Predictive value of the National Institutes of Health Stroke Scale and the Mini-Mental State Examination for neurologic outcome after coronary artery bypass graft surgery

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Objective: We intended to define the role of the National Institutes of Health Stroke Scale and the Mini-Mental State Examination in identifying adverse neurologic outcomes in a large international sample of patients undergoing cardiac surgery.

Methods: We evaluated 4707 patients undergoing cardiac surgery with cardiopulmonary bypass at 72 centers in 17 countries between November 1996 and June 2000. Prespecified overt neurologic outcomes were categorized as type I (clinically diagnosed stroke, transient ischemic attack, encephalopathy, or coma) or type II (deterioration of intellectual function). The National Institutes of Health Stroke Scale and Mini-Mental State Examination were administered preoperatively and on postoperative day 3, 4, or 5. Receiver operating characteristic curves were plotted to determine the predictive value of worsening in National Institutes of Health Stroke Scale and Mini-Mental State Examination scores with respect to type I and II outcomes.

Results: The receiver operating characteristic area under the curve for changes in National Institutes of Health Stroke Scale score (n = 4620) was 0.89 for type I outcomes and 0.66 for type II outcomes. A 1-point worsening in National Institutes of Health Stroke Scale score provided excellent discrimination (86% specificity; 84% sensitivity) of type I outcomes. The receiver operating characteristic area under the curve for changes in Mini-Mental State Examination score (n = 4707) was 0.75 for type I outcomes and 0.71 for type II outcomes. A 2-point worsening in Mini-Mental State Examination score provided only fair discrimination (73% specificity; 62% sensitivity) of type II outcomes.

Conclusion: We used baseline controls and postoperative worsening in National Institutes of Health Stroke Scale and Mini-Mental State Examination scores to predict both serious adverse neurologic outcome and deterioration of intellectual function. Our findings provide the only reference for evaluating these tests that are used in cardiac surgical clinical trials. (J Thorac Cardiovasc Surg 2010;139:901-12)

The National Institutes of Health Stroke Scale (NIHSS) is used to evaluate neurologic impairment. It was designed for use in clinical trials of interventions to ameliorate cerebral damage after acute stroke.[1,2] This widely used scale has been recommended by the Stroke Council of the American Heart Association for serial assessment of patients with acute stroke.[3] Although often used in studies of neurologic outcome after cardiac surgery,[4-6] the NIHSS has never been specifically studied or validated as an appropriate instrument for use in this setting.

The Mini-Mental State Examination (MMSE) is one of the most widely used instruments for screening for dementia,[7,8] particularly for Alzheimer's disease, and measuring cognitive change over time in older adults. It is also used as one of a battery of tests assessing neurocognitive outcome in studies of patients undergoing cardiac surgery.[4,6,9] However, only 1 study (involving 100 consecutive patients) has prospectively evaluated the clinical utility of MMSE for screening in this setting.[10] Although the investigators concluded that MMSE-based detection of cognitive dysfunction should warrant geriatric follow-up after hospital discharge,

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Disclosures: None.

Received for publication Aug 19, 2008; revisions received June 2, 2009; accepted for publication July 22, 2009; available ahead of print Sept 11, 2009.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.07.055

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Abbreviations and Acronyms

AUC = area under the curve
CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
IREF = Ischemia Research and Education Foundation
MMSE = Mini-Mental State Examination
NIHSS = National Institutes of Health Stroke Scale
ROC = receiver operating characteristic

their study was too small to correlate changes on the MMSE with overt neurologic sequelae.

We have previously described the classification of new overt adverse neurologic sequelae after cardiac surgery into 2 general categories: type I (death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack, or stupor or coma at the time of discharge) and type II (new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury).[11] Our prior study, however, used neither the NIHSS nor the MMSE to assess neurologic outcome.[11] In the current study, we wanted to determine whether postoperative changes from baseline in NIHSS scores, MMSE scores, or both would be sensitive or specific to either type I or type II neurologic outcomes. We hypothesized that the NIHSS would be sensitive and specific for detecting overt new postoperative type I outcomes but less so for type II outcomes. However, the MMSE, as a single screening test, might not be sensitive or specific for either type I or type II neurologic outcomes. To test these hypotheses, we analyzed preoperative and postoperative NIHSS and MMSE scores that were gathered prospectively in a large, international, multicenter study.

MATERIALS AND METHODS

Study Design and Patients

The Multicenter Study of Perioperative Ischemia Epidemiology II, funded by the Ischemia Research and Education Foundation (IREF), is a retrospective analysis of prospectively collected data in patients undergoing coronary artery bypass grafting (CABG) surgery at 72 hospitals in 17 countries between November 1996 and June 2000. A systematic sampling scheme[12] was used to select up to 100 patients at each site, aged 18 years or older, undergoing CABG surgery with or without valve repair or replacement while on cardiopulmonary bypass (CPB). All participating sites in the study were required to submit their institutional review board approval to IREF to obtain authorization to join the study. Written informed consent was obtained from each patient before enrollment could ensue.

Of the 5436 patients enrolled (Figure 1), 371 were excluded from the data analyses because of patient withdrawal (n = 32), death before surgery (n = 2), canceled or rescheduled surgery (n = 97), alteration of surgical schedule (n = 132), enrollment in another study (n = 11), or incomplete data collection (n = 97; see Appendix 1). Also excluded were 358 patients who underwent a carotid procedure concurrently with CABG (n = 56), patients who underwent emergency CABG because of life-threatening conditions (n = 12), patients who had severe hematologic disorders (n = 12), patients who had religious beliefs precluding transfusion (n = 5), patients who had a previous deforming injury such as amputation (n = 17), and patients who had a known history of intravenous drug use or alcohol abuse (n = 271).

Test Administration

Standardized NIHSS certification procedures were followed.[13,14] At each site, all personnel planning to administer the NIHSS received training and were required to pass a certification test. A standardized NIHSS training videotape provided demonstration cases and detailed instructions regarding test procedures and scoring of each scale item. Individuals seeking certification then viewed a separate videotape that required completion of the NIHSS for each of 5 standardized patients. Answers were submitted to IREF, an organization accredited for certification. The individual seeking certification was required to have a test score of at least 100 correct answers of a possible total of 105. Each site was notified of the certification status of its research personnel. Certification test data for each test giver from each participating site were stored in the IREF database.

Administration of the MMSE does not require certification. However, all clinical personnel conducting this examination attended a training session. Furthermore, each test giver received printed instructions in his/her native language for each question on the examination.

Data Collection and Management

Data were collected from each patient by independent investigators throughout each patient's hospitalization. The collected data included demographic, historical, clinical, laboratory, electrocardiographic, surgical, and other intraoperative information, and data regarding adverse outcomes and resource use. All data fields for each patient were queried for completeness and accuracy, with all changes documented before database closure. All outcomes were defined in advance and determined by independent investigators blinded to the study question.

The primary outcome variables were type I or II overt neurologic sequelae. Type I outcomes were defined as any of the following: death due to stroke or hypoxic encephalopathy, nonfatal stroke, transient ischemic attack, or stupor or coma at the time of discharge. Type II outcomes were defined, according to a ''2-day, 2-item'' rule, as the presence of 2 or more indications of intellectual dysfunction (eg, confusion, disorientation, agitation, memory deficits, or seizures) on 2 or more days, not necessarily consecutive. All final type I and type II outcomes were determined by committee. The primary predictor variable for both type I and type II outcomes was postoperative worsening in NIHSS or MMSE score from the preoperative baseline score. Receiver operating characteristic (ROC) curves were created and used to determine the predictive value of worsening in NIHSS or MMSE scores with regard to type I and II outcomes. The sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of the NIHSS or MMSE score are reported.

