◆ CLINICAL INVESTIGATION ◆

Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS): 4-Year Outcomes

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Purpose: To examine the 4-year outcomes from Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) in light of the current reimbursement guidelines for carotid artery stenting (CAS) from the Centers for Medicare and Medicaid Services (CMS).

Methods: CaRESS was designed as a prospective, nonrandomized comparative cohort study of a broad-risk population of symptomatic and asymptomatic patients with carotid stenosis. In all, 397 patients (247 men; mean age 71 years, range 43–89) were enrolled and underwent carotid endarterectomy (CEA; n=254) or protected CAS (n=143). More than 90% of patients had >75% stenosis; two thirds were asymptomatic. The primary endpoints included (1) all-cause mortality, (2) any stroke, and (3) myocardial infarction (MI), as well as the composite endpoints of (4) death and any nonfatal stroke and (5) death, nonfatal stroke, and MI. The secondary endpoints were restenosis, repeat angiography, and carotid revascularization. All patients were classified with respect to surgical risk, symptom status, and stenosis grade based on criteria published by the CMS. In addition, separate analyses were performed comparing genders and octogenarians to those <80 years old.

Results: No significant differences in the primary outcome measures were found between the CEA and CAS groups in the 4-year analysis. The incidences of any stroke at 4 years were 9.6% for CEA and 8.6% for CAS (p=0.444); when combined with death, the composite death/nonfatal stroke rates were 26.5% for CEA versus 21.8% for CAS (p=0.361). The composite endpoint of death, nonfatal stroke, and MI at 4 years was 27.0% in CEA versus 21.7% in CAS (p=0.273) patients. The secondary endpoints of restenosis (p=0.014) and repeat angiography (p=0.052) were higher in the CAS arm. There were no differences in any of the subgroups stratified according the CMS guidelines or in the gender comparison. Four-year incidences of death/nonfatal stroke and death/nonfatal stroke/MI were higher in the CEA arm among patients <80 years of age (p=0.049 and p=0.030, respectively). There were no significant differences between these incidences in the octogenarian subgroup.

Funds for the Phase I CaRESS Clinical Trial were provided to the INTERNATIONAL SOCIETY OF ENDOVASCULAR SPECIALISTS, which sponsored the Investigational Device Exemption, by Boston Scientific Corporation, Natick, MA, USA, and by Medtronic CardioVascular, Santa Rosa, CA, USA.

Presented at the Transcatheter Cardiovascular Therapeutics meeting held in Washington, DC, USA, on October 12–17, 2008.

Christopher K. Zarins is a consultant to Medtronic. Rodney A. White and Edward B. Diethrich report no conflicts. Rebecca J. Shackelton and Flora S. Siami are employees of the New England Research Institutes, Inc.

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Conclusion: The risk of death or nonfatal stroke 4 years following CAS with distal protection is equivalent to CEA in a broad category of patients with carotid stenosis. There were no significant differences in stroke or mortality rates between high-risk and non-high-risk patients and no differences in outcomes between symptomatic and asymptomatic patients. After 4 years, CAS had a 2-fold higher restenosis rate compared to CEA. The risk of death/stroke or death/stroke/MI appears to be higher following CEA than CAS among patients <80 years of age, yet there is no statistically significant relationship between death, stroke, or MI among octogenarians.

J Endovasc Ther. 2009;16:397-409

Key words: carotid occlusive disease, carotid stenosis, carotid stent, carotid endarterectomy, outcome analysis, mortality, stroke, octogenarians

In the US, carotid artery stenting (CAS) is emerging as a practical therapeutic alternative to carotid endarterectomy (CEA) in high-risk patients based upon device-specific clinical trials¹⁻⁶ that led to Food and Drug Administration (FDA) approval of a number

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of carotid stenting systems and embolic protection devices. In 2004, after the first carotid stenting systems were approved by the FDA, the Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Decision (NCD)⁷ that provided reimbursement for the treatment of high-risk patients with symptomatic >70% carotid stenosis so long as they were treated with FDA-approved stents and a distal embolic protection device (EPD). Subsequently, the CMS allowed reimbursement for CAS in symptomatic high-risk patients with carotid stenosis between 50% and 69% and asymptomatic high-risk patients with stenosis >80% only if the patients were enrolled and treated in a Category B IDE (Investigational Device Evaluation) clinical trial or post-approval study. In 2007, the CMS considered expanding coverage by removing the clinical study restrictions on these high-risk subsets.⁸ However, the CMS ultimately decided not to implement the proposed expansion of coverage, citing conflicting data and lack of uniform support for such changes.⁹ Today, costs of treatment of symptomatic patients who do not meet the high-risk criteria and those with <80% asymptomatic carotid stenosis are not reimbursed regardless of participation in an approved clinical trial.

