

The association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials

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CONTRIBUTORSHIP STATEMENT

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ABSTRACT

Background: Follow-up infarct volume (FIV) has been recommended as an early indicator of treatment efficacy in acute ischemic stroke patients. Questions remain about the optimal imaging approach for FIV measurement.

Objective: To examine the association of FIV with 90-day mRS and investigate its dependency on acquisition time and modality.

Methods: Data of seven trials were pooled. FIV was assessed on follow-up (12 hours-2 weeks) CT or MR. Infarct location was defined as laterality and involvement of the ASPECTS regions. Relative quality and strength of multivariable regression models of the association between FIV and functional outcome were assessed. Dependency of imaging modality and acquisition time (≤ 48 hours versus > 48 hours) was evaluated.

Results: Of 1665 included patients, 83% was imaged with CT. Median FIV was 41 mL (IQR: 14-120). Large FIV was associated with worse functional outcome (OR=0.88 [95% CI: 0.87-0.89] per 10 mL) in adjusted analysis. A model including FIV, location, and hemorrhage type best predicted mRS. FIV of ≥ 133 mL was highly specific for unfavorable outcome. FIV was equally strongly associated with mRS for assessment on CT and MR, even though large differences in volume were present (48 mL [IQR: 15-131] versus 22 mL [IQR: 8-71], respectively). Associations of both early and late FIV assessments with outcome were similar in strength ($\rho=0.60$ [95% CI: 0.56-0.64] and $\rho=0.55$ [95% CI: 0.50-0.60], respectively).

Conclusions: In patients with an acute ischemic stroke due to a proximal intracranial occlusion of the anterior circulation, FIV is a strong independent predictor of functional outcome and can be assessed before 48 hours, and on either CT or MR imaging.

INTRODUCTION

In current trials investigating stroke treatment, efficacy is generally evaluated by assessment of functional ability and physical limitations of patients rated on a relatively coarse scale such as the modified Rankin Scale (mRS). In the causal chain of acute ischemic stroke, treatments are designed to save or preserve brain tissue, which subsequently translates to improved functional outcome. Following the positive outcome of the five trials proving the efficacy of endovascular treatment (EVT) in patients with anterior circulation acute ischemic stroke due to large vessel occlusion,[1–5] it has been advocated that the volume of ischemic tissue injury may serve as an early signal of treatment efficacy and consequently as a surrogate endpoint for phase II trials.[6] Indeed, most trials also showed benefit of EVT in terms of a smaller infarct volume in patients treated with EVT. Follow-up infarct volume (FIV) is a more direct measurement of biological effect of treatment and can be measured much earlier than the traditional 90-day functional outcome on the mRS. FIV is therefore less likely to be confounded by intervening comorbid illness, rehabilitation therapy, or non-stroke related pathology. Using FIV as a surrogate could allow early-phase trials to be completed sooner and more efficiently, resulting in lower costs and greater speed of therapeutic development. To that end, a strong correlation between the potential surrogate and the clinical endpoint must first be proven. Previous studies examining the relation between FIV and functional outcomes have yielded inconsistent results and reported varying correlations and conclusions.[7–11] Research on the translation of ischemic tissue injury to functional outcome is further complicated by discrepancies in FIV assessment using different imaging approaches. For example, MR may provide more accurate estimates of tissue outcome parameters compared to CT since it is highly sensitive to ischemic tissue. Moreover, the optimal timing of FIV assessment is unclear. Imaging too early may prevent the accurate measurement of ischemic lesions that continue to grow.[12] In contrast, FIV assessment on late (3-7 days) follow-up imaging might be subject to artificial inflation due to cerebral edema. It is currently uncertain what effect these dependencies have on the association of FIV and functional outcome.[6]

Patient-level data of seven major randomized controlled trials that studied the benefit of EVT in acute ischemic stroke provided us with an extensive dataset to examine the association of FIV with 90-day mRS. In addition, this dataset allows the investigation of the dependency of FIV assessment on acquisition time and modality.