The NIHSS and MMSE examinations were routinely performed per the study protocol on postoperative day 3, 4, or 5 by investigators certified in administration of these tests. On the NIHSS, a perfect score is zero, each point on the neurologic deficit scale is assigned a whole number, the maximum number of possible points is 42, and higher scores indicate worsening neurologic function. On the MMSE, a perfect score is 30, each wrong answer is assigned a point value (ie, a whole number), and lower scores indicate worsening neurocognitive dysfunction. To establish the clinical utility of NIHSS and MMSE scores in prediction of postoperative type I or II outcomes in cardiac surgical patients, analyses for ROC curve, sensitivity, and specificity were performed for worsening of score (postoperative score minus preoperative score).

For missing data regarding potential predictors, a combined variables approach was used. For missing NIHSS or MMSE scores, most study patients were examined but had missing records for a few individual questions; thus, imputation was performed by dividing the patients into 4 groups: female aged ≤70 years, male aged ≤70 years, female aged >70 years, and

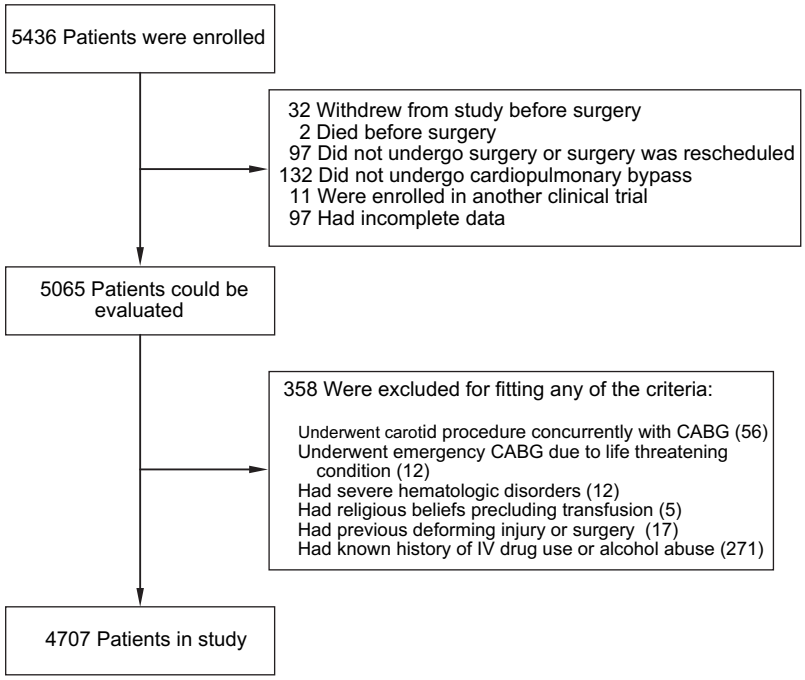

FIGURE 1. Consolidated Standards of Reporting Trials diagram of patient enrollment. *CABG,* Coronary artery bypass grafting.

male aged >70 years. The mean score was calculated for each question on the NIHSS or MMSE, stratified by age and gender, separately for the preoperative and postoperative periods. Missing data for the individual question for each patient were imputed using the mean score of the question and then sum scores for all questions.

Baseline characteristics, which included demographic, historical, preoperative and intraoperative factors, and univariate outcomes, were compared among patients without type I or II outcome, patients with type I outcome, and patients with type II outcome (see Appendix 2). The Kruskal–Wallis test and chi-square test were used for group comparisons among continuous and categorical variables, respectively.

To assess the independent effects of predictors on ''subnormal'' (greater than zero) preoperative or postoperative NIHSS score, a Zero-inflated Negative binomial model with a random effect of country (the NLMIXED procedure in SAS software; SAS Institute, Inc, Cary, NC) was used. This will account for the excess of zeros in NIHSS scores.[15] A Logit model with binomial assumption was used to account for the probability of a zero-NIHSS score. Then a Negative binomial regression was performed to model the count outcome in the not-always-zero group. The preoperative subnormal NIHSS score model was adjusted for baseline characteristics and countries. The additional adjustments for preoperative NIHSS score and intraoperative factors were added in the postoperative adverse NIHSS score model.

To evaluate MMSE scores, we defined a ''subnormal'' MMSE score according to the score distribution and the analysis of ROC curve, sensitivity, and specificity of preoperative or postoperative MMSE scores with regard to type I or II outcomes and literature review.[16,17] Both preoperative and postoperative MMSE scores were categorized as ''high score'' (normal) = 27–30, ''moderate score'' = 24–26, and ''low score'' (subnormal) = 0–23. Generalized estimating equations regression models for ordinal outcomes (the GENMOD procedure) were performed to assess the associations between subnormal MMSE scores and predictors and account for the clustering of patients within countries. The preoperative subnormal MMSE score model was adjusted for baseline characteristics and countries. Additional adjustments for preoperative MMSE score and intraoperative factors were added in the postoperative subnormal MMSE score model.

We developed a series of multivariable models to assess the independent effects of predictors on the type I or II outcome and stroke (fatal or nonfatal). The models were adjusted for baseline characteristics and intraoperative factors. Generalized estimating equations models (the GENMOD procedure) were used to account for the clustering of patients within countries. All analyses were performed with SAS software, version 8.12.

RESULTS

Of the 4707 study patients (Table 1), 2.9% (135/4707) had new postoperative type I outcomes, and 6.4% (301/4707) had type II outcomes. Resource use, measured by length of postoperative intensive care unit and hospital stays and discharge to a facility other than home, was significantly greater among patients with worse outcomes (Table 1). The median time of postoperative NIHSS examination was on the fourth postoperative day. The area under the ROC curve (AUC) for changes in NIHSS score was 0.89 for type I outcomes and 0.66 for type II outcomes (Table 2). There was little change in the AUC when correction factors were applied for age and higher education (college or postgraduate education) (Table 2).

A 1-point worsening in NIHSS score provided 86% specificity and 84% sensitivity for type I outcomes, and a 2-point worsening in the NIHSS score provided 94% specificity and 71% sensitivity (Table 3). For type II outcomes, a 1-point worsening in the NIHSS score provided 88% specificity and 44% sensitivity, and a 2-point worsening in the score provided 95% specificity but only 33% sensitivity (Table 3).

The median time for performance of MMSE examination was postoperative day 4. The AUC for changes in MMSE

