The impact of Centers for Medicare and Medicaid Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry

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Objective: **The Centers for Medicare and Medicaid Services (CMS) require high-risk (HR) criteria for carotid artery stenting (CAS) reimbursement. The impact of these criteria on outcomes after carotid endarterectomy (CEA) and CAS remains uncertain. Additionally, if these HR criteria are associated with more adverse events after CAS, then existing comparative effectiveness analysis of CEA vs CAS may be biased. We sought to elucidate this using data from the SVS Vascular Registry.**
Methods: **We analyzed 10,107 patients undergoing CEA (6370) and CAS (3737), stratified by CMS HR criteria. The primary endpoint was composite death, stroke, and myocardial infarction (MI) (major adverse cardiovascular event [MACE]) at 30 days. We compared baseline characteristics and outcomes using univariate and multivariable analyses.**
Results: **CAS patients were more likely to have preoperative stroke (26% vs 21%) or transient ischemic attack (23% vs 19%) than CEA. Although age ≥80 years was similar, CAS patients were more likely to have all other HR criteria. For CEA, HR patients had higher MACEs than normal risk in both symptomatic (7.3% vs 4.6%; $P < .01$) and asymptomatic patients (5% vs 2.2%; $P < .0001$). For CAS, HR status was not associated with a significant increase in MACE for symptomatic (9.1% vs 6.2%; $P = .24$) or asymptomatic patients (5.4% vs 4.2%; $P = .61$). All CAS patients had MACE rates similar to HR CEA. After multivariable risk adjustment, CAS had higher rates than CEA for MACE (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.0-1.5), death (OR, 1.5; 95% CI, 1.0-2.2), and stroke (OR, 1.3; 95% CI,1.0-1.7), whereas there was no difference in MI (OR, 0.8; 95% CI, 0.6-1.3). Among CEA patients, age ≥80 (OR, 1.4; 95% CI, 1.02-1.8), congestive heart failure (OR, 1.7; 95% CI, 1.03-2.8), EF <30% (OR, 3.5; 95% CI, 1.6-7.7), angina (OR, 3.9; 95% CI, 1.6-9.9), contralateral occlusion (OR, 3.2; 95% CI, 2.1-4.7), and high anatomic lesion (OR, 2.7; 95% CI, 1.33-5.6) predicted MACE. Among CAS patients, recent MI (OR, 3.2; 95% CI, 1.5-7.0) was predictive, and radiation (OR, 0.6; 95% CI, 0.4-0.8) and restenosis (OR, 0.5; 95% CI, 0.3-0.96) were protective for MACE.**
Conclusions: **Although CMS HR criteria can successfully discriminate a group of patients at HR for adverse events after CEA, certain CMS HR criteria are more important than others. However, CEA appears safer for the majority of patients with carotid disease. Among patients undergoing CAS, non-HR status may be limited to restenosis and radiation. (J Vasc Surg 2013;57:1318-24.)**

Over the last 2 decades, carotid artery stenting (CAS) has emerged as an alternative to carotid endarterectomy (CEA) to reduce the risk of stroke in patients with severe carotid artery stenosis. Meanwhile, subsequent trials have shown conflicting results with failure to meet noninferiority between the two revascularization procedures in average-risk patients.[1-4] The Centers for Medicare and Medicaid Services (CMS) have approved reimbursement for CAS in patients who are at "high risk" for CEA with symptomatic ≥70% stenosis unless enrolled in a clinical trial.[5] High-risk (HR) criteria include several medical and anatomic conditions; criteria that many presume are associated with increased operative risk.

As a result of these HR criteria proposed by CMS, there may be over representation of HR and/or symptomatic patients selected for CAS, which may introduce bias into the comparisons of CAS and CEA. Additionally, there is no clear evidence suggesting that the risk with CAS is lower in these HR patients compared with CEA. The HR criteria used by CMS were developed years ago based on outcomes from a randomized trial including mainly asymptomatic patients[6] and several prospective (still ongoing at that time) CAS registries.[7-9] The validity of

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these HR criteria was called into question by several authors.[10-13] However, the results of these studies cannot be justified because they are limited by low numbers of patients or the inability to adequately stratify patients into HR groups using only administrative data.

