Safety and Effectiveness of Endovascular Therapy After 8 Hours of Acute Ischemic Stroke Onset and Wake-Up Strokes

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Background and Purpose—This is a retrospective review of patients who underwent endovascular recanalization ≥8 hours after acute ischemic stroke symptom onset, including wake-up strokes, between June 2005 and June 2008.

Methods—Thirty patients with a premorbid modified Rankin score ≤1 and NIHSS between 5 and 22 were included. All had admission CT, CTA, and CT perfusion scans to evaluate for salvageable brain tissue. Recanalization effectiveness was assessed by angiograms obtained within 30 hours after intervention. Patient, treatment characteristics, and immediate and 3-month outcomes were analyzed.

Results—Mean NIHSS at presentation was 13 (median=12). Mean interval between time last-seen well and angiogram was 12.75 hours (median=10). Twenty-six patients (86.7%) presented with complete-to-near-complete vessel occlusion (thrombolysis in myocardial infarction [TIMI] 0/1); 4 had partial vessel occlusion (TIMI 2). Interventions included intra-arterial pharmacological thrombolysis (n=10), mechanical thrombectomy (n=21); Merici, 16; intracranial stent, 9; extracranial stent, 3), angioplasty (n=14; intracranial, 11; extracranial, 3). Nine patients received GPIIb/IIIa inhibitors (eptifibatide); all received heparin. Partial-to-complete recanalization (TIMI 2/3) was achieved in 20 patients (66.7%). Procedure-related complications included vascular perforations (n=3) and femoral access site complication (n=1). One patient had an embolic anterior cerebral artery infarct during intervention; another had progression of brain stem infarct. Symptomatic intracerebral hemorrhage occurred in 3 patients (10%), with 2 being primarily subarachnoid in location. Total in-hospital mortality including procedural mortality, disease progression, or other comorbidities was 23.3% (n=7). Mean discharge NIHSS was 9.5, representing an overall NIHSS 3.5-point improvement. Overall, mean modified Rankin score at death or last follow-up (mean=10.6 months) was 4.2. At 3 months, total mortality was 33.3% (n=10), 20% had modified Rankin score ≤2, and 33% had modified Rankin score ≤3. Among survivors, mean modified Rankin score at 3-month follow-up was 3.

Conclusion—Our data show that delayed endovascular revascularization of carefully selected patients is safe, effective, and improves clinical outcome. (Stroke. 2009;40:3269-3274.)

Key Words: acute ischemic stroke ■ endovascular therapy ■ outcomes ■ recanalization ■ revascularization time window ■ wake-up strokes

Approximately 795 000 strokes occur in the US annually, of which ≈85% are ischemic.1 The only US FDA-approved medical therapy for acute stroke to date is intravenous tissue plasminogen activator (t-PA) administered within 3 hours of symptom onset.2 However, <5% of patients with acute ischemic stroke in the US receive t-PA, primarily because of a delay in hospital presentation.3 To increase the proportion of acute stroke patients who receive treatment, efforts are ongoing to try to expand the time window for reperfusion therapy beyond 3 hours. These efforts include the development of novel thrombolytic agents,4 mechanical thrombectomy,5 self-expanding stents,6 and use of advanced imaging techniques.7,8 There is increasing evidence that identification of potentially salvageable brain tissue with advanced MR and CT imaging may allow the selection of patients who can be effectively and safely treated with intravenous thrombolysis for up to 9 hours after ictus.9–16

Approximately 16% to 28% of ischemic stroke patients awaken with their deficits.17,18 In these wake-up strokes (WUS), the onset of symptoms is defined as the “time last-seen well” (TLSW). Because this is the time the patient went to sleep, unfortunately, these patients are usually placed outside the window for thrombolysis or ineligible for entry into reperfusion clinical trials. Barreto et al19 reported that patients with WUS have better outcomes when they are treated. There was no significant difference between WUS

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patients and patients treated within 3 hours by intravenous thrombolysis when time of stroke onset was known. Reestablishment of flow to perfuse salvageable brain tissues has been shown to significantly reduce the morbidity and mortality of ischemic stroke. Endovascular techniques to recanalize occluded vessels have overcome some of the limitations of systemic intravenous thrombolysis, such as narrow therapeutic window, poor recanalization rates, high hemorrhage rates, and inability to visualize treatment effectiveness immediately. In this report, we describe our center’s experience using various endovascular therapies to treat ischemic stroke at least 8 hours after stroke symptom onset and including WUS.

