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

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ABSTRACT

Background: CT-perfusion (CTP) and MRI may assist patient selection for endovascular thrombectomy. We aimed to establish whether imaging assessments of ischaemic core and penumbra volumes were associated with functional outcomes and treatment effect.

Methods: In this systematic review and meta-analysis, we pooled patient-level data from all randomised controlled trials comparing endovascular thrombectomy using predominantly stent-retrievers with medical therapy in anterior circulation ischaemic stroke listed in Pubmed 1/Jan/2010-31/May/2017 (HERMES Collaboration). The primary outcome was functional outcome as assessed by the modified Rankin scale (mRS) at 90 days. Irreversibly injured ischaemic core was estimated as CTP relative cerebral blood flow<30% of normal brain or MRI apparent diffusion co-efficient threshold<620μm^2/s. Hypoperfused tissue-at-risk of infarction was estimated using CTP time-to-maximum (Tmax)>6s. Mismatch (estimated penumbral) volume was calculated as tissue-at-risk minus core volume. The association of pre-treatment core and penumbral volumes with 90-day mRS was analysed with multivariable logistic regression (functional independence; defined as mRS 0-2) and ordinal logistic regression (functional improvement by at least 1 mRS category) in all patients and those with >50% endovascular reperfusion, adjusted for baseline prognostic variables. The meta-analysis was prospectively designed, but not registered.

Findings: We identified 7 studies with 1764 patients, all were included in the meta-analysis. Pre-treatment CTP was available for 591(34%) and MRI for 309(18%) . Since functional independence was worse in patients who had pre-treatment CTP versus MRI, after adjustment for ischaemic core volume [odds ratio 0·47(0·30,0·72),

p=0·0007], the modalities were not pooled. Increasing ischaemic core volume was associated with reduced likelihood of functional independence [CTP adjusted OR=0·77(0·69-0·86) per 10mL, p(interaction)=0·29; MRI adjusted OR=0·87(0·81-0·94) per 10mL], p(interaction)=0·94. CTP mismatch volume was not associated with outcome. In CTP-imaged patients with >50% endovascular reperfusion, age(OR 0·83(0·72-0·94), p=0·005), ischaemic core volume(OR 0·82 (0·73-0·92), p=0·001), and imaging-to-reperfusion time(OR 0·79 (0·66-0·95), p=0·01) were independently associated with functional outcome in ordinal logistic regression.

Interpretation: Estimated ischaemic core volume was independently associated with outcome but did not modify treatment effect. Combining ischaemic core volume with age and expected imaging-to-reperfusion time will improve assessment of prognosis and may inform treatment decisions.

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Research in context

Evidence before this study

We did a systematic review of studies in any language in PubMed between 1/Jan/2010-31/May/2017 examining the prognostic effect of penumbral imaging parameters including estimated ischaemic core volume and penumbral mismatch volume in patients with stroke undergoing endovascular stent-thrombectomy using one of 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 outcomes in patients with the penumbral mismatch profile (which required an ischaemic core volume

<70mL) who reperfused (n=46) versus those who not reperfuse (n=32, OR 8·8, 95%CI 2·7-29·0) but there was not a significant benefit of reperfusion in patients without the favourable penumbral mismatch profile (n=21, OR 0·2, 95%CI 0·0-1·6). Two small retrospective studies suggested that reperfusion may benefit patients with large cores defined as either >70mL on diffusion MRI or extensive non-contrast CT hypodensity defined as Alberta Stroke Program Early CT Score (ASPECTS) 0-5. Subanalysis of 175 patients imaged with pre-treatment CTP in the MR CLEAN trial showed that >70mL ischaemic core volume was associated with less favorable 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 analysis of 1764 patients quantifies the independent prognostic effect of ischaemic core volume on functional outcome. A 10mL increase in ischaemic core volume had a similar adverse impact on functional outcome as a 30 minute delay in imaging-to-reperfusion time or a 5 year increase in age. However, the odds of improved outcome and absolute benefit (ie, number needed to treat) 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 hours 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 outcome and determining the most appropriate treatment.

Introduction

Individual patient data meta-analysis of endovascular thrombectomy after large-vessel ischaemic stroke demonstrated remarkable consistency in treatment effect across clinical subgroups, although age and clinical severity remained strongly prognostic[8] and treatment effect declined with delayed reperfusion.[9] However, the positive trials of endovascular thrombectomy 0-6h after ischaemic stroke onset used different clinical and brain imaging selection criteria.[1-7] Imaging selection for ischaemic stroke treatment aims to identify individual pathophysiology, rather than traditional group-average time thresholds.[10]

The presence of ischaemic penumbra (electrically non-functioning but metabolically viable brain tissue that is salvageable with rapid 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 multimodal MRI, when processed in a reproducible manner using validated thresholds, can estimate both the irreversibly injured ischaemic core and potentially salvageable ischaemic penumbra with reasonable accuracy.[13-16] The mismatch between the hypoperfused tissue-at-risk (or territory of the occluded artery) and the ischaemic core estimates the salvageable penumbra.