The Vascular Registry (VR) is the largest published database of CAS in the United States, designed to capture real-world practices. It, therefore, allows stratification of patients undergoing CAS or CEA by symptom status as well as the predefined HR criteria of CMS. In this study, we aimed to assess the validity and the impact of these HR criteria on 30-day outcomes following CAS and CEA and to identify patient factors associated with increased procedural risk.

METHODS

VR data are reported by providers through web-based electronic data capture. The measurement schedule includes baseline (preoperative) demographics, medical history, carotid symptom status, preprocedural diagnostic imaging and laboratory studies, procedural (CAS or CEA) information including clinical utility, intraoperative and predischarge complications, and follow-up information such as postoperative mortality, stroke, myocardial infarction (MI), and other morbidity. Specifically, the VR includes all individual HR criteria outlined by CMS. The VR does not use inclusion or exclusion criteria for patient eligibility and is reliant on site entry of patients in whom CAS or CEA is performed. All data entered into the VR are fully compliant with the Health Insurance Portability and Accountability Act regulations and are auditable. All data reports and analyses performed include only de-identified and aggregated data. New England Research Institutes, Inc (Watertown, Mass) maintains the online database and funding for the administration and database management of the VR has been provided by the Society for Vascular Surgery.

Outcomes. The primary endpoint was a major adverse cardiovascular event (MACE) diagnosed within 30 days of treatment, defined as a composite of death, stroke, and MI. Secondary outcomes were combined stroke and death, death, stroke, and MI at 30 days following CAS and CEA. Stroke is defined as any nonconvulsive, focal neurologic deficit of abrupt onset persisting more than 24 hours. The ischemic event must correspond to a vascular territory. An MI is classified as either Q wave MI in which one of the following criteria is required: (1) chest pain or other acute symptoms consistent with myocardial ischemia and new pathologic Q waves in two or more contiguous electrocardiogram leads, or (2) new pathologic Q waves in two or more contiguous electrocardiogram leads and elevation of cardiac enzymes; or non-Q wave MI, defined as CK ratio >2, and CK-MB >1 in the absence of new, pathologic Q waves. Analysis of 30-day outcomes was based on only those patients who had at least a 30-day post-procedure visit or who experienced a MACE within 30 days of treatment.

Table I. Demographics and clinical characteristics of 10,107 patients undergoing CEA or CAS in SVS VR

	CEA (n = 6370)	*CAS (n = 3737)*	P *value*
Age, years, mean (range)	70.9 (18-96)	70.9 (34-98)	.98
Sex (male)	58.6%	60.4%	.08
White - Caucasian	92.8%	91.9%	.13
Symptom status	38.0%	41.0%	<.01
Preoperative symptoms			
Stroke	21.0%	25.5%	<.001
TIA	19.1%	23.1%	<.001
TMB	5.4%	7.4%	<.001
Etiology of lesion			<.001
Atherosclerosis	98.2%	68.5%	
Radiation	0.1%	5.2%	
Restenosis	1.3%	24.0%	
Diabetes	31.4%	34.0%	<.01
Hypertension	84.3%	83.0%	.08
Current or past smoker	60.8%	61.3%	.65
Coronary artery disease	48.1%	57.8%	<.001
Myocardial infarction	16.3%	22.0%	<.001
Valvular heart disease	7.9%	6.0%	<.001
Cardiac arrhythmia	12.9%	14.4%	.03
Congestive heart failure	7.8%	14.1%	<.001
COPD	17.7%	20.3%	<.01
Chronic renal failure	3.4%	3.8%	.28
Peripheral vascular disease	43.7%	37.2%	<.001
GI ulcer/bleeding	3.0%	4.8%	<.001
Cancer	13.0%	19.8%	<.001
Coagulopathy	1.4%	1.1%	.20
NYHA scale			
Class I or II	95.4%	89.1%	<.001
Class III or IV	4.6%	10.9%	

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *COPD,* chronic obstructive pulmonary disease; *GI,* gastrointestinal; *NYHA,* New York Heart Association; *SVS,* Society for Vascular Surgery; *TIA,* transient ischemic attack; *TMB,* transient monocular blindness; *VR,* Vascular Registry.

