Collaterals at Angiography and Outcomes in the Interventional Management of Stroke (IMS) III Trial

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Background and Purpose—Endovascular strategies provide unique opportunity to correlate angiographic measures of collateral circulation at the time of endovascular therapy. We conducted systematic analyses of collaterals at conventional angiography on recanalization, reperfusion, and clinical outcomes in the endovascular treatment arm of the Interventional Management of Stroke (IMS) III trial.

Methods—Prospective evaluation of angiographic collaterals was conducted via central review of subjects treated with endovascular therapy in IMS III (n=331). Collateral grade before endovascular therapy was assessed with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale, blinded to all other data. Statistical analyses investigated the association between collaterals with baseline clinical variables, angiographic measures of recanalization, reperfusion and clinical outcomes.

Results—Adequate views of collateral circulation to the ischemic territory were available in 276 of 331 (83%) subjects. Collateral grade was strongly related to both recanalization of the occluded arterial segment (P=0.0016) and downstream reperfusion (P<0.0001). Multivariable analyses confirmed that robust angiographic collateral grade was a significant predictor of good clinical outcome (modified Rankin Scale score ≤2) at 90 days (P=0.0353), adjusted for age, history of diabetes mellitus, National Institutes of Health Stroke Scale strata, and Alberta Stroke Program Early CT Score. The relationship between collateral flow and clinical outcome may depend on the degree of reperfusion.

Conclusions—More robust collateral grade was associated with better recanalization, reperfusion, and subsequent better clinical outcomes. These data, from the largest endovascular trial to date, suggest that collaterals are an important consideration in future trial design.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424. (Stroke. 2014;45:759-764.)

Key Words: angiography ■ collateral circulation ■ reperfusion ■ stroke

The degree of collateral circulation to offset impaired blood flow downstream from an arterial occlusion is a principal determinant of ischemic severity in acute stroke.1 The severity and duration of such ischemia mitigated by collateral perfusion influences tissue injury and clinical impairment. In endovascular approaches to treatment of acute ischemic stroke, the amount of collateral perfusion may be associated with the likelihood of recanalization, or opening of an arterial occlusion, and the extent of reperfusion, or restoration of normal blood flow, into the reopened arterial territory.2 The clinical outcomes of patients with stroke treated with endovascular therapies, however, may not always be accurately predicted from the degree of arterial recanalization or reperfusion. Successful revascularization is also not synonymous with subsequent clinical function, because baseline collaterals may determine tissue viability or even hemorrhagic transformation.3 Conventional angiography provides maximal spatial and temporal resolution for the depiction of anatomic and functional capacity of collaterals.4 Endovascular strategies provide a unique opportunity to correlate definitive...
angiographic measures of collaterals at the time of intervention.

We conducted a systematic evaluation of collaterals on conventional angiography in endovascular subjects of the Interventional Management of Stroke (IMS) III trial being treated with intra-arterial tissue plasminogen activator (t-PA) or mechanical thrombectomy subsequent to intravenous t-PA. The primary objective was to establish an association between the degree of collaterals before endovascular therapy and the likelihood of recanalization, reperfusion, and good clinical outcome at 90 days after randomization.

Methods

The evaluation of angiographic collaterals immediately before endovascular treatment was conducted via central review of all endovascular subjects in IMS III. Detailed aspects of trial design and clinical outcomes of the IMS III trial have already been published. For every subject treated with endovascular therapy, the complete cerebral angiography study was submitted in digital format for central review. The images were reviewed in a DICOM viewer. Although not prespecified as part of theangiography procedure or data extraction for primary analyses, blinded evaluation of collaterals was conducted by a central angiography reviewer in the multicenter trial. The central adjudicator had extensive experience in grading collaterals from several other multicenter endovascular studies. All diagnostic runs were evaluated for the presence of adequate information regarding collateral circulation with respect to the arterial occlusive lesion (AOL). Because collateral injections were not mandated as part of trial protocol, variability was noted from case to case in the completeness of such information. Collateral grades before endovascular treatment were assessed with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale on angiography, blind to all other data. The ASITN/SIR grading system is a 5-point scale: with 0=no collaterals visible to the ischemic site; 1=slow collaterals to the periphery of the ischemic site with persistence of some of the defect; 2=rapid collaterals to the periphery of the ischemic site with persistence of some of the defect and to only a portion of the ischemic territory; 3=collaterals with slow but complete angiographic blood flow of the ischemic bed by late venous phase; and 4=complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion. The use of this grading system and scale metrics has been previously reported. Cases with insufficient information regarding collateral status before treatment were excluded from subsequent analyses.