The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS)

received IDE approval in 2001 as one of the few prospective multicenter clinical trials to focus on the broad-risk population of patients with symptomatic and asymptomatic carotid stenosis commonly seen in clinical practice.^{10,11} Both the 30-day and 1-year results of the CaRESS trial showed no difference in outcome between carotid CEA and CAS with distal cerebral protection: both had 2% 30-day combined stroke/death rates.^{12,13}

During the 8 years since CaRESS was conceived, the techniques and devices for CAS have evolved considerably,¹⁴⁻¹⁷ yet reimbursement has remained available for only high-risk patients. Moreover, the aging population has presented new treatment challenges.¹⁸⁻²⁴ In particular, recent data suggest that octogenarians are at particularly high risk for CAS,^{20,23,24} though various single-center experiences have reported the safety of CAS in this subgroup.^{19,21,21,25,26} In this report of the 4-year outcomes of the CaRESS trial, we examine the CMS coverage guidelines for CAS in a series of subgroup analyses that stratify this large, broad-risk patient cohort by risk status, symptomatology, stenosis grade, and age >80 years.

METHODS

Study Design and Patient Population

This CaRESS study was a 14-site, 2-phase clinical trial (Appendix) designed as an equivalence cohort study to determine whether the stroke/death rate in patients treated with CAS under distal cerebral protection was comparable to patients undergoing CEA. Follow-up to 4 years was mandated for Phase I. The

study design, clinical site selection, patient enrollment, treatment selection, procedural techniques, and the 30-day and 1-year results for Phase I have been published.^{10–13} An enrollment goal of 450 subjects (300 CEA, 150 stent) was selected to provide sufficient precision in determining a 3% event rate in the CEA arm and enough carotid stent cases to ensure comparable patients in each treatment cohort.¹² The CAS patients were treated with the Monorail Wallstent (Boston Scientific, Natick, MA, USA) and the GuardWire Plus (Medtronic CardioVascular, Santa Rosa, CA, USA) distal protection device according to their instructions for use.

Follow-up included physical examination, review of medications and adverse events, neurological examination with National Institutes of Health Stroke Scale assessment and quality of life/cerebral events questionnaires,¹³ and carotid ultrasound at 1, 6, and 12 months and annually to 48 months. However, at the annual visits, only symptomatic patients had a neurological examination. Angiography was performed as needed to evaluate symptomatic patients or those with an indication of stenosis >75% on an ultrasound scan.

The primary endpoints included (1) all-cause mortality, (2) any stroke, and (3) myocardial infarction (MI), as well as the composite endpoints of (4) death/any nonfatal stroke and (5) death/nonfatal stroke/MI. The secondary endpoints were restenosis ($\geq 75\%$ narrowing documented by ultrasonography or symptomatic narrowing >50% that required secondary treatment), repeat angiography, and carotid revascularization.

Of the 439 patients enrolled in CaRESS, 397 patients (247 men; mean age 71 years, range 44–89) were treated with carotid endarterectomy ($n=254$) or protected CAS ($n=143$). The demographics, clinical status, and past medical history of the treatment groups have been published.^{12,13} More than 90% of patients had >75% stenosis; about two thirds were asymptomatic. There were no significant differences in baseline patient characteristics between the treatment groups with the exception of a more frequent history of prior CEA (30% CAS versus 11% for CEA, $p<0.0001$) and prior carotid stent placement in the CAS group (6%

versus 0% for CEA, $p=0.0002$). In both groups, the etiology was atherosclerosis in the majority of cases (87% in CEA and 76% in CAS); CAS was performed for restenosis in 17% and post-radiation stenosis in 4%.

Patient Stratification

To complement the 4-year outcome data for the entire CaRESS cohort, additional analyses were performed to compare outcomes according to gender, risk classification, symptom status, stenosis grade, and age >80 years. Risk was dichotomized based on published CMS criteria for carotid stenting,⁹ which differed somewhat from the definition used in CaRESS (Table 1). According to the CMS, patients with one or more of the following were considered to be *high risk*: age ≥ 80 years, New York Heart Association class III/IV for congestive heart failure, Canadian Cardiovascular Society class III/IV, left ventricular ejection fraction <30%, unstable angina, previous MI, end-stage renal disease on dialysis, severe pulmonary disease, previous CEA with recurrent stenosis, prior radiation treatment to the neck, tracheostomy, high cervical internal carotid artery lesion, common carotid artery lesion below the clavicle, contralateral carotid occlusion, and contralateral laryngeal nerve palsy. Of the 397 CaRESS patients, 184 (46%) were classified as “high risk” and 213 (54%) were classified as “non-high risk” according to this CMS definition.

