Neurologic Examination at 24 to 48 Hours Predicts Functional Outcomes in Basilar Artery Occlusion Stroke

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Background and Purpose—Accurate long-term outcome prognostication in basilar artery occlusion strokes may guide clinical management in the subacute stage. We determine the prognostic value of the follow-up neurological examination using the National Institutes of Health stroke scale (NIHSS) and identify 24- to 48-hour NIHSS risk categories in basilar artery occlusion patients.

Methods—Participants of an observational registry of radiologically confirmed acute basilar artery occlusion (BASICS [Basilar Artery International Cooperation Study]) with prospectively collected 24- to 48-hour NIHSS and 1-month modified Rankin scale scores were included. Uni- and multivariable modeling were performed to identify independent predictors of poor outcome. Predictive powers of baseline and 24- to 48-hour NIHSS for poor outcome (modified Rankin scale, 4–6) and 1-month mortality were determined by receiver operating characteristic analyses. Classification and regression tree analysis was performed to identify risk groups.

Results—Three hundred seventy-six of 619 BASICS participants were included, of whom 65.4% had poor outcome. In multivariable analyses, 24- to 48-hour NIHSS (odds ratio=1.28 [1.21–1.35]), history of minor stroke (odds ratio=2.64 [1.04–6.74]), time to treatment >6 hours (odds ratio=3.07 [1.35–6.99]), and age (odds ratio=1.02 [0.99–1.04]) were retained in the final model as predictors of poor outcome. Prognostic power of 24- to 48-hour NIHSS was higher than baseline NIHSS for 1-month poor outcome (area under the curve, 0.92 versus 0.75) and mortality (area under the curve, 0.85 versus 0.72). Classification and regression tree analysis identified five 24- to 48-hour NIHSS risk categories with poor outcome rates of 9.4% (NIHSS 0–4), 36% (NIHSS 5–11), 84.3% (NIHSS 12–22), 96.1% (NIHSS 23–27), and 100% (NIHSS28).

Conclusions—Twenty-four- to 48-hour NIHSS accurately predicts 1-month poor outcome and mortality and represents a clinically valuable prognostic tool for the care of basilar artery occlusion patients. (Stroke. 2016;47:2534-2540. DOI: 10.1161/STROKEAHA.116.014567.)

Key Words: brain ischemia ■ critical care outcomes ■ decision support techniques ■ neurologic examination ■ prognosis ■ stroke ■ vertebrobasilar insufficiency

Basilar artery occlusion (BAO) accounts for 6% to 10% of ischemic strokes and is associated with a higher mortality and morbidity than ischemic stroke in the anterior circulation.1-3 Intravenous thrombolysis is the mainstay of acute treatment, and intra-arterial therapy is currently being investigated in the BASICS trial (Basilar Artery International Cooperation Study).4 Despite intravenous thrombolysis and intra-arterial treatment, disability ensues in the majority of patients.5 Because medical decisions to pursue or withdraw ventilator support, tracheostomy, gastrostomy, long-term rehabilitation, and placement in skilled nursing facilities are often made in the first few days after BAO, early accurate prognostic tools can be clinically meaningful and can guide physicians and family members during decision making.

Fairly good prognostic accuracy (area under the curve [AUC], 0.79–0.80) for long-term outcome in BAO patients can be achieved by incorporating clinical variables (admission National Institutes of Health stroke scale [NIHSS], age, hyperlipidemia, prodromal minor stroke, and time to treatment) and computed tomography imaging data available at the time of presentation.6,7 Severity of neurological deficits can be measured by the NIHSS at admission and has previously been identified to independently predict clinical outcomes in stroke patients. NIHSS often changes during the first 24 hours, and the relationship between the neurological examination and long-term functional outcome strengthens after the first few hours and then begins to plateau.8,9 Early neurological improvement may reflect recanalization of BAO, whereas failure of improvement or clinical decline may reflect persistent occlusion, substantial
infarction, or medical complications. Although prognostication based on admission data can facilitate acute treatment decision making and predict early mortality, the prognostication of long-term functional outcome and decision making regarding prolonging life-sustaining medical and surgical treatments usually occur after the first 24 hours. We recently found that the 24-hour NIHSS is superior to admission NIHSS for the prediction of long-term outcome in anterior circulation large vessel occlusion stroke patients. However, data on the prognostic importance of the follow-up neurological examination in BAO patients are lacking. We sought to determine the prognostic value of the follow-up neurological examination using the NIHSS at 24- to 48-hour poststroke admission in a large cohort of BAO patients and to objectively develop clinically useful prognostic risk categories.