The 2 central angiography core laboratory reviewers for the trial independently evaluated the angiographic measures of recanalization and reperfusion. Recanalization of the target AOl was scored with the AOl score. Reperfusion of the corresponding arterial territory was scored with the modified Thrombolysis in Cerebral Infarction (mTICI) scale, using 50% as the threshold for achieving reperfusion grade 2a or higher. At the completion of the trial, these independent assessments were adjudicated by consensus reading, referring to the prespecified angiography interpretation protocol for the trial.

Because baseline (obtained immediately before endovascular treatment but after intravenous t-PA) and target collateral scores were highly associated (r=0.90), only baseline collateral score was used in the analysis. Collateral score was treated as a categorical variable. The association of collateral grade with baseline characteristics and vascular and clinical outcomes was assessed via Fisher exact test for categorical variables and Kruskal–Wallis test for continuous variables. In addition, the Cochran–Armitage trend test (CA) was performed for vascular and clinical outcomes when association with collateral grade was found. Baseline characteristics included comorbid conditions, demographics, and location and severity of stroke. Vascular outcomes were angiographic recanalization, defined as AOl score of 2 or 3, and angiographic reperfusion, defined as mTICI of ≥2b, or 3, and separately as ≥2a or 3. Clinical outcomes considered were symptomatic intracranial hemorrhage <30 hours of intravenous t-PA initiation, death from all causes <90 days, and functional independence at 90 days, defined as a modified Rankin Scale (mRS) score of 0, 1, or 2. Day 90 mRS, the primary clinical outcome for IMS III, was imputed as >2 if the assessment was not completed or was completed out of the window (before 60 or after 120 days postrandomization).

Logistic regression was used to model the outcome as a function of collateral score and covariates selected using backward selection methodology. Baseline variables potentially associated with outcome (P<0.2) were considered for inclusion in the model. For continuous covariates, linearity in the logit was assessed via Box–Tidwell transformation. After establishing that collinearity was not a concern, significant (P<0.05) variables were included in the final logistic models. In cases where the Hosmer–Lemeshow test suggested lack of fit, interaction terms were considered. The significance (P<0.05) of baseline collateral score as a predictor of outcome was assessed, and odds ratios and 95% confidence intervals (CIs) were estimated for each change in collateral score (eg, 0–1, 1–2).

Results

From 2006 to 2012, of 434 subjects in the endovascular arm, we evaluated 331 subjects treated with endovascular therapy and available imaging for angiographic collateral grade. Adequate views of collateral circulation to the ischemic territory were available in 276 of 331 (83%) subjects. Collateral grade included 19 (6.9%) with grade 0 (no collaterals), 53 (19.2%) with grade 1, 108 (39.1%) with grade 2, 88 (31.9%) with grade 3, and only 8 (2.9%) with grade 4.

Collateral status at angiography was analyzed based on demographics, comorbidities, and other baseline clinical data in IMS III (Table 1). Interestingly, time interval from stroke onset to initiation of intravenous t-PA differed by collateral grade (P=0.0039); this time was numerically longest for subjects with grade 0 (mean, 146.9 minutes; SD, 26.3 minutes) and shortest for subjects with grade 1 (mean, 113.2 minutes; SD, 35.8 minutes). History of hypertension (P=0.0008) and history of congestive heart failure (P=0.0411) were associated with poorer baseline collateral grade. A trend was noted between the severity of Alberta Stroke Program Early CT Score (ASPECTS) on pre-intravenous t-PA brain imaging and collateral grade, where more robust collaterals were noted in those with higher ASPECTS. Table I in the online-only Data Supplement details the relationship between collateral grade and site of initial vascular occlusion. Inadequate power because of limited sample size limited further conclusions, because the numbers become far smaller if the analysis was based on specific occlusion sites.