Patients were classified as *symptomatic* if one or more of the following symptoms were present within the 6 months prior to enrollment: transient ischemic attack (TIA; distinct focal neurological dysfunction persisting <24 hours), focal cerebral ischemia producing a non-disabling stroke (modified Rankin scale <3 with symptoms for ≥ 24 hours), or amaurosis fugax. Based on these criteria, 128 (32%) of the CaRESS patients were symptomatic and 269 (68%) were asymptomatic.

The baseline *degree of stenosis* was determined by preoperative ultrasound, with $\geq 75\%$ diameter reduction representing severe stenosis. For purposes of this analysis, this threshold was considered equivalent to the 80% stenosis guideline used by the CMS

TABLE 1

Centers for Medicare and Medicaid Services (CMS) and CaRESS Definitions of High Surgical Risk

CMS	CaRESS
Age ≥ 80 years	Age ≥ 80 years
Previous MI	Recent MI was an exclusion criterion; used history of MI
LVEF $\leq 30\%$	N/A
Contralateral carotid occlusion	Contralateral stenosis $>50\%$
NYHA class III or IV	NYHA class III or IV
Unstable angina: CCS class III/IV	N/A
Renal failure (ESRD on dialysis)	ESRD was exclusion criterion
CCA lesion(s) below clavicle	N/A
Severe pulmonary disease	Did not collect
Clinically significant cardiac disease (CHF, abnormal stress test, or need for open-heart surgery)	CHF and prior CABG collected
Previous neck radiation	N/A
High cervical ICA lesion	Did not collect
Restenosis of prior CEA	Prior CEA or carotid stent
Tracheostomy	Did not collect
Contralateral laryngeal nerve palsy	Did not collect

MI: myocardial infarction, LVEF: left ventricular ejection fraction, N/A: not available, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society, ESRD: end-stage renal disease, CCA: common carotid artery, CHF: congestive heart failure, CABG: coronary artery bypass graft, ICA: internal carotid artery, CEA: carotid endarterectomy.

for asymptomatic patients. Each patient in the CaRESS trial was then retrospectively assigned to 1 of 4 groups based on CMS guidelines: (1) high risk, symptomatic, $\geq 75\%$ stenosis ($n=39$, 10%); (2) high risk, symptomatic, 50% to 74% stenosis ($n=12$, 3%); (3) high risk, asymptomatic, $\geq 75\%$ stenosis ($n=133$, 34%); or (4) non-high risk, asymptomatic, $<75\%$ ($n=213$, 54%).

Statistical Analysis

Baseline characteristics of the CEA and CAS patient groups were compared using the Student *t* test for continuous variables and the chi-square or Fisher exact test for categorical data. Multivariable regression analysis using the Cox proportional hazards model was performed to identify baseline factors predictive of the outcomes at 4 years for the high-risk cohort; variables with $p < 0.2$ from the univariate analyses were entered into the model. Kaplan-Meier estimates of freedom from events for the primary and secondary endpoints were determined; the log-rank test was used to compare group event rates. Differences were considered significant if $p < 0.05$. Statistical analyses were performed

by the New England Research Institutes, Inc, using SAS statistical software (SAS Institute Inc, Cary, NC, USA).

RESULTS

Entire CaRESS Cohort

No significant differences in the primary outcome measures were found between the CEA and CAS patient groups in the 4-year analysis (Table 2). All-cause mortality was 21.2% in the CEA arm and 18.7% in the CAS arm (Table 3, $p=0.835$). It is interesting that the CAS arm began to show higher mortality compared with CEA at 1–2 years and 2–3 years, but rebounded at 3–4 years, though there were no significant differences in survival at that time.

The incidence of any stroke at 4 years was 9.6% for CEA and 8.6% for CAS ($p=0.444$); when combined with death, the composite rates were 26.5% for CEA versus 21.8% for CAS (Table 3), though this difference was not statistically significant ($p=0.361$). The composite endpoint of death/nonfatal stroke/MI at 4 years was 27.0% in CEA versus 21.7% in CAS (Table 3, $p=0.273$) patients. The corresponding Kaplan-Meier curve (the Figure)

TABLE 2
Kaplan-Meier Event Rates at 4 Years for the Primary Endpoints in the Entire CaRESS Cohort*

	All-Cause Mortality		Stroke		MI		Death/Stroke		Death/Stroke/MI	
	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS
At risk	254	143	254	143	254	143	254	143	254	143
Events	39	23	22	10	19	8	53	27	55	27
Censored	157	69	175	85	180	87	144	68	143	68
Estimate	0.788	0.813	0.904	0.914	0.892	0.924	0.735	0.782	0.730	0.783
SE	0.031	0.035	0.019	0.027	0.024	0.0262	0.033	0.038	0.032	0.037
Event rate, %*	21.2	18.7	9.6	8.6	10.8	7.6	26.5	21.8	27.0	21.7
p	0.835		0.444		0.347		0.361		0.273	

CEA: carotid endarterectomy, CAS: carotid artery stenting, MI: myocardial infarction, SE: standard error.

