ORIGINAL RESEARCH

Observed Cost and Variations in Short Term Cost-Effectiveness of Therapy for Ischemic Stroke in Interventional Management of Stroke (IMS) III

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***Background*—**Examination of linked data on patient outcomes and cost of care may help identify areas where stroke care can be improved. We report on the association between variations in stroke severity, patient outcomes, cost, and treatment patterns observed over the acute hospital stay and through the 12-month follow-up for subjects receiving endovascular therapy compared to intravenous tissue plasminogen activator alone in the IMS (Interventional Management of Stroke) III Trial.

***Methods and Results*—**Prospective data collected for a prespecified economic analysis of the trial were used. Data included hospital billing records for the initial stroke admission and subsequent detailed resource use after the acute hospitalization collected at 3, 6, 9, and 12 months. Cost of follow-up care varied 6-fold for patients in the lowest (0–1) and highest (20+) National Institutes of Health Stroke Scale category at 5 days, and by modified Rankin Scale at 3 months. The kind of resources used postdischarge also varied between treatment groups. Incremental short-term cost-effectiveness ratios varied greatly when treatments were compared for patient subgroups. Patient subgroups predefined by stroke severity had incremental cost-effectiveness ratios of $97 303/quality-adjusted life year (severe stroke) and $3 187 805/quality-adjusted life year (moderately severe stroke).

***Conclusions*—**Detailed economic and resource utilization data from IMS III provide powerful evidence for the large effect that patient outcome has on the economic value of medical and endovascular reperfusion therapies. These data can be used to inform process improvements for stroke care and to estimate the cost-effectiveness of endovascular therapy in the US health system for stroke intervention trials.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Registration number: NCT00359424. **(*J Am Heart Assoc*. 2017;6:e004513. DOI: 10.1161/JAHA.116.004513.)**

Key Words: cost • cost-effectiveness • ischemic • stroke • stroke care • tissue-type plasminogen activator

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/6/5/e004513/DC1/embed/inline-supplementary-material-1.pdf

*A complete list of the IMS (Interventional Management of Stroke) III Investigators is provided in Appendix S1.

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Received August 18, 2016; accepted March 22, 2017.

Stroke is the leading cause of death and disability worldwide.[1,2] Improvements in stroke prevention and acute care have resulted in declines in stroke incidence and mortality over the last decade.[2] However, absolute numbers of strokes continue to rise, fueled by the aging of the population in many countries.[3] Acute care for stroke is costly, but the delivery of timely, guideline-informed care decreases this cost.[4] Much of the economic and caregiver burden of stroke is predicted by the functional outcomes that are achieved poststroke.[2,5] New stroke interventions that increase initial hospital cost may vary in their ability to improve patient outcomes based on the severity of the stroke, the timing of the intervention, and aspects related to the process of care.[4,6] Thus, the implementation of changes in the process of stroke care should be examined in light of their effect on acute care cost, patient outcomes, and effect on the medical/recovery care after discharge from the initial hospitalization.

The IMS (Interventional Management of Stroke) III trial is the first and largest randomized trial of endovascular therapy (EVT) following intravenous (IV) tissue plasminogen activator (t-PA) as compared with IV t-PA alone for acute ischemic stroke. The Trial did not demonstrate differences in recanalization rates and good functional outcome at 3 months poststroke for either treatment arm.[7] Preplanned analyses of patients with a severe baseline neurological deficit demonstrated better functional outcome in EVT patients as compared with t-PA over 12 months of follow-up,[8] and post-hoc analyses indicated a trend to improved 3-month outcomes in those patients with documented arterial occlusion before IV t-PA therapy.[9] Yet, the overall negative primary results of the IMS III Trial, as compared with subsequent endovascular trials,[10–14] reflect the very limited use of stent retriever devices as well as more-limited use of computed tomography angiography CTA in the earlier years of the trial when CTA was just gaining acceptance as a standard diagnostic tool.[15]

Several recent publications have estimated the cost-effectiveness of EVT versus standard medical therapy using 3-month outcome data from the recent randomized endovascular trials of stent retriever technology, as well as cost and quality-of-life data from other sources.[16–22] These reports demonstrate the cost-effectiveness of EVT overall when used in the various populations included in these trials. However, the cost-effectiveness of EVT in these modeling studies is strongly affected by observed efficacy (the most powerful determinant), characteristics of patients enrolled in the trial, the available data regarding costs and resource utilization until trial completion at 3 months, and, most important, major model assumptions regarding costs, resource use, death rates, rates of recurrent stroke, hospitalization, etc, extrapolating results from 3 months until 30 years from stroke onset in 1 model or until death in another.[19,22] To this point, actual costs and resource utilization in the published trials using stent retriever technology include only the first 3 months after randomization, except for 2 years of economic and resource utilization data expected soon from the MR CLEAN trial.[10]

The IMS III trial collected prospective data for 12 months after hospital discharge for all study patients.[23] These data include quarterly measures of patient quality of life, level of disability, and medical care resource utilization. These data are uniquely able to show patterns of resource use and patient-related outcomes for patients treated with EVT after t-PA and those treated with t-PA alone. The objective of this report is to determine variations in measures of cost-effectiveness for treatment subgroups defined by stroke severity or care process factors, as well as the subsequent costs and resource utilization associated with functional outcome at 3 months. This analysis is able to inform the costs associated with medical and EVT given that the data are not modeled or simulated, but rather have been prospectively recorded for each patient.

Methods

Data Collection

The study design, population, and results of the IMS III trial have been reported previously.[7,8] Resource use and cost data were collected on patients enrolled in the United States, Australia, and Canada as part of the clinical trial.[23] The preplanned analysis of the IMS III Trial included subgroup analysis according to stroke severity, which included moderately severe stroke defined as a National Institute of Health Stroke Scale (NIHSS) score of 8 to 19 at baseline and severe stroke as NIHSS of 20 or more. No economic data were collected from patients enrolled in Europe. Data on length of initial hospital stay (LOS) were collected for all patients, but hospital charges for the initial hospital admission were collected from US patients only.

Hospital Cost

The cost per initial (index) hospital admission was calculated by applying the study hospital's cost to charge ratio to the reported charges expressed in 2012 US costs as reported elsewhere.[6] A cost weight per hospital day for the US patients was calculated; this weight was adjusted to reflect systematic difference in LOS between the US admissions and admissions in other countries and used with the recorded LOS to estimate the cost of the initial hospital stay for non-US patients.