Statistical methods. Tests of statistical significance were conducted with χ^2 or Fisher exact tests for categorical variables and two-tailed *t*-test for continuous variable age. Descriptive statistics are listed as percent (frequency) for categorical variables and mean (range) for continuous variable age. Subset analyses were performed using the χ^2 or Fisher exact test, as necessary, for discrete/categorical data. The event rates are calculated per-patient. Unadjusted and adjusted ORs were used to compare the primary outcomes across treatment groups. ORs were adjusted for symptomatic status and HR status in the overall comparison of CEA and CAS. Differences were considered significant if $P < .05$. All statistical analyses were performed by New England Research Institutes, Inc using SAS Statistical Software (SAS Institute, Cary, NC).

RESULTS

Data collected in the VR from November 2001 to September 2011 from 81 institutions (community-based, university-based, private practice, and nonuniversity teaching hospitals) were analyzed; 10,107 patients who underwent CEA (n = 6370; 37.5% symptomatic) and CAS

Table II. CMS qualifying HR factors

	CEA (n = 6370)	*CAS (n = 3737)*	P *value*
Age ≥80 years	19.3%	20.7%	.10
NYHA CHF class III/IV	3.5%	10.4%	<.001
LVEF <30%	0.9%	4.1%	<.001
Unstable angina	0.6%	3.6%	<.001
Recent MI (within 30 days)	0.5%	1.2%	<.001
Restenosis	2.5%	29.5%	<.001
Radical neck dissection	0.1%	4.0%	<.001
Contralateral occlusion	4.3%	13.4%	<.001
Prior radiation to neck	0.3%	8.4%	<.001
Contralateral laryngeal nerve injury	0.1%	0.9%	<.001
High anatomic lesion	1.2%	9.4%	<.001
At least one HR factor	37.0%	90.5%	<.001

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *CHF,* congestive heart failure; *CMS,* Centers for Medicare and Medicaid Services; *HR,* high risk; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NYHA,* New York Heart Association.

(n = 3737; 45.5% symptomatic) with data on 30-day outcomes were identified. The majority of the procedures (71% CAS; 93% CEA) were performed by vascular surgeons. Baseline demographics, patient characteristics, CMS HR status, and individual HR factors are presented in Tables I and II. Mean age was 71 years, and approximately 59% were male and 92% were white. CAS patients were more likely to have a preoperative stroke (25.5% vs 21.0% CEA; $P \leq .001$) or transient ischemic attack (23.1% vs 19.1% CEA; $P \leq .001$) compared with CEA patients. CAS patients also had a significantly higher prevalence of cardiac comorbidities (coronary artery disease [57.8% vs 48.1%], MI [22% vs 16.3%], chronic heart failure [14.1% vs 7.8%]), and nonatherosclerotic disease (recurrent or radiation-induced stenosis [31.5% vs 1.8%]). All individual CMS qualifying HR factors were more prevalent in CAS patients, except for age ≥80 (19.3% CAS vs 20.7% CEA; P = NS). Only 37% of CEA patients met any of the HR factors compared with 90.5% of CAS patients (P <.001).

CEA outcomes. In symptomatic patients, the 30-day rate of MACE was 7.3% in HR patients vs 4.6% ($P = .008$) in non-HR patients. Combined stroke/death and death rates were significantly higher in HR patients compared with non-HR patients (6.4% vs 3.9%; $P = .006$; and 1.8% vs 0.6%; $P = .008$, respectively). Stroke alone did not show significant differences between HR and non-HR symptomatic patients (4.9% vs 3.5%; $P = .09$). The rate of MI was similar between HR and non-HR patients (1.4% vs 1.1%; $P = .57$) (Table III). In asymptomatic patients, the 30-day rate of MACE was 5.0% in HR patients vs 2.2% in non-HR patients ($P < .001$). Combined stroke/death, death, and stroke rates were all significantly higher in HR patients compared with non-HR patients. There was no difference in the rate of MI between HR and non-HR asymptomatic patients (1.6% vs 1.1%; $P = .30$) (Table IV).