* Person-year, calculated as 1 – estimate.

showed a trend toward better outcomes in the CAS arm, but the difference was not statistically significant. The secondary endpoints at 4 years were, in general, higher in the CAS arm, notably for the frequency of restenosis (14.7% versus 5.9% for CEA; $p=0.014$) and repeat angiography (11.2% versus 5.1%; $p=0.052$). A higher proportion of CAS patients had carotid reinterventions (5.6% versus 2.8% for CEA), but the difference was not statistically significant ($p=0.263$).

Stratification

Risk status. Nearly half (184, 46%) of the CaRESS patients met at least one of the CMS-defined criteria of high risk for surgery: 107 (42%) of the 254 patients in the CEA arm and 77 (54%) of the 143 CAS patients. Baseline

demographics and characteristics of the high-risk patients (Table 4) differed between the arms in age only; CEA patients were 3 years older than high-risk CAS patients (76 versus 73 years, $p<0.05$), but there were no significant differences in medical comorbidity rates. CAS patients were more likely to have carotid stenosis $>75\%$ ($p=0.02$) and were more likely to have had a prior carotid endarterectomy ($p<0.001$) or carotid stent ($p=0.03$) with restenosis from these procedures ($p<0.001$). CAS patients also were more likely to have peripheral vascular disease ($p=0.016$).

Table 5 demonstrates outcomes by risk level, symptom status, and age for each treatment group. There was no significant difference between the 4-year death/stroke rate between high-risk CEA (30.1%) and high-risk CAS patients (29.1%, $p=0.820$). Similarly, there were no differences in all-cause mortality or combined death/stroke/MI rates between the high-risk patient subgroups. Adjustment for statistically significant differences at baseline, such as age, gender, stenosis $\geq 75\%$, etiology, history of TIA, history of stroke, congestive heart failure, and history of prior CEA/CAS, did not alter the primary outcome measures at 4 years (data not shown). The 4-year death/stroke rate among the non-high-risk group was higher among patients treated with CEA (24.1%) than patients treated with CAS (12.7%), though this result was not statistically significant ($p=0.104$). As expected, the Kaplan-Meier event rates in the high-risk patients were in general higher than the event rates for the non-high-risk CaRESS.

Figure ♦ Kaplan-Meier curves for freedom from death/nonfatal stroke/MI in the CAS and CEA arms.

TABLE 3
Summary of the Kaplan-Meier Estimates

	Treatment to 30 Days	1-6 Months	6-12 Months	1-2 Years	2-3 Years	3-4 Years
Freedom From Death (p=0.835)						
CEA						
At risk	254	230	217	200	184	153
Events	1	6	7	7	8	10
Censored	23	7	10	9	23	85
Estimate	0.996	0.969	0.937	0.903	0.862	0.788
Event rate, %*	0.4	3.1	6.3	9.7	13.8	21.2
SE	0.004	0.011	0.016	0.020	0.024	0.031
CAS						
At risk	143	137	132	121	109	94
Events	0	2	6	7	6	2
Censored	6	3	5	5	9	41
Estimate	1.000	0.985	0.940	0.884	0.833	0.813
Event rate, %	0.0	1.5	6.0	11.6	16.7	18.7
SE	0.000	0.010	0.021	0.028	0.033	0.035
From Death and Nonfatal Stroke (p=0.361)						
CEA						
At risk	254	224	209	191	174	144
Events	9	10	10	8	7	9
Censored	21	5	8	9	23	79
Estimate	0.964	0.920	0.875	0.838	0.802	0.735
Event rate, %	3.6	8.0	12.5	16.2	19.8	26.5
SE	0.012	0.018	0.022	0.024	0.027	0.033
CAS						
At risk	143	135	129	118	107	93
Events	3	3	6	6	5	4
Censored	5	3	5	5	9	41
Estimate	0.979	0.956	0.912	0.864	0.821	0.782
Event rate, %	2.1	4.4	8.8	13.6	17.9	21.8
SE	0.012	0.017	0.024	0.030	0.034	0.038
Freedom from Death, Nonfatal Stroke, and Myocardial Infarction† (p=0.273)						
CEA						
At risk	254	222	206	189	171	142
Events	11	11	9	9	7	8
Censored	21	5	8	9	22	79
Estimate	0.956	0.908	0.867	0.825	0.790	0.730
Event rate, %	4.4	9.2	13.3	17.5	21.0	27.0
SE	0.013	0.019	0.022	0.025	0.027	0.032
CAS						
At risk	143	135	129	117	107	93
Events	3	3	7	5	5	4
Censored	5	3	5	5	9	41
Estimate	0.979	0.956	0.904	0.864	0.822	0.783
Event rate, %	2.1	4.4	9.6	13.6	17.8	21.7
SE	0.012	0.017	0.025	0.030	0.034	0.037