Materials and Methods
A retrospective review was conducted of a prospectively collected registry of acute ischemic stroke patients undergoing endovascular treatment at a single high-volume stroke center (Millard Fillmore Gates Hospital) between June 2005 and June 2008. Data for the consecutive series of patients who had an angiogram with intent-to-treat at least 8 hours after the time when they were last known to be normal (TLSW) were collected and analyzed. Our Institutional Review Board approved this study.

Patient Selection
All patients who had witnessed or nonwitnessed (including WUS) strokes with TLSW between 7 and 23 hours (treatment initiation between 8 and 24 hours) and had a premorbid modified Rankin score (mRS) score of 0 to 1 and NIHSS between 5 and 22 were included in this study. All patients had cranial CT, CTA, and CT perfusion scans on admission. After the diagnosis of ischemic stroke caused by vessel occlusion had been made and the presence of an intracranial hemorrhage had been excluded by noncontrast CT imaging, CT perfusion scans were analyzed to evaluate for salvageable brain tissue. Endovascular therapy was only implemented on those patients in whom CT perfusion volume maps demonstrated the presence of clinically significant salvageable brain tissue as compared with established core infarct (less than one-third of the middle cerebral artery territory) that was at high risk for hemorrhagic conversion (APSCETS ≥7) as demonstrated by CT perfusion cerebral blood volume maps. Cause of ischemic stroke was determined by a complete neurological–neuroimaging evaluation, including diagnostic angiography, noninvasive imaging, telemetry, and 2-dimensional echocardiography.

CT Perfusion Protocol
Our CT perfusion protocol starts with an axial noncontrast cranial CT scan. If hemorrhage was present, the protocol was aborted and these patients were not included in this review. Most perfusion scans were performed on the Toshiba Aquilion 64-slice CT scanner (Toshiba American Medical Systems, Inc.). Maps obtained by the Aquilion 64 were generated using both Gaussian Fit and single value deconvolution methods using Vitrea software (Vital Images), yielding the following perfusion parameters: time to peak, mean transit time, cerebral blood flow, and cerebral blood volume. Patients with significant salvageable brain tissue were identified and chosen for intervention on the basis of preserved cerebral blood volume, using the criteria of >30% relative cerebral blood volume values, compared with the unaffected hemisphere. If this criterion was satisfied using both analysis methods, the patient was selected for intervention. The few perfusion maps obtained from the Toshiba Aquilion One (320-slice CT scanner that creates whole-brain perfusion maps) were also analyzed by Gaussian fit and single value deconvolution, as well as the newest single value deconvolution plus algorithm, using Vitrea software, yielding the additional perfusion parameters of mean time to peak and a delay map. Patients were chosen for treatment using the same criteria as that for the Aquilion 64 with the additional requirement for preserved volume on the single value deconvolution plus maps. This helped in identifying patients with decreased cerebral blood flow in the same hemisphere if there was a coexisting ipsilateral carotid stenosis.

Treatment Protocol
Endovascular therapy was commonly performed under conscious sedation with a rigid easily detachable headholder, thereby allowing safe road mapping, adequate imaging, and continuous monitoring of the patient’s neurological examination. General anesthesia was used only in cases of large dominant hemisphere strokes or for uncooperative patients. Antiplatelet therapy was instituted or continued on all patients within the first 24 hours. All patients receiving stents were given a loading dose of clopidogrel on the angiogram table via a nasogastric feeding tube. Mechanical revascularization methods were the primary choice in these patients because the use of thrombolytics at a delayed time window increases the risk of hemorrhage. Intra-arterial (IA) pharmacological thrombolysis (t-PA) was used only when the clot was not accessible with available devices or as an adjunct to mechanical strategies. An IA GP IIb/IIIa inhibitor (eptifibatide) was used if thrombus formation was noticed after recanalization. All patients were monitored in a neurosurgical intensive care unit for at least the first 24 hours after intervention. All patients received a postintervention noncontrast cranial CT scan and CT perfusion imaging and CTA on the day after the intervention.