TABLE 1. Characteristics of study patients (n = 4707)*

Characteristic	All patients (n = 4707)	Patients without type I or II outcome (n = 4271)	Patients with type I outcome (n = 135)	Patients with type II outcome (n = 301)	*P* value
Age (y)					<.001
Median	64.9	64.1	69.5	71.3	
Interquartile range	57.5–71.6	57.0–71.0	63.9–74.3	65.2–75.9	
Obesity (BMI > 28 kg/m^2), no. (%)	1861 (39.5)	1690 (39.6)	55 (40.7)	116 (38.5)	.90
Diabetes, no. (%)	1416 (30.1)	1242 (29.1)	56 (41.5)	118 (39.2)	<.001
College or postgraduate education, no. (%)	850 (18.1)	781 (18.3)	26 (19.3)	43 (14.3)	.20
African American, American Indian, or Hispanic ethnicity	355 (7.5)	318 (7.4)	11 (8.1)	26 (8.6)	.72
Medical history or preoperative factor, no. (%)					
Congestive heart failure	282 (6.0)	224 (5.2)	18 (13.3)	40 (13.3)	<.001
Myocardial infarction	2489 (52.9)	2239 (52.4)	74 (54.8)	176 (58.5)	.11
Unstable angina	2638 (56.0)	2357 (55.2)	88 (65.2)	193 (64.1)	.001
Atrial fibrillation or atrial flutter	392 (8.3)	331 (7.7)	21 (15.6)	40 (13.3)	<.001
Dysrhythmia	891 (18.9)	777 (18.2)	35 (25.9)	79 (26.2)	<.001
Neurologic dysfunction	512 (10.9)	420 (9.8)	36 (26.7)	56 (18.7)	<.001
Mental dysfunction	717 (15.2)	619 (14.5)	31 (23.0)	67 (22.3)	<.001
Hypertension	3284 (69.8)	2933 (68.7)	108 (80.0)	243 (80.7)	<.001
Peripheral vascular disease	777 (16.5)	673 (15.8)	31 (23.0)	73 (24.3)	<.001
Carotid vascular disease	714 (15.2)	601 (14.1)	38 (28.1)	75 (24.9)	<.001
Aortic vascular disease	707 (15.0)	610 (14.3)	28 (20.7)	69 (22.9)	<.001
Renal disease	136 (2.9)	106 (2.5)	7 (5.2)	23 (7.6)	<.001
Valve disease	910 (19.3)	758 (17.8)	42 (31.1)	110 (36.5)	<.001
Pulmonary disease	664 (14.1)	578 (13.5)	30 (22.2)	56 (18.6)	.001
Preoperative pulse pressure, mm Hg					<.001
Median	57.0	56.5	62.5	60.0	
Interquartile range	48.0–67.5	48.0–67.0	52.0–76.0	48.0–71.0	
Preoperative insertion of IABP	34 (0.7)	31 (0.7)	0 (0.0)	3 (1.0)	.52
Redo operation	311 (6.6)	267 (6.3)	15 (11.1)	29 (9.6)	.008
Surgical factor, no. (%)					
Concomitant current procedure	655 (13.9)	541 (12.7)	34 (25.2)	80 (26.6)	<.001
Concurrent CABG and valve (aortic/mitral) surgery	508 (10.8)	419 (9.8)	26 (19.3)	63 (20.9)	<.001
Bypass of > 3 proximal aortic anastomoses	191 (4.1)	160 (3.7)	13 (9.6)	18 (6.0)	<.001
Intraoperative use of antifibrinolytics†	2751 (67.6)	2477 (67.1)	84 (70.6)	190 (74.2)	.05
Intraoperative hypertension‡	1678 (36.4)	1478 (35.4)	62 (46.6)	138 (46.5)	<.001
Intraoperative atrial fibrillation or atrial flutter	345 (7.3)	296 (6.9)	18 (13.3)	31 (10.3)	.002
Intraoperative homologous red blood cell transfusion	1767 (37.6)	1525 (35.7)	61 (45.2)	181 (60.1)	<.001
Intraoperative homologous fresh-frozen plasma transfusion	487 (10.4)	395 (9.3)	27 (20.0)	65 (21.6)	<.001

TABLE 1. Continued

Characteristic	All patients (n = 4707)	Patients without type I or II outcome (n = 4271)	Patients with type I outcome (n = 135)	Patients with type II outcome (n = 301)	*P* value
Intraoperative homologous platelets transfusion	424 (9.0)	346 (8.1)	19 (14.1)	59 (19.6)	<.001
Return to CPB	210 (4.5)	175 (4.1)	13 (9.6)	22 (7.3)	<.001
Duration of CPB (min)					<.001
Median	96.0	94.0	107.0	109.0	
Interquartile range	74.0–123.0	73.0–121.0	86.0–136.0	82.0–142.0	
Postoperative factor, no. (%)					
Postoperative renal composite§	226 (4.8)	145 (3.4)	30 (22.2)	51 (16.9)	<.001
Length of ICU stay (d)					<.001
Median	1.3	1.2	3.9	4.2	
Interquartile range	0.9–2.8	0.9–2.3	1.5–9.3	1.8–8.0	
Length of hospital stay (d)					<.001
Median	8.0	8.0	13.0	11.0	
Interquartile range	6.0–11.0	6.0–10.0	10.0–21.0	8.0–18.0	
Discharge to facility other than home	1533 (33.6)	1321 (31.7)	64 (56.1)	148 (53.4)	<.001
Patient died in hospital	151 (3.2)	106 (2.5)	21 (15.6)	24 (8.0)	<.001

BMI, Body mass index; *IABP*, intraaortic balloon pump; *ICU*, intensive care unit; *CABG,* coronary artery bypass graft; *CPB,* cardiopulmonary bypass. *Continuous variables are summarized by medians and interquartile ranges, and *P* values were calculated by the Kruskal–Wallis test; categorical variables are summarized by numbers and percentages, and *P* values were calculated by the chi-square test. Missing data for patients with neurologic dysfunction: 5 without type I or II outcome and 1 with type II outcome; missing data for patients with valve disease: 2 without type I or II outcome; missing data for preoperative pulse pressure: 7 without type I or II outcome; missing data for bypass of > 3 proximal aortic anastomoses: 1 without type I or II outcome; missing data for intraoperative use of anti-fibrinolytics: 579 without type I or II outcome, 16 with type I outcome, and 45 with type II outcome; missing data for intraoperative hypertension: 91 without type I or II outcome, 2 with type I outcome, and 4 with type II outcome; missing data for intraoperative homologous red blood cell transfusion: 4 without type I or II outcome; missing data for intraoperative fresh-frozen plasma transfusion: 6 without type I or II outcome; missing data for intraoperative platelets transfusion: 6 without type I or II outcome; missing data for those discharged to facility other than home: 106 without type I or II outcome, 21 with type I outcome, and 24 with type II outcome. †Intraoperative use of antifibrinolytics was defined as administration of > 2,000,000 KIU aprotinin intravenously before the end of surgery, > 10 g aminocaproic acid, or > 1 g tranexamic acid. ‡Intraoperative hypertension was defined as highest systolic blood pressure > 160 mm Hg pre-CPB or post-CPB, highest mean arterial pressure > 110 mm Hg pre-CPB or during-CPB or post-CPB, or highest systolic blood pressure > 160 mm Hg after end of protamine infusion, 0–5 min, 6–15 min, or 16–30 min. §Postoperative renal composite was defined as renal dysfunction requiring a postoperative serum creatinine level of at least 177 μmol per liter with an increase over preoperative baseline levels of at least 62 μmol per liter or renal failure defined as dysfunction requiring dialysis or in-hospital death with evidence at autopsy of acute renal failure.

score was 0.75 for type I outcomes and 0.71 for type II outcomes (Table 2). There was little change in the AUC when correction factors were applied for age and higher education (college or postgraduate education) (Table 2). A 2-point worsening in MMSE score provided only 73% specificity and 63% sensitivity for type I outcomes (Table 3). For type II outcomes, a 2-point worsening in the MMSE score provided 73% specificity and 62% sensitivity (Table 3).

For the NIHSS, 37% of patients were tested on postoperative day 3, 30% of patients were tested on postoperative day 4, and 22% of patients were tested on postoperative day 5. For the MMSE, 38% of patients were tested on postoperative day 3, 30% of patients were tested on postoperative day 4, and 22% of patients were tested on postoperative day 5. There were small, statistically significant but clinically unimportant differences in the NIHSS and MMSE results according to the postoperative date of testing (on postoperative day 3, 4, or 5). These differences are reported in Appendices 3 and 4.

We also examined the predictive value of both the NIHSS and MMSE if only nonfatal or fatal stroke outcomes are considered. The sensitivity and specificity of both the NIHSS and MMSE were better for stroke only (Table 4). The AUC for changes in NIHSS score was 0.95, and the AUC for changes in MMSE score was 0.77.