METHODS

Trial investigators of ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, MR CLEAN, PISTE and THRACE established the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration.[1–5,13,14] These seven randomized controlled trials investigated the benefit of EVT using second-generation mechanical devices in anterior circulation ischemic stroke patients. Design features and inclusion criteria of the contributing trials have been described previously.[13–15] Each of the seven trials was approved by a local central medical ethics committee and the research boards of all participating centers. Written informed consent was acquired from all patients or legal representatives.

According to the original trial imaging protocols, all participating sites were required to perform 24-hour follow-up imaging and were free to choose between CT and MR. Participating centers from MR CLEAN and THRACE were additionally requested to perform follow-up imaging at 5 days, or at hospital discharge. In EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT and PISTE, 5-day follow-up imaging was at the discretion of the intervention site. We included all patients with follow-up non-contrast CT (NCCT) or MR done at least 12 hours and up to 2 weeks (336 hours) after stroke symptom onset.

Imaging assessment

Tissue outcome was assessed on follow-up NCCT or MR. If multiple follow-up scans were available, the latest scan was selected for analysis with an upper limit of two weeks after onset. If both NCCT and MR were performed, MR was the modality of choice. FIVs were initially outlined using previously validated software.[16] Manual adjustment of lesion boundaries was performed by an expert neuroradiologist (WvZ, LFB or CBM) when appropriate. Areas with parenchymal hemorrhage

(within or adjacent to the infarct), cerebral edema extending into the contralateral hemisphere, and those causing ventricular and sulcal effacement were included in the lesion. In case of decompressive hemicraniectomy with no available pre-surgery scan, only the ischemic lesion within the theoretical boundaries of the skull was included. A consensus reading with 2 neuroradiologists was performed to resolve cases with any discrepancies. All imaging assessments were performed blinded to treatment assignment, study trial, and clinical findings (apart from baseline imaging to identify and eliminate old infarcts from the analysis). FIVs were calculated in milliliters (mL) by multiplying the number of voxels of the segmented ischemic lesions with its voxel size. Infarct location was assessed by the same neuroradiologists (WvZ, LFB or CBM) and defined by laterality (left or right hemisphere) and involvement of the 10 distinct anatomical regions of the Alberta Stroke Program Early CT score (ASPECTS) template.[17] In case of MR, $\geq 20\%$ infarction within an ASPECTS region was classified as an infarct positive region. The total follow-up ASPECTS score was calculated. Hemorrhagic transformations (HT) were scored according to the anatomical description of the Heidelberg Classification.[18] In case of multiple intracranial hemorrhages, all were scored.

Outcomes

The primary outcome was the degree of disability as scored on the modified Rankin Scale (mRS) at 90 days, considered as an ordinal outcome.[19] The mRS is a common measure of patient functional outcome after stroke, ranging from 0 (no symptoms) to 6 (death). Dichotomized functional outcomes were patients with excellent outcome, defined as mRS 0-1 vs. 2-6; patients with functional independence, defined as mRS 0-2 vs. 3-6; and death (mRS 6 vs. 0-5).

Statistical Analysis

A detailed description of the statistical analysis plan is provided in the Online-only Supplements. Dichotomous variables were presented as proportions while continuous variables were tested for normality (Shapiro-Wilk test) and presented as mean \pm SD if normally distributed, or as median and interquartile range (IQR) if not.

All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria). P-values were two-sided and $p < 0.05$ indicated statistical significance in all analyses.

Association of FIV and mRS

The association between FIV and ordinal mRS was estimated with adjusted and unadjusted ordinal and binary logistic regression models, and expressed as odds ratios (OR) with 95% confidence intervals (CI). For the primary outcome, ordinal logistic regression was performed. For dichotomized secondary outcomes, binary logistic regression was employed. All multivariable regression analyses included the pre-specified prognostic variables age and baseline National Institute of Health Stroke Scale score (NIHSS). Missing variables were included after imputation of the relevant covariate with median values of the non-missing data. To account for between-trial variance, we used mixed-effects modelling with a random effect for trial incorporated in all regression models.