Data Collected
Data collected were patient characteristics (age, sex, comorbid conditions, antithrombotic agent intake, presentation NIHSS score, TLSW); treatment characteristics (angiography-catheterization time, occlusion site, occlusion grade [TICI grading], recanalization time [time interval between catheterization and revascularization], type of intervention, adjunctive heparinization, procedural complications, extent of recanalization [TICI]); immediate posttreatment outcomes (symptomatic intracerebral hemorrhage, presence of parenchymal hemorrhage [ECASS II grading], subarachnoid hemorrhage, discharge NIHSS score, discharge destination, hospital stay, morbidity, and mortality); and 3-month follow-up data (mRS, mortality [evaluated by the interventionist and NIHSS-certified members of his team]).

Results
Patient Characteristics
Thirty patients who presented with acute ischemic stroke at least 8 hours after the TLSW (including WUS) were selected for endovascular revascularization after clinical assessment and imaging. There were 17 men and 13 women, with a mean age of 72 years (range, 24–91 years), who presented with a mean NIHSS of 13 (median, 12; range, 5–22). Twenty-seven patients had anterior-circulation ischemia and 3 had posterior-circulation ischemia. Stroke risk factors included hypertension in 21 patients (70%), smoking in 11 (36.6%), hyperlipidemia in 10 (33.3%), atrial fibrillation in 13 (43.3%), diabetes mellitus in 10 (33.3%), previous stroke in 2 (6.6%; 1 ipsilateral), transient ischemic attacks in 2 (6.6%; both ipsilateral), myocardial infarction in 3 (10%), and hypercoagulable state in 3 (10%). Nine patients (30%) had concomitant coronary artery disease, 2 (6.6%) had cardiomyopathy, and 7 (23.3%) had cardiac valvulopathy. At presentation, 11 patients (36.6%) were using aspirin, 4 were using clopidogrel (13.3%), 7 (23.3%) each were using warfarin and a statin, and 1 was using aspirin/extended-release dipyridamole. Overall, 19 (63.3%) patients were receiving some form of antiplatelet or anticoagulant therapy at presentation. The etiology for ischemic stroke was determined to be arterioem-
bollic in 7 patients (23.3%), cardioembolic in 13 (43.3%),
left-to-right cardiac shunt in 1, and unknown in 9 (30%).
Oclusion sites were cervical ICA in 2 patients, petrous ICA
in 2, intracranial ICA in 4, proximal M1 in 7, distal M1 in 13,
M2 in 7, vertebrobasilar junction to superior cerebellar artery
in 2, superior cerebellar artery to basilar artery bifurcation in
2, A1 in 1, and A2 in 1. Eight patients had multiple intracranial occlusions (ICA terminus, A1, and M1-3; M1 and
M2-5), and 1 patient had tandem cervical ICA and intracra-
nial M1 occlusions. Twenty-six of 30 patients (86.7%)
presented with complete to near-complete vessel occlusion
(TIMI 0/1); 4 patients presented with partial vessel occlusion
(TIMI 2).

Treatment Characteristics
Mean interval between TLSW and angiography-catheteriza-
tion was 12.75 hours (median, 10 hours; range, 8–27.5
hours). Mean time from emergency department door to
angiography-catheterization time was 3.5 hours (median, 3
hours; range, 0.25–8.0 hours). Interventions included IA
pharmacological thrombolysis in 10 patients (8 alone; 2 in
combination with mechanical measures), mechanical throm-
boectomy in 21 patients (Merci [Concentric Medical], 16;
intracranial stent, 9; extracranial stent, 3), and balloon angi-
oplasty in 14 (intracranial, 11; extracranial, 3). A total of 9
patients received IA (8 patients) or intravenous (6 patients)
eptifibatide in combination with endovascular therapy. Hepar-
arin was used in all patients to an activated coagulation time
measured at 250 seconds.