In univariate analysis, patients with contralateral occlusion had significantly higher risks of MACE (symptomatic, 16.1%; asymptomatic, 8.8%), stroke/death (symptomatic, 16.1%; asymptomatic, 7.2%), death (symptomatic and asymptomatic 2.2%), and stroke (symptomatic, 15.1%; asymptomatic, 5.0%) compared with patients without contralateral occlusion. A multivariable model showed that symptomatic status, age ≥80, CHF class III/IV, left ventricular ejection fraction <30%, angina, contralateral occlusion and high anatomic lesion were independent predictors for MACE (Table V). The same factors were identified as predictors for stroke/death with the exception of age ≥80. CHF, angina, restenosis, and contralateral occlusion were risk factors for death. For stroke alone,

Table III. Thirty-day event rates for symptomatic patients undergoing CEA and CAS stratified by risk group

	CEA patients		
	HR (n = 936)	*Non-HR (n = 1470)*	P *value*
MACE	7.3%	4.6%	<.01
Stroke, death	6.4%	3.9%	<.01
Mortality	1.8%	0.6%	<.01
Stroke	4.9%	3.5%	.09
MI	1.4%	1.1%	.57
	CAS patients		
	HR (n = 1538)	*Non-HR (n = 162)*	P *value*
MACE	9.1%	6.2%	.25
Stroke, death	7.9%	4.9%	.21
Mortality	2.4%	1.9%	1.00
Stroke	6.7%	3.7%	.18
MI	1.4%	1.2%	1.00

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *HR,* high risk; *MACE,* major adverse cardiovascular events; *MI,* myocardial infarction.

Table IV. Thirty-day event rates for asymptomatic patients undergoing CEA and CAS stratified by risk group

	CEA patients		
	HR (n = 1418)	*Non-HR (n = 2546)*	P *value*
MACE	5.0%	2.2%	<.001
Stroke, death	3.7%	1.4%	<.001
Mortality	1.3%	0.5%	<.01
Stroke	2.7%	1.1%	<.001
MI	1.6%	1.1%	.30
	CAS patients		
	HR (n = 1844)	*Non-HR (n = 193)*	P *value*
MACE	5.4%	4.2%	.61
Stroke, death	4.8%	3.6%	.59
Mortality	1.7%	1.6%	1.00
Stroke	3.4%	2.6%	.68
MI	1.1%	1.0%	1.00

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *HR,* high risk; *MACE,* major adverse cardiovascular events; *MI,* myocardial infarction.

Table V. Predictors for 30-day outcomes of CEA

	MACE		*Stroke/death*		*Stroke*		*Death*		*MI*	
Risk factors	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Symptomatic	1.8	1.4-2.4	2.3	1.7-3.1	2.5	1.8-3.5	-	-	-	-
Age ≥80 years	1.4	1.0-1.8	-	-	-	-	-	-	-	-
CHF class (III/IV)	1.7	1.0-2.8	1.8	1.0-3.2	-	-	3.5	1.5-7.8	-	-
LVEF <30%	3.5	1.6-7.7	3.2	1.3-7.6	-	-	-	-	-	-
Angina	3.9	1.6-9.9	3.2	1.1-9.6	-	-	5.9	1.6-21.4	6.8	2.0-22.5
Contralateral occlusion	3.2	2.1-4.7	3.7	2.4-5.8	4.1	2.6-6.6	2.5	1.0-5.9	-	-
High anatomic lesion	2.7	1.3-5.6	3.0	1.4-6.5	3.4	1.5-7.6	-	-	-	-
Restenosis	-	-	-	-	-	-	3.6	1.4-9.3	-	-

CEA, Carotid endarterectomy; *CHF,* congestive heart failure; *CI,* confidence interval; *LVEF,* left ventricular ejection fraction; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *OR,* odds ratio.

Table VI. Predictors for 30-day outcomes of CAS

	MACE		*Stroke/death*		*Stroke*		*Death*		*MI*	
Risk factors	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Symptomatic	2.0	1.5-2.6	1.6	1.2-2.1	2.0	1.5-2.7	-	-	-	-
Age ≥80 years	-	-	-	-	1.5	1.1-2.1	-	-	2.1	1.1-3.8
Recent MI	3.2	1.5-7.0	4.0	2.0-8.3	-	-	8.0	3.4-18.9	-	-
Angina	-	-	-	-	-	-	2.4	1.1-5.6	-	-
Contralateral occlusion	-	-	-	-	-	-	1.9	1.1-3.4	-	-
Restenosis	0.6	0.4-0.8	0.6	0.5-0.9	-	-	-	-	-	-
Prior radiation to neck	0.5	0.3-0.9	0.5	0.3-0.9	-	-	-	-	-	-

CAS, Carotid artery stenting; *CI,* confidence interval; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *OR,* odds ratio.

symptomatic status, contralateral occlusion, and a high anatomic lesion were predictive. Angina was the only risk factor identified for MI.