The DAWN[17] and DEFUSE3[18] trials demonstrated benefit of thrombectomy beyond 6h in patients with favourable CTP or MR penumbral imaging. However, the role of penumbral imaging selection within 6h of stroke onset remains uncertain. Patients estimated to have a large ischaemic core are sometimes excluded from reperfusion therapies[2-5] and the thrombectomy trials used variable non-contrast CT, CT-

angiographic collaterals, CTP and multimodal MRI criteria. There are limited data characterising clinical benefit of endovascular thrombectomy as ischaemic core volume increases. The DEFUSE2 prospective cohort study demonstrated benefit of endovascular reperfusion in patients with favourable perfusion-diffusion MRI (criteria included diffusion lesion volume<70mL).[12] No benefit was observed among patients without the favourable imaging profile. In contrast, two retrospective observational studies suggested benefit of reperfusion in patients with MRI-diffusion lesions>70mL[19] or Alberta Stroke Program Early Computed Tomography Score (ASPECTS)<6 which correlates with large ischaemic core.[20] Sub-analysis of pre-treatment CTP from MR-CLEAN (n=175) found no interaction between ischaemic core volume and treatment effect.[21]

We did a systematic review and meta-analysis of all randomised controlled trials of stent-retriever thrombectomy versus medical therapy within 6h published between 1/01/2010 and 31/05/2017 to assess the influence of ischaemic core volume (estimated using CTP and MRI-diffusion), and the volume of hypoperfused tissue-at-risk (estimated using CTP) on functional outcome after thrombectomy.

Methods

Search strategy and selection criteria

This study was a systematic review and meta-analysis, performed according to PRISMA guidelines, comparing endovascular thrombectomy predominantly performed with stent-retrievers versus medical therapy in patients with anterior circulation ischaemic stroke. We searched PubMed for randomised controlled trials published in any language between 1/01/2010 and 31/05/2017 using the search string ((“randomized 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 trials: MR-CLEAN,[1] EXTEND-IA,[2] ESCAPE,[3] SWIFT-PRIME,[4] REVASCAT,[5] PISTE[6] and THRACE[7] were pooled in the Highly Effective Reperfusion using Multiple Endovascular Devices (HERMES) collaboration.[8] 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 available in the appendix.

Data analysis

Statistical analysis was performed using SAS v.9.4 (SAS Institute, Cary, NC, USA) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria). Qualitative assessment of between-trial differences including patient eligibility and assessment of bias are presented in appendix.

An independent core laboratory (Los Angeles, USA) collated imaging data, assigning a random HERMES ID to blind assessors to trial of origin. Individual CTP and MRI-diffusion data were uniformly reprocessed using RAPID software (v4.6, iSchemaView, Menlo Park, California) as used in EXTEND-IA[2] and SWIFT-PRIME.[4] All automated output was visually verified and artefacts removed by a stroke neurologist with extensive neuroimaging analysis experience, blinded to treatment allocation and all other imaging and clinical information. For CTP, irreversibly injured ischaemic core was estimated as relative cerebral blood flow<30% of normal brain.[13] For MRI-diffusion, ischaemic core was defined using apparent diffusion co-efficient (ADC)<620$\mu m^2/s$.[22] Tissue-at-risk of infarction was estimated using CTP-Tmax>6s.[23] Penumbral mismatch volume was calculated as the difference between Tmax>6s

and ischaemic core lesion volumes and penumbral mismatch ratio as Tmax>6s divided by ischaemic core lesion volume.

The primary outcome was modified Rankin scale (mRS) at 90 days. Regression analyses were adjusted for 7 baseline prognostic variables: 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 noncontrast-CT ASPECTS, and site of vessel occlusion. To account for between-trial variance we used mixed-effects modeling with a random effect for trial incorporated in all 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 logistic regression for functional independence (mRS 0-2) and ordinal logistic regression for the 6-level mRS (merging categories 5-6). Since imaging modality was a prognostic factor, these data were treated separately for the main analysis. The treatment effect in the prespecified subgroups with ischaemic core volume <70mL vs >70mL was examined using ordinal logistic regression (6-level mRS). Symptomatic intracerebral haemorrhage was assessed as a safety outcome using the definitions applied in the original trials (appendix).

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

Modeling of the effect of ischaemic core and penumbral mismatch volumes on functional outcome was performed using mRS0-2 (functional independence) and the utility-weighted mRS score, a patient-centered, linear disability measure that converts each mRS score to a utility score between 1(perfect health) and 0(death)[24]: mRS 0=1, mRS 1=0·91, mRS 2=0·76, mRS 3=0·65, mRS 4=0·33, mRS 5=0, mRS 6=0. Reduction in utility score can therefore be expressed as a percentage increased disability.

