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Characteristics that define high risk in carotid endarterectomy from the Vascular Study Group of New England

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Abstract

Objective—The Stenting with Angioplasty and Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared carotid endarterectomy (CEA) to carotid artery stenting (CAS) among high-risk patients using a model of risk that has not been validated by previous publications. The objective of our study was to determine the accuracy of this high-risk model and to determine the true risk factors that result in patients being at high risk for CEA.

Methods—Prospectively collected data for 3098 CEAs between 2003 and 2011 at 20 Vascular Surgery Group of New England (VSGNE) centers were used. SAPPHIRE general inclusion criteria and primary outcomes were assessed. Factors that were associated with the primary outcome by analysis of variance ($P < .10$) and not linearly dependent, as determined by a Pearson correlation analysis, were further assessed for an independent association by multivariate logistic regression. A risk index model was developed for these significant predictors to accurately define high-risk CEA.

Results—The average patient age was 69.9 ± 9.5 years, 60% were male, and 45.7% were asymptomatic. The 1-year composite outcome event rate, defined as postoperative myocardial infarction and stroke or death, was 14.2%. Multivariate analysis ($P < .05$) found the following

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Analysis and interpretation: FS, RB
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independently significant risk factors: age in years (95% confidence interval [CI], 1.0–1.1; $P < .001$), preadmission living in a nursing home (95% CI, 1.2–6.6; $P = .020$), congestive heart failure (95% CI, 1.4–2.8; $P < .001$), diabetes mellitus (DM; 95% CI, 1.1–1.3; $P < .001$), chronic obstructive pulmonary disease (95% CI, 1.2–1.5; $P < .001$), any previous cerebrovascular disease (95% CI, 1.1–1.9; $P = .003$), and contralateral internal carotid artery stenosis (95% CI, 1.0–1.2; $P = .001$). Three of the SAPPHIRE high-risk criteria—abnormal stress test, recurrent stenosis after CEA, and previous radiotherapy to the neck—were not independently associated with an adverse outcome. Independently significant risk factors not included in the SAPPHIRE criteria are inclusion of ages <80 years, preadmission living in a nursing home, DM, contralateral carotid stenosis, and any previous cerebrovascular accident. The risk index predictors are age in years (40–49: 0 points; 50–59: 2 points; 60–69: 4 points; 70–79: 6 points; 80–89: 8 points), living in a nursing home (4 points), any cardiovascular disease (2 points), congestive heart failure (5 points), chronic obstructive pulmonary disease (3 points), DM (2 points), degree of contralateral stenosis (<50%: 0 points; 50%–69%: 1 point; 70%-near occlusion: 2 points; occlusion: 3 points). High-risk CEA is defined as >13 points, representing adverse outcome rate of 22.5%.

Conclusions—SAPPHIRE and other previously reported high-risk CAS inclusion criteria do not include all of the factors found to be independently associated with outcomes. Further studies are required to determine whether CAS is inferior to CEA in high-risk patients using a validated model of risk. In addition, this preoperative assessment includes novel criteria that can be used to stratify risks.

Carotid artery stenting (CAS) has emerged as an alternative to carotid endarterectomy (CEA) for treating asymptomatic and symptomatic carotid artery disease. The Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) trial was one of the first controlled randomized trials to evaluate CAS compared with CEA. Their investigators focused on patients with coexisting conditions, which potentially increased the risk of complications after CEA.[1]

The SAPPHIRE trial concluded that CAS with an embolic protection device was not inferior to CEA in high-risk patients. The patients who underwent stenting had a 39% lower risk of their primary end point (composite stroke, death, or myocardial infarction [MI] ≤30 days).[1] One of the limitations of the SAPPHIRE trial was that the definition of “high-risk” was based on the investigators’ opinions and was never validated in an evidence-based manner.[1] The objective of this study was to evaluate the true accuracy of the high-risk definition proposed by the SAPPHIRE trial.

METHODS

Data set

Approval was given by the Vascular Study Group of New England (VSGNE) Research Advisory Committee to obtain a prospectively collected, deidentified data set (no patient consent required) for all patients who underwent CEAs between January 2003 and November 2011.

Patients

All patients undergoing CEA were listed in the VSGNE database. The study group was determined as shown in the Fig, yielding 3098 patients to included in an analysis of variance (ANOVA). From the original data sample, 23 patients were excluded due to missing SAPPHIRE general inclusion criteria, and an additional 1225 were excluded because they did not meet these criteria. Inclusion criteria matched SAPPHIRE general inclusion criteria: age ≥18 years, symptoms plus stenosis of >50% of the luminal diameter, and asymptomatic plus stenosis of >80% of the luminal diameter. The degree of stenosis was determined by any or all of duplex ultrasound imaging, computed tomography angiogram, magnetic resonance angiogram, or arteriogram. A patient was determined as symptomatic if a transient ischemic attack or stroke (major or minor) had occurred. Subsequently, an additional 4506 were excluded because they were missing 1-year outcome data. After ANOVA, 259 patients were excluded due to missing variable data.