CEA: carotid endarterectomy, CAS: carotid artery stenting, SE: standard error.

* Person-year, calculated as 1 - estimate.

† Myocardial infarctions were counted only during the first year.

Symptom status. A third (32%) of patients in the CaRESS trial were symptomatic, including 84 CEA and 44 CAS patients. There was no difference in the 30-day death/stroke rate in

symptomatic patients between the CEA (7.2%) and CAS (4.7%) arms (Table 5). However, at 4 years, in symptomatic patients, the death/stroke rate in the CEA subgroup (33.5%) was

TABLE 4
Baseline Characteristics of the 184-Patient CMS-Defined High-Risk Subset by Treatment Arm

	CEA (n=107)	CAS (n=77)	p*
Demographics			
Age, y	76.3± 7.9	73.4± 10.1	0.041
Men	71 (66.4%)	43 (55.8%)	0.147
Caucasian	102 (95.3%)	71 (92.2%)	0.379
Clinical status			
Symptomatic	33 (30.8%)	18 (23.4%)	0.264
Asymptomatic	74 (69.2%)	59 (76.6%)	
Percent stenosis			
50%–75%	11 (10.3%)	1 (1.3%)	0.015
>75%	96 (89.7%)	76 (98.7%)	
Etiology of carotid disease			
Atherosclerosis	93 (86.9%)	58 (75.3%)	0.043
Restenosis	1 (0.9%)	24 (31.2%)	<0.001
Radiation	1 (0.9%)	1 (1.3%)	0.814
Medical history			
TIA	26 (24.3%)	12 (15.6%)	0.150
Stroke	16 (15.0%)	20 (26.0%)	0.063
TIA or stroke	37 (34.6%)	29 (37.7%)	0.667
CEA prior to study	12 (11.2%)	37 (48.1%)	<0.001
Carotid stent prior to study	0 (0.0%)	4 (5.2%)	0.017
Prior peripheral angioplasty	1 (0.9%)	1 (1.3%)	0.814
Contralateral stenosis >50%	45 (42.1%)	26 (33.8%)	0.254
CAD or previous stroke	88 (83.0%)	63 (84.0%)	0.861
CHF	32 (29.9%)	14 (18.2%)	0.070
Hypertension	87 (81.3%)	63 (81.8%)	0.930
Hypercholesterolemia	73 (68.2%)	55 (71.4%)	0.641
Diabetes mellitus	28 (26.2%)	21 (27.3%)	0.867
Peripheral vascular disease	42 (39.3%)	44 (57.1%)	0.016
Smoking (past or current)	81 (75.7%)	61 (79.2%)	0.575

Continuous data are presented as means ± standard deviation; categorical data are given as counts (percentages). CEA: carotid endarterectomy, CAS: carotid artery stenting, TIA: transient ischemic attack, CAD: coronary artery disease, CHF: congestive heart failure.

* Based on Fisher exact test.

higher than in corresponding CAS patients (12.5%, $p=0.019$), primarily due an increase in overall mortality. There was no significant difference in stroke rate between CEA (17.8%) and CAS (7.2%, $p=0.124$) at 4 years. Among asymptomatic patients, there were no differences between CEA and CAS in 4-year mortality (19.7% CEA versus 22.2% CAS, $p=0.384$) and the combined death/stroke rate (23.2% CEA versus 25.8% CAS, $p=0.551$).

Gender. There were 161 men and 93 women in the CEA arm and 86 men and 57 women in the CAS cohort. There was only 1 death at 30 days: a woman from the CEA group. In late follow-up, 13/93 women and 26/161 men in the CEA arm died, which did not differ significant-

ly from the 6/57 women and 17/86 men in the CAS arm who died (results not shown).