The collateral grade was related to the degree of recanalization, degree of reperfusion, and clinical outcomes at 3 months in unadjusted (Table 2) and multivariable analyses. Recanalization of the occluded arterial segment (AOL ≥2) was more frequent in those subjects with more robust collaterals (P<0.0001), with AOL ≥2 recanalization present in only 53% of subjects with no collaterals and in 88% of those with complete collateral filling. Similar analyses revealed that the proportion of cases with downstream recanalization (mTICI ≥2) increased (Figure) with more robust collaterals on pretreatment angiography (CA trend test; P<0.0001), with 44% of subjects attaining mTICI ≥2 reperfusion at collateral grade 0 and 86% mTICI ≥2 reperfusion in subjects with grade 3 collaterals. The proportion of cases with mTICI ≥2b reperfusion also increased with more robust collaterals (CA trend test;
P < 0.0001. If we consider variables with significance < 0.2 for inclusion in a multivariable model relating collateral score to reperfusion, we will need adjustments in ASPECTS, hypertension, black race, and age. However, after the backward selection procedure, only collateral score remained in the model. As collateral grade increased, so did the proportion of subjects with good clinical outcomes (mRS ≤ 2) at day 90 (CA trend test; P = 0.0002). Whereas only 21% of those with grade 0 or no collaterals attained good clinical outcomes, more than half of all subjects with complete or grade 3 to 4 collaterals...
had good functional outcomes 3 months later. Importantly, all of the subjects with no collaterals and good clinical outcome had distal arterial occlusions, whereas good clinical outcome was never attained in subjects with an internal carotid artery or proximal M1 occlusion and absence of collaterals. A trend for higher mortality was noted in those with worse angiographic collaterals (CA trend test; \( P = 0.0118 \)), and no relationship could be demonstrated between collaterals and symptomatic hemorrhagic transformation, limited by small numbers of available cases.

Collateral score remained significantly associated with recanalization (AOL \( \geq 2 \)) and reperfusion (mTICI \( \geq 2 \)) when adjusted for systolic blood pressure, the only covariate remaining after backward selection. There was a significant interaction between collateral score and baseline systolic blood pressure for both vascular outcomes. Because of the complicated relationship between collateral score and systolic blood pressure with respect to both recanalization and reperfusion, the multivariable model was not used to estimate odds ratios; unadjusted odds ratios are detailed in Table 3. A marginally significant difference was found between subjects with baseline collateral grades of 1 and 2, with subjects with a grade of 2 being 2.07 times (95% CI, 1.00–4.27) more likely to achieve (AOL \( \geq 2 \)) recanalization compared with subjects with grade 1 collaterals. Similar analyses confirmed the association with downstream reperfusion (mTICI \( \geq 2 \)). Subjects with grade 2 collaterals were 2.49 times (95% CI, 1.23–5.06) more likely to achieve (mTICI \( \geq 2 \)) reperfusion compared with subjects with grade 1 collaterals; subjects with collateral grade 3 were 2.14 times (95% CI, 1.01–4.52) more likely to achieve (mTICI \( \geq 2 \)) reperfusion compared with subjects with grade 2 collaterals.

Finally, multivariable analyses confirmed that angiographic collateral grade was associated with good clinical outcome (mRS \( \leq 2 \)) at 90 days (\( P = 0.0353 \)), adjusted for age, history of diabetes mellitus, National Institutes of Health Stroke Scale (NIHSS) strata, and ASPECTS. Table 3 shows the adjusted odds ratios for 90-day mRS \( \leq 2 \) for subjects with adjacent baseline collateral grades. A significant difference was noted between subjects with collateral grade 2 and 3, with grade 3 collateral subjects 2.12 times (95% CI, 1.12–4.00) more likely to achieve good clinical outcome compared with subjects with grade 2 collaterals, adjusted for previously mentioned covariates.