Follow-up Data Collection

Follow-up economic and quality of life data consisted of the EQ-5D, a health-related quality-of-life measure instrument, as well as elicited resource use for subsequent hospital admissions, rehabilitation institutional stays, physician office visits, visits with rehabilitation providers for physical, occupational, and speech therapy, home health visits, and homemaker visits at 3, 6, 9, and 12 months. These data were collected by patient and/or proxy report for patients in the United States, Australia, and Canada. Nursing home stay or residence was indicated by a yes/no variable. A total of 475 patients had 1 or more records for quality of life and/or resource use variables during the 12-month follow-up period. These patients were included in the follow-up cost and quality-of-life analysis. The economic data collection protocol was not implemented for patients in Europe who were enrolled in the clinical trial. Details of the populations included in the economic analyses are provided in Figure 1.

Costing Approach

Each type of care resource (hospital days, emergency department visits, medical visits, rehabilitation therapy visits for physical, occupational, and speech therapy, etc) was calculated from resource use data collected for the initial hospital admission and for the 12-month follow-up period. The follow-up resource data were first summed by resource type for each patient and then assigned a standard cost weight calculated from 2012 Medicare billing data. The calculation of the medical care cost weights were based on Medicare data for patients in the year poststroke and performed as follows. Mean payment for emergency department visits for poststroke patients were calculated using Medicare data for poststroke patients. All emergency department costs for the visit, tests, and provider bills were summed and the mean value per emergency department visit was used as the cost weight in the study. Mean charges for medical office visits were calculated by summing the charges for the visit and any concurrent bills for tests or treatments at each visit. Mean allowable charges of care for physical, occupational, and speech therapy were calculated by summing the relevant charges by visit. Mean daily payments for outpatient rehabilitation were used to estimate outpatient rehabilitation costs. Home health visits were calculated as the mean payment amount per visit, and skilled nursing home stays were calculated as the mean payment per day. These cost weights were attached to the resource units reported by patients or their proxy at each follow-up visit. Patient reports were used when available. For patients unable to respond, we used the resource use reports by a proxy. The cost weights used for the estimates are listed in Table 1.

Total follow-up costs for each patient were calculated using the cost weights in Table 1. The initial hospital cost included data for patients who were discharged dead. These

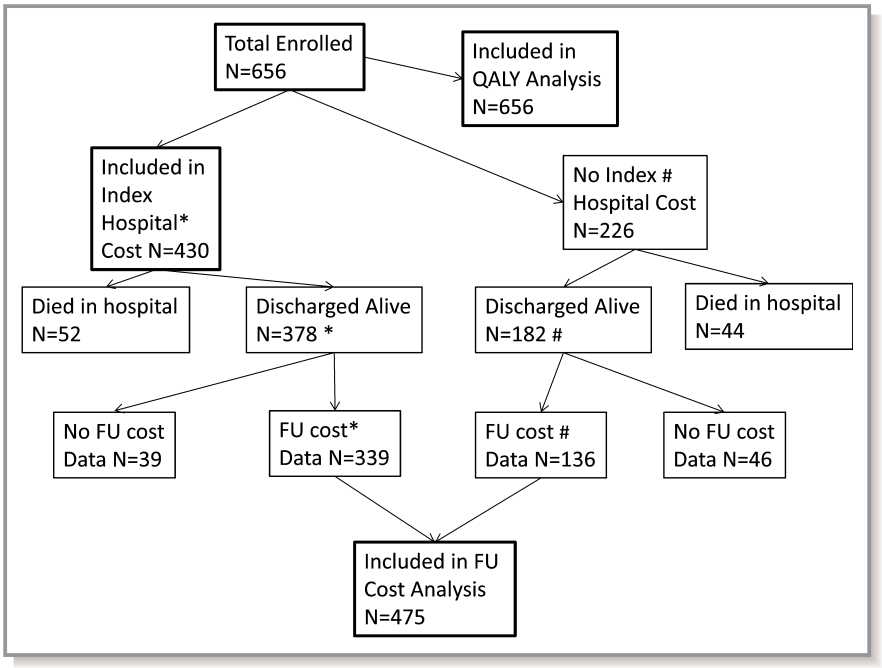

Figure 1. Details of the populations included in the economic analyses. *US subjects; #non-US subjects. *Note:* The index hospital admission is the initial admission for stroke. FU costs are calculated from resource use data collected at the 3-, 6-, 9-, and 12-month follow-up visit or call. FU indicates follow-up; QALY, quality-adjusted life year.

Table 1. Cost Weights Derived From Medicare Billing Data for 2012

Resource Type	Mean Cost Weight (SD)	No. of Cost Records Used
Stroke hospital day	$4051 (3709)	574
Nonstroke hospital day	$2167 (1844)	636
Emergency visit	$1682 (1309)	831
Medical office visit	$237 (303)	5592
Physical therapy visit	$164 (83)	2216
Occupational therapy visit	$360 (384)	793
Speech therapy visit	$286 (302)	1197
Mean therapist visit cost	$236 (202)	4206
Home health visit	$173 (99)	6778
Skilled nursing home day	$330 (267)	618
Inpatient rehabilitation day	$1471 (639)	193
Home chore help*	$40*	

*Not recorded in Medicare data, estimated at 2 hours @$20 per hour based on provider reports.

patients were assigned zero follow-up costs and zero health-related quality-of-life values for the follow-up time. The analytical data set for the follow-up time period included data from all 656 randomized patients for health-related quality of life and for 656 patients with cost estimates. However, only 475 patients with economic follow-up data contributed to the mean follow-up cost estimates reported because 181 patients had died in hospital and thus had 0 follow-up costs or they had missing follow-up records. Follow-up cost for patients in Europe who did not have detailed resource-use data were imputed based on the patient's treatment and recorded survival.

Statistical Analysis

Data were aggregated at the patient level to identify total estimated cost of care and quality-adjusted days of survival for patients during the follow-up time period of 12 months. Follow-up costs were compared by main treatment groups and prespecified subgroups using gamma-distributed generalized linear log-transformed models, adjusting for age, reported prestroke modified Rankin Scale (mRS), and NIHSS. SAS software was used (version 9.4; SAS Institute Inc, Cary, NC) and a P value of <0.05 was defined as a statistically significant difference. Mean cost for each type of medical care resource used were calculated by treatment group for each quarter of the follow-up period to describe treatment patterns over time. In addition, mean hospital cost and the follow-up costs summed at the patient level were estimated for the subset defined by categories of NIHSS at day 5 (or discharge if earlier) from randomization. Mean follow-up costs were also estimated by mRS at 3 months poststroke. For these descriptive analyses, patients who died during the initial hospital admission or who had no score at day 5 or at 3 months were not included in the follow-up cost estimates. The health-related quality-of-life measure used for the IMS III Trial was EQ-5D[8] (formerly known as EuroQol). The EQ-5D-3L was obtained at 5 days and at 3, 6, 9, and 12 months. Quality-adjusted days in the study were estimated for the 12 months (365 days) poststroke using linear interpolation between measurements and calculating area under the curve. We used the last observation carried forward for the quality-adjusted days calculation, which is expected to result in the most conservative cost utility estimate. The quality-adjusted days were summed for each subject and divided by 365 days to represent quality-adjusted life years (QALYs). Details on the estimation of quality-adjusted life years (QALYs) have been described previously.[8]

The mean cost by group was estimated separately for the initial hospital admission and for the follow-up period. The values were combined with follow-up cost set as 0 for patients who died in the hospital. Thus, the total cost reported reflects cost per group over 12 months.