CAS outcomes. In both symptomatic and asymptomatic CAS patients, no significant difference was detected in MACE between HR and non-HR patients (9.1% vs 6.2%; $P = .25$ symptomatic; 5.4% vs 4.2%; $P = .6$ asymptomatic) (Tables III and IV). Stroke/death, mortality, stroke, and MI rates were similar in both groups for both symptomatic and asymptomatic patients.

In a multivariable model, symptom status (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.3-2.2) and recent MI (OR, 3.4; 95% CI, 1.7-7.0) were independent predictors for MACE, whereas restenosis (MACE rate, 3.5%, OR, 0.6; 95% CI, 0.4-0.8) and previous cervical radiation therapy (MACE rate, 4.6%; OR, 0.4; 95% CI, 0.2-0.8) were protective (Table VI). The same predictors were identified for combined stroke/death. Angina (OR, 2.4; 95% CI, 1.1-5.6), previous MI (OR, 8.0; 95% CI, 3.4-18.9), and contralateral occlusion (OR, 1.9; 95% CI, 1.1-3.4) were risk factors for mortality. Independent predictors for stroke alone were symptom status and age ≥80 years. Age ≥80 was the only predictor for MI (OR, 2.1; 95% CI, 1.1-3.8).

Anatomic HR factors. In symptomatic patients with contralateral occlusion, the 30-day MACE rate was 16.1% after CEA and 9.3% after CAS ($P = .13$). In asymptomatic patients, MACE rates were 8.8% after CEA vs 6.9% after CAS ($P = .58$). Risk for MACE in patients with symptomatic restenosis was 7.9% after CEA vs 6.7% ($P = .79$) after CAS and 7.1% vs 3.5% ($P = .10$) in asymptomatic patients. Patients with prior neck radiation undergoing CAS (n = 315) had a MACE risk of 4.5% (symptomatic patients) and 2.5% (asymptomatic patients). Only 19 patients with prior neck irradiation had CEA without any adverse events. For patients with a high anatomic lesion (C2 or higher), symptomatic patients had a risk for MACE of 11.9% after CEA vs 13.2% after CAS ($P = 1.0$). In asymptomatic patients, the MACE rate was 12.2% after CEA vs 4.52% after CAS ($P = .13$).

CAS vs CEA outcome. No significant differences in MACE were identified between CAS and CEA within the strata of the non-HR and HR groups. Symptomatic HR patients had 9.1% MACE risk following CAS vs 7.3% after CEA (OR, 1.3; 95% CI, 0.95-1.73; $P = .11$). MACE risk in asymptomatic HR patients was 5.4% after CAS vs 5.0% after CEA (OR, 1.1; 95% CI, 0.79-1.47; $P = .65$). In the non-HR group, symptomatic patients undergoing CAS had a MACE risk of 6.2% vs 4.6% in patients undergoing CEA (OR, 1.4; 95% CI, 0.69-2.69; $P = .38$). For asymptomatic non-HR patients, the MACE risk was 4.2% after CAS vs 2.2% after CEA (OR, 1.92; 95% CI, 0.90-4.09; $P = .09$). In unadjusted models assessing outcome across treatment groups, CAS patients had higher ORs for MACE (OR, 1.7; 95% CI, 1.4-2.0), combined stroke and death (OR, 1.9; 95% CI, 1.6-2.3), mortality (OR, 2.3; 95%

Table VII. Thirty-day outcome of CAS vs CEA, unadjusted and adjusted for HR and symptomatic patients

	Unadjusted CAS vs CEA			*Adjusted CAS vs CEA*		
	OR	*95% CI*	P *value*	*OR*	*95% CI*	P *value*
MACE	1.7	1.4-2.0	<.001	1.2	1.0-1.5	.04
Stroke, death	1.9	1.6-2.3	<.001	1.3	1.1-1.7	.01
Death	2.3	1.6-3.2	<.001	1.5	1.0-2.2	.04
Stroke	1.9	1.5-2.4	<.001	1.4	1.1-1.7	.02
MI	0.9	0.7-1.4	.91	0.9	0.6-1.3	.46

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *HR,* high risk; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *OR,* odds ratio.