Outcomes

The primary outcome measure was identical to the SAPPHIRE trial: cumulative incidence of death, stroke, or 30-day MI; or, death or ipsilateral stroke ≤1 year. This study used postoperative MI instead of 30-day MI because the VSGNE only collected in-hospital MI. Stroke was defined by the VSGNE database as a major disabling or minor nondisabling neurologic event as determined by the surgeon or trained data entry assistant at each institution. MI was defined as a troponin T/I elevation, electrocardiogram abnormalities, or clinical presentation (determined at each institution).

Definitions of preoperative variables

The SAPPHIRE trial determined by expert opinion that a patient who had at least one of the following coexisting conditions was at high-risk for undergoing CEA: (1) clinically significant cardiac disease, (2) severe pulmonary disease, (3) contralateral carotid occlusion (CCO), (4) contralateral laryngeal-nerve palsy, (5) previous radical neck surgery or radiotherapy to the neck, (6) recurrent stenosis after endarterectomy, or (7) age >80 years. To determine which criteria were associated with high-risk for undergoing CEA using an evidence-based approach, all 99 prospectively collected VSGNE database preoperative variables were analyzed. Variables were collected from patient demographics, admission data, presenting symptoms, medical and surgical history, medications, and radiographic studies. Notably, data on laryngeal-nerve palsy and radical neck surgery were not collected in the database, so no analysis was performed using these factors.

“Clinically significant cardiac disease” was defined in the SAPPHIRE trial as congestive heart failure (CHF), abnormal stress test result, or need for open heart surgery. In this study, these factors were analyzed separately and combined to determine significance. An abnormal stress test result was defined as showing ischemia, MI, or both. Requiring open heart surgery was not a variable included in our data set; however, surrogate variables (any coronary artery disease [CAD] symptoms, stable angina, unstable angina, MI ≤6 months of treatment date, and concomitant coronary artery bypass grafting) were studied. Pulmonary disease or chronic obstructive pulmonary disease (COPD) was defined as the presence of any COPD, COPD with home oxygen, COPD on medication, or untreated COPD. In

addition, recurrent stenosis after CEA was not delineated in the SAPPHIRE trial; therefore, all degrees of stenosis between repeated CEAs were included.

Statistical analysis

Baseline characteristics of the patient population and the incidence of adverse outcomes were assessed for similarity to the SAPPHIRE trial by an independent *t*-test for interval data and the χ^2 test for nominal data. ANOVA was used to identify variables associated with perioperative MI, any stroke ≤30 days, ipsilateral stroke ≤1 year, or death ≤1 year. $P = .1$ was used. Significant interactions between variables were identified using a two-tailed Pearson correlation analysis, and the variable with the most significant association with the outcome was chosen. A multivariate logistic regression analysis was performed on the remaining variables to discover which were independently significant predictors of the primary outcome. $P = .05$ was used. A qualified statistician performed all analyses with SPSS 19.0 software (IBM Corp, Armonk, NY).

Development of the risk index

The independently significant variables were used to construct a risk index system to predict the primary outcome. Multivariate logistic regression was rerun using the variables of age, degree of contralateral stenosis, any cerebrovascular disease (major or minor stroke or documented cerebrovascular atherosclerosis), CHF, COPD, diabetes mellitus (DM), and preadmission living in a nursing home. Regression coefficients were obtained along with the intercept for the regression. Convenient categories were created for the interval and ordinal data. Age was divided into decades 40 to 89 years. The degree of contralateral stenosis was analyzed by the reported categories of <50%, >50%, >60%, >70%, >80%, and occluded. Owing to small differences in the regression coefficients, these categories were collapsed into four groups with a detectable difference: <50%, 50% to 69%, 70%-near occlusion, and occlusion. A point system was developed using a common denominator for the regression coefficients to achieve convenient integers. Finally, the risk associated with each point was calculated using the multiple logistic regression equation, as described by Sullivan et al.[2]

RESULTS

Patient characteristics

Compared with the SAPPHIRE trial, the VSGNE patients were younger (72.6 vs 69.9 years; $P < .001$), current smokers (16.4% vs 28.9%; $P < .001$), had COPD (13.8% vs 23.4%; $P < .003$), and had a symptomatic stenosis (27.7% vs 54.3%; $P < .001$). The patient population from the SAPPHIRE trial was more likely to have CAD (75.5% vs 34.5%, $P < .001$), CHF (19.6% vs 8.4%; $P < .001$), CCO (25.3% vs 6.6%; $P < .001$), and present with recurrent stenosis after CEA. Selected demographics and patient characteristics reported in the SAPPHIRE trial are listed in Table I.