Measures of Efficiency

Only the cost values (observed or imputed) for the total patient cohort of 656 subject were used to estimate the 1-year limited incremental cost-effectiveness ratio (ICER). ICERS were used to explore potential economic differences between important patient subgroups. All ICER calculations used cost and health-related quality of life from the relevant subgroup of the 656 patients with any missing cost values imputed. The subgroups included in the sensitivity analysis are: (1) patients with moderately severe and severe stroke; (2) patients who had documented occlusion shown on baseline CTA[24]; (3) patients with severe stroke where the cost of the index hospital admission excluded cost of anesthesia, unless this was medically indicated in the trial record[6]; and (4) subgroups defined by occlusion. The subgroup analyses are strictly descriptive and statistics for these values were not calculated because of the small sample sizes.

Sensitivity Analysis

Because the ICER statistic is a ratio of differences between 2 random variables, with either having possible values of 0, there is no mathematically tractable formula for the variance of an ICER.[25] Consensus has emerged that nonparametric bootstrapping, combined with cost-effectiveness acceptability curves be used to show the variability in the ICER.[25–27] To

show the potential effect of chance on the ICERs, we used 1000 bootstrap replications[25] of all 656 study patients with costs for patients with missing cost values estimated based on their hospital LOS and their number of days in the follow-up period (Figure 1). We also performed 1000 bootstrap replications for patients with complete data to present the effect of differences between the total population estimates and those calculated on patients with recorded cost data. Cost-effectiveness acceptability curves were used to show the distribution of the ICERs. The ICERs reflect the cost perspective of the US healthcare system and payment rates expected for Medicare patients in 2012. Other payers and health systems may have lower or higher costs.

Results

Variations in Cost and Care Patterns

We examined the variations in cost of care over 12 months poststroke. We report costs separately for the initial hospital admission and for the follow-up time after hospital discharge so that differences over the continuum of care can be identified. For the EVT group, the mean acute care hospital cost ($35 223) was higher than the postacute care costs ($30 375) over 12 months ($P<0.0001$; Table 2). In contrast, for the IV t-PA only group, the mean acute care hospital costs ($25 907) was not different from the postacute care costs ($27 454; $P=0.5108$). The majority of the mean cost difference between the EVT and IV t-PA only groups was in the initial hospitalization ($9316) as compared with postacute care ($2921). EVT patients were most often discharged to a rehabilitation hospital (43%) and home (30%) with a small proportion discharged to a nursing home (6%). Participants treated with IV t-PA alone were most frequently discharged to a rehabilitation hospital (45%) and home (27%) with a small proportion discharged to a nursing home (9%).

Differences in initial hospital cost and follow-up cost were estimated for patient subgroups defined by outcome measures (NIHSSS and mRS) to provide information on the association between outcomes and cost of care (Table 3). When costs were stratified by outcomes at day 5 poststroke across the treatment groups, there was a 6-fold difference in the cost of postacute care by lowest (NIHSS=0; $9984) and highest NIHSS (NIHSS=20+; $62 283) at day 5 ($P<0.0001$). Similarly, large differences were observed across outcome categories for the mRS measured at 3 months ($P<0.0001$). Costs reported by NIHSS and mRS varied for the 2 treatment groups, but these cost differences were not statistically significant. In addition, participants treated with EVT who had a thrombolysis in cerebral infarction score 2b-3 (good reperfusion) had around $30 000 less annual costs as compared with those with thrombolysis in cerebral infarction score of 0-2a (no or poor reperfusion; Table 4).

Differences in Postdischarge Healthcare Utilization

The differential pattern of utilization between the EVT and the IV t-PA alone arms over the year for the study overall and for the severe stroke subgroup only are detailed in Figures 2 and 3. In the severe stroke subgroups, participants randomized to EVT had greater postacute hospitalization costs (presumed mostly for rehabilitation or long-term acute hospital costs), outpatient rehabilitation therapy visits, and home health visits than those in the t-PA alone group in the first 2 quarters. These data reflect that these participants were more likely to have mild-to-moderate deficits post-treatment that were amenable to more-intensive therapy in the rehabilitation setting or at home. The EVT patients also had greater physician visits in the first quarter, which likely reflects greater posthospital follow-up with EVT physicians and rehabilitation physicians after discharge from rehabilitation hospital. In contrast, the t-PA alone group had higher utilization of skilled nursing facilities from the very first quarter, which increased as the year progressed, as well as increasing utilization of home health visits.

Only a $310 difference in mean postacute hospitalization care costs was observed between the EVT and the IV t-PA alone groups, but there were marked differences in the distribution of costs (Figure 3). This distribution reflects the

Table 2. Mean Quality-Adjusted Years*, Cost*, and Cost by Treatment Group

Outcome Measure	Endovascular	IV t-PA	Difference
QALY (95% CI)	0.5181 (0.4854–0.5508)	0.4737 (0.4279–0.5195)	0.0444
Initial hospitalization (95% CI)	$35 223 (33 028–37 565)	$25 907 (23 679–28 344)	$9316†
Follow-up cost (95% CI)	$30 375 (26 612–34 354)	$27 454 (23 259–33 536)	$2921
Total cost difference			$12 237

IV t-PA intravascular tissue plasminogen activator; QALY, quality-adjusted life years.
*Multivariable model controlling for age, baseline modified Rankin Scale score, and stroke severity.
†$P<0.05$.