CI, 1.6-3.2,) and stroke (OR, 1.9; 95% CI, 1.5-2.4) but not for MI (OR, 0.9; 95% CI, 0.7-1.4). After adjusting for symptom and HR status, CAS patients had still higher ORs for MACE (OR, 1.2; 95% CI, 1.0-1.5), mortality (OR, 1.5; 95% CI, 1.0-2.2), and stroke (OR, 1.4; 95% CI, 1.0-1.7), whereas there was no difference in stroke/death and MI. (Table VII).

DISCUSSION

Patients with symptomatic or asymptomatic severe carotid stenosis and HR status have an increased risk for MACE following CEA compared with non-HR patients undergoing CEA. Of the CMS HR criteria, age ≥80, CHF, angina, contralateral occlusion, and high anatomic lesion predict MACE after CEA. For CAS, 30-day outcomes between HR and non-HR patients were similar. Prior MI predicted MACE after CAS, whereas previous radiation and restenosis proved to be protective conditions. By comparing CAS and CEA after adjusting for symptoms and HR status, CAS patients had significantly higher rates than CEA for MACE, combined stroke/death, mortality, and stroke, whereas there was no difference in MI.

Our results emphasize that some, but not all, CMS HR criteria identify patients at increased risk for MACE after CEA. However, these patients do not per se seem to benefit from CAS. CMS reimbursement for CAS covers HR symptomatic patients, as long as stenting is performed using FDA-approved systems with embolic-protection devices and at CMS-approved facilities. This policy was mainly based on favorable endovascular results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, designed to compare CAS vs CEA in an HR population.[6,14] The applicability of the results was however questioned by several others. In SAPPHIRE, the 30-day stroke, death, and MI rates in the CEA arm were as high as 9.8% (vs 4.8% CAS; $P = .09$). The MI rate of 6.6% strongly influenced this combined endpoint. Also, approximately 70% of the study population was asymptomatic. Outcomes of our VR real-world data looking at the same HR population consequently do not compare with the SAPPHIRE trial, with a MACE rate of 5.0% (MI rate, 1.6%) after CEA in asymptomatic patients and 7.3% in symptomatic patients. Noteworthy, the primary end point in SAPPHIRE did not differ significantly in symptomatic patients at 30 days and at 1 year (16.8% CAS vs 16.5% CEA; $P = .95$), one of the major reimbursement criteria from CMS.

Several other studies have retrospectively sought to evaluate medical,[10,13] anatomical,[15-17] or a combination of HR criteria[11,12,18,19] outlined by CMS. Most of these studies analyzed risk factors against a non-HR group in only one treatment arm (CAS or CEA). Our prior analysis[10] using the Nationwide Inpatient Sample identified significantly lower stroke/death rates after CEA compared with CAS with a stratified analysis by symptom status and HR status, questioning the validity of the HR criteria. In that analysis, medical HR status was associated with worse outcome (stroke/death, mortality) following CEA compared with non-HR patients undergoing CEA. Outcomes with CAS, however, were not improved in these HR patients (combined stroke/death CAS vs CEA in symptomatic patients: 14.4% vs 6.9%; $P < .001$). However, anatomic HR could not be determined and medical HR could not be precisely quantified because of the limitations of administrative data. Additionally, outcome events other than death may not be reliably documented with administrative data.

We undertook the current analysis to perform a thorough identification of HR factors and better discrimination of pre- and postoperative outcomes. We found that recent angina was a predictor for all major outcomes after CEA except for stroke alone and also a predictor for death after CAS. We also found that those patients aged ≥80 years had an increased risk for MACE after CEA and for stroke and MI after CAS. A differential effect of advancing age on outcome was also observed in the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) lead in and the randomized trial, where older patients had significantly better outcomes after CEA and younger patients had a nonsignificant trend toward better outcomes after CAS.[20-22]