Outcomes

Death rates between the VSGNE database and the SAPPHIRE trial were similar (Table II), 285 (9.2%) and 19 (12.9%), respectively ($P = .163$). The 1-year stroke rate was 7.7% (n = 11) in the SAPPHIRE trial vs 3.8% (n = 118) in the VSGNE cohort ($P = .032$). On further

analysis, major ipsilateral and minor nonipsilateral stroke differed significantly between the two groups, five (3.5%) vs 41 (1.3%; $P = .043$) and three (2.1%) vs 19 (0.6%), respectively ($P = .044$). The rates of MI also differed significantly; the SAPPHIRE trial included MI through 1-year of follow-up (8.1%), whereas the VSGNE database only included perioperative MI (2.6%; $P < .001$). Despite this, the primary end point of death, stroke, or MI at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year was similar to the VSGNE database, 30 (20.1%) vs 440 (14.2%; $P = .053$). The conventional end point, stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year, was also similar, 11 (7.5%) vs 380 (12.3%), ($P = .066$), indicating equivalence between these data sets.

Correlates of high risk

Of the 99 preoperative variables analyzed, 64 correlated with the primary outcome ($P < .10$) by ANOVA. The following variables were also significant by ANOVA but were removed from further analysis due to excessive missing data (any variable with >25% of results missing) preventing multivariate ANOVA (MANOVA): dialysis, American Society of Anesthesiologists class, hemoglobin concentration, and positive stress test result. Hispanic or Latino ethnicity was similarly removed from further analysis with only six patients (0.002%).

A Pearson correlation analysis excluded 43 of these variables due to a significant correlation coefficient ($P < .05$) with another variable that was more significantly associated with the primary outcome, leaving the remaining correlates in Table III. These 21 variables were analyzed by MANOVA, and the correlates listed in Table IV found an independent association with the primary outcome. Variables that trended towards significance by MANOVA included male gender (n = 1868; 95% confidence interval [CI], 1.0–1.6; $P = .071$), previous arterial bypass (n = 191; 95% CI, 1.0–2.2; $P = .083$), previous arterial aneurysm repair (n = 92; 95% CI, 0.9–2.9; $P = .086$), and previous neck irradiation (n = 27; 95% CI, 90-1.3; $P = .089$).

Risk index model

The resulting weighted point system is included in Table V. The range of possible points was from 0 to 27, with an associated range in risk from 2.7% to 78.3%. High-risk CEA was defined as >25.2%, this is the rate of stroke or death as described in the North American Symptomatic Carotid Endarterectomy Trial for medically managed symptomatic patients with moderate stenosis.[3] This correlates to >13 points (Table VI). A naïve bootstrap analysis was then created for each parameter and the 95% CI for kurtosis. The parameters of the sample are within the values estimated by our bootstrapping analysis, suggesting our sample is representative (at least to a similar population as that sampled by the VSGNE data set; Table V).

DISCUSSION

CEA is an effective and durable procedure for stroke prevention in symptomatic and asymptomatic patients previously validated by several reported clinical trials.[3–8] With CAS

emerging as an alternative to open surgery, there is a need to more accurately define the "high-risk" patient population. The SAPPHIRE trial was used as comparison for being one of the first large-scale trials to define what constituted high-risk with a set of subjectively chosen variables. Their definition is currently used by the Centers for Medicare & Medicaid Services and the U.S. Department of Health and Human Services to create the Medicare National Coverage Determinations.[1,4,9,10] However, our results show the SAPPHIRE comorbidities do not necessarily correlate with an adverse outcome after CEA. The four SAPPHIRE risk factors we found were not independently predictive of high-risk CEA: CAD, abnormal stress test result, previous neck irradiation, and recurrent stenosis. Also, the SAPPHIRE definition of high-risk—age >80 years and contralateral ICA occlusion—were not found to be sensitive; instead, age >71 years and contralateral stenosis >50% were optimal thresholds. Our study revealed two novel variables not included in the SAPPHIRE definition of high-risk patients: living in a nursing home preadmission and DM. The only two SAPPHIRE variables associated with high-risk were a history of CHF and COPD.