Four mixed models were constructed; model A included FIV, model B included FIV and infarct location (laterality and ASPECTS involvement), model C included FIV and hemorrhage type, and model D included FIV, infarct location, and hemorrhage type. The likelihood function test Akaike's Information Criterion (AIC) was used to determine which model provided the best relative quality, where lower AIC values represent a better fitting model to the data.

Effect of age and baseline NIHSS

Three-dimensional surface plots were constructed to show the relation between favorable outcome, FIV, and the prognostic variables age and baseline NIHSS.

Discriminative power of FIV

The discriminative capability of FIV to predict dichotomized mRS was assessed by receiver operating characteristic (ROC) analysis. This was performed for FIVs assessed on either imaging modality and

for FIVs assessed on MR only. Thresholds for FIV were calculated for predicting unfavorable outcome (mRS 3-6) with specificities of 80, 90, and 95%.

Dependency on imaging modality and acquisition time

Outcome characteristics were compared to assess differences in subjects imaged with CT versus MR, and in subjects whom had imaging acquired within 48 hours of onset versus after 48 hours (and up to two weeks). The Mann–Whitney U test was performed to test for differences in FIV. We selected the multivariable regression model that provided the best relative quality, and tested whether the relation between FIV and mRS was different among imaging modalities and timing of follow-up image acquisition. The strength of association of FIV with mRS per imaging modality and follow-up acquisition time was calculated using partial Spearman correlations correcting for age, baseline NIHSS, and treatment assignment to control for potential confounding effects of those covariates.

RESULTS

Of the 1764 patients, 1690 (95.8%) had follow-up imaging acquired at least 12 hours after stroke symptom onset and before 2 weeks. Twenty-five patients were additionally excluded because of poor image quality or difficulties precluding accurate lesion determination, leading to a total of 1665 included patients. These difficulties included; large diffuse hemorrhages (n=12), extreme motion artefacts (n=8), diffuse cerebral ischemia (n=2), bihemispheric ischemic lesions (n=2), and incomplete image reconstruction (n=1). Baseline characteristics of the total population are presented in Online supplementary table S1.

Among 1665 patients, median age was 68 (IQR 57-76) years, and 781 (46.9%) were female. Median baseline NIHSS was 17 (IQR 13-21), 740 (47.9%) had a left sided infarct, 844 (50.7%) were randomized to EVT and 1496 (90%) received intravenous thrombolysis. The majority (n=1383; 83%) had follow-up NCCT and the remainder MR. Median FIV was 41mL (IQR 14-120mL) and median mRS at 90 days was 3 (IQR 2-4), with 651 (39.0%) achieving functional independence (mRS 0-2).

Eight-hundred-ninety-four (56%) of the 1598 patients with timing reported had follow-up imaging within 48 hours.

Association of FIV and mRS

The distribution of FIV per mRS category is depicted in Figure 1, which demonstrates progressively larger FIVs with increasing mRS scores (Spearman’s ρ correlation coefficient, 0.58; $p < 0.001$). Results of the four multivariable regression models of the association between FIV and mRS, and AICs are shown in Table 1.

Table 1. Association of follow-up infarct volume with ordinal modified Rankin Scale and AICs of the multivariable models			
Model	Odds Ratio for FIV per 10mL	95% CI	Likelihood function test (AIC)
A	0.88	0.87 – 0.89	4842
B	0.91	0.90 – 0.93	4781
C	0.88	0.87 – 0.90	4825
D	0.92	0.90 – 0.94	4775

Odds ratio’s towards shift in better outcome on modified Rankin Scale
 All multivariable regression models (A – D) included age and National Institutes of Health and Stroke Scale score. In addition, Model A included FIV; Model B included FIV and location (laterality and Alberta Stroke Program Early CT score); Model C included FIV and hemorrhage type, and Model D included FIV, location and hemorrhage type.
 Abbreviations: FIV, follow-up infarct volume; CI, confidence interval; AIC, Akaike’s Information Criterion.