Table 3. Estimated* Initial Hospital Cost and FU Cost by NIHSS Category at Day 5 and FU Cost by mRS Category at 3 Months by Treatment Group

NIHSS Category Measured at Day 5	Endovas-cular Hospital Cost (N=214)	IV t-PA Alone Hospital Cost (N=113)	Endovascular FU Cost (N=304)	IV t-PA Alone FU Cost (N=150)	mRS Measured at 3 Months	Endovascular FU Cost (N=314)	IV t-PA Alone FU Cost (N=150)
0	$23 242	$16 308	$9984	$12 348	0	$5871	$10 137
1 to 9	$28 140	$20 377	$14 674	$16 542	1	$10 419	$10 683
10 to 19	$38 588	$27 649	$52 325	$35 815	2	$17 839	$18 936
20+	$61 289	$62 147	$62 283	$54 294	3	$29 889	$27 304
					4	$69 015	$49 263
					5	$80 857	$64 712
					6	$9431	$9006

FU indicates follow-up; IV t-PA, intravascular tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.
*Adjusted for age. NIHSS differences in hospital cost by treatment P=0.2535 and follow-up cost by treatment P=0.1268. mRS differences in follow-up cost by treatment P=0.1800. If mRS=6, then FU cost includes only patients who were discharged alive from the hospital and who died within 91 days of discharge.

overall better functional outcome in the EVT subgroup with severe stroke, which requires more costs associated with initial intensive utilization of rehabilitation and therapy, but less nursing home costs.

Variations in Benefits

The total possible follow-up time in the study was 365 days. Therefore, a patient in perfect health could contribute a maximum 1.0 QALY. However, patients with acute ischemic stroke would each be expected to contribute less than 1.0 QALY. Thus, the mean number of QALYs per group is less than 1 because of the 12-month follow-up time. Overall, there was a small estimated nonsignificant benefit of 16.2 days (or 0.044 QALYs) in quality-adjusted survival for patients randomized to receive EVT (P=0.49; Table 2). The overall ICER for participants randomized to EVT compared to IV t-PA alone is $262 207 based on data from all 656 subjects and $275 608/QALY if only observed cost data are used for the estimate. The World Health Organization (WHO) benchmark

Table 4. Sensitivity Analysis Results for Cost-Effectiveness Estimates for Patient Subgroups

	EVT Total Cost	t-PA Only Total Cost	EVT QALY	t-PA Only QALY	ICER
Base estimate: all 656 patients*	$60 590	$48 948	0.5181	0.4737	$262 207
Observed cost only	$65 598	$53 361	0.5181	0.4737	$275 608
Patients with moderately severe stroke	$61 700	$48 630	0.5825	0.5784	$3 187 805
Patients with severe stroke	$77 478	$68 098	0.3995	0.3030	$97 303
All patients with baseline occlusion by CTA	$64 820	$54 929	0.5671	0.4904	$128 936
Patients with moderate or severe stroke and baseline occlusion by CTA	$64 935	$57 014	0.6164	0.5945	$361 396
Patients with severe stroke and baseline occlusion by CTA	$64 559	$50 619	0.4548	0.2740	$77 092
EVT patients with baseline occlusion and TICI 2b/3 reperfusion	$59 730	. . .	0.6382	. . .	. . .
EVT patients with baseline occlusion and TICI 0/2a reperfusion	$89 056	. . .	0.4613	. . .	. . .
Patients with severe stroke, with cost including only medically indicated intubation	$58 841	$47 709	0.3995	0.3030	$71 433
Patients with severe stroke, with cost including estimated physician payment in hospital	$88 798	$66 956	0.3995	0.3030	$106 566
Patients with severe stroke, with cost including estimated physician payment in hospital and only medically indicated intubation	$84 200	$76 986	0.3995	0.3030	$74 825

CTA indicates computed tomography angiography; EVT, endovascular therapy; ICER, incremental cost-effectiveness ratio; IV t-PA, intravascular tissue plasminogen activator; TICI, thrombolysis in cerebral infarction scale.
*Using recorded health-related quality of life and observed or imputed cost for all 656 patients in the study. QALYs=quality-adjusted life years calculated for 12-month follow-up only.

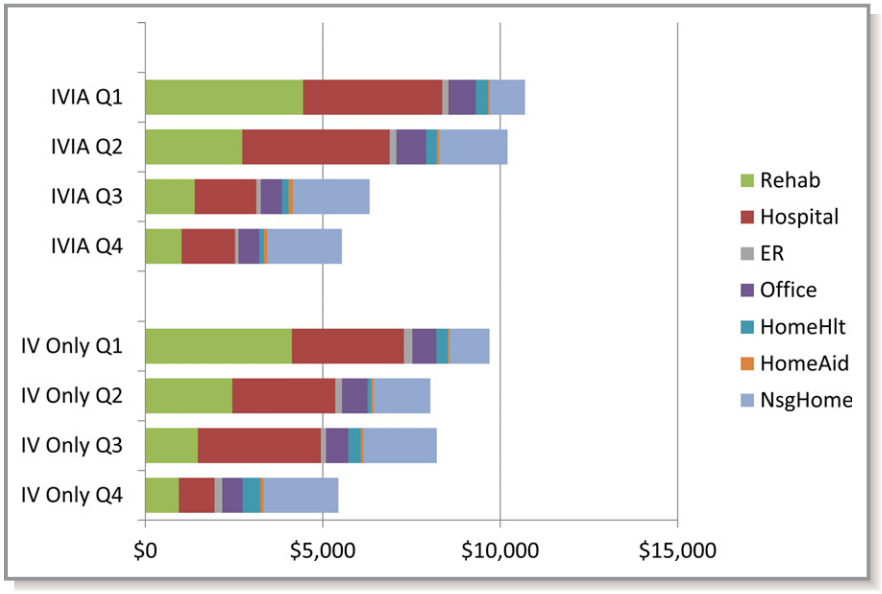

Figure 2. Distribution of costs after initial acute stroke hospitalization by type of resources used over the 12 months by treatment group. EVT indicates subjects randomized to endovascular therapy; IV Only are subjects who are randomized to receive only intravenous tissue plasminogen activator; Q1 through Q4 indicate first through fourth quarter year in the study; Rahab, cost for rehabilitation care; Hospital, cost of hospital admissions; ER, cost of emergency visits; Office, cost of medical office visits; HomeHlt, cost of home health care; HomeAid, cost of care delivered by home health aids; NsgHome, cost of days in a skilled nursing facility.

for measuring "good value for money" for healthcare interventions is 1 to 3 times the mean annual income. For the United States in 2013, this was between $51 000 and $153 000. Thus, the estimated ICER for the overall study of around $276 000/QALY is not cost-effective for the United States based on the WHO criteria of a maximum acceptable