Because this study was a retrospective review of a large-scale, self-reported database, we did find some differences amongst the studied populations. The proportion of patients with CAD, CHF, previous CEA, contralateral stenosis, recurrent stenosis, asymptomatic status, and smoking history was significantly greater than in the SAPPHIRE study. The primary end points of both studies, however, were comparable. Our population had a lower rate of stroke (3.8% vs 7.7%; $P = .032$) and MI (2.6% vs 8.1%) compared with the SAPPHIRE trial, which could possibly be explained by the increased proportion of patients who had cardiovascular comorbidities in SAPPHIRE. The rate of MI among our population, conversely, was comparable to that reported by Press et al,[9] who found the postprocedure rate of MI of 1.2% for all patients undergoing CEA as well as the 2.3% rate reported by the recent Carotid Revascularization Endarterectomy Versus Stenting Trial.[40]

Several studies evaluated the medical and anatomic high-risk characteristics outlined by Centers for Medicare & Medicaid Services vs matched non-high-risk patients undergoing CEA.[11–14] In a study published by Kang et al[13] using the National Quality Improvement Program Database, the authors looked at CEA in high-risk patients as defined by the SAPPHIRE criteria vs non-high-risk patients and found no difference in the 30-day stroke/death rate (2.5% vs 2.0%; $P = .371$). They then evaluated 27 preoperative variables, including the defined high-risk variables, and found many SAPPHIRE variables were not significantly associated with their outcome after multivariate analysis. Similar to our study, functional status was a significant marker of increased postoperative death (odds ratio, 7.05; $P < .0001$).[13] One of the disadvantages of the Kang et al study[13] was that postoperative MI was not analyzed, potentially making their definition of high-risk incomplete. In addition, many vascular specific variables were unavailable in their database.

Flanigan et al[15] also questioned the validity of the SAPPHIRE "high-risk" definition. Their study compared 207 "high-risk" patients with 235 standard-risk patients, evaluating 30-day outcomes and long-term outcomes.[15] Results showed no difference between the groups for all strokes, death, MI, all strokes or death, or all stroke or death or MI, both in the perioperative period and during follow-up.[15] Another retrospective review performed between 1998 and 2002 at the Mayo Clinic examined high-risk and low-risk patients and

found no difference in perioperative stroke/death rates (2.5% vs 1.1%).[16] These results support our analysis, leading to questioning the validity of "high-risk" proposed by the SAPPHIRE trial.

One of the new high-risk characteristics that emerged was living in a nursing home preadmission, a surrogate for poor functional status. Age also was a significant indicator of postoperative risk, instead of age >80 years; however, age >71 years was more closely associated with the primary end points. Researchers have raised the question of the safety of CEA in the elderly and frail population for many years.[17–19] A subgroup analysis of patients from the Asymptomatic Carotid Surgery Trial failed to find a stroke risk-reduction benefit in patients aged ≥80 years and suggested that CEA only be performed in asymptomatic patients with a life expectancy of at least 5 years.[20]

However, findings in several other studies that evaluated octogenarians vs younger patients suggest an increased risk with CEA in younger patients. One hypothesis is that young patients with critical carotid disease may represent a population with premature atherosclerosis, labile plaques, or undiagnosed hypercoagulable disorders that place them at higher-risk for complications.[14,16,21] Another report using North American Symptomatic Carotid Endarterectomy Trial data demonstrated that patients aged ≥75 years with 50% to 99% symptomatic carotid stenosis demonstrated greater benefit from CEA than younger patients.[21] Conversely, a meta-analysis of randomized controlled trials and registries completed by Bond et al[22] showed that age had a small effect on the risk of complications after CEA. The question of the relationship between age and poor postoperative outcomes after CEA remains unanswered. Evidence strongly suggests that risks among octogenarians for poor outcomes are much higher for those undergoing CAS.[23–26] Hobson et al[26] reported that octogenarians undergoing stenting had a 30-day stroke or death rate of 12.1%, and in the Carotid ACCULINK/ACCUNET Post- Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) trial, they reported a 30-day stroke, death or MI rate of 17.1%.[27] The higher complication rate may be attributed to unfavorable anatomy, such as tortuous and severely calcified vessels, increasing risk for embolization during stent placement.[28,29]

It is important to highlight that a challenge of this study is that the projected life expectancy of octogenarians and nursing home patients is unknown and cannot be factored into the analysis, and little delineation has been made between patients aged >80 years (noting there is often a large difference in life expectancy between patients who are 80 vs 89). Despite this, the data do support the accepted conclusion that the beneficial effects of CEA are limited in those with a decreased life expectancy (such as in the frail/elderly) and may make them high-risk surgical candidates. In addition, even as high-risk candidates, the alternative, CAS, may not yield better outcomes.