The ORs of each variable within the four multivariable regression models are presented in Online supplementary table S2. FIV was independently associated with mRS in addition to age and baseline NIHSS ($p < 0.001$ for all three variables across all models). Model D, which includes location and hemorrhage type was the superior model with the lowest AIC. This best relative quality was principally due to the presence of infarct in the Internal Capsule (OR 0.45; $p < 0.001$) and to a lesser extent in the M5 ASPECTS regions (OR 0.77; $p = 0.042$), intraventricular hemorrhage (OR 0.29; $p = 0.002$), and hemorrhagic infarct type 2 (OR 0.71; $p = 0.043$). Laterality ($p = 0.36$) was not an independent predictor of functional outcome.

Effect of age and baseline NIHSS

Three-dimensional surface plots of the effects of age, baseline NIHSS and FIV on the likelihood of reaching favorable outcome are depicted in Online supplementary figure 1a and 1b for the total

population, and in Online supplementary figure 2a and 2b for patients who had FIV assessed on MR imaging only. These figures illustrate the importance of age, and show that even with a small FIV, the chance of reaching functional independence is drastically reduced in older patients. Moreover, patients can still achieve favorable outcomes despite having stroke-related neurologic deficit at baseline.

The relation between FIV adjusted for pre-specified prognostic variables and estimated probability for excellent outcome, favorable outcome, and death is displayed in Online supplementary figure 1c. Online supplementary figure 2c shows this relation for MR imaging only.

Discriminative power of FIV

Analysis of the ROC to classify between favorable and unfavorable outcome by FIV showed an AUC of 0.80. ROC analysis for all dichotomized outcomes are shown in Online supplementary figure 3a for the total population, and in Online supplementary figure 3b for FIVs assessed on MR. Thresholds for FIV with high specificities for an unfavorable outcome (mRS 3-6) are displayed in Table 2. These thresholds indicate that unfavorable outcome is almost inevitable when an infarction exceeds 133mL.. Thresholds calculated per imaging modality are presented in Online supplementary table S3.

Table 2. Follow-up infarct volume thresholds with high specificity for unfavorable outcome (modified Rankin Scale score of 3-6)		
Specificity	Follow-up infarct volume threshold in mL	95% CI for unfavorable outcome
95%	133	(92.3%, 97.1%)
90%	96	(87.0%, 92.5%)
80%	32	(77.3%, 82.6%)

Abbreviations: CI, confidence interval

Dependency on imaging modality and acquisition time

Outcome characteristics stratified by imaging modality and follow-up acquisition time are presented in Online supplementary table S4 and S5. We found significantly lower FIVs in subjects imaged with MR (median of 22mL) compared to subjects imaged with CT (median of 48mL) (p<0.001). Also, patients who underwent MR had lower 90-days mRS scores and rates of hemorrhagic infarct type 2 (HI-2), higher reperfusion rates, and shorter time from onset to follow-up imaging. Lower rates of hemorrhagic infarct type 1 (HI-1) and remote parenchymal hemorrhage were observed in patients who

were imaged with CT. We found that mRS was not significantly different ($p=0.28$) for patients in whom FIV was assessed on CT compared to MR in model D, which incorporated lesion location and hemorrhage type as a predictor in addition to age and baseline NIHSS.

A significant difference in FIV was found between patients who had early versus late follow-up imaging, with a median of 32 mL in images acquired up to 48 hours versus 56 mL in those acquired past 48 hours ($p=0.042$). Our results show that the relation between FIV and mRS was not significantly different between follow-up acquisition times ($p=0.36$).

The strength of correlation between FIV and mRS was moderate and statistically significant with a Spearman's ρ of 0.58 ($p<0.0001$). The correlations of FIV measurements per imaging modality and follow-up acquisition time with mRS are shown in Table 3, and are all similar in strength, ranging from a Spearman's ρ of 0.55 for FIV assessment on imaging after 48 hours to a Spearman's ρ of 0.60 for FIV assessment on imaging up to 48 hours.