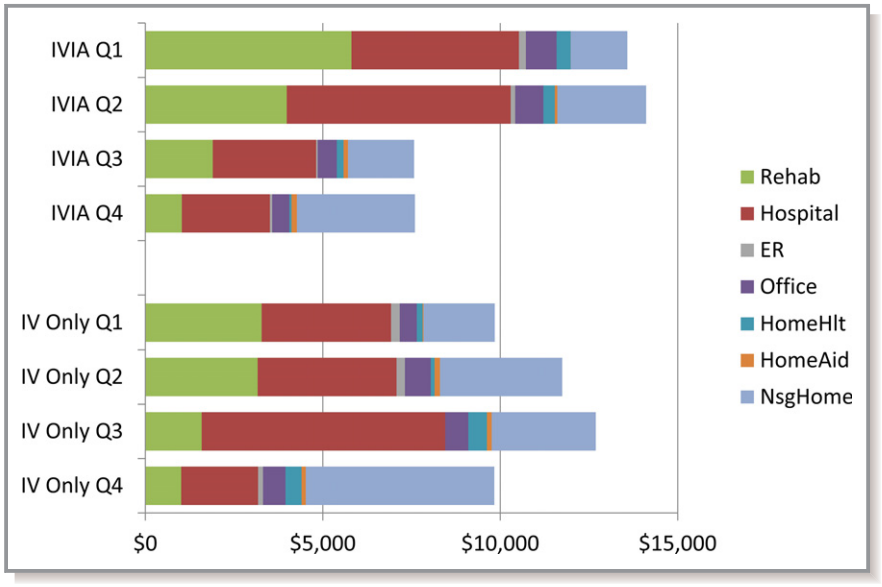

Figure 3. Severe stroke only: distribution of costs after initial acute stroke hospitalization by type of resources used over the 12 months by treatment group. EVT indicates subjects randomized to endovascular therapy; IV Only are subjects who are randomized to receive only intravenous tissue plasminogen activator; Q1 through Q4 indicate first through fourth quarter year in the study; Rahab, cost for rehabilitation care; Hospital, cost of hospital admissions; ER, cost of emergency visits; Office, cost of medical office visits; HomeHlt, Cost of home health care; HomeAid, cost of care delivered by home health aids; NsgHome, cost of days in a skilled nursing facility.

cost-effectiveness ratio below 3 times a country's per capita gross domestic product.[26]

Variations in Cost-Effectiveness

The prespecified subgroup analysis showed that outcomes and cost differed greatly by baseline stroke severity (Table 4). The ICER for comparing treatment for the EVT arm to the IV t-PA alone arm for patient subgroups with moderate stroke is over $3 million per QALY gained. The ICER for patients with severe stroke at baseline who were randomized to EVT is around $97 000/QALY gained as compared with those randomized to IV t-PA alone. The sensitivity analysis scatter plot and the Treshold analysis for this estimate is provided in Figure 4. The use of EVT in patients with severe stroke in the United States is associated with an ICER below the maximum WHO threshold[26] and may be expected to be cost-effective, especially given that the WHO benchmark assumes a time horizon until death, and our time horizon is only 1 year Additional subgroup explorations showed that the ICER for all participants with a documented arterial occlusion at baseline before to IV t-PA was $128 936/QALY, although there still was a difference in ICERs for participants who had a baseline occlusion with moderately severe stroke ($361 396) and severe stroke ($77 092). These findings provide support for the favorable ICERs reported in cost-effectiveness modeling studies that are based on newer clinical trial data and lifetime benefit assumptions.[21,22]

Sensitivity Analysis

In addition to the subgroup analyses, we evaluated the expected effect of including estimated physician payments for services during the initial hospital admission. Physician payment data were not collected in the study, so the values used in the sensitivity analysis for this cost are less precise than our other costs data. We also examined the effects of cost reduction that could be achieved if the process of care was changed to limit intubations to the inclusion of cost only for medically indicated cases.[24] We estimated mean daily Medicare Part B payments from a 5% sample of Medicare patients who received t-PA. The mean daily cost was $1054 for patients who received t-PA and $1331 for patient who received t-PA and had a thrombectomy procedure code. The addition of the estimated physician costs to the main model estimates increased the ICER for moderate stroke patients from $3.2 to $3.7 million per QALY, and the ICER for severe stroke patients from $97 000 to $106 700 per QALY.

We also examined the effect of the use of nonmedically indicated general anesthesia and intubation as standard of practice during the EVT procedure versus conscious sedation on the cost of the index hospital admission.[24] Use of conscious sedation as a standard approach, except for those patients in whom intubation is medically indicated, may be expected to reduce the ICER for patients with moderately severe stroke from $3 187 805 to $2 701 320 and the ICER for severe stroke patients from $97 303 to $71 433 per

