There is a mounting evidence in support of the notion that vessel recanalization has the most powerful effect on clinical outcomes in acute ischemic stroke. A concept fundamental to the rationale for instituting reperfusion therapy is that of mismatch between ischemic core and ischemic penumbra. After vessel occlusion, attributable to progressive collateral failure, there is continuous growth of the core at the expense of the penumbra. The aim of recanalization therapy is to halt this process by salvaging the penumbra with the consequence of limiting final infarct size.

Whereas final infarct volume represents the accepted outcome measure in most experimental models of focal ischemia, it is not the standard outcome measure in human studies where scales assessing disability status are typically chosen for this purpose. This is in part attributable to the fact that human studies attempting to correlate final infarct volumes to clinical outcomes have yielded contradictory results. Significant limitations of these studies include the heterogeneous nature of vascular occlusion sites particularly with respect to anterior and posterior circulations and small sample sizes. We sought to study the relationship between clinical outcomes, recanalization, and final infarct volume in a homogeneous patient population with regard to the territory at risk composed of patients with middle cerebral artery (MCA)-M1 segment occlusion who underwent endovascular therapy.

Methods
We identified 201 patients with middle cerebral artery occlusion. Patients with other occlusive lesions were excluded. Baseline clinical/radiological characteristics, procedural outcomes (including thrombolysis in cerebral infarction scores), clinical outcome scores (modified Rankin scores), and final infarct volumes on diffusion weighted imaging were retrospectively analyzed from a prospectively collected database. Favorable outcome is defined as 90-day modifyed Rankin score ≤2.

Results—Successful recanalization (thrombolysis in cerebral infarction grade 2b or 3) was achieved in 63.2% and favorable outcomes in 46% of cases. Mean infarct volume was 50.1 mL in recanalized versus 133.9 mL in non-recanalized patients (P<0.01) and 40.4 mL in patients with favorable outcomes versus 111.8 in patients with unfavorable outcomes (P<0.01). In multivariate analysis, thrombolysis in cerebral infarction ≥2b, baseline National Institute of Health Stroke Scale, Alberta Stroke Program Early Computed Tomography scores, and age were identified as independent predictors of outcome. However, when infarct volumes were included in the analysis only final infarct volume and age remained significantly associated.

Conclusions—Successful recanalization leads to improved functional outcomes through a reduction in final infarct volumes. In our series, age and final infarct volume but not recanalization were found to be independent predictors of outcome, supporting the use of final infarct volume as surrogate marker of outcome in acute stroke trials.
ischemic stroke treated with endovascular therapy at single high volume academic center from 2000 to 2010. Patients receiving intra-arterial (IA) stroke treatment at the University of Pittsburgh Medical Center are included in an Institutional Review Board approved prospective database after written informed consent is obtained by the patient or proxies. All patient information was de-identified and analyzed in compliance with the Health Insurance Portability and Accountability Act. To study a homogeneous population with respect to vascular occlusion site, only patients with MCA-M1 segment occlusion were included and to determine final infarct volumes based on the most accurate imaging method, only patients who underwent post-procedure magnetic resonance imaging (MRI) were included. Follow-up MRI was obtained within 24 to 48 hours after completion of the procedure in all patients.

### Patient Selection

All patients presenting with acute ischemic stroke symptoms underwent a baseline head Computed Tomography (CT) scan. In general, as a first step, patients with anterior circulation stroke were selected for IA therapy if CT showed an Alberta Stroke Program Early CT score (ASPECTS) of ≥6 or less than one third of hypodensity of the MCA territory. Most patients underwent additional imaging studies (CT angiography/CT perfusion) or MRI/magnetic resonance angiography and were considered for interventional therapy based on assessment of mismatch between the extent of infarcted brain relative to the extent of threatened but viable brain. In patients undergoing CT/CT perfusion, the ratio of low cerebral blood volume (threshold ≤2.0 mL x 100 gm⁻¹)/elevated mean transit time maps and the severity of clinical deficit (National Institute of Health Stroke Scale [NIHSS]) was factored in treatment decision. The minimum amount of mismatch necessary for treatment selection varied according to patient specific considerations and stroke neurologist/interventionalist specific practice patterns. In general, patients with a core volume of less than one third of MCA territory in the presence of M1 occlusion and corresponding clinical deficit (NIHSS ≥6-8) or severe perfusion deficit (TTP >6s) involving greater than or equal to two thirds of the MCA territory were considered potential treatment candidates. Computer-generated volumetric analysis was not available and manual calculation of volumes is too lengthy a process to be useful for selection in the setting of acute stroke. Therefore, volumes were estimated based on visual mismatch. Time from stroke onset was not considered a limiting factor. All patients who underwent IA treatment had baseline modified Rankin score (mRS) ≤2.