Table 3. The strength of association of follow-up infarct volume with functional outcome of the total population, and per imaging modality and follow-up acquisition time.			
FIV assessment	Spearman ρ	95% CI	p-value
Full population	0.58	(0.55-0.62)	<0.0001
CT	0.57	(0.53-0.61)	<0.0001
MR	0.59	(0.51-0.66)	<0.0001
<48 hours	0.60	(0.56-0.64)	<0.0001
>48 hours	0.55	(0.50-0.60)	<0.0001
Abbreviations: FIV, follow-up infarct volume; CI, confidence interval			

DISCUSSION

Our analysis of the HERMES dataset shows that FIV is an independent predictor of functional outcome in patients with acute ischemic stroke due to a proximal intracranial occlusion of the anterior circulation in addition to age and baseline NIHSS. We found a strong association between FIV and 90-day mRS indicating that it might be suitable as a surrogate biomarker for functional outcome after acute ischemic stroke presenting within the 0-6 hour window.

The relation between FIV and functional outcome was consistent across all models, in which FIV proved to be an independent predictor. Addition of lesion location and hemorrhage type increased the

predictive value of the models. The negative effect of outcome ASPECTS involvement on functional outcome was mainly driven by the influence of the internal capsule and the M5 region. These regions may include the corticospinal tract and the motor cortex, which emphasizes the pivotal role of damage to these areas in determining functional independence of patients.

The Stroke Treatment Academy Industry Roundtable (STAIR) IX report questioned the optimal imaging modality and timing for FIV assessment.[6] In our study, we observed larger volumes when FIV was assessed on CT. This is supposedly because trials, which had stricter inclusion criteria towards smaller cores at baseline, routinely performed more MR than others. Despite the fact that we observed large differences in FIV between modalities, our model showed that functional outcomes of CT and MR assessed patients were similar. This is most likely due to the diluting effect of the infarct location on the relation of FIV with functional outcome. What is important is that we demonstrated similar correlations with functional outcome for both CT and MR.

Differences in FIV between early and late follow-up imaging were observed. The reasons for this include both lesion growth (evolving ischemia) and the development of infarct-associated vasogenic edema, which results in larger appearing infarcts. Our data suggest that FIV assessment on early follow-up imaging predicts functional outcome with similar strength as assessment on imaging after 48 hours. Similar findings were reported in MR CLEAN, in which FIV measured at 24 hours and at 1 week were compared.[12]

Several studies have previously assessed the relation between FIV and functional outcome on the 90-days mRS after proximal anterior circulation stroke.[9,10,20,21] All these studies report that FIV is a strong predictor of functional outcome, independent from other known important factors such as age and baseline NIHSS. Our study confirms these results in the largest patient-level dataset on EVT to date. This unique dataset also allowed us to answer questions on how different imaging approaches affected the interaction of FIV and functional outcome. Of note is that once FIV and baseline NIHSS were included in our models, infarct laterality was not an independent predictor of outcome, suggesting that baseline NIHSS captures most of the stroke lateralization effect. Our results also show

that, in cases with HT, hemorrhagic infarct type 2 (HI-2) was a stronger predictor of functional outcome than parenchymal hematoma type 2 (PH-2). In contrast, previous studies have reported PH-2 to be more strongly associated with clinical deterioration because of its space occupying effect.[22,23] These conflicting results could possibly be attributed to the fact that most of the mass effect of PH-2 was captured by FIV in our models, since parenchymal hematomas were considered part of the lesion volume, leading to a diminished independent effect. Another explanation might be that PH-2 often leads to extensive damage, resulting in leakage of blood into other spaces.[24] Therefore, the unfavorable effect of PH-2 may have been captured by intraventricular hemorrhage in our models, which in our study is associated with poor clinical outcome.

