaemic stroke who have the potential to benefit.

Contributors

BCVC prepared the first draft of the report based on an analysis plan agreed by the HERMES executives (BCVC, MG, DWJD, AMD, SBra, PW, AD, CBLMM, FG, KWM, JLS, TGJ, MDH, and PJM) who also contributed to study interpretation. SBro did the statistical analyses. DSL co-ordinated the central imaging repository. GS and NY assisted with image processing. All authors participated in patient enrolment and data collection, critically reviewed the report, and approved the final version.

Declaration of interests

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