To investigate the effect of reperfusion/recanalization on the relationship between collateral scores and clinical outcome, we also looked at proportions of good clinical outcome by collateral score separately for reperfusers, defined as mTICI \( \geq 2 \), and nonreperfusers, defined as mTICI <2 (and likewise for recanalizers, defined as AOL \( \geq 2 \), and nonrecanalizers, defined as AOL <2) via the CA trend test. Because of

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Collateral Grade, no. (%)</th>
<th>0 (n=19)</th>
<th>1 (n=53)</th>
<th>2 (n=108)</th>
<th>3 (n=88)</th>
<th>4 (n=8)</th>
<th>Fisher P Value</th>
<th>Cochran–Armitage Trend P Value</th>
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</thead>
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<tr>
<td>Recanalization (AOL ≥2)</td>
<td></td>
<td>10 (53)</td>
<td>34 (64)</td>
<td>85 (79)</td>
<td>77 (88)</td>
<td>7 (88)</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Reperfusion (mTICI ≥2)*</td>
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<td>8 (44)</td>
<td>27 (54)</td>
<td>79 (75)</td>
<td>75 (86)</td>
<td>7 (88)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Symptomatic ICH &lt;30 h of intravenous t-PA</td>
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<td>2 (11)</td>
<td>3 (6)</td>
<td>6 (6)</td>
<td>6 (7)</td>
<td>0 (0)</td>
<td>0.8918</td>
<td>0.6346</td>
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<tr>
<td>Clinical outcome mRS ≤2 at 3 mo</td>
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<td>4 (21)</td>
<td>13 (25)</td>
<td>37 (34)</td>
<td>46 (52)</td>
<td>4 (50)</td>
<td>0.0039</td>
<td>0.0002</td>
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<tr>
<td>Death from all causes &lt;3 mo</td>
<td></td>
<td>5 (26)</td>
<td>14 (26)</td>
<td>21 (19)</td>
<td>11 (13)</td>
<td>0 (0)</td>
<td>0.1402</td>
<td>0.0118</td>
</tr>
</tbody>
</table>

AOL indicates arterial occlusive lesion; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; and t-PA, tissue plasminogen activator.

*Eleven subjects with missing mTICI score due to clot location (basilar, vertebral, or posterior cerebral artery).
Table 3. Association Between Collateral Grade and Outcome After Endovascular Therapy

<table>
<thead>
<tr>
<th>Recanalization (AOL)</th>
<th>Unadjusted OR</th>
<th>95% Wald confidence limits</th>
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</thead>
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<tr>
<td>Collateral grade 1 vs 0</td>
<td>1.61</td>
<td>0.56 - 4.65</td>
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<tr>
<td>Collateral grade 2 vs 1</td>
<td>2.07</td>
<td>1.00 - 4.27</td>
</tr>
<tr>
<td>Collateral grade 3 vs 2</td>
<td>1.89</td>
<td>0.87 - 4.14</td>
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<tr>
<td>Collateral grade 4 vs 3</td>
<td>1.00</td>
<td>0.11 - 8.92</td>
</tr>
</tbody>
</table>

Reperfusion (mTICI ≥2) | Unadjusted OR | 95% Wald confidence limits |
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<tbody>
<tr>
<td>Collateral grade 1 vs 0</td>
<td>1.47</td>
<td>0.50 - 4.34</td>
</tr>
<tr>
<td>Collateral grade 2 vs 1</td>
<td>2.49*</td>
<td>1.23 - 5.06</td>
</tr>
<tr>
<td>Collateral grade 3 vs 2</td>
<td>2.14*</td>
<td>1.01 - 4.52</td>
</tr>
<tr>
<td>Collateral grade 4 vs 3</td>
<td>1.12</td>
<td>0.13 - 9.93</td>
</tr>
</tbody>
</table>