DM was the second novel high-risk factor found. The literature is, unfortunately, not clear on the potential increased risk in patients with DM undergoing carotid surgery. Axelrod et al[30] and other investigators found DM was an independent risk factor for a poor outcome after any major vascular surgery, and patients with DM had a significantly higher incidence of death or cardiovascular complications after CEA (3.5% vs 2.5%; $P = .023$). Ballotta et al,[31] specifically looking at carotid disease, evaluated 547 CEAs and found patients with

DM had a significantly higher incidence of cardiac-related complications ($P = .01$). An earlier study by Ahari et al[32] also found patients with DM had a higher 30-day mortality rate of 3.2% vs 1.4% ($P = .02$) as well as a 1-year mortality rate of 7.9% vs 4.4% ($P = .008$) compared with patients without DM. Skydell et al[33] and Salenius et al[34] found that patients with DM had increased neurologic complications after CEA compared with their nondiabetic counterparts. Salenius et al[34] evaluated 331 patients who underwent CEA. Patients with DM had a 20% postoperative stroke rate compared with 8.2% in nondiabetic patients. Tu et al[41] also found that DM was a significant independent predictor for 30-day death or stroke after CEA (odds ratio, 1.28; 95% CI. 1.01–1.63). Skydell et al,[33] however, evaluated patients who presented with post-CEA hypertensive crisis and found a significant correlation with the presence of DM, most likely due to the known negative effects that DM has on cerebrovascular autoregulation.[17]

In contrast, a few studies have disputed that DM may be an independent risk factor for poor outcomes after CEA.[14,35,36,42] Hamdan et al[43] analyzed 6565 major vascular operations and found that DM alone did not confer a higher rate of cardiac morbidity or mortality, even though long-term survival among patients with DM was reduced. Akbari et al[12] reported 732 CEAs, 284 in patients with DM, and found there was no significant difference in perioperative stroke or mortality. Similarly, Pistolese et al[35] reviewed 781 CEAs, 193 in patients with DM, and also found no significant difference in perioperative stroke MI, mortality, or long-term survival. Our current study supports DM as a marker of patients who are at high risk for postoperative complications; however, this may need review in the future with a prospective trial.

The SAPPHIRE variables that we found were still significant predictors of the primary end points are CHF and COPD. CAD and previous abnormal stress test result were not significant in our analysis, and in the literature, there is controversy about their inclusion or exclusion as high-risk variables. Because of the differences in definition of postoperative MI (SAPPHIRE, MI at 30 days; VSGNE, MI during hospitalization), some MIs could have been missed in the VSGNE data set that could possibly have validated the definition of high-risk, which included these cardiac variables, from the SAPPHIRE trial. However, in many other studies, the proportion of patients with severe cardiac comorbidities seems to be much smaller then that represented by the SAPPHIRE data, indicating patients may be receiving better medical optimization before surgery. Further investigation will be needed to determine their true effect on postoperative events.

Another variable defined as high-risk by SAPPHIRE criteria is CCO. Our results found that contralateral disease with >50% stenosis was a more precise threshold, potentially refining the high-risk category. Many recent studies have challenged the assumption that CEA is unsafe in the presence of a CCO; however, there is much controversy in the literature.[15,16,24,30,37–40] Unfortunately, few studies have specifically looked at the degree of contralateral stenosis vs a CCO to determine a difference in outcomes. Gasecki et al examined patients with severe carotid stenosis who had a recent ischemic event and reviewed whether outcomes were altered by the degree of contralateral stenosis or occlusion.[40] They looked at 659 patients and grouped them into contralateral stenosis <70%, contralateral stenosis of 70% to 90%, or CCO. Results showed perioperative stroke and

death rate were higher in patients with a CCO (14.3% risk) compared with severe (4.0% risk) or mild-to-moderate contralateral stenosis (5.1% risk). The Gasecki et al results are limited by only including patients with previous symptoms and high-grade ipsilateral stenosis and thus not adequately representing all-comers for CEA. Future studies are still needed to evaluate the true effect of contralateral carotid disease.

With the variability of what defines a patient as “high-risk,” we believe this label should be based on the accumulation of unfavorable preoperative variables instead of just one. We developed a risk index model including the variables that we found were independently significant in our initial analysis. The weighted point system can be used to calculate the overall risk for every patient. For example, a 71-year-old man living in a nursing home with history of CHF would have 15 points (Table IV). This correlates with a risk of an adverse event with open surgery of 29.4% and puts this patient in the high-risk category compared with optimal medical management alone. Using a risk index model when approaching patient selection could give physicians a more accurate way of predicting postoperative complications.

Reed et al[14] also investigated an additive risk analysis for patients undergoing CEA. They looked at outcomes in patients with multiple risk factors and found that in 1370 patients evaluated, 30-day mortality was significantly greater in patients with two or more risk factors and that 5-year survival for patients with two or more risk factors was also notably diminished.[14] The Reed study did not address whether all risk factors conferred equal risk.