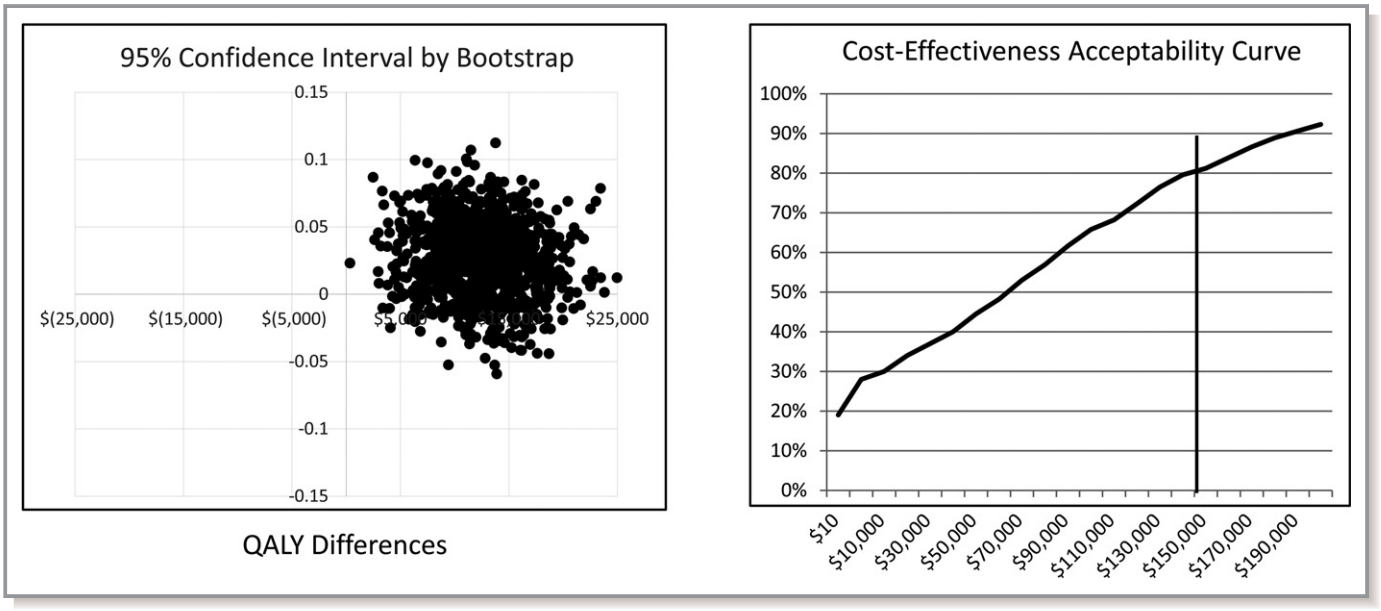

Figure 4. Variations in differences in cost and QALYs for patients with severe stroke based on 1000 bootstrap replications. *Note:* The panel on the left shows the distribution of cost and QALYs from 1000 bootstrap estimates for patients with severe stroke. The right-hand panel shows the cost-effectiveness acceptability curve for the ICERs produced by 1000 bootstrap replications for subjects with severe stroke based on observed QALYs and observed or estimated costs for all subjects with severe stroke at baseline. ICERs indicates incremental cost-effectiveness ratios; QALYs, quality-adjusted life years.

QALY. The sensitivity analysis scatter plot for this estimate is provided in Figure 5. When only patients with baseline occlusion determined by CTA were examined, the ICER improved to $128 936 from the baseline value of $275 608. The sensitivity analysis scatter plot for this estimate is provided in Figure 5. When physician payments were added and procedural intubation costs were removed, the ICER for the moderate stroke group was $3 102 365/QALY and $74 825/QALY for the severe stroke group (Table 4). The sensitivity analysis scatter plot for this estimate is provided in Figure 5.

Because the calculation of CIs are not recommended for ICERs,[25] we examined the effect of variations in the cost and QALY data in the study using a bootstrap[26] approach and present the results as a 95% cost-effectiveness plane and an ICER acceptability plot (Figure 4). Overall, 82.1% of the replications showed a greater number of QALYs for severe stroke patients who received EVT therapy. The cost-effectiveness acceptability curve based on the bootstrap estimates for all patients with cost data and patients where cost data were calculated based on LOS and days surviving posthospital discharge showed that 74% of the ICERs fell below the WHO Benchmark of $153 000/QALY (Figure 4). Additional scatter plots for subgroup ICERs are provided in Figure 5.

Because of the short time horizon of the study, we also examined the potential effect on the ICERs of a longer follow-up period. If one extrapolates the QALY and cost differences observed at the 12-month visit for patients in the severe stroke subgroup, then the ICER for the subgroup would continue to decrease by around $6000 per additional quarter that the quality of life and cost differences persist beyond our 12-month time horizon.

Discussion

EVT using primarily first-generation technology following IV t-PA, as tested in IMS III, was not cost-effective overall for participants with moderate and severe stroke overall as

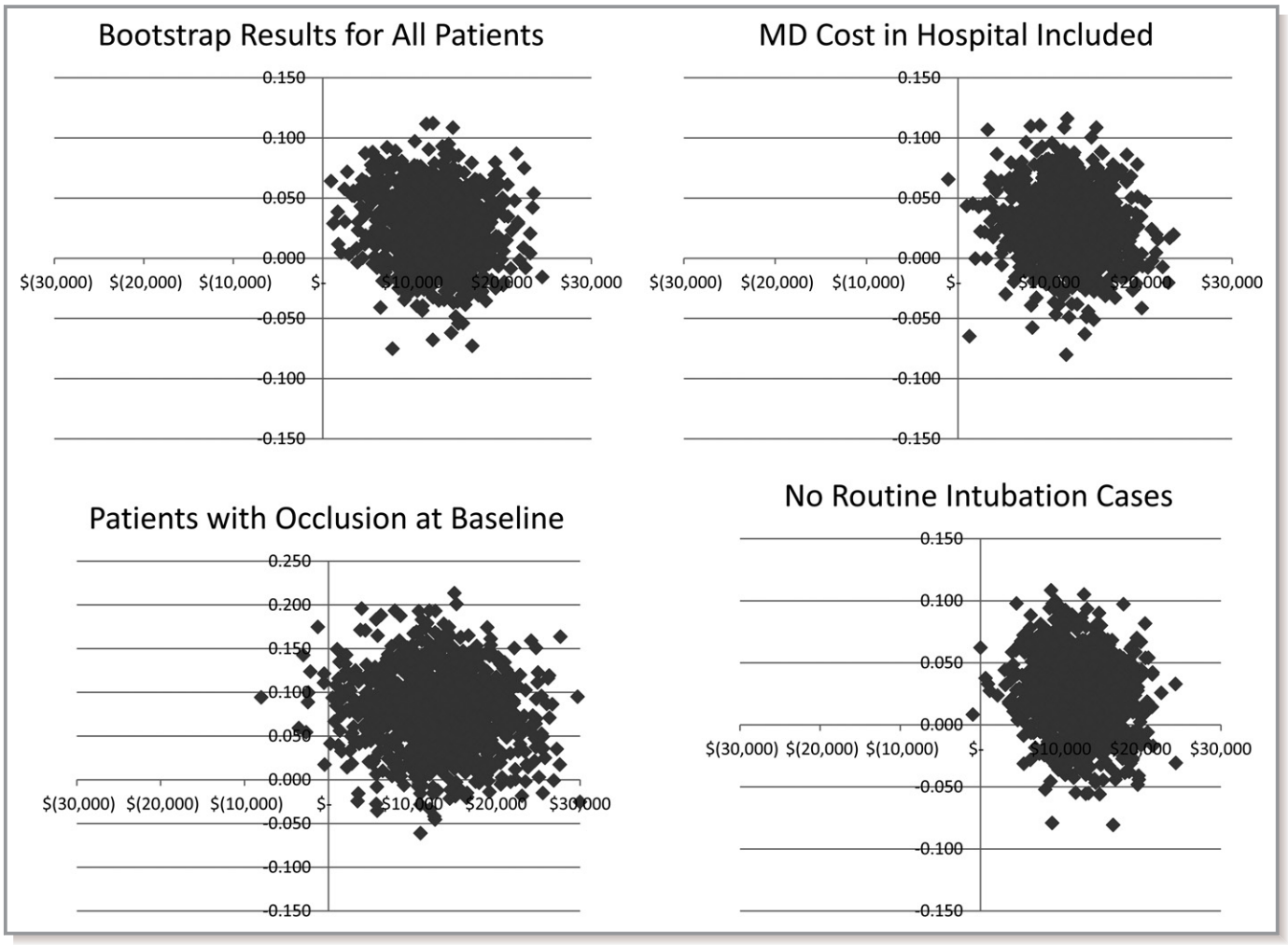

Figure 5. Effect of uncertainty on ICERs presented in Table 4. *Note:* The panels show the distribution of cost and QALYs from 1000 bootstrap estimates for the respective patient groups. ICERs indicates incremental cost-effectiveness ratios; MD, physician costs included; QALYs, quality-adjusted life years.