Methods

Study Population, Measurements, and Outcome Measures

BASICS was a prospective, observational registry of 619 consecutive patients who presented with an acute symptomatic and radiologically confirmed BAO between November 1, 2002, and October 1, 2007. The study protocol, demographic, clinical, and outcome data have been previously published (see online-only Data Supplement for the complete BASICS Study Group member list). BAO was confirmed radiographically by computerized tomography, magnetic resonance angiography, or conventional angiography. Baseline NIHSS and 24- to 48-hour follow-up NIHSS were obtained by trained investigators as part of the study protocol. Modified Rankin scale (mRS) at 1 month was determined prospectively as part of the BASICS study protocol. The outcome measure for this analysis was mRS at 1 month, and primary end point was poor outcome, defined as mRS 4 to 6 at 1 month. Secondary end points were all-cause mortality at 1 month and severe dependency or death (mRS 5–6) at 1 month.

Statistical Analysis

For comparison of included and excluded BASICS participants, categorical variables were compared using χ2 (or Fisher exact) tests, whereas continuous variables were compared using independent sample 2-way t test for parametric and Mann–Whitney U test for nonparametric variables. Relationship between continuous variables was assessed using scatterplots. Univariable logistic regression was performed using clinical variables and previously identified predictors of stroke outcome. Significant variables (P<0.05) from univariable analyses were used for multivariable logistic regression using backward elimination based on the likelihood method (entry threshold 0.05 and elimination threshold 0.15) to model mRS 4 to 6 at 1 month. Calibration of the final model was assessed by comparing observed and predicted probabilities across 24- to 48-hour NIHSS deciles and the Hosmer–Lemeshow statistic was calculated (P=0.05 indicating satisfactory calibration). Missing data points (1-month mRS and 24- to 48-hour NIHSS) were not imputed in either database. Receiver operator characteristic curve analysis was performed to determine the discriminative power (AUC) of 24- to 48-hour NIHSS for 1-month poor outcome (mRS 4–6), as well as for 1-month mortality. AUCs for poor outcome were also determined and compared in patients intubated and not intubated at the time of assessment. AUCs of 24- to 48-hour NIHSS were compared with baseline NIHSS, absolute change in NIHSS over 24 to 48 hours, and relative change in NIHSS over 24 to 48 hours for patients with NIHSS recorded at both time points, using the Hanley and McNeil method. Classification and regression tree analysis was performed using predictors of poor outcome retained in the final regression model to identify risk groups that best segregate patients based on rates of poor outcomes (minimum change in improvement=0.001) and cross-validation was performed (10 sample folds). Classification accuracy of the classification and regression tree analysis result was evaluated. SPSS version 22 was used for all statistical analyses.