This study has some limitations. Follow-up NIHSS, a strong predictor of 90-day mRS, was not included in our models, as this was not recorded in most of the trials included in our meta-analysis. Secondly, infarct location assessment was restricted to follow-up ASPECTS regions combined with lateralization. A more detailed analysis on the location of brain tissue injury may improve the strength of the relation between FIV and functional outcome, as this more closely resembles brain eloquence.[25] Finally, we compared different populations to assess the optimal imaging modality and timing for FIV measurement. As some trials routinely performed more MR imaging than others, and had different inclusion criteria, this could have biased our results. However, the distribution of patients with MR-based assessments was fairly even across the different trials, minimizing this effect. In contrast, as almost all late follow-up imaging were from MR CLEAN and THRACE, this finding is heavily confounded by study effect. MR CLEAN had no restrictions with regard to baseline parenchymal imaging except for the presence of intracranial hemorrhage. As a consequence, most patients with large FIVs on early follow-up imaging were from MR CLEAN. In addition, reperfusion rates varied per study, which also contributes to infarct size. In order to fully explore and understand the interaction between imaging modality and timing on FIV assessment, comparisons must be performed in an intra-patient, rather than an inter-patient design. We strove to overcome this limitation by using adjusted partial Spearman correlations to control for potential confounding effects. Nevertheless, adequate validation can only be addressed in prospective studies with pre-specified time

points for FIV assessment, making this a hypothesis generating study that does not provide level 1 evidence.

Our study provides useful estimates of high specificity FIV thresholds that may help to identify patients for whom reaching functional independence at 90 days is unlikely, potentially influencing patient management after stroke, particularly on decisions taken on disposition. Large differences in FIV thresholds with high specificity for unfavorable outcome between CT and MR were revealed. Underestimation of infarct size on CT could possibly explain why these thresholds were lower for CT. Generally, FIV measurements might be less accurate on CT, as CT is less sensitive to ischemia in the early phase as compared to diffusion-weighted MR imaging. A phenomenon like ‘fogging’, where regions of cortical ischemia regains a near-normal appearance, might also have contributed to underestimation of the infarct size. Despite these large differences, we found that FIV assessed on CT offers an association with functional outcome of similar strength compared to MR. This is favorable, as CT is currently still cheaper and more widely available in many countries. Furthermore, the HERMES data suggest that FIV can be measured as soon as after 12 hours, with the major advantage that most patients are still at the intervention hospital, which would minimize loss to follow-up.

FIV has been suggested as surrogate endpoint in early-phase EVT trials, where the aim is to rapidly evaluate direct biological effect of therapy. In order for a potential surrogate endpoint to substitute the clinical endpoint, the effect of therapy on that surrogate endpoint must accurately reflect and predict the effect on the clinical endpoint.[26] We found a strong association between FIV and 90-day mRS, regardless of imaging approach, which is a crucial first step for a potential surrogate endpoint. Future studies must examine the full potential of FIV as a surrogate through formal testing of the causal chain of treatment to FIV to functional outcome.

CONCLUSIONS

In summary, this analysis of HERMES confirms that FIV is a strong independent predictor of functional outcome at 90 days in patients with acute ischemic stroke due to a proximal intracranial occlusion of the anterior circulation presenting within 6 hours after onset. Our data suggest that FIV

might be suitable as a prognostic biomarker for functional outcome in acute ischemic stroke, irrespective of imaging modality and time to follow-up imaging.

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All four criteria for authorship are met: AMMB and IGHJ prepared the first draft. AMMB, IGHJ, MG, and MDH conducted the literature research. AMMB, CBLMM, HAM, WHvZ, HFL, AJY, DSL, MG, MDH, AMD, BCVC, PJM, DWJD, and PW participated in study design. AMMB, CBLMM, WHvZ, RJvO, AvdL, LFMB, AJY, DSL, NA, MB, SBracard, FG, JLM, TM, CO, SS, JT, JHH, MAA, AMD, BKM, BCVC, RGN, PJM, RdMdR, PW, KWM MMB, DWJD, YBWEMR, AD, TGJ, and MR participated in data collection. SBrown did the statistical analysis. AMMB, IGHJ, CBLMM, HAM, WHvZ, HFL, RJvO, AvdL, IGHJ, AJY, SBrown, DSL, NA, SBracard, FG, JLM, TM, CO, JT, MG, MDH, AMD, BKM, BCVC, RGN, GWA, KWM, LSR, MR, JB, PC, DWJD, TGJ, and LA participated in data interpretation. All authors critically reviewed the manuscript and approved the final version. AMMB and IGHJ contributed equally, as did CBLMM and HAM.