The number needed to treat (NNT) to achieve mRS 0-1, 0-2, 0-3 or at least 1 unit improvement in mRS with endovascular treatment versus control was calculated for a range of ischaemic core volumes, based on model-derived adjusted treatment effects (absolute risk reduction). NNT was calculated as 1/absolute risk reduction.
The association between pre-treatment ischaemic core and penumbral mismatch volumes and the 90-day mRS was examined by treatment status. The subgroup with >50% endovascular reperfusion (post-procedure, core-lab adjudicated, modified Treatment in Cerebral Infarction (mTICI)2b-3) was also examined.[25]

Role of the funding source

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

Of 1764 patients included in the 7 RCTs, penumbral imaging was performed and assessable in 900(51%). Pre-treatment CTP was obtained in 625(35%) and assessable in 591(34%) after exclusion of 34 patients (11 severe motion, 7 no lesion within coverage, 2 contrast bolus failure, 14 data corruption during transfer from site). Of the 591 patients, 289(49%) were randomised to endovascular thrombectomy and 302(51%) to control group. Baseline characteristics were similar between endovascular and control patients with pre-treatment CTP (table 1). Median CTP-estimated ischaemic core volume was 10mL(IQR 3-28mL), appendix). Pre-treatment MRI-diffusion was obtained in 309/1764(18%) patients, 153/309(50%) randomised to endovascular thrombectomy and 156/309(50%) to control group. No significant differences were observed in baseline characteristics between endovascular and control patients with pre-treatment MRI-diffusion. Median MRI-diffusion estimated ischaemic core volume was 21mL(IQR 10-52mL, appendix). Imaging was performed within 6h of stroke onset in 887/900(99%) patients. MRI-perfusion was available for only 33 patients and was not analysed.

In logistic regression, ischaemic core volume was associated with reduced independent functional outcome (OR 0·85, 95%CI 0·80-0·90, p<0·0001) and worse outcome in ordinal logistic regression analysis of mRS (cOR 0·86 95%CI 0·83-0·89, p<0·0001), per 10mL increase, after adjustment for the 7 prespecified covariates and imaging modality (CTP or MRI). Imaging modality was independently associated with reduced independent functional outcome (OR 0·47, 95%CI 0·30-0·72, p=0·0007) and worse outcome in ordinal logistic regression analysis of mRS (cOR 0·51 95%CI 0·36-0·72, p=0·0001). There was no interaction between imaging modality and treatment effect (p=0·86), indicating that the relative effect on outcome per 10mL increase in core was consistent between modalities. Given these differences in predicted

functional outcome modeled on core volume between the MRI and CTP groups, these data were not pooled for subsequent analyses.

Larger ischaemic core volume estimated using CTP was associated with lower probability of independent functional outcome (mRS0-2) in endovascular (OR 0·79 95%CI 0·69-0·90) and control patients (OR 0·71 95%CI 0·56-0·90) per 10mL increase in volume in the 7-covariate adjusted model. Benefit from thrombectomy was not modified by ischemic core volume (core*treatment interaction p=0·29, figure 1). When ASPECTS (which was correlated with ischaemic core volume but not independently associated with outcome) 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 10mL increase in ischaemic core volume was associated with reduced odds of independent functional outcome (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). The odds ratio relating core volume to independent functional outcome was similar in the subgroup of endovascular patients with >50% reperfusion (n=186, OR 0·83 95%CI 0·71-0·97 per 10mL increase in ischaemic core volume). At 100mL ischaemic core volume, the absolute increase in independent functional outcome was 25.4%, 95%CI 0.8-49.9% if endovascular reperfusion was achieved versus the control group.

Larger CTP-estimated ischaemic core volume was also associated with worse disability outcome using utility-weighted mRS. Utility was significantly reduced by 3%, 95%CI 1-4% per 10mL increase in ischaemic core volume for endovascular patients and by 2%, 95%CI 1-3% for control patients. Though 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 1). In endovascular-treated patients with >50% reperfusion (n=186), utility was significantly reduced by 3%, 95%CI 1-5% per 10mL increase in ischaemic core volume (appendix). In ordinal logistic regression including both endovascular and control patients, ischaemic core volume had cOR 0·85, 95%CI 0·81-0·91 per 10mL increase with the other significant covariates being age, baseline NIHSS, endovascular treatment and site of vessel occlusion (appendix).

In the pre-planned subgroup analysis of patients with ischaemic core >70mL using CTP (n=50, median 100mL(IQR 82-144mL), 2(8%) of 25 thrombectomy and 0/25(0%) control patients achieved functional independence (OR infinite). Thrombectomy patients had improved functional outcome in unadjusted ordinal logistic regression analysis of the mRS: cOR 3·1 95%CI 1·0-9·4 (figure 2). However, despite similar age in both treatment groups, NIHSS was higher in the control group than in the thrombectomy group (median 22 versus 18, p=0·005) and the ischaemic core volume was numerically larger in controls than in the thrombectomy patients (median 110mL versus 85mL, p=0·12, ASPECTS 5 versus 8, p=0·001). There was insufficient sample size to include the full 7-co-variates in the >70mL subgroup but adjustments for age and NIHSS resulted in cOR 1·8, 95%CI 0·3-12·5, p=0·53. In this subgroup, there was no difference in symptomatic intracerebral haemorrhage between endovascular patients 0/25(0%) versus 3/25(12%) control patients, p=0·24 (appendix).

MRI-diffusion lesion volume was independently associated with independent functional outcome in endovascular (OR 0·88, 95%CI 0·78-0·97) and control patients

(OR 0·87 95%CI 0·79-0·96) per 10mL increase in volume (figure 1, appendix) but did not significantly interact with thrombectomy treatment effect (p=0·94). Similarly, increasing MRI-diffusion lesion volume was independently associated with a reduction in utility score in endovascular (2%, 95%CI 1-3%) and control patients (2%, 95%CI 1-3%) per 10mL increase in volume; p-interaction=0·58. The relationship between ischaemic core and functional outcome in endovascular patients with >50% reperfusion (n=186) was similar to that observed in the CTP reperfusion subgroup (appendix). Patients with >70mL MRI-diffusion lesions (n=59) achieved functional independence in 7/23(30%) thrombectomy versus 7/36(20%) control group (OR 1.8, 95%CI 0.5-6.3, cOR 2.1, 95%CI 0.8-5.6, unadjusted, Figure 2).