Results

Study Population

Patient characteristics and outcomes in BASICS have been previously published. Of 619 patients enrolled in BASICS, 376 had an NIHSS documented at the 24 to 48 hours, as well as 1-month mRS, and were included in our analysis. Our study cohort had a mean age of 63 (SD=15) years and median baseline NIHSS of 21 (interquartile range, 11–30). Of these 376 patients, 246 (65.4%) had poor outcome (mRS 4–6 at 1 month), whereas 92 (24.5%) achieved mRS 0 to 2 and 38 (10.1%) achieved mRS of 3 at 1 month. Of the 376 included patients, 143 (38%) were intubated at the time of the 24- to 48-hour examination. There were no significant differences in patient characteristics or stroke severity (admission NIHSS) between patients with and without available 24- to 48-hour NIHSS (Table 1). Patients with missing 24- to 48-hour NIHSS had a higher risk of poor outcome than those with available data (RR=1.15 [1.04–1.28]). Patients with missing 24- to 48-hour NIHSS had unknown intubation status at 24 to 48 hours, and the reason for missingness of NIHSS data could not be determined in the majority of patients. Mortality within 48 hours accounted for 45 of 243 patients with missing 24- to 48-hour NIHSS data. The rates of intubation and the reasons for intubation (procedural versus nonprocedural indications) at the time of initial presentation were the same in patients with and without 24- to 48-hour NIHSS data. Of the 177 included patients who were intubated at presentation, 119 (67.2%) remained intubated at the 24- to 48-hour time point. However, of the 189 included patients who were not intubated at initial presentation, only 21 (11.1%) were subsequently intubated by the 24- to 48-hour time point.

NIHSS at 24 to 48 Hours Strongly Predicts 1-Month Clinical Outcomes and 1-Month Mortality

NIHSS at 24 to 48 hours was positively correlated with 1-month mRS (Figure 1A). In univariable analyses, predictors of poor outcome (mRS 4–6 at 1 month) were age, current smoking, hyperlipidemia, time to treatment, intubation at 24 to 48 hours, intubation at initial presentation, history of minor stroke, baseline NIHSS, and 24- to 48-hour NIHSS (Table 2). In multivariable logistic regression analysis (Table 2), age (odds ratio=1.02 [0.99–1.04]), time to treatment >6 hours (odds ratio=3.07 [1.35–6.99]), history of minor stroke (odds ratio=2.64 [1.04–6.74]), and 24- to 48-hour NIHSS (odds ratio=1.28 [1.21–1.35]) were retained in the final model. The calibration of the final model was satisfactory (Hosmer–Lemeshow statistic P value, 0.91). The discriminative power of the final model for poor outcome was 0.93, whereas that of NIHSS at 24 to 48 hours alone was 0.92. NIHSS at 24 to 48 hours had similar discriminative power in nonintubated (AUC=0.87) and intubated (AUC=0.84) patients at 24 to 48 hours. NIHSS at 24 to 48 hours also had excellent discriminative power for mRS 5 to 6 (AUC=0.87) at 1 month. NIHSS at 24 to 48 hours had superior discriminative power for poor outcome compared with baseline NIHSS (AUC, 0.92 versus 0.75; P<0.001). NIHSS at 24 to
48 hours was also superior to our previously published 5-vari-
model that includes age, baseline NIHSS, hyperlipidemia,
prodromal or minor stroke, and time to treatment (AUC, 0.92
versus 0.80; \( P < 0.001 \); Figure 1B).\(^7\) The discriminative abili-
ties of the absolute change in NIHSS (AUC=0.75) and relative
change in NIHSS over 24 to 48 hours (AUC=0.79) were also
inferior (\( P < 0.001 \)) to that of the total 24- to 48-hour NIHSS.
NIHSS at 24 to 48 hours had higher discriminative power
for 1-month mortality (AUC=0.85) compared with baseline
NIHSS (AUC=0.71; \( P < 0.001 \)) and the previously published
5-variable model (AUC=0.75; \( P < 0.01 \)).