Age. Patients 80 years of age and older comprised 19% of the CaRESS population: 52 (20%) of the 254 CEA patients and 25 (17%) of the 143 CAS patients. All-cause mortality at 4 years for octogenarian CEA patients (26.8%) was not statistically different from octogenarian CAS patients (41.7%, $p=0.158$). At 4 years, the combined death/stroke rate for octogenarians treated with CEA (35.4%) was not significantly different from the death/stroke rate for octogenarians treated with CAS (54.1%, $p=0.204$). There was no difference in overall mortality between non-octogenarian CEA patients (20.0%) and CAS patients

TABLE 5

Outcomes by Treatment Arm at 30 Days and 4 Years According to Risk Level, Symptom Status, and Age

	All-Cause Mortality		Stroke		MI		Death/Stroke		Death/Stroke/MI	
	30-Day	4-Year	30-Day	4-Year	30-Day	4-Year	30-Day	4-Year	30-Day	4-Year
RISK LEVEL										
High risk										
CEA (n=107)	NA	20 (25.7%)	NA	9 (9.9%)	NA	7 (10.2%)	NA	25 (30.1%)	NA	25 (30.0%)
CAS (n=77)	NA	17 (24.5%)	NA	8 (12.9%)	NA	4 (6.4%)	NA	20 (29.1%)	NA	20 (28.8%)
p		0.976		0.900		0.529		0.820		0.828
Non-high risk										
CEA (n=147)	NA	19 (18.2%)	NA	13 (9.3%)	NA	12 (11.2%)	NA	28 (24.1%)	NA	30 (25.0%)
CAS (n=66)	NA	6 (11.3%)	NA	2 (3.4%)	NA	4 (9.2%)	NA	7 (12.7%)	NA	7 (12.7%)
p		0.358		0.123		0.545		0.104		0.066
SYMPTOM STATUS										
Symptomatic										
CEA (n=84)	1 (1.3%)	15 (24.9%)	6 (7.2%)	13 (17.8%)	0 (0.0%)	7 (12.6%)	6 (7.2%)	23 (33.5%)	6 (7.2%)	23 (33.5%)
CAS (n=44)	0 (0.0%)	4 (10.4%)	2 (4.7%)	3 (7.2%)	0 (0.0%)	2 (7.1%)	2 (4.7%)	5 (12.4%)	2 (4.7%)	5 (12.4%)
p	0.476	0.093	0.571	0.124	—	0.236	0.571	0.019	0.571	0.019
Asymptomatic										
CEA (n=170)	0 (0.0%)	24 (19.7%)	3 (1.8%)	9 (5.7%)	2 (1.2%)	12 (10.1%)	3 (1.8%)	30 (23.2%)	5 (3.0%)	32 (24.0%)
CAS (n=99)	0 (0.0%)	19 (22.2%)	1 (1.0%)	7 (9.2%)	0 (0.0%)	6 (7.9%)	1 (1.0%)	22 (25.8%)	1 (1.0%)	22 (25.6%)
p	—	0.384	0.606	0.654	0.280	0.688	0.606	0.551	0.293	0.734
AGE										
>80 Years										
CEA (n=52)	0 (0.0%)	9 (26.8%)	2 (4.2%)	7 (17.2%)	0 (0.0%)	1 (3.4%)	2 (4.2%)	13 (35.4%)	2 (4.2%)	13 (35.4%)
CAS (n=25)	0 (0.0%)	10 (41.7%)	1 (4.0%)	6 (31.3%)	0 (0.0%)	1 (6.7%)	1 (4.0%)	13 (54.1%)	1 (4.0%)	13 (54.1%)
p	—	0.158	0.989	0.513	—	0.686	0.989	0.204	0.989	0.199
≤80 Years										
CEA (n=202)	1 (0.5%)	30 (20.0%)	7 (3.5%)	15 (8.0%)	2 (1.0%)	18 (12.4%)	7 (3.5%)	40 (24.6%)	9 (4.5%)	42 (25.3%)
CAS (n=118)	0 (0.0%)	13 (13.3%)	2 (1.7%)	4 (3.7%)	0 (0.0%)	7 (7.8%)	2 (1.7%)	14 (13.8%)	2 (1.7%)	14 (13.8%)
p	0.447	0.246	0.355	0.135	0.283	0.260	0.355	0.049	0.192	0.030

Data are given as counts (percentages).

NA: not analyzed, MI: myocardial infarction.