Increasing CTP ischaemic core volume was not associated with a significant reduction in absolute treatment effect or increased NNT, assessed using common dichotomies and ordinal logistic regression analysis of mRS (Figure 3). Notably the lower confidence interval for treatment effect in ordinal analysis remained >0 for ischaemic core volumes up to 150mL. The NNT point estimate remained less than 10 for most outcomes and less than 5 for ordinal shift in patients with ischaemic core volumes up to ~125mL, noting wide confidence intervals. Absolute risk reduction by MRI-diffusion lesion volume and NNT is displayed in the appendix.

In multivariable logistic regression analysis within the CTP-imaged, endovascular-treated patients who achieved >50% reperfusion (n=186), age, imaging-to-reperfusion time and ischaemic core volume were associated with both ordinal improvement in mRS and functional independence (table 2). Surface plots display the effect of age and imaging-to-reperfusion time on functional outcome for a given

CTP ischaemic core volume in patients with >50% endovascular reperfusion (figure 4).

The median volume of CTP penumbral mismatch was 96mL(IQR 64-138mL), 0-10ml was present in 5 patients (<1%), 10-60ml in 125 (21%) patients, and ≥60ml in 453 (78%) patients. Motion artefacts excluded 8/591(1.4%) patients from this analysis. The median penumbral mismatch ratio was 9·4(IQR 3·6-33·7), 556/583(95)% had a ratio>1·8 as originally applied in SWIFT PRIME and 580/583(99·5%) had a ratio>1·2 as applied in EXTEND-IA. CTP penumbral mismatch volume was correlated with ischaemic core volume (rho=0·13, p=0·002). In univariate analysis, CTP penumbral mismatch volume was associated with ordinal mRS (OR per 10ml=0·96, 95%CI 0·93-0·99, p=0·009) and utility-weighted mRS (beta per 10ml=-0·007, 95%CI -0·011 to -0·002, p=0·001) but not functional independence (OR per 10ml=0·97, 95%CI 0·93-1·00, p=0·08). When ischaemic core volume was included in the model, mismatch was not associated with either outcome (utility-weighted mRS beta per 10ml=-0·001, 95%CI -0·006 to 0·004, p=0·60, mRS0-2 OR per 10ml=1·01, 95%CI 0·97-1·05, p=0·65).

There were 34/583(6%) patients with no CTP penumbral mismatch by SWIFT PRIME criteria (14 in the endovascular group and 20 in the control group). These patients had no benefit 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, 95%CI 0·67-0·90, p=0·002). The interaction between CTP penumbral mismatch status and endovascular treatment effect was not significant (p=0·15), although power was limited by the small number of patients without penumbral mismatch.

Discussion

Larger estimated ischaemic core volume was independently associated with worse outcome in patients treated with endovascular thrombectomy and in those who received medical therapy. Every 10ml increase in pretreatment ischaemic core volume reduced the odds of favourable outcomes by 20-30%. However, large ischaemic core did not prevent benefit of endovascular thrombectomy versus medical therapy in patients who otherwise met eligibility for these trials. At every ischaemic core volume level, favorable outcomes were more likely with thrombectomy than with medical care 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 may inform more individualized decision-making in patients with larger ischaemic core volumes. The volume of mismatch between the ischaemic core and hypoperfused Tmax>6s lesion was not associated with outcomes independent of ischaemic core volume and did not interact with treatment effect. However, few patients had no mismatch and there was no signal of benefit from endovascular thrombectomy in this group.

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 cores, even in this large pooled dataset, and the power to probe for treatment effect modification by ischaemic core volume was constrained. Moreover, similar odds ratios (and hence lack of statistical interaction) can mask substantial differences in absolute treatment effect, which may be clinically relevant. Importantly, the absolute benefit and number needed to treat point estimates for different functional outcomes

across the spectrum of ischaemic core volumes remained clinically meaningful. In ordinal analysis of the modified Rankin scale, confidence intervals indicated that a clinically significant benefit of at least 1 point improvement was maintained up to approximately 150mL of CT/MRI ischaemic core volume. In addition, there was no signal of harm as symptomatic intracerebral haemorrhage was not increased in patients with large ischaemic core in the included trials.

In patients with >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 model it was strongly related to functional outcome, non-contrast CT ASPECTS was no longer associated with outcome and the effect of stroke onset-to-imaging time became weak and of borderline significance. 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 10mL increase in ischaemic core volume was approximately equivalent to a 30min delay in imaging-to-reperfusion or a 5yr increase in age. Chronological age is not an ideal selection criterion and physiological robustness and functional reserve may be more valid in clinical practice, albeit harder to quantify objectively. Our data illustrate the principle that weighing patient functional status, the volume of irreversible injury at the time of imaging and the expected time to achieve reperfusion (particularly when transfer to another hospital may 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 6h of stroke onset.[24] In contrast, penumbral imaging is central to selecting patients who benefit from thrombectomy beyond 6h.[17,18] However, our data demonstrate strong prognostic relationships that substantially improve estimation of outcome versus non-contrast CT and clinical variables. As illustrated in figure 4, the absolute probability of meaningful improvement in a patient with a large ischaemic core, in addition to clinical poor prognostic factors, may be sufficiently low that thrombectomy may be regarded as futile, even within 6h of stroke onset.