**Development of 24- to 48-Hour NIHSS Risk Categories**

Using classification and regression tree analysis with poor
outcome as the dependent variable and 24- to 48-hour NIHSS,
age, time to treatment, and history of minor stroke as predictor
variables, we arrived at 5 risk categories solely based on
24- to 48-hour NIHSS (Figure 2): 0 to 4 (poor outcome=9.4
[95% confidence interval, 4.4–19]; \( n = 64 \)), 5 to 11 (poor
outcome=36.4 [27–47]; \( n = 88 \)), 12 to 22 (poor outcome=82.3
[72–89]; \( n = 79 \)), 23 to 27 (poor outcome=96.1 [87–99];
\( n = 51 \)), and \( \geq 28 \) (poor outcome=100 [95–100]; \( n = 94 \)).
Cross-
validation was performed, and overall classification accuracy
was 85.6% (87.7% for mRS 0–3 and 84.6% for mRS 4–6).
The distribution of mRS scores across the five 24- to 48-hour
NIHSS risk groups is shown in Figure 3A. Severe dependency
or death (mRS 5–6 at 1 month) was observed in 135 of 145
patients (93.1%), with a 24- to 48-hour NIHSS \( \geq 22 \). Observed
rates of poor outcomes in the NIHSS 12 to 22, 23 to 37, and
\( \geq 28 \) risk groups were similar in patients who were nonintu-
bated, as well as those intubated at the time of the NIHSS
assessment (Figure 3B). Intubation at 24 to 48 hours was not
common in NIHSS 0 to 4 (\( n = 1 \)) and 5 to 11 (\( n = 5 \)) groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Available (n=376)</th>
<th>Not available (n=243)</th>
<th>P-Value*</th>
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<td>Age, y (SD)</td>
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<td>Sex (male), n (%)</td>
<td>243 (64.6)</td>
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<td>Diabetes mellitus, n (%)</td>
<td>86 (22.9)</td>
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<td>Hypertension, n (%)</td>
<td>223 (59.3)</td>
<td>160 (65.8)</td>
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<tr>
<td>Atrial fibrillation, n (%)</td>
<td>79 (21.0)</td>
<td>54 (22.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>109 (29.0)</td>
<td>58 (23.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Intubation at presentation, n (%)</td>
<td>177 (47.1)</td>
<td>98 (40.3)</td>
<td>0.12</td>
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</table>

**Indication for initial intubation, n (%)†**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Available (n=376)</th>
<th>Not available (n=243)</th>
<th>P-Value*</th>
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</thead>
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<tr>
<td>Procedural</td>
<td>21 (11.9)</td>
<td>7 (7.1)</td>
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<tr>
<td>Nonprocedural</td>
<td>156 (88.1)</td>
<td>91 (92.9)</td>
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Discussion

Our analysis of BAO patients in the BASICS registry demonstrates the prognostic value of the follow-up neurological assessment using the NIHSS at 24 to 48 hours and emphasizes the importance of using follow-up clinical information in the subacute stage, as opposed to information available at the time of admission, while attempting long-term prognostication in stroke patients. Previous studies limited primarily to anterior circulation ischemic stroke have suggested that the 24-hour NIHSS is highly predictive of long-term clinical outcomes.\(^8\) The inherently higher morbidity and mortality associated with BAO, as well as the unique neuroanatomical features of the brain stem, and other posterior circulation regions do not allow for extrapolation of results from anterior circulation by guest on July 23, 2017 http://stroke.ahajournals.org/ Downloaded from

<table>
<thead>
<tr>
<th>Table 2. Identification of Predictors of Poor Outcome</th>
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<tr>
<td>Univariable Analysis*</td>
</tr>
<tr>
<td>Variable</td>
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<td>Age, y</td>
</tr>
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<tr>
<td>History of minor stroke</td>
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<tr>
<td>Admission NIHSS</td>
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<tr>
<td>24 to 48 h NIHSS</td>
</tr>
<tr>
<td>Intubation at 24–48 h</td>
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<tr>
<td>Intubation at initial presentation</td>
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<tr>
<td>Smoking</td>
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</tr>
<tr>
<td>4–6 h</td>
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<tr>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Atrial fibrillation</td>
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</table>

CI indicates confidence interval; OR, odds ratio; and NIHSS, National Institutes of Health stroke scale.

*Variables not significant in univariable analyses included sex, diabetes mellitus, hypertension, atrial fibrillation, and alcohol use.