With the index developed in this study, not only can the effect of additive risk be calculated but also the weighted effects of the statistically significant variables. To fully appreciate the use of this type of risk index, further studies will need to be done to validate it based on another large data set or on a prospectively collected sample. Potentially, however, this or another similar index could be used on all patients with carotid disease preoperatively to aid in decision making and to predict risk of adverse events with open surgery qualifying them as normal-risk or high-risk candidates.

The strengths of this study include that it is a large, multicenter study using prospectively collected data of current practice. A large number of preoperative variables were collected to allow for discovery of any novel high-risk variables previously overlooked. The primary outcome was extended beyond the perioperative period to include 1 year of follow-up. Also, through rigorous statistical analysis we attempted to eliminate any covariance in our data that might have affected outcomes.

Limitations to this study relate to the study design and data collection. The SAPPHIRE outcomes could not be exactly matched with the VSGNE collected data. The SAPPHIRE trial used 30-day MI, whereas we had to use MI during hospitalization. An additional limitation was lack of compatibility with the SAPPHIRE inclusion criteria and missing 1-year outcome data in 4506 patients in the VSGNE registry for unknown reasons (patient related vs center related). In the original SAPPHIRE trial of the 167 patients assigned to surgery, only 151 underwent treatment and all were followed up at 1 year. Another limitation was the amount of missing data in the database requiring exclusion of certain variables

(dialysis, American Society of Anesthesiologists class, hemoglobin concentration, and positive stress test result) from further analysis, which could have affected the results. A type I error is always possible and is more likely in this study due to the amount of variables analyzed for association with the primary outcome. Stroke, prognosis, life expectancy, operative risk, and functional status are different between the two studies, and applying a single algorithm to define perioperative risk could lead to misleading results. It is important to evaluate each patient individually when determining treatment options.

CONCLUSIONS

The SAPPHIRE trial high-risk CEA definition is only partially valid. We propose a new, evidence-based definition of high-risk CEA that includes (1) age, (2) preadmission nursing home, (3) CHF, (4) COPD, (5) DM, (6) any previous cerebrovascular accident, and (7) degree of contralateral ICA stenosis. The CEA risk index model may assist clinicians in patient counseling and surgical selection. Future studies should aim to evaluate the usefulness of a risk index model in patient selection criteria. Future studies should also examine whether this newly defined high-risk patient would benefit from CAS vs CEA, because the previously identified noninferiority of CAS found in the SAPPHIRE trial in high-risk patients, as the previous definition, was not statistically validated.

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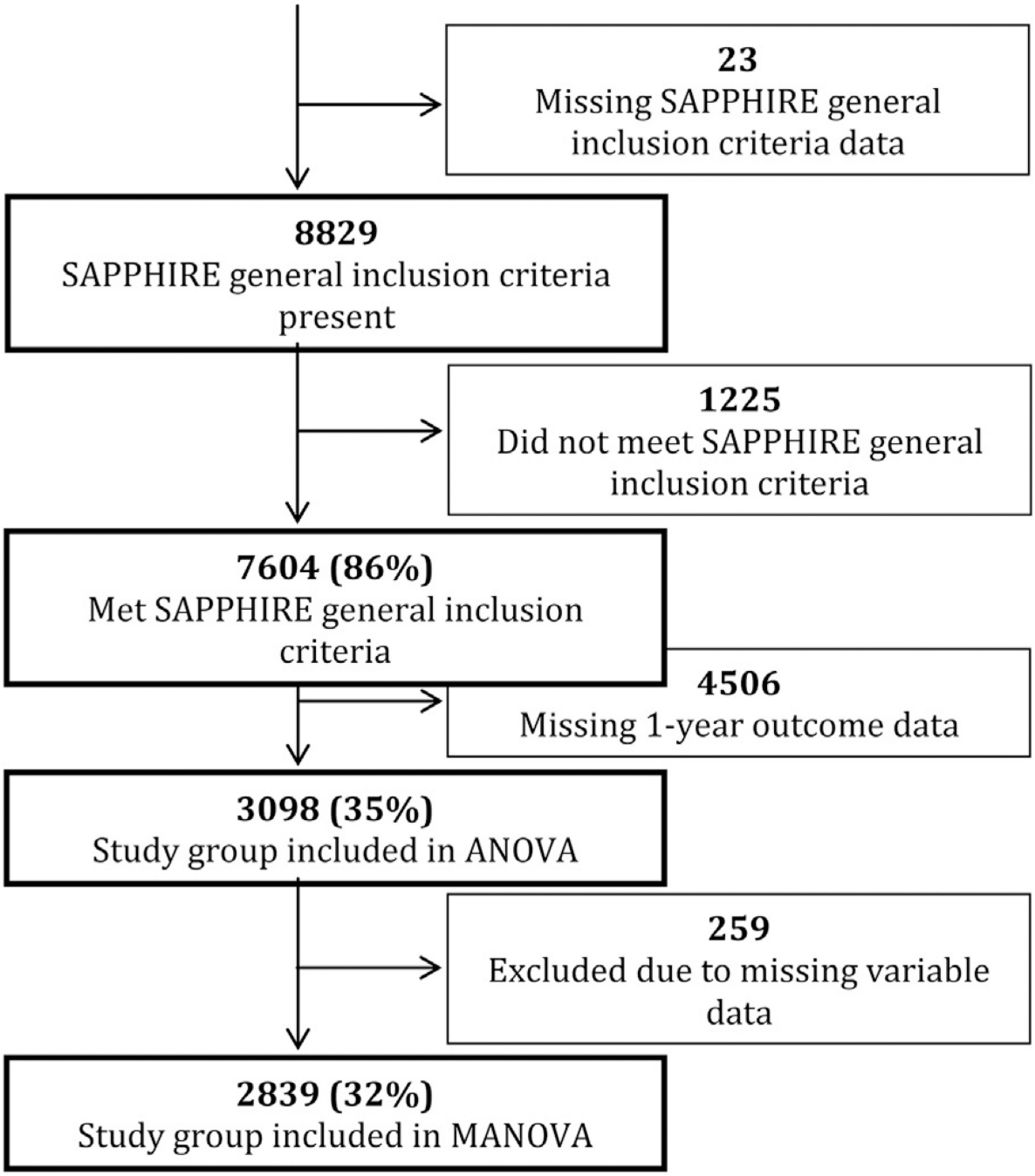