Interestingly, CTP and MRI ischaemic core volume versus outcome curves were offset (MRI was associated with better outcome at any estimated core volume). However, the lack of statistical interaction indicated that the prognostic influence per mL increase in ischaemic core was similar. Whether this modality difference occurred due to underestimation of infarct volume by CTP, overestimation by DWI, a trial-specific effect (with the majority of MRI data coming from a single trial) or some combination of these factors remains unclear. Regardless, there was no evidence of a difference in prognostic accuracy between MRI and CTP.

Study limitations include that CTP was not required in all trials and therefore imaging acquisition protocols varied. Overestimation of the actual core volume could potentially explain good outcome in some patients with large estimated ischaemic core. However, analyses using follow-up infarct volume in this dataset,[26] SWIFT PRIME[27] and EXTEND-IA[2] showed substantial overestimation of the core volume using CTP processed with RAPID was rare. RAPID software 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 may not apply. The majority of MRI data came from one trial (THRACE). Although all analyses were adjusted by trial, some residual trial effect may have persisted in the MRI data. The component trials were of high quality and risk of bias was overall assessed to be low, apart from the unblinded outcome assessment in THRACE. The multivariable model for favourable outcome among CTP-imaged patients with >50% reperfusion and figure 4 were based on 186 patients. Collection of large patient datasets with baseline CTP and MRI-diffusion, successful reperfusion, and 90 day functional outcomes is desirable to validate and improve precision of the prognostic model.

In conclusion, this large series of patients with pre-treatment CTP and MRI-diffusion demonstrated the potential for clinically meaningful benefit in patients with large baseline ischaemic core when treated within 6h of stroke onset. This was particularly evident in younger patients with fast imaging-to-reperfusion times. Patients should therefore not be excluded from therapy solely based on large ischaemic core. Clinical judgment is required based on the individual patient's overall health status, location of the core relative to highly eloquent structures, 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 large ischaemic core at initial imaging is crucial to ensure that thrombectomy is available to the broadest possible range of appropriate large vessel ischaemic stroke patients with potential to benefit.

Contributors

BCVC prepared the first draft of the report based on an analysis plan agreed by the HERMES Executive (BCVC, MG, DWJD, AMD, S Bracard, PW, AD, CBLM, FG,

KWM, JLS, TJG, MDH, PJM) who also contributed to study interpretation. S Brown performed the statistical analyses. DSL co-ordinated the central imaging repository. GS and NY assisted with image processing. All authors participated in patient enrolment, data collection, critically reviewed the report and approved the final version. S Bracard, KWM, DWJD, MG, JLS, TGJ, MDH and PJM contributed equally.

Declaration of interests

Declaration of interests

B.C.V. Campbell: reports research support from the National Health and Medical Research Council of Australia (GNT1043242, GNT1035688), Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, National Heart Foundation, National Stroke Foundation of Australia and unrestricted grant funding for the EXTEND-IA trial to the Florey Institute of Neuroscience and Mental Health from Covidien (Medtronic).

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T.G. Jovin: has received personal fees for consultancy from Codman Neurovascular and Neuravi, holds stock in Silk Road, Anaconda, Route 92, FreeOx Biotech and Blockade; has acted as an unpaid consultant to Stryker as PI of the DAWN trial.
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Figure legends

Figure 1: Association of ischaemic core volume with functional outcome.

CT perfusion (CTP) ischaemic core volume versus A) functional independence, B) disability (utility scores derived from modified Rankin Scale (mRS).

MRI ischaemic core volume versus C) functional independence, D) disability. Point estimate (solid) and 95% confidence interval (dashed), models adjusted for 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 noncontrast CT ASPECTS, site of vessel occlusion with a random effect for trial.