†Backward elimination using likelihood ratio method (entry level 0.05, exit level 0.15) was used for multivariable analysis. n=361 for the final multivariable model.
studies to the posterior circulation. Our study for the first time demonstrates the high predictive power and potential clinical utility of the follow-up NIHSS in the BAO population. Furthermore, an NIHSS \( \leq 4 \) at 24 to 48 hours is highly associated with a favorable outcome at 1 month, whereas an NIHSS \( \geq 28 \) universally portends a poor outcome. These NIHSS thresholds could serve as early surrogates of long-term outcomes while studying the BAO population.

Key confounders of the neurological examination in BAO patients are intubation and sedation, both of which may

Figure 2. Identification of 24- to 48-hour National Institutes of Health stroke scale (NIHSS) risk groups. Classification and regression tree analysis performed with modified Rankin Scale (mRS) 4 to 6 at 1 month as the outcome variable and 24- to 48-hour NIHSS and history of minor stroke as predictor variables. Cross-validation was performed (sample fold=10).

Figure 3. Observed outcomes in 24- to 48-hour National Institutes of Health stroke scale (NIHSS) risk categories. A, Distribution of modified Rankin Scale (mRS) outcomes in the five 24- to 48-hour NIHSS risk groups; (B) comparison of observed rates of poor outcomes in 24- to 48-hour NIHSS risk groups based on intubation status at the time of assessment.
artificially inflate the NIHSS. Interestingly, we observed that intubation status at the time of the NIHSS did not affect the predictive power of 24- to 48-hour NIHSS for poor outcome and after controlling for 24- to 48-hour NIHSS, was no longer retained in our final model as a predictor of poor outcome. The NIHSS captures level of consciousness domains that are influenced by sedation, as well as language/speech domains that can be influenced by intubation. The fact that a patient is intubated at 24 to 48 hours is likely reflective of severity of the stroke and degree of brain stem injury, and therefore directly linked to functional outcome. In our cohort, patients intubated at the time of 24- to 48-hour NIHSS assessment had a higher median NIHSS than nonintubated patients. Because the predictive power of the 24- to 48-hour NIHSS was the same for intubated and nonintubated patients, it is likely that intubated patients in the BASICS registry who were included in our study had been examined off sedation, although we are unable to confirm this directly. However, whether the prognostic importance of the 24- to 48-hour NIHSS in intubated patients included in our study is similar to intubated patients who were excluded from our analysis is unclear.

Our analysis adds to our previous model that was based on the BASICS registry and that identified age, hyperlipidemia, prodromal minor stroke, baseline NIHSS, and longer time to treatment as predictors of poor clinical outcome (mRS 4–6 at 1 month). In the current study, we found that 24- to 48-hour NIHSS, age, time to treatment, and history of prodromal minor stroke were predictors of poor outcome, although the discriminative power of 24- to 48-hour NIHSS alone was the same as that of our final model and was superior to the previously published 5-variable Greving model. These observations highlight the prognostic importance of the 24- to 48-hour NIHSS over and above admission variables. A possible explanation for the high predictive power of the 24- to 48-hour NIHSS for poor outcome is that the NIHSS may be partly influenced by multiple factors, including medical comorbidities, frailty, stroke location, and size, as well as early poststroke complications.