Fig.

Defining the study group. *ANOVA*, Analysis of variance; *MANOVA*, multivariate analysis of variance; *SAPPHIRE*, Stenting with Angioplasty and Protection in Patients at High Risk for Endarterectomy.

Table I

Comparing characteristics of patients in the Stenting with Angioplasty and Protection in Patients at High Risk for Endarterectomy (*SAPPHIRE*) trial and Vascular Study Group of New England (*VSGNE*) database

Characteristic	SAPPHIRE CEA (n = 167)	VSGNE (n = 3098)	*P* value
Age, mean ± SD, years	72.6 ± 8.9	69.9 ± 9.5	<.01[a]
Age >80 years, %	20.5	13.2	<.01[a]
Male sex, %	67.1	60.3	.08
DM, %	27.5	31.5	.28
History of hypertension, %	85.1	87.6	.33
Current smoking, %	16.4	28.9	<.01[a]
CAD, %	75.5	34.5	<.01[a]
Previous PTA, %	23.4	NA	NA
Previous CABG, %	30.8	NA	NA
Previous CABG or PTCA, %	NA	31.2	NA
CHF, %	19.6	8.4	<.01[a]
Renal insufficiency, %	7.5	5.8[b]	.28
COPD, %	13.8	23.4	<.01[a]
History of transient ischemic attack, %	34	36.6	.52
History of stroke, %	23.8	18.9	.11
Symptomatic stenosis, %	27.7	54.3[c]	<.01[a]
Asymptomatic stenosis >80%, %	72.3	45.7	<.01[a]
CCO, %	25.3	6.6	<.01[a]
Previous CEA, %	26.7	13.8	<.01[a]
Recurrent stenosis after CEA, %	22.2	4.1[d]	<.01[a]

CABG, Coronary artery bypass grafting; *CAD*, coronary artery disease; *CCO*, contralateral carotid occlusion; *CEA*, carotid endarterectomy; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *NA*, no available data; *PTA*, percutaneous transluminal angioplasty; *PTCA*, percutaneous transluminal coronary angioplasty; *SD*, standard deviation.

[a] Significant difference ($P < .05$).

[b] Defined as creatinine >1.78 mg/dL.

[c] Defined as >50% carotid stenosis and any neurologic event or evidence of an ipsilateral stroke by computed tomography or magnetic resonance imaging.

[d] History of CEA with recurrence of at least 50% ipsilateral stenosis.