(13.3%, $p=0.246$). However, non-octogenarians treated with CAS rather than CEA had nearly half the incidence of combined death/stroke ($HR=0.55$). The death/stroke rate among non-octogenarians treated with CEA was 24.6%, while this rate was 13.8% among CAS patients ($p=0.049$). For CEA patients, the 30-day death/stroke rate for octogenarians (4.2%) was not different from CEA patients <80 years of age (3.5%; Table 5). Similarly, for CAS patients, the 30-day death/stroke rate for octogenarians (4.0%) was not different from CAS patients <80 years of age (1.7%).

Stratification by CMS Guidelines

High risk, symptomatic, $\geq 75\%$ stenosis (currently reimbursed by CMS). Patients in

this category comprised 10% of the CaRESS trial population, including 22 patients in the CEA and 17 patients in the CAS group. There was no difference in the 30-day death/stroke rates between CEA 0.0% and CAS 5.9% (Table 6) and no difference in the 4-year death/stroke rate between the groups (CEA 25.3% versus CAS 12.6%, $p=0.444$).

High risk, symptomatic, 50% to 74% stenosis and high risk, asymptomatic, stenosis $\geq 75\%$ (reimbursed by CMS under clinical trial criteria). Because only 3% of the CaRESS trial population fell into the high risk, symptomatic, 50% to 74% stenosis group (11 CEA patients and 1 CAS patient), this group was combined with the 33% of CaRESS patients who were in the high risk, asymptomatic, $\geq 75\%$ stenosis cohort (74 CEA patients and 59

CAS patients). There was no difference in death/stroke rates between CEA (3.6%) and CAS (1.7%) at 30 days or at 4 years (CEA 31.5% and CAS 33.5%).

Non-high risk, asymptomatic, <75% stenosis. Of the 213 (54%) patients in this group, 147 were CEA patients and 66 were CAS patients. There were no differences in 30-day or 4-year death/stroke rates.

DISCUSSION

The CaRESS trial is unique in that it is the only prospective multicenter trial comparing CEA to CAS with distal cerebral protection in a broad-risk category of patients with carotid stenosis, representative of standard clinical practice. The overall trial results demonstrate equivalence between the procedures out to 4 years, with no differences in the all-cause mortality, stroke, or combined death/stroke endpoints at 30 days or at 4 years. Analyzing the high-risk patients alone revealed no statistically significant differences in primary outcome measures.

The outcomes in CaRESS compare favorably with the published results in high-risk carotid stent registries using distal protection.^{1–6} Although the CaRESS trial likely reflects more accurately the true decision-making process when treating patients with carotid stenosis, the results of the randomized, prospective Carotid Revascularization Endarterectomy versus Stent Trial (CREST) trial are anxiously anticipated to provide needed level I proof to support the selection of CEA or CAS for these patients. In the interim, the midterm results were published from two other trials designed to test the hypothesis that CAS is not inferior to CEA for treating patients with severe symptomatic carotid artery stenosis. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial²⁷ concluded after 4 years that CAS was as effective as CEA for midterm prevention of ipsilateral stroke, but CAS had a higher periprocedural risk of any stroke. At the same time, the 2-year results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial²⁸ found no differences between the CAS and CEA groups in the rates of

ipsilateral ischemic strokes up to 2 years or of any periprocedural stroke or death.

At nearly the same time, several meta-analyses were published to examine a variety of outcomes for CAS versus CEA.^{29–33} Murad et al.²⁹ used a random-effects meta-analysis to evaluate the death, stroke (disabling and non-disabling), and nonfatal MI rates at 30 days in 10 randomized controlled trials representing 3182 patients. They based equivalency of the 2 procedures on an absolute difference in events of <2%. They found moderate-quality evidence for equivalence with respect to death and nonfatal MI, but only low-quality evidence of equivalence in stroke. Brahmanandam et al.³⁰ likewise looked at the differences in risk of stroke or death at 30 days in 10 trials (n=3580). They found that CAS patients overall had a higher risk of 30-day stroke/death (RR 1.30 versus CEA), which was evident in trials enrolling only symptomatic patients (RR 1.63) but not in trials including both symptomatic and asymptomatic patients (RR 0.89). Using random- and fixed-effects meta-analyses of 9 trials (n=3138), Jeng et al.³¹ found no differences for stroke, death, or MI in the random-effects models, but there were significantly higher 30-day event rates after CAS for death or any stroke by the fixed effects model. From these data, they concluded that CAS was not safer than surgery nor associated with a better short-term outcome. Ringleb et al.³² drew much the same conclusions after updating their earlier analysis to include 8 trials (n=2985).