### IA Treatment Protocol

The general approach regarding IA treatment at our center has been described previously. In most cases, the procedure was performed under conscious sedation. Subjects with airway compromise, significantly impaired comprehension, and agitation were intubated before the procedure. IA treatment was categorized as pharmacological only, mechanical only, or combination pharmacological and mechanical. If eligible, patients were administered IV tPA prior to intervention. Mechanical thrombectomy was performed as first line. In cases of unsuccessful recanalization with this approach,
a combination of IA pharmacological and mechanical treatment was used. Sixty-six patients (33.1%) received IV Ipa before the procedure. Most patients underwent MERCI (Concentric Medical, Mountain View, Ca) thrombectomy which was performed in 144 of 201 (71.6%) cases. Manual aspiration15 in conjunction with MERCI thrombectomy was applied in 64 (31.9%) cases. Another 38 patients (18.9%) underwent PENUMBRA (Penumbra Inc, Alameda, CA) clot evacuation. Intracranial stenting was performed in 18 subjects (8.9%). IA tPA was administered in 90 patients (47.1%). Sixty-two patients (30.8%) received glycoprotein Ib/IIIa inhibitors. Combination pharmacological and mechanical IA treatment was performed in 110 cases (54.7%). Successful recanalization was considered if thrombolyis in cerebral infarction (TICI) 2b or 3 (defined according to previously published TICI recanalization scores)11 was achieved.

Infarct Volume Calculation

Post-treatment infarct volumes were calculated by vascular neurologists (S.Z. and M.J.), blinded to recanalization grade. The acute infarct was determined by visual inspection on the magnetic resonance diffusion weighted imaging (DWI) sequence. Final outlines were manually edited. If present, hemorrhagic changes were incorporated in the final infarct volumes. Volume viewer 2 software (Voxtools; GE Healthcare, Milwaukee, WI) on an Advantage Workstation 4.3 (GE Healthcare) was used to calculate total infarct volume.

Patient Follow-Up

On discharge, patients were scheduled for follow-up appointments in the stroke neurology clinic at 30 and 90 days and 90-day mRS was charted on follow-up appointment. If patients were physically unable to present for follow-up, they or next of kin were reached by a vascular neurologist or other mRS certified investigator, and mRS was obtained over the phone. Good clinical outcome was defined as mRS score of ≤2. Symptomatic hemorrhage was defined as any parenchymal hematoma (PH) according to European Cooperative Acute Stroke Study criteria.12

Statistical Analysis

Variables collected included patient demographics, stroke risk factors, admission NIHSS score, ASPECT score, time from symptom onset to first diagnostic baseline angiographic run, IA treatment used (pharmacologic, mechanical, or both), pre- and post-treatment TICI reperfusion grade, final DWI volumes, rates of symptomatic hemorrhage and hemorrhagic transformation, inpatient mortality rate, and 90-day mRS. All tests were performed using the STATA 10 software (StataCorp LP, College Stanton, TX). Normal distribution of all variables was confirmed, with and without recanalization using t test or Mann–Whitney test for continuous variables and χ² or Fisher exact tests for categorical variables. In univariate analysis, several variables of interest were correlated to good functional outcome as binary outcome measure. Subsequently all covariates with a P value <0.2 were then entered into a multivariate stepwise logistic regression model. Significant association was considered for a P value of <0.05. A multivariate logistic regression model was used to assess the effects of clinical and radiological variables on functional outcome and mortality. Because ASPECTS and final infarct volumes are related variables that are correlated to each other (spearman ρ 0.68, P<0.01) multivariate analyses were performed, with and without inclusion of the ASPECT score. Level of significance was established at a 2-tailed P value of <0.05.