Considering anatomic HR factors, we found that patients with contralateral occlusion were at HR for adverse outcomes following CEA and CAS. Controversy regarding the benefit of CEA exists in patients with contralateral occlusion, with some studies reporting similar outcomes after CEA,[17,23] whereas others show increased risk of adverse events.[24,25] However, little data exist to evaluate the impact on CAS outcomes.[26] Our data suggest that the risk for adverse outcome after both CEA and CAS was increased in patients with contralateral occlusion, in both symptomatic and asymptomatic patients. We were not able to assess shunt use during CEA, which might impact perioperative outcome. For patients with restenosis, this was not true. With an OR of 3.6 (95% CI, 1.4-9.3), restenosis was predictive for death after CEA, but proved to be a protective condition for MACE and stroke/death after CAS. However, MACE rates were similarly high

between symptomatic patients undergoing CAS and CEA, but for asymptomatic patients, the MACE rate with CAS was one-half that of CEA (3.5% vs 7.1%; P = NS). This expands the evidence of a prior report of the VR, were no differences in stroke/death/MI rate between CAS patients with atherosclerotic disease compared with nonatherosclerotic disease (eg, restenosis and prior radiation therapy) were identified.[15] These findings suggest that asymptomatic patients with restenosis or prior radiation therapy might be considered as the only "low" risk group in CAS. Differences in histology may explain this observation because intimal hyperplasia and radiation-induced plaque have been shown to be more stable compared with atherosclerotic plaque.[27,28] Additionally, patients with high anatomic lesions suffered from high MACE risks after both procedures (>10% in symptomatic patients), far beyond the accepted complication rates after carotid revascularization and, thus, questioning the benefit of revascularization over medical treatment in these patients. No such trials exist today, and accepted rates are, however, based on trials in which these patients were specifically excluded, such as CREST.[29]

Results of the CREST trial showed that both symptomatic and asymptomatic patients had equal low risks after CAS and CEA for combined stroke/death/MI.[22] Stroke rates alone were lower following CEA, whereas an increased risk for MI was seen compared with CAS. Symptomatic patients had lower stroke and death rates with CEA compared with CAS.[30] As stated above, most HR criteria outlined by the CMS (except for age ≥80 years and contralateral occlusion) were exclusion criteria in this trial. The study also required that interventionalists have documented prior performance of at least 35 CAS procedures, emphasizing that CAS might be a safe procedure under specific conditions in selected patients treated by selected physicians. Unadjusted data from a regional quality improvement registry (Vascular Study Group of New England) showed increased in-hospital risk for stroke/death/MI in symptomatic patients undergoing CAS (5.8%) compared with CEA (2.7%) but equal results in asymptomatic patients.[31] In the real-world data from the VR, the vast majority (90.5%) of the CAS patients meet CMS HR criteria and had more comorbid conditions than CEA patients where only 37% were HR, making unadjusted comparison difficult to interpret and likely biased.

This study has several limitations. Self-reporting bias by treating physicians and institutions is inherent to any registry-based study and the potential effect of reporting bias within the VR has been investigated and discussed. Given that 90% of CAS patients were HR, there were a relatively small number of patients in the non-HR group available for stratified analysis. It is possible that a type II error prevented finding a significant difference in subgroup comparisons stratified by symptom status and non-HR status. It is also possible that some of the patients considered non-HR were in fact HR and were mislabeled. Given that CMS reimbursement and site approval for performance of CAS in Medicare patients is dependent upon this documentation, we believe that this is unlikely. Non-HR patients may be entered into clinical trials and have CMS reimbursement. Because the VR data are capturing real-world data, it is reliant on site entry of patients without predefined exclusion or inclusion criteria. Therefore, differences in patient selection may have occurred for both CAS and CEA. Lastly, the combined outcome of MACE is flawed in that it equates death, stroke, and MI. Although there has been considerable debate about the relative importance of stroke vs MI,[32-34] we do not think that this impacts our findings, as we had similar findings using the stroke/death outcome that had previously been considered the standard.

In conclusion, we find that certain CMS HR criteria are associated with adverse outcomes after CEA. However, outcomes in HR patients are not improved after CAS, and patients treated with CEA fare better than CAS after adjustment for symptom status and HR status. Therefore, our study finds little advantage for CAS over CEA in patients at HR for perioperative complications and suggests that the strongest advantage of CAS over CEA lies in patients with restenosis or prior neck radiation, compared with those patients with HR medical conditions.