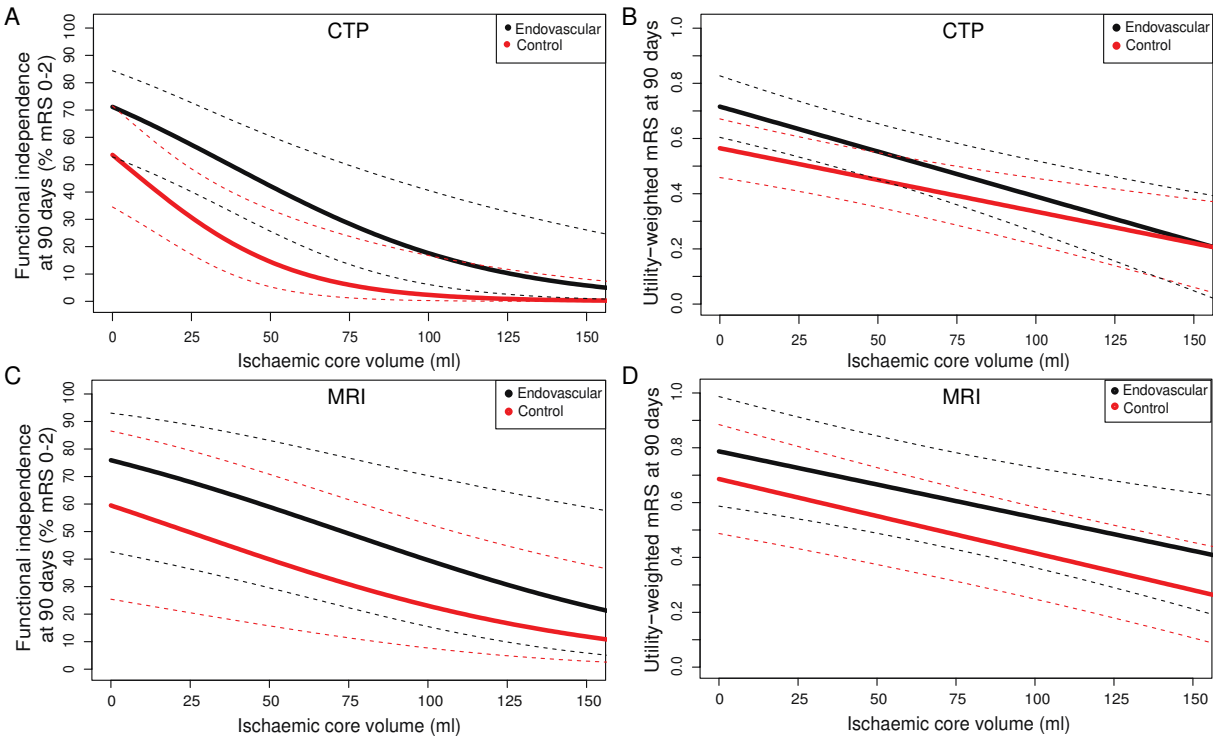

Figure 2: Functional outcome at day 90 stratified by ischaemic core volume

A) CTP ischaemic core volume </> 70mL B) MRI ischaemic core volume </>70mL.