compared with patients treated with IV t-PA alone. However, even with the limited follow-up time horizon of 12 months, EVT was cost-effective for the predefined subgroup of participants with a severe stroke who had an ICER of $97 303 in the first year and lower estimated ICERs expected in subsequent years as relatively increased nursing facility costs in the IV t-PA alone group continue to accrue.

Our cost-effectiveness data are driven by the powerful logarithmic relationship between differences in the level of disability at 3 months and costs during the first year after discharge from the initial acute hospitalization. Not surprisingly, only in the predefined IMS III subgroup of participants with an NIHSS ≥20 and better functional outcomes after EVT, compared with IVT alone over the first year, was there any evidence of cost-effectiveness for EVT.

IMS III was limited by the use of older EVT technology, longer time from onset to reperfusion and the less frequent use of CTA angiography to identify patients with large artery occlusion as compared with more-recent endovascular trials. The economic impact of higher rates of excellent reperfusion with stent retriever technology, as compared with older clot retrieval devices, is reflected in our data in which participants who had poor reperfusion post-EVT had $30 000 greater annual costs following their stroke as compared with those with good or excellent reperfusion. Yet, the detailed and prospectively collected documentation of resource utilization over 1 year among IMS III study patients, linked to 5-day and 3-month outcomes, provides a rich data set that can inform cost-effectiveness analyses of the other stent retriever trials, or any reperfusion trial, at least for resource utilization in the United States. Except for MR CLEAN,[10] none of the other EVT trials have resource-use data collection beyond 3 months after randomization, and thus cost-effectiveness analyses examining a longer time horizon will be heavily dependent upon many assumptions.[16–22]

Strengths and Limitations

Our cost data provide unique insights into current US costs associated with both IV t-PA and EVT and reflect not only the amount, but also the timing and type of resource utilization, which are not currently included in current cost-effectiveness models of EVT for acute stroke. For example, after the initial increased up-front costs during the acute stroke hospitalization associated with EVT (costs of devices, endovascular procedure, and anesthesia costs), there was little difference in postacute hospitalization costs between the 2 treatment groups. However, EVT patients with a severe stroke at baseline had much higher outpatient and inpatient rehabilitation costs during the first 2 quarters of the year (Figure 3) as compared with participants treated with t-PA alone. In contrast, t-PA alone treated participants had higher nursing home costs that were increasingly greater than the EVT patients as the year progressed. Thus, while there was little difference in postacute hospitalization costs between the 2 treatment groups over the year, the distribution of costs differed greatly. The EVT group had more up-front postacute hospitalization costs related to therapy and rehabilitation because they were functionally better after treatment as compared with the IV t-PA alone group. After the initial 3 months of postacute care, the healthcare costs continued to separate between the 2 groups because nursing home costs begin to dominate as therapy visits and rehabilitation came to an end. Thus, we estimate that the ICER for EVT in severe stroke patients will continue to decrease and cost-effectiveness increase if the difference in nursing home utilization continues over subsequent years. Our data show that postacute care costs in the first year equal that of the initial hospitalization, particularly for those treated with IV t-PA. However, these postacute care costs do not include indirect costs, such as personal or societal financial costs because of loss of employment, modification of home for disability, etc, which are difficult to measure.[28]

Stroke recurrence and readmissions have a significant impact on the economics of stroke. Both add to the total cost of care for the patient. However, the biggest effect on the ICER is usually not related to the cost of readmissions or recurring stroke. ICERs are most sensitive to the loss of life, or quality of life. Better patient survival, and better quality of life for surviving patients, has the greatest effect on the ICER. This is an important point for all analyses of acute ischemic stroke interventions. As seen in Table 3, the improvement of 1 point in the mRS score at 3 months from a score of 4 to one of 3 may be expected to reduce the 12-month follow-up cost of care by 53%. This is a powerful economic incentive for investment in improvements in the care process for acute ischemic stroke.

Our findings have several limitations. The resource-use data records on which the follow-up cost estimates are based depend on patient or proxy recall of medical care use over a 3-month period. The protocol for the collection of cost data for the index hospital admission was limited to study sites that routinely report hospital charges. Data collection did not include physician charges that would be greater for the EVT group nor the costs of transportation from an initial emergency department to a comprehensive stroke center for patients treated in the “drip and ship” paradigm.[29] Thus, it is likely that the ICER in the first year for the severely affected stroke patients may be higher than reported here.

Only US study sites were included in the collection of cost data for the initial hospital admission, but resource-use and follow-up data were collected in other countries (see Figure 1). It is well known that US and Canadian hospital costs differ on both the mean LOS and on cost per day and

per admission.[29] Thus, it is quite likely that index hospital costs are different for stroke patients outside the United States. The resource-use data on which the study follow-up cost calculation are based were limited to sites in the United States, Canada, and Australia. Patients who were enrolled in the clinical sites in Europe contributed survival data, but not individual resource use data, to the follow-up cost estimation, which required us to impute their follow-up cost based on their survival. Thus, the costing perspective of this economic analysis is that of the US healthcare system with greatest relevance to Medicare patients. Economic inferences for other US payers and other countries will require cost weights that reflect the practice patterns, resource utilization, and cost structure of these insurers and medical care delivery systems.

The emphasis in the collection of follow-up resource use was on capturing important cost drivers, such as hospital readmission and outpatient rehabilitation costs.

Data collection on nursing home stays were limited to information that the patient had been discharged to or resided in a nursing home. Thus, nursing home costs were estimated based on mean number of days observed for stroke patients in the Medicare 2012 billing database that was used for calculating the cost weights. The follow-up cost analysis used standard cost weights based on mean resource use unit cost calculated for Medicare patients. It is probable that these cost weights would be different if another data source was used. The use of standard costs in the economic analysis decreases the variation in cost estimates for the follow-up costs and the standard deviation reported here for the follow-up costs are narrower than if actual cost data had been available for the patients. Furthermore, the large variation in participation of the clinical sites in the economic data collection for the index hospital admission, and for the follow-up data collection, limits our ability to link the index hospital and the follow-up cost data across patients. We have therefore presented these data separately and used the mean values for the 2 cost estimates in our main calculations of ICERs and included estimates for all patients in the sensitivity analysis shown in Figure 4.