REFERENCES

- 1 Berkhemer O, Fransen P, Beumer D, *et al.* A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *New Engl J Med* 2015;**372**:11–20. doi:10.1056/NEJMoa1411587
- 2 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**:2285–95. doi:10.1056/NEJMoa1415061
- 3 Campbell BC V, Mitchell PJ, Kleinig TJ, *et al.* Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;**372**:1009–18. doi:10.1056/NEJMoa1414792
- 4 Jovin TG, Chamorro A, Cobo E, *et al.* Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. *N Engl J Med* 2015;**372**:1–11.
- 5 Goyal M, Demchuk AM, Menon BK, *et al.* Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;**372**:1019–30. doi:10.1056/NEJMoa1414905
- 6 Warach SJ, Luby M, Albers GW, *et al.* Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials. *Stroke* 2016;**47**:1389–98. doi:10.1161/STROKEAHA.115.012364
- 7 Wardlaw JM, Keir SL, Bastin ME, *et al.* Is diffusion imaging appearance an independent predictor of outcome after ischemic stroke? *Neurology* 2002;**59**:1381–7. doi:10.1212/01.WNL.0000032495.71720.C3
- 8 Saver JL, Johnston KC, Homer D, *et al.* Infarct Volume as a Surrogate or Auxiliary Outcome Measure in Ischemic Stroke Clinical Trials. *Stroke* 1999;**30**:293–8. doi:10.1161/01.STR.30.2.293
- 9 Zaidi SF, Aghaebrahim A, Urrea X, *et al.* Final infarct volume is a stronger predictor of outcome than recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy. *Stroke* 2012;**43**:3238–44. doi:10.1161/STROKEAHA.112.671594
- 10 Al-Ajlan FS, Goyal M, Demchuk AM, *et al.* Intra-Arterial Therapy and Post-Treatment Infarct

- Volumes: Insights From the ESCAPE Randomized Controlled Trial. *Stroke* 2016;**47**:777–81. doi:10.1161/STROKEAHA.115.012424
- 11 Yoo AJ, Chaudhry ZA, Nogueira RG, *et al.* Infarct volume is a pivotal biomarker after intra-arterial stroke therapy. *Stroke* 2012;**43**:1323–30. doi:10.1161/STROKEAHA.111.639401
 - 12 Bucker A, Boers AM, Bot JCJ, *et al.* Associations of Ischemic Lesion Volume With Functional Outcome in Patients With Acute Ischemic Stroke. *Stroke* 2017;**48**:1233–40. doi:10.1161/STROKEAHA.116.015156
 - 13 Muir KW, Ford GA, Messow C-M, *et al.* Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry* 2017;**88**:38–44. doi:10.1136/jnnp-2016-314117
 - 14 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**:1138–47. doi:10.1016/S1474-4422(16)30177-6
 - 15 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**:1723–31. doi:10.1016/S0140-6736(16)00163-X
 - 16 Boers AM, Marquering HA, Jochem JJ, *et al.* Automated Cerebral Infarct Volume Measurement in Follow-up Noncontrast CT Scans of Patients with Acute Ischemic Stroke. *Am J Neuroradiol* 2013;**34**:1522–7. doi:10.3174/ajnr.A3463
 - 17 Pexman JH, Barber PA, Hill MD, *et al.* Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *Ajnr Am J Neuroradiol* 2001;**22**:1534–42.
 - 18 von Kummer R, Broderick JP, Campbell BCV, *et al.* The Heidelberg Bleeding Classification. *Stroke* 2015;**46**:2981–6. doi:10.1161/STROKEAHA.115.010049