Table II

Cumulative incidence of adverse events ≤1 year[a]

Event	SAPPHIRE CEA[b] (n = 151), No. (%)	VSGNE (n = 3098), No. (%)	*P* value
Death			.16
Stroke	11 (7.7)	118 (3.8)	.03[c]
Major ipsilateral	5 (3.5)	41 (1.3)	.04[c]
Major nonipsilateral	1 (0.7)	13 (0.4)	.66
Minor ipsilateral	3 (2.2)	54 (1.7)	.82
Minor nonipsilateral	3 (2.1)	19 (0.6)	.04[c]
MI	12 (8.1)	80 (2.6)[d]	<.01[c]
Q wave	2 (1.3)	NA	NA
Non-Q wave	10 (6.7)	NA	NA
Cranial-nerve palsy	8 (5.3)	193 (6.2)	.64
Carotid artery reintervention	6 (4.6)	9 (0.3)	<.01[c]
Conventional end point[e]	11 (7.5)	380 (12.3)	.07
Primary end point[f]	30 (20.1)	440 (14.2)	.05

MI, Myocardial infarction; *NA*, for no available data; *SAPPHIRE*, Stenting with Angioplasty and Protection in Patients at High Risk for Endarterectomy; *VSGNE*, Vascular Study Group of New England.

[a] Patients may have had more than one event.

[b] Outcomes for actual treatment analysis.

[c] Significant difference ($P < .05$).

[d] Perioperative MI only for VSGNE.

[e] Stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year.

[f] Death, stroke, or MI (perioperative MI only for VSGNE) at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 year.

Table III

Univariate correlates predictive of the Stenting with Angioplasty and Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) primary outcome of myocardial infarction (MI), stroke, or death[a]

Variable	95% CI	*P* value
Age (1 year)	1.024–1.047	<.001
Gender	0.996–1.498	.054
BMI (kg/m^2)	0.959–0.996	.017
Preadmission nursing home	1.965–8.588	<.001
CAD	1.118–1.414	<.001
CHF	2.439–4.298	<.001
Hypertension	1.083–2.171	.016
Diabetes	1.102–1.321	<.001
COPD	1.260–1.590	<.001
Cerebrovascular disease	1.247–1.890	<.001
Previous bypass	1.477–2.951	<.001
Previous aneurism repair	1.192–3.176	.008
Previous PTA stent	1.304–2.680	.001
Previous major amputation	1.643–7.942	.001
Previous radiation	0.024–1.287	.087
>30 days use β-blocker	1.015–1.534	.036
Plavix[b]	1.141–1.900	.003
Aspirin	0.537–0.926	.012
>80% ipsilateral stenosis	0.572–0.948	.018
Contralateral ICA stenosis (10%)	1.051–1.168	<.001
Creatinine (0.1 mg/dL)	1.180–1.785	<.001

BMI, Body mass index; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ICA*, internal carotid artery; *PTA*, percutaneous transluminal angioplasty.

[a]Variables with statistical significance of $P < .10$.

[b]Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ.

Table IV

Multivariate correlates of the primary outcome of myocardial infarction (MI), stroke, or death[a]

Variable	95% CI	*P* value
Age in years	1.0–1.1	<.001
Preadmission nursing home	1.2–6.6	.02
CHF	1.4–2.8	<.001
DM	1.1–1.3	<.001
COPD	1.2–1.5	<.001
Any previous cerebrovascular disease	1.1–1.9	.003
Contralateral ICA stenosis (10%)	1.0–1.2	.001

CHF, Congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ICA*, internal carotid artery.

[a]Variables with statistical significance of $P < .05$.

Table V

Risk index system

Risk factor	Categories	Points	Bootstrap analysis
Age	40–49	0	−0.50 to −0.29 (−0.40)
	50–59	2	
	60–69	4	
	70–79	6	
	80–89	8	
Nursing home	No	0	76.3 to 183 (106)
	Yes	4	
CVD	No	0	−1.68 to −1.47 (−1.59)
	Yes	2	
CHF	No	0	5.77 to 8.51 (6.94)
	Yes	5	
DM	No	0	−1.48 to −1.22 (1.36)
	Yes	2	
COPD	No	0	−0.69 to −0.17 (−0.44)
	Yes	3	
Degree of contralateral ICA stenosis	<50%	0	−0.47 to −0.11 (−0.30)
	50%–69%	1	
	70%-near occlusion	2	
	Occluded	3	

CHF, Congestive heart failure; *CVD*, cardiovascular disease; *COPD*, chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *ICA*, internal carotid artery.

Table VI

Estimate of risk associated with risk index model

Point total	Estimate of risk, %	Point total	Estimate of risk, %
0	2.7	14	25.8
1	3.2	15	29.4
2	3.9	16	33.3
3	4.6	17	37.4
4	5.4	18	41.7
5	6.4	19	46.1
6	7.6	20	50.6
7	9.0	21	55.1
8	10.6	22	59.5
9	12.4	23	63.7
10	14.5	24	67.8
11	16.9	25	71.6
12	19.5	26	75.1
13	22.5	27	78.3