The time horizon for this study is limited to 1 year, except for the sensitivity analysis that examines the effect of extrapolating the data from 9 to 12 months. This is both a strength and limitation of the study. The short time horizon allows us to report cost and QALY estimates *as we observed them in the trial data*. Thus, our estimates come as close as possible to reflecting actual resource-use patterns and costs over the first year. It is also a limitation, insofar as this short time horizon makes us unable to capture the total potential economic benefit that will accrue over time for patients with better outcomes and less use of healthcare resources.

Other researchers have presented economic analyses for EVT with longer time horizons after stroke of up to 20 years or until end of life.[16–22] These studies use modeling approaches that require a large number of assumptions, some of which may not be valid, and that are not needed if one limits the time horizon to the data collection period. As expected, others report ICERs that are more favorable to EVT because these modeling studies predict cost and outcomes over the lifetime of all patients treated. In addition, several of the published studies based their effect estimates on the outcomes reported from clinical trials, such as MR CLEAN,[10] that used stent retrievers and a new generation of thrombotic devices, which was not available for most IMS patients. Ganesalingam et al[21] report an ICER of $11 651 for patient outcomes modeled over 20 years and treated under UK cost assumptions and efficacy measures from 5 recent trials. Our ICERS were higher because our effects were smaller, the time horizon was only 1 year, and US costs are known to be higher than cost of care in the United Kingdom. However, our findings, and those of others, agree that the use of EVT may be expected to be a cost-effective intervention for appropriately selected patients with acute ischemic stroke.

However, our study adds some important information, beyond cost-effectiveness. We observed a number of associations that require further study. Careful patient selection may make a substantial economic difference. Clearly, the use of EVT in patients with severe stroke may be expected to give the highest economic benefit, and the use of CTA improves this even more. Our finding related to the higher ICER associated with intubation requires further study to elucidate how this procedure influences cost and outcomes.

Conclusion

Detailed patient outcome data combined with resource utilization and cost data from IMS III provide powerful insight into the effect of good patient outcomes on the costs of stroke and illustrates how new, more costly, but effective medical therapies may differentially affect the stroke-cost continuum depending on patient characteristics and the process of care used. The short-term economic benefits of early clinical improvements during the initial hospitalization and functional outcomes at 3 months are exceptional and show the large potential that incremental improvements in the management of acute stroke may be expected to have on costs. The data presented here may be used to inform considerations for improving care processes for acute stroke and for estimating the cost-effectiveness of improvements in endovascular therapy and other new stroke interventions in the US health system stroke studies.

Author Contributions

Palesch, PhD, Yeatts, PhD, Foster, MS, Annie Simpson, PhD, Kit N. Simpson, DrPH, and Broderick, MD, were responsible

for the analyses used in this article. Kit N. Simpson, DrPH, Palesch, PhD, and Broderick, MD, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The remaining authors contributed to the design and execution of the study and to the critical revision of the manuscript.

Sources of Funding

This work was supported by NIH/NINDS grant numbers: UC U01NS052220, U01NS054630, and U01NS077304. Genentech Inc supplied study drug used for intra-arterial tPA in the Endovascular group. EKOS Corp, Concentric Inc, and Cordis Neurovascular, Inc supplied study catheters during Protocol Versions 1 to 3. In the United States, IMS III investigator meeting support was provided, in part, by Genentech Inc, EKOS Corp, and Concentric Inc. In Europe, IMS III investigator meeting support was provided, in part, by Boehringer Ingelheim. This publication was partially supported by the South Carolina Clinical & Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, through NIH-NCATS Grant Number UL1 TR001450. Data support for the study was provided through the CEDAR core funded by the MUSC Office of the Provost.

Disclosures

Broderick reports research monies to Department of Neurology from Genentech for PRISMS Trial and travel to Australian stroke conference paid for by Boerhinger Ingelheim. Study medication from Genentech for IMS III Trial and study catheters supplied during Protocol Versions 1 to 3 by Concentric Inc, EKOS Corp, and Cordis Neurovascular. Palesch reports honoraria for her role as a statistical DSMB member for Brainsgate Ltd trials. Demchuk reports honoraria for CME and unrestricted grant to support the ESCAPE trial from Covidien. Yeatts reports research monies from Genentech for statistical role in PRISMS Trial. Khatri's Department of Neurology receives research support from Genentech, Inc, for her role as Lead PI of the PRISMS trial, Penumbra, Inc, for her role as Neurology PI of the THERAPY trial, and Biogen, Inc, for her role as DSMB member. Kleindorfer reports research grant funding NIH-IMS III Trial, Genentech speakers bureau. Goyal reports honoraria for teaching engagements as a consultant from Covidien; partial funding for ESCAPE trial provided by Covidien through an unrestricted grant to the institution; and stockholder in NoNo Inc, Calgary Scientific. Mazighi reports consulting for Servier and funding for travel from Covidien, Boehringer Ingelheim, Zeneca, and Bayer. Yan received research funding from Codman (Johnson & Johnson), speaker's honorarium from Stryker and from Bio CSL, and an educational grant from Bayer. von Kummer reports personal fees from Lundbeck, Penumbra, Covidien, and Synarc. Hill reports consulting fees from Vernalis Group; grant support from Covidien and Hoffmann–La Roche Canada; lecture fees from Hoffmann–La Roche Canada, Servier Canada, and Bristol-Myers Squibb Canada; stock ownership in Calgary Scientific; and financial support from Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut and Alberta Innovates–Health Solutions. Jauch reports research support to Division of Emergency Medicine from Penumbra, Covidien, and Stryker for POSITIVE Study and from Genentech for PRISMS Trial. Jovin reports consulting and stock ownership Silk Road Medical. Anderson reports speaker fees from Covidien. Engelter reports funding for travel or speaker honoraria from Bayer and Boehringer Ingelheim; he has served on scientific advisory boards for Bayer, Boehringer Ingelheim, BMS/Pfizer, and Covidien and on the editorial board of *Stroke*. He has received an educational grant from Pfizer and research support from the Science Funds (Wissenschaftsfonds) of the University Hospital Basel, the University Basel, the Swiss Heart Foundation, and the Swiss National Science Foundation. The other authors report no conflicts.

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