AUTHOR CONTRIBUTIONS

Conception and design: MS
Analysis and interpretation: MS, MF, CK, FS
Data collection: FS
Writing the article: MS, MF, CK, FS
Critical revision of the article: MS, MF, PG, ED, JJ, CK, FS, RW
Final approval of the article: MS, MF, PG, ED, JJ, CK, FS, RW
Statistical analysis: CK, FS
Obtained funding: RW
Overall responsibility: MS

REFERENCES

1. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004;18:69-74.
2. Mas J-L, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin J-P, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006;355:1660-71.
3. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
4. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. J Vasc Surg 1998;28:326-34.
5. 100-03 P. Medicare National Coverage Determinations. 2010.
6. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
7. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the

BEACH trial 30 day results. Catheter Cardiovasc Interv 2006;67: 503-12.
8. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg 2006;44:258-68.
9. Iyer SS, White CJ, Hopkins LN, Katzen BT, Safian R, Wholey MH, et al. Carotid Artery revascularization in high-surgical-risk patients using the carotid WALLSTENT and FilterWire EX/EZ: 1-year outcomes in the BEACH Pivotal Group. J Am Coll Cardiol 2008;51:427-34.
10. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML. Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. J Vasc Surg 2010;52:1497-504.
11. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. J Vasc Surg 2003;37:40-6.
12. Kang JL, Chung TK, Lancaster RT, LaMuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: is there a high-risk population? A National Surgical Quality Improvement Program report. J Vasc Surg 2009;49:331-9.e1.
13. Yuo TH, Goodney PP, Powell RJ, Cronenwett JL. "Medical high risk" designation is not associated with survival after carotid artery stenting. J Vasc Surg 2008;47:356-62.
14. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med 2008;358:1572-9.
15. White RA, Sicard GA, Zwolak RM, Sidawy AN, Schermerhorn ML, Shackelton RJ, et al. Society of vascular surgery vascular registry comparison of carotid artery stenting outcomes for atherosclerotic vs nonatherosclerotic carotid artery disease. J Vasc Surg 2010;51: 1116-23.
16. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. Stroke 2012;43:793-801.
17. Rockman CB, Su W, Lamparello PJ, Adelman MA, Jacobowitz GR, Gagne PJ, et al. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: surgical results in symptomatic and asymptomatic patients. J Vasc Surg 2002;36:668-73.
18. Reed AB, Gaccione P, Belkin M, Donaldson MC, Mannick JA, Whittemore AD, et al. Preoperative risk factors for carotid endarterectomy: defining the patient at high risk. J Vasc Surg 2003;37:1191-9.
19. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. J Vasc Surg 2004;39:958-65; discussion: 965-6.
20. Hobson RW II, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. J Vasc Surg 2004;40:1106-11.
21. Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC III, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke 2011;42:3484-90.
22. Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke 2010;41:S31-4.
23. AbuRahma AF, Robinson P, Holt SM, Herzog TA, Mowery NT. Perioperative and late stroke rates of carotid endarterectomy contralateral to carotid artery occlusion: results from a randomized trial. Stroke 2000;31:1566-71.
24. Goodney PP, Likosky DS, Cronenwett JL. Factors associated with stroke or death after carotid endarterectomy in Northern New England. J Vasc Surg 2008;48:1139-45.
25. Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJM. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. J Neurosurg 1995;83:778-82.
26. Sabeti S, Schillinger M, Mlekusch W, Nachtmann T, Lang W, Ahmadi R, et al. Contralateral high-grade carotid artery stenosis or occlusion is not associated with increased risk for poor neurologic outcome after elective carotid stent placement. Radiology 2004;230:70-6.
27. Hellings WE, Moll FL, de Vries JP, de Bruin P, de Kleijn DP, Pasterkamp G. Histological characterization of restenotic carotid plaques in relation to recurrence interval and clinical presentation: a cohort study. Stroke 2008;39:1029-32.
28. Fokkema M, den Hartog AG, van Lammeren GW, Bots ML, Pasterkamp G, Vink A, et al. Radiation-induced carotid stenotic lesions have a more stable phenotype than de novo atherosclerotic plaques. Eur J Vasc Endovasc Surg 2012;43:643-8.
29. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. Stroke 2011;42:e420-63.
30. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2011;42:675-80.
31. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012;56:990-6.
32. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA, et al. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. J Vasc Surg 2009;49:71-9.
33. Naylor AR. Hearts and minds. Eur J Vasc Endovasc Surg 2012;43:1-3.
34. Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al. Myocardial infarction after carotid stenting and endarterectomy/clinical perspective. Circulation 2011;123:2571-8.

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