Multivariate analysis determined that the common predictors of worsening postoperative NIHSS and MMSE scores included age increment, performance on the preoperative NIHSS and MMSE, a history of neurologic dysfunction,

TABLE 2. Receiver operating characteristic for worsening in National Institutes of Health Stroke Scale or Mini-Mental State Examination scores predicting type I or II outcomes*

Test	Adjustment	ROC for prediction of type I outcome	ROC for prediction of type II outcome
NIHSS	Without adjustment	0.89	0.66
NIHSS	Adjustment for age† and education‡	0.89	0.73
MMSE	Without adjustment	0.75	0.71
MMSE	Adjustment for age† and education‡	0.75	0.77

ROC, Receiver operating characteristic; *NIHSS,* National Institutes of Health Stroke Scale; *MMSE,* Mini-Mental State Examination. *Type I, event(s) before postoperative NIHSS test or MMSE test, or type I–neurologic death. †Age, age > 60 y and per 5 y thereof, and > 80 y. ‡Education, with higher education (college or postgraduate education) vs without higher education.

TABLE 3. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of National Institutes of Health Stroke Scale or Mini-Mental State Examination score for type I or II outcomes

CNS type I or II outcome	Worsening in NIHSS or MMSE score	ROC curves	Specificity	Sensitivity	Positive predictive value	Negative predictive value	Likelihood ratio–positive test result	Likelihood ratio–negative test result
Type I*	NIHSS change ≥1	0.85	0.86	0.84	0.10	1.00	6.20	0.19
Type I*	NIHSS change ≥2	0.83	0.94	0.71	0.19	0.99	12.79	0.30
Type I*	NIHSS change ≥3	0.75	0.97	0.54	0.25	0.99	18.22	0.48
Type I*	NIHSS change ≥4	0.74	0.98	0.49	0.35	0.99	28.85	0.52
Type II	NIHSS change ≥1	0.66	0.88	0.44	0.19	0.96	3.66	0.63
Type II	NIHSS change ≥2	0.64	0.95	0.33	0.31	0.96	6.95	0.70
Type II	NIHSS change ≥3	0.61	0.98	0.24	0.38	0.95	9.84	0.78
Type II	NIHSS change ≥4	0.57	0.98	0.16	0.38	0.95	9.60	0.86
Type I*	MMSE change ≤ −1	0.66	0.54	0.79	0.03	0.99	1.71	0.39
Type I*	MMSE change ≤ −2	0.68	0.73	0.63	0.05	0.99	2.29	0.51
Type I*	MMSE change ≤ −3	0.69	0.84	0.54	0.06	0.99	3.30	0.55
Type I*	MMSE change ≤ −4	0.69	0.90	0.48	0.09	0.99	4.84	0.57
Type II	MMSE change ≤ −1	0.65	0.54	0.75	0.10	0.97	1.63	0.46
Type II	MMSE change ≤ −2	0.68	0.73	0.62	0.14	0.97	2.35	0.51
Type II	MMSE change ≤ −3	0.66	0.85	0.48	0.18	0.96	3.18	0.62
Type II	MMSE change ≤ −4	0.65	0.91	0.39	0.23	0.96	4.48	0.67

CNS, Central nervous system; *NIHSS,* National Institutes of Health Stroke Scale; *ROC,* receiver operating characteristic; *MMSE,* Mini-Mental State Examination. *Type I, event(s) before postoperative NIHSS test or MMSE test, or type I–neurologic death.

diabetes, intraoperative transfusion of red blood cells, and duration of CPB (Table 5). For the NIHSS, additional predictors of worsening score included congestive heart failure, hypertension, and pulmonary disease. For the MMSE, additional predictors of worsening score included female gender, a history of renal disease, valvular heart disease, and intraoperative hypertension, whereas higher education was ''protective.''

In regard to the predictors of type I and type II outcomes, multivariate analysis determined that the common predictors of these overt adverse events were age increment, diabetes, and intraoperative fresh-frozen plasma transfusion (Table 5). For type I outcomes, additional predictors included neurologic dysfunction, congestive heart failure, high pulse pressure, and more than 3 proximal aortic anastomoses. For type II outcomes, additional predictors included a history of myocardial infarction, renal disease, or valvular heart disease, as well as intraoperative hypertension and intraoperative transfusion of red blood cells. If only nonfatal or fatal stroke outcomes are considered, multivariate analysis confirmed that preoperative predictors were neurologic dysfunction, carotid disease, pulmonary disease, high pulse pressure, and redo surgery (Table 6).

The median preoperative NIHSS score was zero (zero being a perfect score) with an interquartile range of 0 to 0; 85% of study patients had a preoperative NIHSS score of zero. The median preoperative MMSE score was 29 (30 being a perfect score) with an interquartile range of 27 to 30. Common preoperative predictors of ''poor'' preoperative NIHSS (Figure 2, *A*) or MMSE (Figure 2, *B*) scores were age increment, congestive heart failure, and valvular heart disease. For the NIHSS, additional preoperative

TABLE 4. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio of National Institutes of Health Stroke Scale or Mini-Mental State Examination Score for nonfatal or fatal stroke (n = 92 patients)

Worsening in NIHSS or MMSE score	ROC* curves	Specificity	Sensitivity	Positive predictive value	Negative predictive value	Likelihood ratio–positive test result	Likelihood ratio–negative test result
NIHSS change ≥1	0.91	0.86	0.95	0.09	1.00	6.96	0.06
NIHSS change ≥2	0.88	0.94	0.82	0.17	1.00	14.38	0.19
NIHSS change ≥3	0.80	0.97	0.63	0.23	0.99	20.49	0.38
NIHSS change ≥4	0.78	0.98	0.58	0.32	0.99	32.44	0.43
MMSE change ≤ −1	0.68	0.54	0.83	0.03	0.99	1.79	0.32
MMSE change ≤ −2	0.70	0.73	0.67	0.04	0.99	2.44	0.45
MMSE change ≤ −3	0.70	0.84	0.57	0.05	0.99	3.47	0.51
MMSE change ≤ −4	0.71	0.90	0.53	0.08	0.99	5.20	0.52

NIHSS, National Institutes of Health Stroke Scale; *MMSE,* Mini-Mental State Examination; *ROC,* receiver operating characteristic. *Nonfatal stroke, stroke before postoperative NIHSS test or MMSE test.

TABLE 5. Model-adjusted ratios for type I or type II cerebral outcome, or worsening National Institutes of Health Stroke Scale or Mini-Mental State Examination scores associated with selected factors*