Limitations of this study need to be acknowledged. First, failure to improve neurologically or a poor neurological examination at 24 to 48 hours may have been considered during decision making for early withdrawal of care or institution of comfort measures, leading to a self-fulfilling prophecy that may have overestimated the rate of poor outcome in patients with high 24- to 48-hour NIHSS. Information regarding early withdrawal of care was not available for analysis. Future prospective validation studies must collect data on medical decision making, physician and patient/family preferences, and the cognitive heuristics that govern early decisions to withdraw or limit care in BAO patients. Second, the primary outcome measure (mRS) was obtained at 1 month in BASICS, as opposed to the traditionally used 3-month time point in the stroke literature. Because significant neurological recovery can occur between 1 and 3 months after ischemic stroke and many patients with intermediate levels of disability at 1 month may achieve functional independence at 3 months or later, the prognostic importance of the 24- to 48-hour NIHSS will need to be evaluated to address longer-term outcomes, but as suggested before, the prognostic accuracy of the 24- to 48-hour examination is likely to remain the same because patients who make an early improvement are likely to do much better in the long-term. To partly overcome this limitation, we also assessed the predictive power of the 24- to 48-hour NIHSS for 1-month mortality and confirmed high predictive power supporting the possibility that 24- to 48-hour NIHSS is likely to have high predictive value for outcomes at later time points as well. Third, 243 patients in BASICS (39%) did not have a 24- to 48-hour NIHSS and were excluded from analysis. Forty-five excluded patients had died within 48 hours explaining why the group of 243 excluded patients had a slightly higher rate of poor outcome; however, they were similar to the included patients in all other aspects, including demographics, clinical stroke severity, as well as the need for initial intubation. Because the NIHSS score at 24 to 48 hours obviously cannot be applied to patients who died within the first 48 hours and because of the observed similarity of included and excluded patients, we do not think that the generalizability of our findings has been limited. Fourth, we were unable to account for the effect of postdischarge variables, such as rehabilitation, access to care, and family support, all of which can influence the long-term outcome and potentially improve the prognostic accuracy of our multivariable model. In addition, outcomes at later time points such as 3 or 6 months were not collected in the BASICS registry, limiting our ability to analyze the discriminative power of the 24- to 48-hour NIHSS for these outcome measures. The BASICS registry also did not include patients more than the age of 85 years, thereby limiting the applicability of our findings to patients over this age limit. Lastly, the relationship between 24- to 48-hour NIHSS and patient’s long-term quality of life was not assessed in our study and should be evaluated in future prospective studies.

In conclusion, the 24- to 48-hour neurological assessment using the NIHSS can be used to accurately predict 1-month rates of poor outcome and mortality and can serve as a valuable clinical tool to aid early prognostication and guide decision making in the care of BAO patients. NIHSS thresholds of ≤4 and >22 strongly predict high rates of favorable and poor outcome, respectively, and may represent early outcome measures in the study of BAO patients.

Sources of Funding
Dr Rangaraju is a recipient of a clinical research training fellowship from the American Brain Foundation. This study was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures
Dr Nogueira was the PI for Trevo-2 trial (sponsored by Stryker Neurovascular—modest) and is the DAWN trial PI (Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention; no compensation). He was on the Steering Committee of SWIFT trial (Solitaire Flow Restoration Device Versus the Merci Retriever in Patients With Acute Ischaemic Stroke; modest) and SWIFT Prime (no compensation). He received compensation from the STAR trial (Solitaire FR Thrombectomy for Acute Revascularisation; Angiographic Core Laboratory—significant). He is also part of the Executive Committee for the Penumbra 3D separator trial (no compensation). He is also
Editor-In-Chief of the Interventional Neurology Journal (no compensation). Dr Jovin reports nonfinancial (travel) support from Fundació Ictus Malaltia Vascular (PI REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset]), nonfinancial (travel) support from Covidien/Medtronic consulting fees from Silk Road Medical, Anaconda, Blockade Medical, Neuravi (Steering Committee) and Johnson and Johnson (Data Safety Monitoring Board), and is the DAWN trial PI (no compensation). Dr Schonewille was the PI of the BASICS registry (no compensation) and is currently the PI of the BASICS trial (no compensation). The other authors report no conflicts.

References
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Stroke. 2016;47:2534-2540; originally published online September 1, 2016;
doi: 10.1161/STROKEAHA.116.014567

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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USA – Stanford Stroke Center, Palo Alto (Christine AC Wijman, Anna Finley Caulfield, Maarten Lansberg, Neil Schwartz, Chitra Venkatasubramanian), University of Texas, Houston (Zolt Garami, Simon van den Bogaard, Frank Yatzu, James Grotta).