- 19 Saver JL. Novel End Point Analytic Techniques and Interpreting Shifts Across the Entire Range of Outcome Scales in Acute Stroke Trials. *Stroke* 2007;**38**:3055–62.
doi:10.1161/STROKEAHA.107.488536
- 20 Yoo AJ, Chaudhry ZA, Nogueira RG, *et al.* Infarct Volume Is a Pivotal Biomarker After Intra-Arterial. 2012;**I**:1323–30. doi:10.1161/STROKEAHA.111.639401
- 21 Albers GW, Goyal M, Jahan R, *et al.* Relationships Between Imaging Assessments and Outcomes in Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke. *Stroke* 2015;**46**:2786–94.
doi:10.1161/STROKEAHA.115.010710
- 22 Berger C, Fiorelli M, Steiner T, *et al.* Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001;**32**:1330–5.
- 23 Fiorelli M, Bastianello S, von Kummer R, *et al.* Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 1999;**30**:2280–4.
- 24 Lisk DR, Pasteur W, Rhoades H, *et al.* Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. *Neurology* 1994;**44**:133–9. doi:10.1212/WNL.44.1.133
- 25 Ernst M, Boers AMM, Aigner A, *et al.* Association of Computed Tomography Ischemic Lesion Location With Functional Outcome in Acute Large Vessel Occlusion Ischemic Stroke. *Stroke* 2017;**48**:2426–33. doi:10.1161/STROKEAHA.117.017513
- 26 Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med* 1989;**8**:431–40.

COMPETING INTERESTS

MG reports grants from Covidien, personal fees from Covidien, during the conduct of the study; MG has a patent for diagnosing strokes (PCT/ CA2013/000761) licensed to GE Healthcare. BKM reports membership of the Steering and Executive Committee, ESCAPE trial that received support from Covidien Inc., Site Principal Investigator, SOCRATES Trial, sponsored by Astra Zeneca, honoraria from Penumbra Inc., a provisional patent 62/086077 for triaging systems in ischemic stroke, research funding from CIHR, HSFC, AIHS, HBI and the Faculty of Medicine, University of Calgary and board membership of QuikFlo Health Inc. WHvZ reports Honoraria; Modest; Stryker (paid to Institution). DWJD reports honoraria; Modest; Stryker (paid to Institution). PJM reports unrestricted grant funding for the EXTEND-IA trial to the Florey Institute of Neuroscience and Mental Health from Covidien (Medtronic), has served as an unpaid consultant to Codman Johnson and Johnson, his organization has received unrestricted research funding and grants from Codman Johnson and Johnson, Medtronic, and Stryker. AMD reports grant support and personal fees from Covidien (Medtronic). AD reports consultant/Advisory Board; Modest; Medtronic Neurovascular (Steering Committee STAR). CBLMM reports speakers' Bureau; Modest; Stryker (paid to institution). GAD reports grants from the Australian National Health & Medical Research Council, non-financial support from, and has served on advisory boards for Boehringer Ingelheim, Astra Zeneca, Bristol Meyers-Squibb, Merck Sharp & Dohme outside the submitted work. BCVC 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). MDH reports unrestricted grant funding for the ESCAPE trial to University of Calgary from Covidien (Medtronic), and active/in-kind support consortium of public/charitable sources (Heart & Stroke Foundation, Alberta Innovates Health Solutions, Alberta Health Services) and the University of Calgary (Hotchkiss Brain Institute, Departments of Clinical Neurosciences and Radiology, and Calgary Stroke Program); personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, outside the submitted work; MDH has a patent Systems and Methods for Assisting in Decision-Making and

Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software. AMMB and HAM own stock in Nico-lab BV, a company that focuses on medical imaging software. TGJ has consulted for Codman Neurovascular and Neuravi, holds stock in Silk Road and Blockade; has acted as an unpaid consultant to Stryker as PI of the DAWN trial and served as an unpaid member of a Medtronic Advisory Board. SMD reports lecture fees from Covidien (Medtronic). SBrown acts as consultant for Medtronic. All other authors have nothing to disclose.

FIGURE LEGENDS

Figure 1: Follow-up infarct volume (FIV) distribution per modified Rankin Scale score (mRS).