Partial-to-complete recanalization (TIMI grade 2/3) was
achieved in 20 of 30 patients (66.7%). The mean time to
recanalization from angiography-catheterization time was 87
minutes (median, 83 minutes; range, 30 minutes to 4 hours).
Procedure-related complications included vascular perfora-
tions in 3 patients and a femoral access site complication in 1.
One patient required a craniotomy because of inability to
open the initial middle cerebral artery M1 occlusion (with
subsequent hemispheric infarct, edema, and impending her-
niation from mass effect); 1 patient had an anterior cerebral
artery (ACA) infarct attributable to embolus during interven-
tion, despite attempting IA thrombolysis and IA eptifibatide
for the embolus; and another had progression of brain stem
infarct and underwent percutaneous endoscopic gastrostomy
placement.

Immediate Posttreatment Outcomes
Postprocedure hemorrhage (subarachnoid hemorrhage or
ICH) was radiologically detected in 9 patients (33.3%). Eight
(26.7%) patients had subarachnoid hemorrhages and 8 had
parenchymal hemorrhages (HI 1-3, HI 2-1, PH 1-3, PH 2-1
[ECASS II23 grades]). Symptomatic intracerebral hemorrhage
was present in 3 patients (10%), with 2 of these being
primarily subarachnoid in location (and 1 being a PH2). Of
these, all 3 had Merci clot retrieval, stents placed, and IA
t-PA; 1 had additional balloon angioplasty; and 1 had
intravenous bolus eptifibatide. Four patients (13.3%) were
discharged home, 15 (50%) were discharged to rehabilitation
(acute and subacute), and 4 (13.3%) were sent to chronic care
facilities. The total in-hospital mortality rate including pro-
cedural mortality, progression of disease, or other comorbid-
ties was 23.3% (7 patients). Mean discharge NIHSS was 9.5,
representing an overall NIHSS improvement of 3.5 points.

Three-Month Outcomes
At 3 months, total mortality rate was 33.3% (10 patients).
Overall, mean mRS at death or last follow up (mean, 10.6
months) was 4.2. Twenty-percent (6 patients) had good
outcomes (mRS ≤2) and 33% (10 patients) had acceptable
outcomes (mRS ≤3). Among survivors, mean mRS at the
time of the 3-month follow up was 3.

Discussion
Until the recent publication of ECASS III,13 there had been no
level 1 evidence in the form of a randomized controlled trial
with primary clinical outcome measures for intravenous t-PA
(or, indeed, clot retrieval) beyond 3 hours. The results of this
trial have extended the time window to 4.5 hours for
intravenous t-PA.15 Furthermore, there is strong evidence for
IA thrombolysis in middle cerebral artery occlusion up to 6
hours, based on the PROACT II results.24 The pooled analysis
by Hacke et al25 demonstrates a treatment effect up to 4.5
hours, and the meta-analysis by Wardlaw et al26 demonstrates
a treatment effect up to 6 hours, thus formally providing level
1 evidence (meta-analysis of randomized controlled trials),
even in patients selected by “only” noncontrast CT. There is
increasing evidence that identification of potentially salvage-
able brain tissue with advanced MR and CT imaging may
allow selection of patients who can be effectively and safely
treated with intravenous thrombolysis for up to 9 hours after
ictus.9–16 Although MR imaging-based perfusion imaging is a
useful imaging modality for determining salvageable tissue,
CT perfusion has been shown to be comparable27,28 and is
widely available. In this study, we used CT perfusion images
to define the core and penumbra in acute ischemic stroke.

The Table compares our study to the NINDS Recombinant
t-PA Stroke Study,2 prominent studies of endovascular treat-
ments for acute ischemic stroke,5,24,29 and the recently pub-
lished DIAS-2 study because the time window in this study
was up to 9 hours and the investigators used MR imaging to
assess salvageable brain tissue for treatment selection.16 Our
recanalization rate of 66.7% was comparable to previous
series using endovascular interventions for opening up
acutely occluded vessels. The use of GP IIb/IIIa inhibitors
changes the prothrombotic–anti thrombotic balance in the
intracranial vessels, thus probably facilitating and maintain-
ing recanalization.30,31 The rates of complications, symptom-
atic intracerebral hemorrhage, and mortality at 3 months are
comparable to previous studies in which patients were treated
within a shorter duration after stroke onset.