Results

From January 2002 through December 2010, 562 endovascular stroke treatments were performed. Patients with posterior circulation (N=76, 14.1%), intracranial ICA and ICA terminus (N=116, 21.6%), proximal carotid (N=44, 8.1%), and isolated MCA M2 segment (N=50, 9.2%) occlusive lesions were excluded. A total of 251 (46.7%) patients with MCA-M1 segment occlusion were identified. Another 50 of these patients were excluded because of lack of post-treatment MRI. Clinical and radiological characteristics of remaining 201 (35.7%) patients are outlined in Table. Five patients were lost to follow-up and 90-day clinical outcomes are available for 196 patients (97.7%). The median number of days from intervention to MRI was 1. Nineteen patients (9.4%) developed PH, of which 9 (47.3) died and only 2 patients (10.5%) had favorable outcome at 90 days. The incidence of perforation was 5 of 201 (2.3%). Overall mortality was 24.3% (49/201). TICI ≥2b and 3 recanalization was achieved in 127 patients (63.2%), whereas TICI ≥2a, b, and 3 was achieved in 159 cases (79.1%). Figure 1 shows an inverse linear association between TICI recanalization grade and infarct volume. Higher recanalization grades corresponded to lower infarct volume (P<0.01 by ANOVA). Recanalized patients had significantly lower mean infarct volumes as compared with non-recanalized patients irrespective of their functional outcomes (mRS 0–2: 31.1 versus 74.9 mL, P<0.01; mRS 3–6: 74.1 versus 154.9 mL, P<0.01).

Figure 2 shows the relationship between recanalization, infarct volume, and 90-day clinical outcomes. Overall 90 patients (46.1%) had a favorable outcome at 3 months, of which 71 (78.9%) recanalized and 19 (21.1%) did not recanalize (P<0.01). Irrespective of recanalization grade, patients achieving functional independence at 3 months were younger (mean age 60.1, 95% CI 57.0–62.9, versus 71.7, 95% CI 69.6–76.6, P<0.01) and had significantly lower mean infarct volumes (40.4, 95% CI 31.8–49.7 mL versus 111.8 mL, 95% CI 89.7–126.8, P<0.01).

In univariate analysis, older age, higher baseline NIHSS, female gender, history of hypertension or atrial fibrillation, intubated state during the procedure, and the development of PH were associated with lower chances of independent functional outcomes at 90 days. Conversely, higher baseline ASPECT score, successful recanalization, lower final infarct volumes, and current smoking status were associated with higher chances of independent functional outcomes at 90 days. We attributed the latter observation to the fact that current smoking status was found predominantly in younger patients (mean age in smoker versus nonsmokers 54 versus 71, P<0.01).

In multivariate logistic regression analysis TICI ≥2b, baseline NIHSS, baseline ASPECT scores, and age were identified as independent predictors of outcome. However, when final infarct volumes were included in the model only final infarct volume (mRS=2: odds ratio [OR] 0.98, 95% CI 0.97–0.99, P<0.01; mortality: OR 1.01, 95% CI 1.01–1.02, P=0.01) and age (mRS=2: OR 0.93, 95% CI 0.88–0.95, P<0.01; mortality: OR 1.07, 95% CI 1.03–1.08, P=0.016) remained significantly associated with outcomes. These predictors, that is, age (OR 0.91, 95% CI 0.87–0.94, P<0.01) and infarct volume (OR 0.97, 95% CI 0.97–0.99, P<0.01) remained significantly associated with outcome when baseline ASPECTS and final infarct volumes were simultaneously added in the model. A receiver operating characteristics curve depicting various final infarct volume points as predictors of favorable outcome was constructed (Figure 3). At 40 mL infarct volume cutoff, the prediction sensitivity and specificity for favorable outcome are 63% and 72%, respectively (area under curve 0.75, 95% CI 0.38–0.72).
Of the 50 subjects excluded because of lack of post-treatment scan, 20 patients had MRI contraindication attributable to cardiac pacemaker, shrapnel injury, etc. Eight patients could not tolerate MRI scanning because of agitation or claustrophobia. In the remaining 22 patients, there was no evident contraindication to MRI. The recanalization and PH rate for this cohort are 14 (66%) and 3 (14%), respectively. Fifty-nine percent died (13/22) and only 5 subjects (23.8%) were functionally independent at 90 days. These patients had high-inpatient mortality 50% (11/22) and the lack of MR imaging may be attributable to clinical instability, early mortality, or withdrawal of care attributable to perceived poor chances of meaningful recovery by the treating physicians or family members. Procedural results and outcomes for the CT only group compared with the analyzed group are as follows: TICI 2b and 3 recanalization: 14 (66%) versus 127 (63.2%), respectively, \( P = 0.78 \); PH: 3 (13.6%) versus 19 (9.4%), respectively, \( P = 0.65 \); favorable outcomes: 5 (22.8%) versus 90 (46.1%), respectively, \( P = 0.03 \); mortality at 90 days: 13 (59%) versus 49 (24.3%), respectively, \( P = 0.02 \).