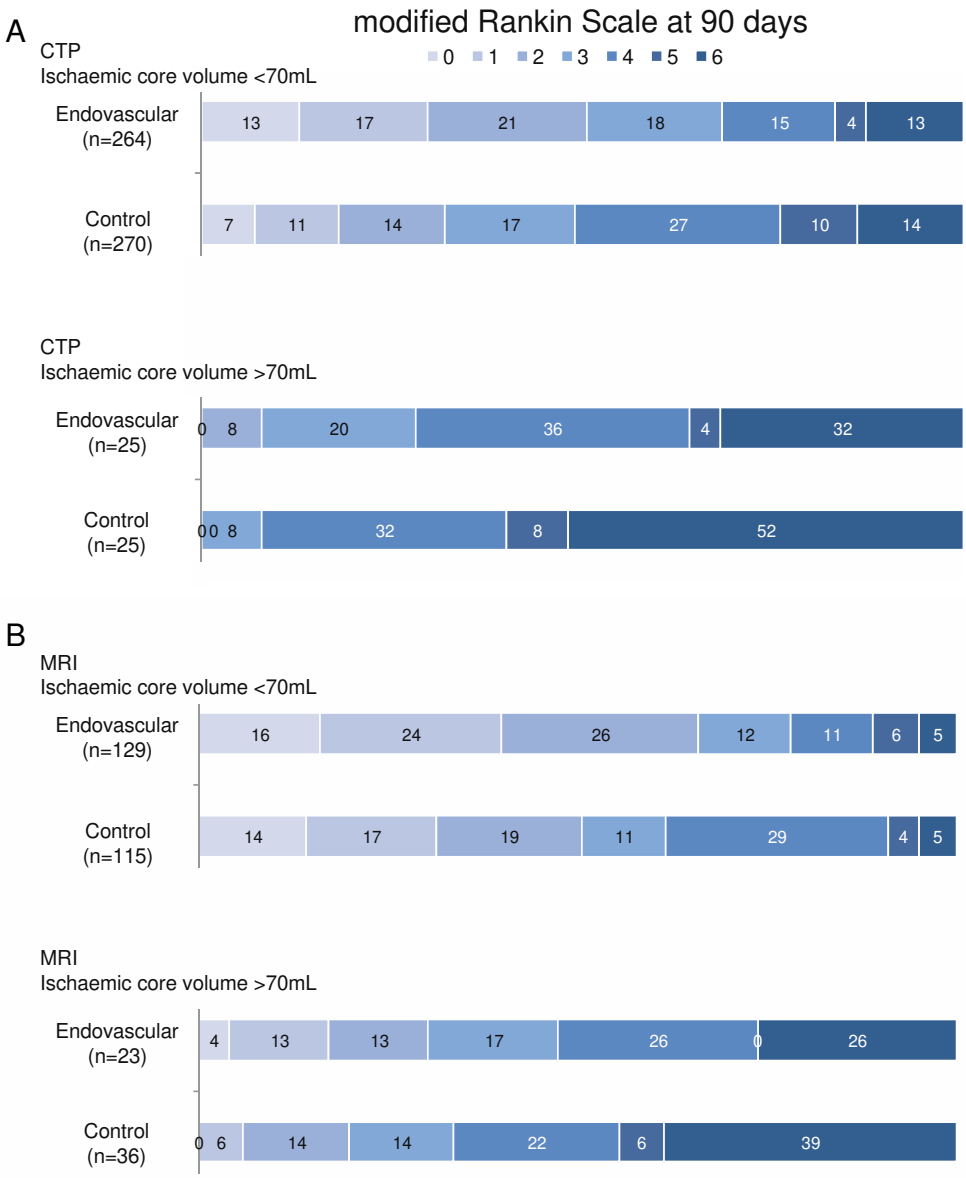

Figure 3: Treatment effect of endovascular thrombectomy versus medical therapy by CTP ischaemic core volume A) excellent functional outcome (mRS 0-1), B) functional independence (mRS 0-2) C) mRS 0-3, D) improvement by at least 1 mRS category (point estimate and 95% confidence interval). N=591 patients. NNT - number needed to treat. Models adjusted for 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 noncontrast CT ASPECTS, site of vessel occlusion with a random effect for trial.

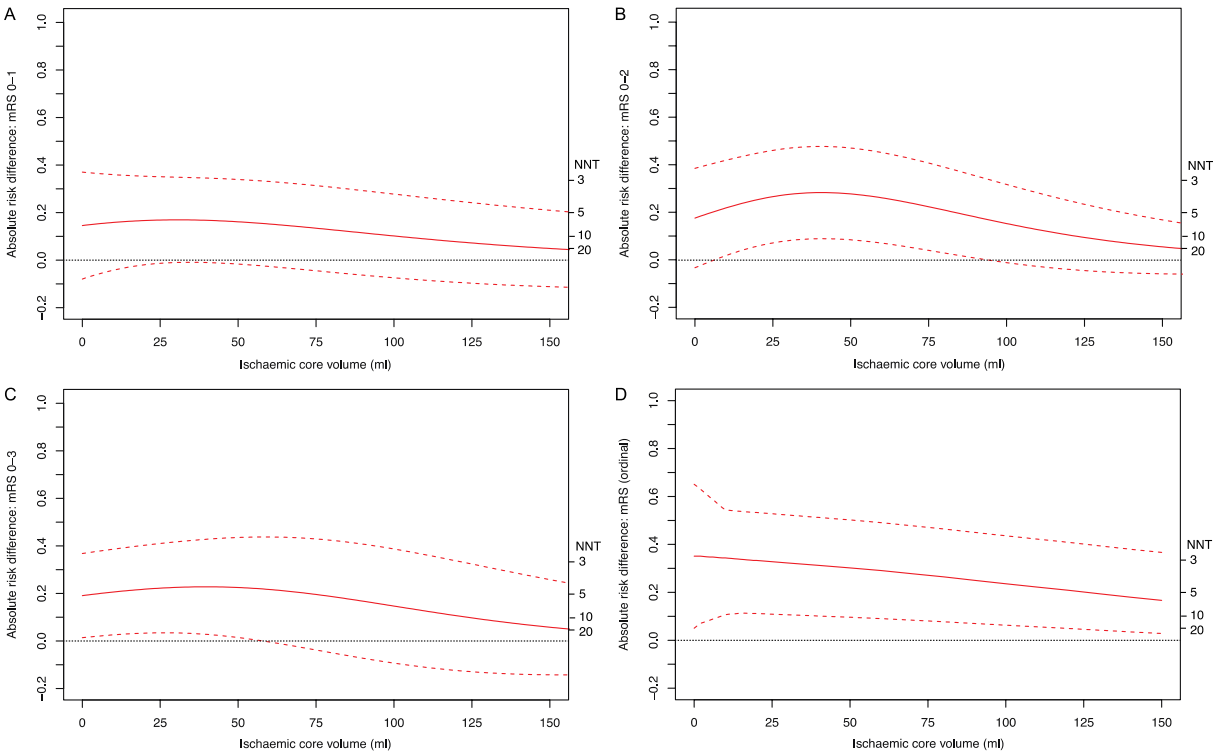

Figure 4: Effect of CT perfusion ischaemic core volume, age and imaging-to-reperfusion time on functional outcome after endovascular reperfusion.

90 day functional outcome dichotomized at A) modified Rankin scale (mRS) 0-2 and B) mRS 0-3 in patients who had >50% endovascular reperfusion (n=186) see expanded figure in appendix. Patients with small (10mL) ischaemic core often achieve functional independence (mRS 0-2) despite advanced age and/or extended delays between imaging and reperfusion. Patients with large (75mL) or very large (125ml) ischaemic core are unlikely to achieve functional independence unless reperfusion is achieved very shortly after imaging (panel A). However, many patients would prefer mild disability (mRS 3) to nursing home care or death and this is achievable, even for relatively elderly patients with large ischaemic core, if rapid reperfusion is possible (panel B).