All 3 patients with posterior circulation ischemia had
basilar artery occlusions and were selected for intervention
based on CT perfusion imaging. They presented with NIHSS
scores of 18, 5, and 18 with TLSW–angiography-catheteriza-
tion time of 19.5, 19, and 9.5 hours, respectively. Merci
device was used in the first patient, but we were not able to
reopen the vessel and there was a perforation with subarachn-
oid hemorrhage. The second patient had TIMI 3 flow after
Merci, IA t-PA, and IA eptifibatide. The third patient had

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TIMI 2 flow after Wingspan stent (Boston Scientific) placement. The first 2 patients did not recover from their original insult and died within 30 days. The third patient had a brain stem infarct, underwent percutaneous endoscopic gastroscopy placement for swallowing difficulty, and had an mRS of 4 at 3 months. Of the 3 patients who had perforations, 2 had a perforation during attempted stent placement—1 after angioplasty before balloon-mounted stent placement and another after attempted self-expanding stent placement. Both these patients underwent intubation and were managed conservatively in the intensive care unit but did not survive for more than 24 hours. The first 2 patients did not recover from their original insult and died within 30 days. The third patient had a brain stem infarct, underwent percutaneous endoscopic gastroscopy placement for swallowing difficulty, and had an mRS of 4 at 3 months.

Janjua et al used clinical diffusion mismatch criteria (patients with NIHSS >8 with limited abnormality on DWI imaging) to evaluate the benefit of endovascular interventions in 11 patients with large vessel occlusion presenting >8 hours after stroke symptom onset. At 1 week after treatment, 72% of the total and 100% of successfully revascularized patients in their study had a decrease of >4 points in NIHSS score. The DAWN trial is an ongoing multicenter trial designed to study safety and efficacy of endovascular treatment in MR or CT perfusion-selected patients with acute ischemic stroke attributable to a proximal large-vessel anterior circulation occlusion (eg, ICA and/or middle cerebral artery M1 segment) who present “beyond the typical therapeutic window” (>8 hours including “wake-up”) events. The main hypothesis of this trial is that MR or CT perfusion-based endovascular treatment in wake-up and late-presenting stroke patients is at least as safe and effective as standard endovascular treatment performed within 8 hours of symptoms onset and leads to improved outcomes when compared to best medical treatment. The results of this trial may provide more evidence of the benefits of treatment in this group of patients.

### Conclusions

Our study sheds light on the safety, effectiveness, and feasibility of endovascular therapy for patients presenting after 8 hours of stroke symptom onset and WUS. The recanalization rate with endovascular therapy is superior to that reported using intravenous t-PA, whereas the rate of symptomatic intracerebral hemorrhage is low. There is a moderate improvement in outcome at 3 months in these patients in their study had a decrease of >4 points in NIHSS score. The DAWN trial is an ongoing multicenter trial designed to study safety and efficacy of endovascular treatment in MR or CT perfusion-selected patients with acute ischemic stroke attributable to a proximal large-vessel anterior circulation occlusion (eg, ICA and/or middle cerebral artery M1 segment) who present “beyond the typical therapeutic window” (>8 hours including “wake-up”) events. The main hypothesis of this trial is that MR or CT perfusion-based endovascular treatment in wake-up and late-presenting stroke patients is at least as safe and effective as standard endovascular treatment performed within 8 hours of symptoms onset and leads to improved outcomes when compared to best medical treatment. The results of this trial may provide more evidence of the benefits of treatment in this group of patients.