Measurement of post-treatment CT infarct volume in these patients yielded larger infarcts than in the analyzed group (median post-treatment CT volume 126 mL (interquartile range 50–355 mL) versus 51 mL, (interquartile range 21–111 mL), \( P = 0.03 \).

**Discussion**

The main conclusion of this study is that in patients with acute ischemic stroke because of MCA occlusion treated with endovascular therapy, final infarct volumes in conjunction with age are the strongest predictors of clinical outcomes. Whereas this concept may be intuitive, it has not been convincingly demonstrated previously, as studies investigating the association between final infarct volumes and clinical outcomes have yielded contradictory results.
On the contrary, a strong relationship between prethrombolytic infarct volumes and outcomes has been well established. The DEFUSE investigators showed that among other MRI signatures, pretreatment DWI MRI volume of >100 mL predicts a malignant clinical course. Among patients with anterior circulation occlusions treated with endovascular therapy, Yoo et al showed that regardless of recanalization results a preprocedural magnetic resonance DWI volume of ≥70 mL has a high likelihood of yielding poor clinical outcomes. The EPITHET investigators reported that in patients treated with intravenous tPA between 3 and 6 hours from symptoms onset, a preprocedure DWI infarct volume of ≤25 mL is associated with a high likelihood of obtaining a favorable outcome. The final infarct volume cutoff of 40 mL found in our cohort to best differentiate between favorable and unfavorable outcomes falls in the middle of the final infarct volume range described by these studies.

Saunders et al using DWI MRI derived infarct volumes in untreated patients with MCA distribution stroke but unspecified site of vascular occlusion reached similar results to those noted in our study. These investigators reported that a final infarct volume of 80 mL was found to best differentiate between the likelihood of obtaining a good versus unfavorable outcome. In keeping with our results, Yoo et al has also shown an independent association between final infarct volume together with age and outcomes. Other investigators have not been able to detect a strong relationship between final infarct and outcomes. We believe that this lack of association is explained primarily by studying a heterogeneous patient population with respect to vascular occlusion without knowledge of vessel patency status. To account for these important confounding factors, we chose to study only patients with a homogenous vascular occlusion site whose vessel patency status could be determined as all patients underwent endovascular therapy.

Because young patients can still achieve functional independence despite higher final infarct volumes the association between final infarct volume and favorable clinical outcome is influenced in a major way by age. The clinical outcome measure captured in our database consisted of the mRS, which primarily reflects physical disability status after stroke. This scale was chosen because it is a widely used outcome measure in endovascular acute stroke therapy trials. Other stroke related sequelae, such as mood, cognition, and overall quality of life, were not captured prospectively in our database and, as such, our study could not assess the extent to which final infarct volumes may be correlated to these important patient-centered outcome measures. We feel that this represents an important question to be addressed by future prospective studies.

Previous studies have suggested that infarct location enhance the predictive value of infarct volume with respect to clinical outcomes. Consequently, the construction of topographic atlases was proposed to account for the different relevance in terms of outcomes of the regions affected. Unlike our report, these studies did not limit inclusion criteria to the presence of a single large artery occlusion (MCA) and as such the volumes of infarct in the patients included were smaller than those observed in our study. Because of the size of the infarcts seen in our group of patients as well as the multiplicity of areas within the MCA territory involved, a detailed topographical differentiation of ischemic lesions on follow-up MRI would have posed significant challenges and, therefore, an analysis of outcome prediction based on infarct location is beyond the scope of this article. The extent to which infarct location influences outcomes in patients with MCA occlusion should be explored by future studies. With regard to side of infarction, no relationship with outcomes could be found in our study. Therefore, it appears that in patients with larger infarcts, lesion side may not have a critical impact on outcome especially when outcomes are measured in a rather crude way through scales of disability such as the mRS. This contention is supported by the findings from several randomized hemicraniectomy trials in which no association between infarct side and likelihood of obtaining a favorable outcome was found.

We were able to detect a strong association between degree of recanalization and final infarct volumes with highest recanalization scores translating into lowest infarct volumes. These findings suggest that recanalization is a powerful means of achieving a reduction in final infarct size, a mechanism that explains why recanalization has a powerful effect on clinical outcomes. Indeed recanalization has been shown in virtually all IA thrombolytic trials to be a significant predictor of favorable clinical outcome. This association was confirmed by our study as we were able to detect a significant relationship between vessel recanalization and clinical outcomes when final infarct volume was not introduced in the statistical model. However, when final infarct volumes are taken into account they override the importance of recanalization. Thus rather than independently predicting outcome, recanalization appears to merely represent a means of achieving a small final infarct volume which in turn is a strong predictor of outcome. If for various reasons (mainly related to robust collateral status) the final infarct volume is low, good clinical outcomes can be obtained despite lack of recanalization. Conversely, successful recanalization will not result in a good outcome, if before recanalization a large infarct has already developed.