Predictor	Type I CNS outcome	Type II CNS outcome	Postoperative NIHSS Score†		Postoperative MMSE score‡
			Logit portion	Negative binomial portion	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	RR (95% CI)	OR (95% CI)
Age > 60 y and per 5 y thereof and > 80 y	1.27 (1.14–1.41)¶	1.43 (1.34–1.53)¶	0.84 (0.76–0.92)¶	1.17 (1.11–1.24)¶	1.29 (1.21–1.38)¶
College or postgraduate education					0.68 (0.55–0.83)¶
Women					1.24 (1.08–1.43)
Medical history/preoperative factor					
Preoperative NIHSS/MMSE score				1.20 (1.13–1.27)¶	1.51 (1.45–1.58)¶
Neurologic dysfunction	2.38 (1.58–3.58)¶			1.54 (1.25–1.89)¶	1.32 (1.10–1.59)
Congestive heart failure	2.03 (1.00–4.10)			1.33 (1.02–1.74)	
Myocardial infarction		1.42 (1.12–1.78)			
Hypertension				1.43 (1.17–1.76)¶	
Pulse pressure (per 10 mm Hg increment)§	1.17 (1.05–1.30)				
Pulmonary disease				1.52 (1.23–1.88)¶	
Diabetes	1.54 (1.17–2.04)	1.48 (1.18–1.85)¶		1.42 (1.18–1.69)¶	1.25 (1.14–1.38)¶
Renal disease		2.20 (1.12–4.32)			1.74 (1.31–2.32)¶
Intraoperative factors					
>3 proximal aortic anastomoses	2.43 (1.41–4.17)				
Valvular heart disease		1.77 (1.40–2.24)¶			1.29 (1.15–1.44)¶
Intraoperative hypertension‖		1.36 (1.17–1.59)¶			1.17 (1.03–1.32)
Intraoperative homologous RBC transfusion		1.48 (1.14–1.92)		1.36 (1.12–1.64)	1.34 (1.14–1.56)¶
Intraoperative homologous FFP transfusion	1.99 (1.54–2.58)¶	1.54 (1.14–2.09)			
CPB time per 30-min increment			0.87 (0.78–0.97)	1.06 (1.001–1.13)	1.15 (1.09–1.22)¶

CNS, Central nervous system; *NIHSS,* National Institutes of Health Stroke Scale; *MMSE,* Mini-Mental State Examination; *OR,* odds ratio; *CI,* confidence interval; *RR,* rate ratio; *RBC,* red blood cells; *FFP,* fresh-frozen plasma; *CPB,* cardiopulmonary bypass. *Models were adjusted for the patients' demographic characteristics, medical history, preoperative or intraoperative factors, and countries.†Zero-inflated Negative binomial model is used to assess the association between postoperative NIHSS score and predictors; a Logit model is used to model the probability of zero-NIHSS score, and then a Negative binomial model is performed to model count outcomes in the not-always-zero group. Rate ratio for preoperative NIHSS score was calculated per 1 unit increase. ‡Generalized estimating equations model for ordinal outcome is used to assess the association of worsening postoperative MMSE score and predictors; postoperative MMSE score is categorized as high (27–30), moderate (24–26), and low (<24). Odds ratio for preoperative MMSE score was calculated as per 1 unit decrease. §Pulse pressure per 10 mm Hg increment above a threshold of 40 mm Hg. ‖Intraoperative hypertension was defined as highest systolic blood pressure > 160 mm Hg pre-CPB or post-CPB, highest mean arterial pressure > 110 mm Hg pre-CPB or during-CPB or post-CPB, or highest systolic blood pressure > 160 mm Hg after end of protamine infusion 0–5 min, 6–15 min, or 16–30 min. ¶*P* value < .001.

predictors of a ''poor'' score were a history of neurologic dysfunction and renal disease. For the MMSE, additional preoperative predictors of a ''poor'' score were a history of mental dysfunction, unstable angina, and peripheral vascular disease, whereas higher education was ''protective.''

DISCUSSION

We have reported preoperative and postoperative NIHSS and MMSE scores in a large international sample of patients undergoing cardiac surgery with CPB and the relationship of these scores to type I and II neurologic sequelae of surgery. Our findings provide the only reference for evaluating changes in NIHSS or MMSE scores from baseline, when these tests are used in clinical trials designed to diagnose, mitigate, or treat adverse neurologic outcome after cardiac surgery. We also defined predictors for type I and II adverse neurologic outcomes and compared these with predictors for postoperative worsening in NIHSS and MMSE scores. Finally, we explored patient characteristics that predict preoperative subnormal NIHSS and MMSE scores.

The NIHSS is a reliable[2,13,14] and validated[1,18,19] measure of stroke-related neurologic impairment. It measures several aspects of brain function, including consciousness, vision, sensation, movement, speech, and language, with a maximal score of 42 representing the most severe and devastating stroke. A normal score is zero (no stroke), a score of 1 to 4 indicates a minor stroke, a score of 5 to 15 indicates a moderate stroke, a score of 15 to 20 indicates a moderate-to-severe stroke, and a score of 21 to 42 indicates a severe stroke.[20] The NIHSS is frequently used in therapeutic trials of stroke rehabilitation as the primary serial measure of the efficacy of interventions designed to ameliorate sequelae

TABLE 6. Model-adjusted odds ratios for nonfatal or fatal stroke (n = 92 patients) associated with preoperative risk factors*

Predictor	OR (95% CI)	*P* value
Medical history/preoperative factor		
Neurologic dysfunction	1.81 (1.35–2.42)	<.001
Carotid disease	1.75 (1.07–2.87)	.03
Pulmonary disease	2.11 (1.15–3.88)	.02
Pulse pressure (per 10 mm Hg increment)†	1.36 (1.25–1.48)	<.001
Redo surgery‡	2.47 (1.50–4.08)	<.001

OR, Odds ratio; *CI,* confidence interval. *Excluded were 13 patients with missing values for at least one of the risk factors in the model, including the covariates. †Pulse pressure per 10 mm Hg increment above a threshold of 40 mm Hg. ‡Redo surgery was defined as with previous CABG, valve, cardiac, noncardiac, or bypass graft surgery.

after documented stroke.[21-23] It is often chosen for its simplicity of administration, its high reproducibility of results among allied health personnel, and the ease with which results can be transformed for database collection and statistical analysis. Although previously used in the setting of cardiac surgery to screen for postoperative neurologic changes in patients with and without suspected acute stroke,[4-6] the NIHSS had not been previously validated as a tool for diagnosing and quantifying the degree of neurologic injury (or lack thereof) in this setting. Our findings indicate that postoperative worsening of the NIHSS score is an excellent predictor of type I outcome after CABG surgery.

The MMSE is a brief, standardized, and validated instrument that was originally used to screen for Alzheimer's disease and is now also used to screen for dementia.[7,8,24] It is commonly used in both clinical and research settings to measure cognitive impairment in various disease states, document intellectual changes over time, and assess the effects of potential therapeutic agents on cognitive function. The MMSE is attractive because it is brief, easily administered, and easily scored. Estimates of internal consistency[25] and interrater reliability[7,26] are good. Premorbid intelligence and educational attainment affect MMSE scores, in that less intelligent or less educated individuals tend to score lower