Clinical outcomes (90-day mRS ≤2)† | Adjusted OR | 95% Wald confidence limits |
<table>
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<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Collateral grade 1 vs 0</td>
<td>0.96</td>
<td>0.25 - 3.66</td>
</tr>
<tr>
<td>Collateral grade 2 vs 1</td>
<td>1.50</td>
<td>0.68 - 3.32</td>
</tr>
<tr>
<td>Collateral grade 3 vs 2</td>
<td>2.12*</td>
<td>1.12 - 4.00</td>
</tr>
<tr>
<td>Collateral grade 4 vs 3</td>
<td>0.61</td>
<td>0.12 - 3.14</td>
</tr>
</tbody>
</table>

AOL indicates arterial occlusive lesion; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; and OR, odds ratio.
*P<0.05.
†Collateral grade, age, history of diabetes mellitus, National Institutes of Health Stroke Scale strata, and Alberta Stroke Program Early CT Score included as covariates in the model.

Reperfusion (mTICI ≥2)†

Discussion

The evaluation of the role of collateral circulation in acute ischemic stroke from the IMS III trial constitutes the largest study to date using the reference standard of conventional angiography.† Our results provide definitive evidence that collateral status is closely related to revascularization success, defined alternatively as recanalization or reperfusion, and most importantly clinical outcomes. Collateral grade, measured by the ASITN scale on angiography before endovascular therapy, is feasible in the vast majority of cases using routine acquisitions or injections.5

Our findings also confirm that collaterals are an influential factor in the angiographic and clinical outcomes across a diverse population of cases based on the site of arterial occlusion and particular endovascular strategies, including local thrombolytic, aspiration, and mechanical thrombectomy approaches in combination with intravenous t-PA. Previous studies on the impact of collaterals in acute ischemic stroke have largely focused on particular sites of vascular occlusion or, alternatively, specific endovascular techniques.9 Recanalization success may be associated with more robust collaterals due to hemodynamic factors, including increased distribution of thrombolytics to the clot surface, potentially making the clot more susceptible to thrombolysis or thrombectomy. Reperfusion of the downstream territory may also be more complete after opening of an arterial occlusion, if such regions are sustained by robust collateral perfusion.

This systematic evaluation of collaterals on conventional angiography provides important data on the relationship with clinical variables commonly encountered in acute stroke. In contrast to recent analyses, we found no significant relationship between age and angiographic collateral grade.10 Similarly, we noted no significant relationship with sex or baseline NIHSS score. These data suggest that collateral status may be difficult to infer based on such brief information during triage of a stroke patient. In fact, our data reveal wide variability in the range of collateral grade without direct links with many clinical factors. We noted a broad distribution of collateral grade, including many cases with partial filling of the territory and few with rapid, complete collateral perfusion. The potential relationship of collateral grade with history of cardiovascual risk factors, such as hypertension or congestive heart failure, time from stroke onset to treatment, and ASPECTS score, requires further study because these variables may exhibit complex interactions. Similarly, the relationship between blood pressure and collateral grade mandates further consideration.

No randomized trial, including the IMS III trial, has yet confirmed that endovascular therapy can effectively achieve successful outcomes in a broad population of stroke patients.11 However, the relationship of collateral grade with angiographic and clinical outcomes helps inform who is most likely to benefit from endovascular revascularization but also indicates that collateral flow by itself is not enough to guarantee who will benefit from endovascular therapy, at least in the time window of patients treated in IMS III. Increased degree of baseline collateral flow was strongly associated with a good functional outcome in subjects with mTICI ≥2 reperfusion, but no such relationship was seen in subjects without reperfusion. In subjects with no or minimal collateral flow, 27% of those with reperfusion had a mRS of 0 to 2, and only 23% of those without reperfusion had good clinical outcomes, although this was largely driven by distal arterial occlusions. Our interpretation is that the degree of collateral flow helps to predict the likelihood of a good outcome with mTICI ≥2 reperfusion, but the absence of collateral flow should not be used to obviate endovascular therapy. Whether there are similar relationships regarding collateral status with noninvasive imaging techniques such as CT angiography is currently being investigated in the IMS III data set. Further analyses are needed to discern whether critical thresholds in collateral grade, as shown in Table 3, are pivotal and whether the relationship of collaterals with angiographic and clinical outcomes endures in the era of stent retriever device use.12,13
Limitations of our study relate to the nature of such subgroup analyses confined to only 83% subjects treated with endovascular therapy and with collaterals evaluated. Although noninvasive imaging selection criteria were not routinely used, selection biases may have influenced collateral status in our sample. Standard angiography acquisitions were prescribed but not universally adhered to, allowing for variability in image quality and limitations in the use of ASITN/SIR scale. Collateral scoring by an expert rater may also not be indicative of future scale use by a local investigator. The impact of collateral grade may vary by individual site of arterial occlusion (limited in our analyses) or by treatment variables not considered, such as rehabilitation. Finally, as with any subgroup analyses, caution is advised in the interpretation of statistical significance due to both increased likelihood of false-positive test results arising from multiple testing and limited sample sizes.