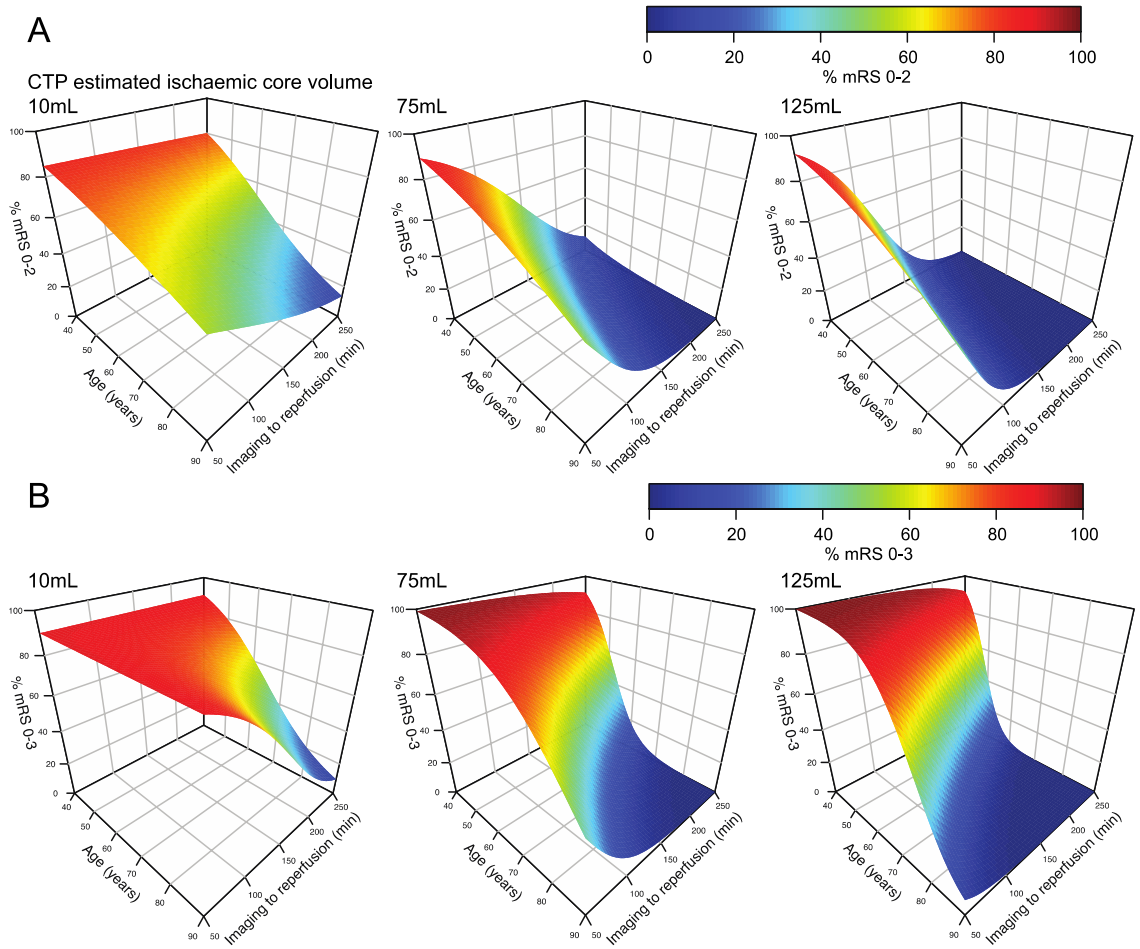

Table 1: Baseline characteristics of patients

Characteristic	CTP		MRI		Overall HERMES (n=1764)
	Endovascular (n=289)	Control (n=302)	Endovascular (n=153)	Control (n=156)	
Age mean	65·5 (13·7)	65·7 (13·0)	63·1 (13·1)	63·6 (14·0)	65·6 (13·5)
Sex Male Female	 137 (47%) 152 (53%)	 168 (56%) 134 (44%)	 94 (61%) 59 (39%)	 73 (47%) 83 (53%)	 929 (53%) 835 (47%)
Initial NIHSS median	17 (14-20)	17 (13-21)	18 (14-21)	17 (14-21)	17 (13-21)
Initial ASPECTS median	8 (7-9)	8 (7-9)	7 (6-8)	7 (5-8)	8 (7-9)
Site of arterial occlusion ICA M1 M2 Unknown	 79 (27%) 171 (59%) 28 (10%) 11 (4%)	 78 (26%) 189 (63%) 24 (8%) 11 (4%)	 25 (16%) 112 (73%) 5 (3%) 11 (7%)	 33 (21%) 101 (65%) 8 (5%) 14 (9%)	 442 (25%) 1073 (61%) 131 (7%) 116 (7%)
Onset to ED (min) median	110 (57-183)	110 (54-197)	105 (75-139)	110 (80-159)	105 (60-180)
ED to arterial access (min) median	103 (75-150)	NA	107 (85-140)	NA	115 (80-165)
Received IV Alteplase	248 (86%)	269 (89%)	145 (95%)	154 (99%)	1572 (89%)
Baseline ischaemic core volume (mL) median	10 (3-30)	9 (2·5-24)	18 (9-41)	23 (12-63)	NA
Baseline Tmax>6s perfusion volume (mL) median	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. CTP=CT perfusion. NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta stroke program early CT score. ICA=internal carotid artery. 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). ED=emergency department. IV=intravenous. NA=not applicable

Table 2: Independent functional outcome in patients imaged with CT-perfusion who achieved >50% endovascular reperfusion

Predictor among patients with endovascular reperfusion (n=186)	**Multivariable ordinal logistic regression**		**mRS 0-2 (multivariable logistic regression)**	
	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
tPA 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**