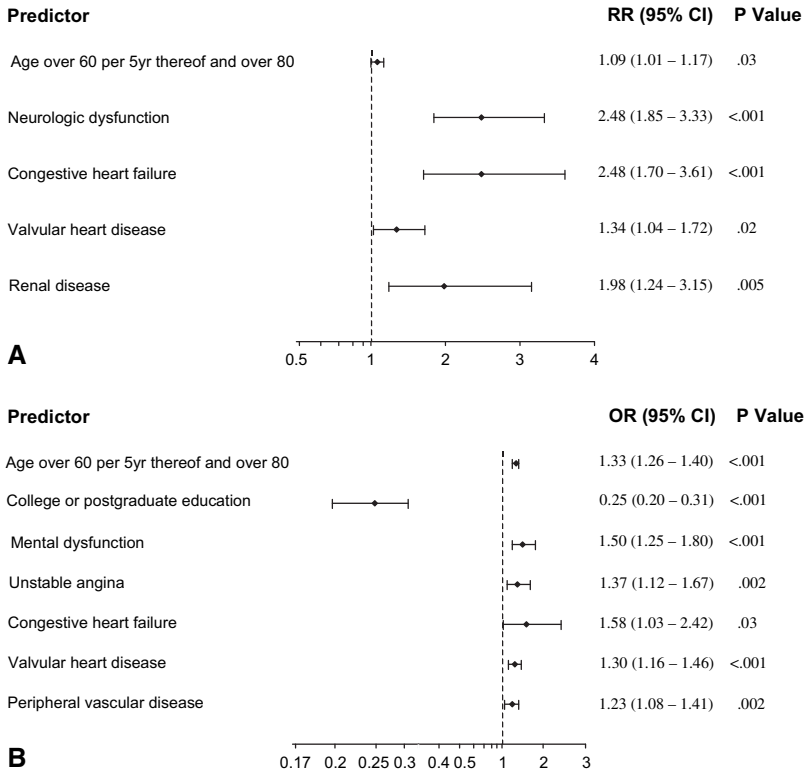

FIGURE 2. Multivariable predictors of adverse preoperative NIHSS or MMSE scores. A, Zero-inflated Negative binomial model for preoperative NIHSS score. A Logit model with binomial assumption is used to determine whether an individual count outcome is from the always-zero or the not-always-zero group, and then a Negative binomial model for count data is performed to model outcomes in the not-always-zero group. For the logistic portion, age increment is related to NIHSS score of zero with a 30% decrease in odds (OR = 0.70; 95% CI, 0.55–0.91, $P = .008$); higher education increases the odds to 3-fold (OR = 3.56; 95% CI, 1.57–8.05, $P = .003$). For the Negative binomial portion, age increment, neurologic dysfunction, congestive heart failure, valvular heart disease, and renal disease increase the risk of increasing NIHSS score (adverse NIHSS score). B, Generalized estimating equations model for ordinal outcome analysis for preoperative MMSE score. MMSE score was categorized as high (27–30), moderate (24–26), and low (<24). Age increment, mental dysfunction, unstable angina, congestive heart failure, valvular heart disease, and peripheral vascular disease increase the risk of decreasing MMSE score category (adverse MMSE score); higher education decreases the risk of adverse MMSE score. Country was adjusted for in both NIHSS (A) and MMSE (B) models. *OR,* Odds ratio; *RR,* rate ratio; *CI,* confidence interval.

than do more intelligent (ie, higher IQ) or more educated individuals.[17,25,27] Also, MMSE scores decrease with advancing age, from a median score of 29 at 18 to 24 years of age to a median of 25 at ≥80 years of age.[24,27] Although the MMSE has been used in the setting of cardiac surgery to measure cognitive change in patients with and without suspected changes in intellectual function,[4,6,9] the preoperative and postoperative clinical utility of MMSE scores has not been published for a large population of surgical patients of any type. Our patients scored relatively well on this test in the preoperative period (median MMSE score of 29 with an interquartile range of 27–30.). Not unexpectedly, we have confirmed that preoperative MMSE scores are related to age and education. Our findings indicate that postoperative worsening of the MMSE score provides only fair discrimination for type I or II outcomes after CABG surgery.

Common predictors of deterioration in NIHSS or MMSE and overt type I or II adverse outcomes included older age, a history of neurologic dysfunction (due to stroke or transient ischemic attack), and diabetes, as well as intraoperative red blood cell transfusion and duration of CPB. These risk factors have been identified as being associated with adverse neurologic outcome.[11,28-32] If only nonfatal or fatal stroke outcomes are considered, multivariate analysis confirmed some of the same preoperative predictors, notably a history of neurologic dysfunction. These findings may have clinical implications, in that perhaps patients with a known history of stroke or transient ischemic attack should undergo myocardial revascularization in hospitals having immediately available services for the treatment of acute stroke.[32]

In our previous study,[11] completed in 1993, we did not formally assess neurologic function with any recognized scale or scoring system in either the preoperative or postoperative periods. In both the previous and the current study, individual investigators at each site assessed type I deficits or type II dysfunction in whatever manner they deemed clinically suitable. Notably, the incidence of type I outcomes in the present study was similar to that in our previous study (2.9% vs 3.1%), whereas the incidence of type II outcomes was somewhat higher in the present study (6.4% vs 3.0%).[11] This may be because patients in the current era are older and more likely to have mild preoperative or postoperative cognitive deficits, although, fortunately, advances in cardiac surgical techniques and extracorporeal circulation technology have prevented increases in the incidence of frank stroke.[5]

As in our previous study,[11] we examined conservative measures of resource use, namely, the duration of intensive care, the total duration of the hospital stay after surgery, and the rate of discharge to intermediate- or long-term care facilities. All 3 measures were markedly prolonged for patients with either type I or type II adverse neurologic outcomes. Compared with patients without adverse neurologic outcomes, patients with type I outcome stayed an additional $2\frac{1}{2}$ days in the intensive care unit and an additional 5 days on the ward, suggesting that regardless of institutional practice, substantial resources are consumed by such patients. Furthermore, compared with patients without adverse neurologic outcomes, patients with type II outcomes stayed an additional 3 days in the intensive care unit and 3 days on the ward. (These data are included in Table 1.) On the basis of conservative estimates of boarding charges of approximately $3700 per day in an intensive care unit and $1700 per day on a ward, type I neurologic events are responsible for approximately $18,000 in additional costs per patient in in-hospital boarding costs, and type II events are responsible for approximately $16,000 in additional costs per patient. Furthermore, the costs of changes in discharge planning and long-term out-of-hospital medical and rehabilitative services undoubtedly result in considerable additional expenditure.

Study Limitations

Several limitations of the present study may affect the generalizability and utility of its findings. The data are approximately 10 years old, and the patients were only at moderate risk for adverse outcomes. Although overt neurologic adverse events were a relatively small percentage of the total, our incidence of type I outcome (2.9%) is not dissimilar from other more recent series.[29-31] As in our previous study,[11] although data were collected prospectively, the study is limited by its purely observational design. The study was conducted with data collected from medical centers throughout the world, a diversity that is both a strength and a potential weakness. The assessments were made by multiple investigators who were not neurologists, and the assessments were not always made by the same investigator within an institution. Furthermore, we were not able to consistently obtain objective evidence of acute cerebral ischemic events (eg, computed tomography or magnetic resonance imaging scans) in the postoperative period. In addition, only 87.2% of patients (4105 of 4707) completed the preoperative and postoperative NIHSS tests, and even fewer completed the MMSE test (2868 of 4707 [60.9%]). Finally, a complete battery of neurocognitive tests were not administered, only the MMSE. In the absence of more extensive evaluation of neurocognitive dysfunction, we did attempt to be rigorous in identifying type II outcomes, mandating that 2 or more indications of ''intellectual dysfunction'' be present on 2 or more days of a patient's hospitalization.

Despite these limitations, our current findings warrant additional investigations. Future studies should examine the long-term outcomes associated with unexpected postoperative worsening of either test score. Outcomes of interest would include worsening in patient scores several years after surgery[33]; ability to return to employment; functional outcomes as measured by quality of life assessment tools;

need for rehospitalization; and postdischarge morbidity due to depression, late stroke, or death.

CONCLUSIONS

Standardized scores on the NIHSS and MMSE tests are used for the quantitative assessment of adverse neurologic events after cardiac surgery. We have provided a reference defining the clinical utility of assessment of baseline scores and postoperative worsening in scores on these tests, which will be useful in the evaluation of results of clinical trials designed to diagnose, mitigate, or treat adverse neurologic outcomes after cardiac surgery.

The authors are indebted to Stephen N. Palmer, PhD, ELS, for editorial support.