Conclusions
Collateral circulation was available and evaluated in the largest endovascular therapy trial for stroke conducted to date. More robust collateral grade was associated with better recanalization, reperfusion, and subsequent better clinical outcomes. The role of collaterals in selection criteria or to modify treatment strategies is an important consideration in the design of future endovascular trials.

Acknowledgments
We extend our gratitude for the efforts of the IMS III investigators.

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Disclosures
Dr Liebeskind was central angiography reader for IMS III; scientific consultant regarding trial design and conduct to Stryker (modest) and Covidien (modest). He was employed by the University of California (UC), which holds a patent on retriever devices for stroke at the time of this work. Dr Tomsick was Co-Principal Investigator, Interventional PI, Core Lab for Angiography Analysis IMS III. Dr Foster received funding from National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) through medical University of South Carolina (MUSC) for her role as unblinded statistician on the IMS III trial. Dr Yeatts received funding from NIH/NINDS through MUSC for her role as unblinded statistician on the IMS III trial. She was a member of the PRISMS Steering Committee. Dr Demchuk was consultant to Covidien for speaking engagements. Dr Jovin has stock ownership in Silk Road Medical. Dr Khatri—Penumbra Inc: research support to UC, Department of Neurology, for her role as Neurology Principal Investigator of THERAPY trial; Genentech Inc: research support to UC, Department of Neurology, for her role as Principal Investigator of PRISMS trial. von Kummer was a consultant for Lundbeck AC, Penumbra Inc, and Synarc. Dr Sugg was in speaker bureau for Genentech Inc. Dr Zaidat was consultant for Penumbra, Stryker, Covidien, and Microvention. Dr Goyal was consultant to Covidien-ev3 for trial design, execution, and for speaking engagements. Dr Menon received salary support from Heart and Stroke Foundation of Canada, and research support (modest) from the Faculty of Medicine, University of Calgary, and Canadian Institutes of Health Research. Dr Broderick received alteplase from Genentech Inc for NIH/NINDS-funded CLEARER (IMS III) trials, and $65,000 educational grant to the American Academy of Neurology for 2012 annual meeting program 2AC.007 “What’s in a Stroke Center: Members, Services, Organization and Roles,” which he directed. He is a member of the Executive Committee for the PRISMS study research grant. He received catheter devices for IMS III clinical trial from EKOS Corporation and drug for NIH-NINDS CLEARER trial from Schering Plough.

References
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for the IMS III Investigators

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SUPPLEMENTAL MATERIAL
Supplemental Table I. Collateral Grade Based on Site of Initial Vascular Occlusion.

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<th>Collateral Grade</th>
<th>Occlusion Location</th>
<th>Extracranial</th>
<th>ICAT</th>
<th>Other intracranial</th>
<th>ACA</th>
<th>M1</th>
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Supplemental Figure I. Proportion (95% CI) of Good Clinical Outcome (90 day mRS≤2) by Collateral Grade and Reperfusion.
Supplemental Figure II. Proportion (95% CI) of Good Clinical Outcome (90 day mRS≤2) by Collateral Grade and Recanalization.