Stroke is a heterogeneous condition with multiple factors determining eventual clinical outcomes. These include age, premorbid functional status, comorbid conditions, as well as...
poststroke care including access to rehabilitation and social factors (family support, socioeconomic status, etc). Because of the inherent complexities associated with clinical outcome measurement in IA thrombolytic stroke therapy trials, recanalization scores are increasingly being used as surrogate markers for efficacy of endovascular therapy. Our findings, however, indicate that final infarct volumes may represent a more accurate indicator of procedural success and, therefore, should be used in preference to recanalization scores as surrogate markers of outcome in reperfusion trials for acute stroke.

The main limitation of this study derives from its retrospective design. Patients were selected for endovascular treatment based on different imaging methods with different selection criteria, and treatment methods were heterogeneous. The heterogeneous nature both of imaging paradigms used for selection and of treatment modalities reflects the dynamic nature of the rapidly evolving field of acute stroke interventions, over the time span this study was conducted. We do not believe, however, that this lack of uniformity affects the main message of our article which, from an imaging standpoint, is based mainly on calculation of follow-up infarct volumes that have been obtained in a uniform fashion.

Patients were included in the study only if they underwent a post-procedure MRI. We chose these inclusion criteria specifically to preserve uniformity in follow-up infarct assessment method and because it is well established that MRI is more accurate than CT in delineating the extent of infarction. As such, the possibility of selection bias is a valid concern. However, we do not feel that this has altered the conclusions of our study in a significant way because a post-procedure MRI within the first 24 to 48 hours is performed as a matter of standard of care at our center. Patients who did not undergo an MRI scan were essentially those with contraindications to the study. The fact that a large proportion (201 of 251) of patients with MCA-M1 occlusion treated at our center during the duration of the study was included supports this contention. In addition, patients who underwent follow-up CT only had significantly larger follow-up infarcts along with significantly higher proportions of poor outcomes than those in the analyzed group, a finding that is in keeping with the main conclusion of this study.

Because of the retrospective nature of our study a blinded assessment of recanalization results by a core lab, whereas optimal was not feasible. This represents another limitation of this current study. Nonetheless, we feel that our prospectively recorded recanalization scores at the end of the procedure are validated by the infarct volume analysis performed by independent investigators, different from the interventionalist performing the procedure and blinded to recanalization results. This analysis reveals a strong correlation between TICI scores and final infarct volumes (Figure 1).

Another significant concern is the MRI sequence (DWI) and timing (24–48 hours) used for final infarct assessment. Several studies have shown that a FLAIR sequence performed at 3 to 5 days may be the most accurate early indicator of true infarct volume. However, the timing of this imaging sequence may result in loss to follow-up as some patients may not be available to undergo the study because of either death or early discharge. In addition, at that point in time, the FLAIR sequence incorporates a certain element of edema that may result in overrepresentation of the final infarct lesion. To explore ways to overcome these limitations, Campbell et al have investigated the accuracy of 24-hour DWI volume in predicting final infarct burden as assessed by FLAIR sequence at 90 days. The 2 sequences were found to be highly correlated indicating that early DWI MRI may be comparable to FLAIR at 5 days in outlining the final infarct. The timing of 24 hours chosen for most of the patients in our study is likely to represent the earliest time point for accurate delineation of final infarct volume. An earlier time point (eg, 6–12 hours) after intervention would likely lead to underestimation of infarct size because during this timeframe, continuous infarct growth is still common. Although Campbell et al findings validate our approach, the question of optimal sequences and timing for infarct measurements on MRI can only be addressed by conducting prospective studies with prespecified time points for infarct measurement. Such studies are currently ongoing and further light will be shed on whether differences in magnetic resonance sequence or timing of measurement have a major impact on measurement accuracy and most importantly whether these differences are clinically relevant in terms of correlations with outcomes.

Disclosures
Dr Nogueira is on scientific advisory board for Concentric Medical, Co-Axia, and eV3. Dr Jovin has received consulting and speaker fees from Covidien, Stryker, Codman, and Silk Road. The other authors have no conflicts to report.

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Final Infarct Volume Is a Stronger Predictor of Outcome Than Recanalization in Patients With Proximal Middle Cerebral Artery Occlusion Treated With Endovascular Therapy

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