References

1. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-70.
2. Lyden P, Raman R, Liu L, Grotta J, Broderick J, Olson S, et al. NIHSS training and certification using a new digital video disk is reliable. *Stroke*. 2005;36:2446-9.
3. Duncan PW, Zorowitz R, Bates B, Choi JY, Glasberg JJ, Graham GD, et al. Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. *Stroke*. 2005;36:e100-43.
4. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291:1720-9.
5. Cook DJ, Huston J III, Trenerry MR, Brown RD Jr, Zehr KJ, Sundt TM III. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. *Ann Thorac Surg*. 2007;83:1389-95.
6. Shernan SK, Fitch JC, Nussmeier NA, Chen JC, Rollins SA, Mojcik CF, et al. Impact of pexelizumab, an anti-C5 complement antibody, on total mortality and adverse cardiovascular outcomes in cardiac surgical patients undergoing cardiopulmonary bypass. *Ann Thorac Surg*. 2004;77:942-9.
7. Folstein MF, Folstein SE, McHugh PR. ''Mini-mental state'': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-98.
8. Hensel A, Angermeyer MC, Riedel-Heller SG. Measuring cognitive change in older adults: reliable change indices for the Mini-Mental State Examination. *J Neurol Neurosurg Psychiatry*. 2007;78:1298-303.
9. Fitch JC, Rollins S, Matis L, Alford B, Aranki S, Collard CD, et al. Pharmacology and biological efficacy of a recombinant, humanized, single-chain antibody C5 complement inhibitor in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass. *Circulation*. 1999;100:2499-506.
10. Weissrock S, Levy F, Balabaud V, Thiranos JC, Dupeyron JP, Steib A. [Interest of the Mini Mental State Examination to detect cognitive defects after cardiac surgery]. *Ann Fr Anesth Reanim*. 2005;24:1255-61.
11. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. *N Engl J Med*. 1996;335:1857-63.
12. Mangano DT. Aspirin and mortality from coronary bypass surgery. *N Engl J Med*. 2002;347:1309-17.
13. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. *Arch Neurol*. 1989;46:660-2.
14. Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale: extension to non-neurologists in the context of a clinical trial. *Stroke*. 1997;28:307-10.
15. Vickers AJ, Altman DG. Statistics notes: analyzing control trials with baseline and follow-up measurements. *BMJ*. 2001;323:1123-4.
16. O'Bryant SE, Humphreys JD, Smith GE, Ivnik RJ, Graff-Radford NR, Petersen RC, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. *Arch Neurol*. 2008;65:963-7.
17. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40:922-35.
18. Lyden P, Lu M, Jackson C, Marler J, Kothari R, Brott T, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. *Stroke*. 1999;30:2347-54.
19. Tong DC, Yenari MA, Albers GW, O'Brien M, Marks MP, Moseley ME. Correlation of perfusion and diffusion-weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology*. 1998;50:864-70.
20. Wkhloo AK, Sandhu JS. Principles of endovascular therapy. In: Bradley WG, Daroff RB, Fenichel GM, Jancovic J, eds. Neurology in clinical practice: principles of diagnosis and management. 4th ed. Philadelphia: Elsevier; 2004:993-1025.
21. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53: 126-31.
22. Young FB, Weir CJ, Lees KR. Comparison of the National Institutes of Health Stroke Scale with disability outcome measures in acute stroke trials. *Stroke*. 2005;36:2187-92.
23. Bruno A, Saha C, Williams LS. Using change in the National Institutes of Health Stroke Scale to measure treatment effect in acute stroke trials. *Stroke*. 2006;37: 920-1.
24. Spreen O, Strauss E. A compendium of neuropsychological tests: administration, norms, and commentary. 2nd ed. New York: Oxford University Press; 1998.
25. Tombaugh TN, McDowell I, Kristjansson B, Hubley AM. Mini-Mental State Examination (MMSE) and the Modified MMSE (3MS): a psychometric comparison and normative data. *Psychol Assess*. 1996;8:48-59.
26. Foster JR, Sclan S, Welkowitz J, Boksay I, Seeland I. Psychiatric assessment in medical long-term care facilities: reliability of commonly used rating scales. *Int J Geriatr Psychiatry*. 1988;3:229-33.
27. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA*. 1993;269: 2386-91.
28. Baker R, Hallsworth LJ, Knight RB. Stroke after coronary artery bypass grafting. *Ann Thorac Surg*. 2005;80:1746-50.
29. Anyanwu AC, Filsoufi F, Salzberg SP, Bronster DJ, Adams DH. Epidemiology of stroke after cardiac surgery in the current era. *J Thorac Cardiovasc Surg*. 2007; 134:1121-7.
30. Lisle TC, Barrett KM, Gazoni LM, Swenson BR, Scott CD, Kazemi A, et al. Timing of stroke after cardiopulmonary bypass determines mortality. *Ann Thorac Surg*. 2008;85:1556-63.
31. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2008;22:814-22.
32. Dafer RM. Risk estimates of stroke after coronary artery bypass graft and carotid endarterectomy. *Neurol Clin*. 2006;24:795-806.
33. Selnes OA, Grega MA, Bailey MAM, Pham LD, Zeger SL, Baumgartner WA, et al. Cognition 6 years after surgical or medical therapy for coronary artery disease. *Ann Neurol*. 2008;63:581-90.

Appendix 1.

The IREF is an independent nonprofit foundation, formed in 1987, that develops clinical investigators via observational studies and clinical trials addressing ischemic injury of the heart, brain, kidney, and gastrointestinal tract. The IREF provided all funding for execution of the study, collection of the data, and analysis and publication of the findings. The Multicenter Study of Perioperative Ischemia Research Group, formed in 1988, is an association of 160 international medical centers located in 23 countries organized through and supported by grants from the IREF.

The following institutions and persons coordinated the Multicenter Study of Perioperative Ischemia Research Group EPI-II study. Study Chairman—D. Mangano; Senior Editors—J. Levin, L. Saidman; Study Design and Analysis Center: Ischemia Research and Education Foundation—P. Barash, C. Dietzel, A. Herskowitz, K. Huang, Y. Miao, I. C. Tudor, S. Wang, Y. Weng; Editorial/Administrative Group—D. Beatty, I. Lei, B. Xavier.