### Table. Comparison of Our Study With Previous Acute Ischemic Stroke Studies

<table>
<thead>
<tr>
<th></th>
<th>NINDS2</th>
<th>DIAS-216</th>
<th>PROACT I39</th>
<th>PROACT II44</th>
<th>Multi MERCI5</th>
<th>Our Study</th>
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<tr>
<td>Revascularization strategy</td>
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<td>IV desmoteplase</td>
<td>IA r-proUK vs placebo</td>
<td>IA r-proUK + heparin vs heparin</td>
<td>Recent Merci + IA t-PA</td>
<td>IA t-PA, Angioplasty, Merci, Stents + Heparin + GP IIb/IIIa</td>
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<td>Time window</td>
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<td>3–9 hours MR perfusion</td>
<td>6 hours</td>
<td>6 hours</td>
<td>8 hours</td>
<td>8–27.5 hours (including WUS)</td>
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<td>Primary end points</td>
<td>Part 1: 4-point NIHSS improvement or resolution of deficit within 24 hours; Part 2: BI, mRS, GOS, NIHSS at 3 mon</td>
<td>Recanalization at 2 hours. NIHSS, mRS, BI at 7, 30, and 90 days; SICH</td>
<td>mRS &lt;2 at 90 days</td>
<td>Recanalization rate, complications</td>
<td>NIHSS at discharge, recanalization rate, complications, SICH</td>
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<td>Not mentioned</td>
<td>MCA recanalization, SICH, mortality</td>
<td>mRS and mortality at 90 days</td>
<td>mRS at 3 mon and mortality</td>
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<td>Not mentioned</td>
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<td>Recanalization rate</td>
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<td>66%</td>
<td>70%</td>
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<td>SICH</td>
<td>6.4%</td>
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<td>15.4%</td>
<td>10%</td>
<td>9.8%</td>
<td>10%</td>
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<td>NIHSS improvement</td>
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<td>19 to not reported</td>
<td>13 to 9.5</td>
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<td>mRS &lt;2 or &lt;1* at 3 mon</td>
<td>39%*</td>
<td>40%</td>
<td>30.8%*</td>
<td>40%</td>
<td>36.7%</td>
<td>20%</td>
</tr>
<tr>
<td>Mortality at 3 mon</td>
<td>17%</td>
<td>21%</td>
<td>26.9%</td>
<td>26%</td>
<td>26%</td>
<td>33.3%</td>
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</table>

*BI indicates Barthel Index; DIAS-2, Desmoteplase in Acute Ischemic Stroke-2; GOS, Glasgow Outcome Scale; GP, glycoprotein; IA, intraarterial; IV, intravenous; MCA, middle cerebral artery; MERCI, Mechanical Embolus Removal in Cerebral Ischemia; MR, magnetic resonance; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study; PROACT, Prolyse in Acute Cerebral Thromboembolism; SICH, symptomatic intracranial hemorrhage; UK, urokinase.
patients when they are carefully selected with perfusion imaging, without an increase in morbidity or mortality. Prospective randomized controlled trials are needed to assess the role of endovascular intervention after 8 hours of stroke symptom onset and WUS.

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Disclosures

Dr Hopkins has an ownership interest in AccessClosure, Boston Scientific, Micrus, and Square One, Inc. ($<10,000 each); serves as a consultant to/member of the advisory board for Abbott, AccessClosure, Bard, Boston Scientific, Cordis, and Micrus ($<10,000 each). Dr Levy receives research grant support, other research support (devices), and honoraria from Boston Scientific ($<10,000) and research support from Micrus Endovascular ($>10,000) and ev3 ($<10,000); has ownership interests in Intratech Medical Ltd. ($<10,000) and Mynx/AccessClosure ($>10,000); serves as a consultant on the board of Scientific Advisors to Cordis Neurovascular, and as a consultant receiving fees on a per-project per-hour basis only for Micrus Endovascular, ev3, and TheraSyn Sensors, Inc; and receives fees for carotid stent training from Abbott Vascular and ev3 ($>10,000). Dr Siddiqui has received a research grant from the University at Buffalo ($<10,000); is a consultant to Codman/Cordis, Concentric Medical, ev3, Micrus Endovascular, and Neocure ($<10,000 each); serves on the speakers’ bureaus for Cordis and Genentech ($<10,000 each); and has received honoraria from Genentech, Neocure, an American Association of Neurological Surgeons’ course, an Emergency Medicine Conference, and from Cordis for training other neurointerventionists ($<10,000 each). Dr Ionita, Dr Natarajan, and Dr Snyder have nothing to disclose.

References


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