The following institutions and persons participated in the *McSPI* EPI-II Study. Centers and investigators: United States—University of Chicago, Weiss Memorial Hospital—S. Aronson; Beth Israel Hospital—M. Comunale; Massachusetts General—M. D'Ambra; University of Rochester — M. Eaton; Baystate Medical Center—R. Engelman; Baylor College of Medicine—J. Fitch; Duke Medical Center—K. Grichnik; UTHSCSA-Audie Murphy VA, UTHSCSA-University Hospital—C. B. Hantler; St. Luke's Roosevelt Hospital—Z. Hillel; New York University Medical Center—M. Kanchuger, J. Ostrowski; Stanford University Medical Center—C. M. Mangano; Yale University School of Medicine—J. Mathew, M. Fontes, P. Barash; University of Wisconsin—M. McSweeney, R. Wolman; University of Arkansas for Medical Sciences—C. A. Napolitano; Discovery Alliance, Inc.—L. A. Nesbitt; VA Medical Center, Milwaukee—N. Nijhawan; Texas Heart Institute, Mercy Medical Center—N. Nussmeier; University of Texas Medical School, Houston—E. G. Pivalizza; University of Arizona—S. Polson; Emory University Hospital—J. Ramsay; Kaiser Foundation Hospital—G. Roach; Thomas Jefferson University Hospital, MCP Hahnemann University Hospital— N. Schwann; VAMC Houston—S. Shenaq; Maimonides Medical Center—K. Shevde; Mt. Sinai Medical Center—L. Shore-Lesserson, D. Bronheim; University of Michigan—J. Wahr; University of Washington—B. Spiess, I. Wright; VA Medical Center, S. F.—A. Wallace; Austria—University of Graz—H. Metzler; Canada—University of British Columbia—D. Ansley, J. P. O'Connor; The Toronto Hospital—D. Cheng; Laval Hospital, Quebec—D. Côte; Health Sciences Centre-University of Manitoba—P. Duke; University of Ottawa Heart Institute—J. Y. Dupuis, M. Hynes; University of Alberta Hospital—B. Finegan; Montreal Heart Institute—R. Martineau, P. Couture; St. Michael's Hospital, University of Toronto—D. Mazer; Colombia—Fundacion Clinico Shaio—J. C. Villalba, M. E. Colmenares; France—CHRU Le Bocage—C. Girard; Hospital Pasteur—C. Isetta; Germany—Universität Wrzburg—C. A. Greim, N. Roewer; Universität Bonn—A. Hoeft; University of Halle—R. Loeb, J. Radke; Westfalische Wilhelms-Universität Munster—T. Mollhoff; Universität Heidelberg—J. Motsch, E. Martin; Ludwig-Maximillians Universität—E. Ott; Universität Krankenhaus Eppendorf—J. Scholz, P.Tonner; Georg-August Universität Göttingen—H. Sonntag; Ludwig-Maximillians Universität (Department of Cardiac Surgery)—P. Ueberfuhr; Hungary—Orszagos Kardiologiai Intezet—A. Szekely; India—Escorts Heart Institute—R. Juneja; Apollo Hospital—G. Mani; Israel—Hadassah University Hospital—B. Drenger, Y. Gozal, E. Elami; Italy—San Raffaele Hospital, Universita de Milano—C. Tommasino; Mexico—Instituto Nacional de Cardiologia—P. Luna; The Netherlands—University Hospital Maastricht—P. Roekaerts, S. DeLange; Poland—Institute of Cardiology—R. Pfitzner; Romania—Institute of Cardiology—D. Filipescu; Thailand—Siriraj Hospital—U. Prakanrattana; United Kingdom—Glenfield Hospital—D. J. R. Duthie; St. Thomas' Hospital—R. O. Feneck; The Cardiothoracic Centre, Liverpool—M. A. Fox; South Cleveland Hospital—J. D. Park; Southampton General Hospital—D. Smith; Manchester Royal Infirmary—A. Vohra; Papworth Hospital— A. Vuylsteke, R. D. Latimer.

Appendix 2. Demographic characteristics

Age, or age > 60 y and per 5 y thereof and > 80 y
Gender
Obesity (BMI > 28)
Regular or current smoke
College or postgraduate education
Race or ethnicity
Medical history or preoperative factors
Stroke
TIA
Preoperative neurologic dysfunction (history of stroke or TIA)
Preoperative mental dysfunction
Myocardial infarction
Unstable angina
Congestive heart failure
Hypertension
Pulse pressure
Controlled hypertension
Uncontrolled hypertension
Atrial fibrillation/atrial flutter
Dysrhythmia
Tachyarrhythmias
Cardiomegaly abnormality (preoperative chest x-ray)
Valvular stenosis
Valvular insufficiency

ACD

Appendix 2. Continued

Preoperative valve (aortic/mitral) calcification: chest x-ray/cardiac catheterization
Any valve (aortic/mitral) disease (stenosis/insufficiency/calcification) on admission or
Preoperation
Redo surgery
Preoperative IABP
Preoperative aortic vascular disease
Peripheral vascular disease
Carotid vascular disease
Pulmonary disease
Diabetes
Renal disease
Liver disease
Hematologic disorder
Previous carotid endarterectomy
Intraoperative and surgical factors
Concurrent combined surgery
Bypass of > 3 proximal aortic anastomoses

Appendix 2. Continued

Aortic vascular disease (history or preoperative or intraoperative image/palpation)
All vascular disease, carotid vascular disease, peripheral vascular disease, or aortic vascular disease (history, preoperative, or intraoperative image/palpation)
Valve stenosis (history, preoperative, or prebypass)
Valve insufficiency (history, preoperative, or prebypass)
Valvular calcification (preoperative or intraoperative)
Any valve (aortic/mitral) disease (stenosis/insufficiency/calcification) (on admission or preoperative or intraoperative)
Intraoperative hypertension
Intraoperative atrial fibrillation/atrial flutter
Intraoperative homologous red blood cell transfusion
Intraoperative homologous fresh-frozen plasma transfusion
Intraoperative homologous platelets transfusion
Return to CPB
CPB time (min)

BMI, Body mass index; *TIA,* transient ischemic attack; *IABP,* intraaortic balloon pump; *CPB,* cardiopulmonary bypass.

Appendix 3. Receiver operating characteristic curves, sensitivity, and specificity of National Institutes of Health Stroke Scale score by postoperative day of National Institutes of Health Stroke Scale test

CNS type I* outcome	POD of NIHSS test	Test of NIHSS	ROC curve	Specificity	Sensitivity
Type I	POD3	NIHSS change $\geq$1	0.87	0.88	0.86
Type I	POD3	NIHSS change $\geq$2	0.79	0.96	0.62
Type I	POD3	NIHSS change $\geq$3	0.75	0.98	0.52
Type I	POD3	NIHSS change $\geq$4	0.73	0.98	0.48
Type I	POD4	NIHSS change $\geq$1	0.82	0.88	0.76
Type I	POD4	NIHSS change $\geq$2	0.80	0.95	0.65
Type I	POD4	NIHSS change $\geq$3	0.72	0.98	0.47
Type I	POD4	NIHSS change $\geq$4	0.70	0.99	0.41
Type I	POD5	NIHSS change $\geq$1	0.84	0.85	0.83
Type I	POD5	NIHSS change $\geq$2	0.84	0.93	0.75
Type I	POD5	NIHSS change $\geq$3	0.77	0.96	0.58
Type I	POD5	NIHSS change $\geq$4	0.78	0.98	0.58

CNS, Central nervous system; *POD,* postoperative day; *NIHSS,* National Institutes of Health Stroke Scale; *ROC,* receiver operating characteristic. *Type I, event(s) before postoperative NIHSS test or MMSE test, or type I–neurologic death.

Appendix 4. Receiver operating characteristic curves, sensitivity, and specificity of Mini-Mental State Examination score by postoperative day of Mini-Mental State Examination test

CNS type I* outcome	POD of MMSE Test	Test of NIHSS	ROC curve	Specificity	Sensitivity
Type I	POD3	MMSE change ≤ -1	0.61	0.55	0.67
Type I	POD3	MMSE change ≤ -2	0.64	0.73	0.54
Type I	POD3	MMSE change ≤ -3	0.67	0.84	0.50
Type I	POD3	MMSE change ≤ -4	0.68	0.91	0.46
Type I	POD4	MMSE change ≤ -1	0.68	0.56	0.80
Type I	POD4	MMSE change ≤ -2	0.65	0.75	0.55
Type I	POD4	MMSE change ≤ -3	0.65	0.85	0.45
Type I	POD4	MMSE change ≤ -4	0.63	0.91	0.35
Type I	POD5	MMSE change ≤ -1	0.72	0.53	0.92
Type I	POD5	MMSE change ≤ -2	0.72	0.72	0.71
Type I	POD5	MMSE change ≤ -3	0.75	0.83	0.67
Type I	POD5	MMSE change ≤ -4	0.76	0.89	0.63

CNS, Central nervous system; *ROC,* receiver operating characteristic; *POD,* postoperative day; *NIHSS,* National Institutes of Health Stroke Scale; *MMSE,* Mini-Mental State Examination. *Type I, event(s) before postoperative NIHSS test or MMSE test, or type I–neurologic death.