The 30-day and 4-year outcomes in CaRESS clearly show that CAS is not inferior to CEA in terms of the death/stroke/MI rates for the entire cohort and for all subgroups analyzed. In fact, though the differences were not statistically significant, rates for CAS were slightly better in nearly all comparisons except restenosis rate and advanced age. This is in contrast to the initial analysis from the Society for Vascular Surgery's (SVS) Vascular Registry (VR) of more than 6400 patients.³⁴ Their 30-day data favored CEA in nearly every outcome measure, including the combined stroke/death/MI endpoint (2.63% versus 5.72% for CAS, $p<0.001$). Notably, more of the registry's CAS patients were

TABLE 6

Outcomes at 30 Days and 4 Years by Treatment Arm in Patients Stratified According to the CMS Guidelines

	All-Cause Mortality		Stroke		MI		Death/Stroke		Death/Stroke/MI	
	30-Day	4-Year	30-Day	4-Year	30-Day	30-Day	4-Year	30-Day	4-Year	30-Day
High risk, symptomatic, $\geq 75\%$ stenosis										
CEA										
(n=22)	0 (0.0%)	3 (18.8%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	2 (14.3%)	0 (0.0%)	4 (25.3%)	0 (0.0%)	4 (25.3%)
CAS										
(n=17)	0 (0.0%)	2 (12.9%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	2 (12.6%)	1 (5.9%)	2 (12.6%)
p	N/A	0.639	0.255	0.928	N/A	0.157	0.255	0.444	0.255	0.444
High risk, symptomatic, 50%–74% stenosis and high risk, asymptomatic, $\geq 75\%$ stenosis										
CEA										
(n=85)	0 (0.0%)	17 (27.5%)	3 (3.6%)	8 (10.8%)	0 (0.0%)	5 (9.4%)	3 (3.6%)	21 (31.5%)	3 (3.6%)	21 (31.5%)
CAS										
(n=60)	0 (0.0%)	15 (27.7%)	1 (1.7%)	7 (15.0%)	0 (0.0%)	4 (8.3%)	1 (1.7%)	18 (33.5%)	1 (1.7%)	18 (33.3%)
p	N/A	0.786	0.479	0.917	N/A	0.994	0.479	0.920	0.479	0.909
Non-high risk, asymptomatic, $< 75\%$ stenosis										
CEA										
(n=147)	1 (0.7%)	19 (18.2%)	6 (4.1%)	13 (9.3%)	2 (1.4%)	12 (11.2%)	6 (4.1%)	28 (24.1%)	8 (5.5%)	30 (25.0%)
CAS										
(n=66)	0 (0.0%)	6 (11.3%)	1 (1.5%)	2 (3.4%)	0 (0.0%)	4 (9.2%)	1 (1.5%)	7 (12.7%)	1 (1.5%)	7 (12.7%)
p	0.504	0.358	0.330	0.123	0.345	0.545	0.330	0.104	0.189	0.067

Data are given as counts (percentages).

CMS: Centers for Medicare and Medicaid Services, MI: myocardial infarction.

symptomatic (49% versus 42% for CEA, $p<0.001$), which is not only different from the CaRESS cohort (~30% in both arms) but also other comparative studies.¹⁻⁶ The CAS patients also had significantly more cardiovascular and cerebrovascular comorbidities, which likely account for the significant differences in the death ($p=0.004$) and MI ($p=0.003$) endpoints. There are notable differences between this registry, with its lack of inclusion/exclusion criteria, predefined surveillance protocol, complete follow-up data, and adjudication, and the many observational and controlled clinical trials comparing the two methods of carotid revascularization. Particularly worrisome are the self-reporting biases typical of any registry. On the other hand, this voluntary registry has an order of magnitude more patients than CaRESS, albeit from a diverse group of centers with no defined participation standards.

It is interesting that one of the only statistically significant differences in the CaRESS study was found in the 4-year composite endpoints of death/stroke (25% CEA versus 14% CAS, $p=0.049$) and death/stroke/MI (25%

CEA versus 14% CAS, $p=0.030$) in patients <80 years old, a subgroup analysis that the SVS VR did not explore. This observation in the CaRESS patients may have been due to clopidogrel treatment in the CAS group (CEA patients were not specifically treated with clopidogrel). This treatment to prevent MI may be more important in the younger (<80) age group than in the patients >80 years. While octogenarians experienced higher all-cause mortality in the CAS arm compared with open surgery, the difference was not statistically significant, perhaps due to other factors associated with this age category, such as vessel tortuosity, arch elongation, and calcification.

Of special note, our analysis of the CaRESS database found no significant differences in outcomes when patients were categorized according to CMS reimbursement categories (risk class, symptom status, or stenosis grade). This observation becomes particularly significant when one considers that only 10% of patients treated in CaRESS would have been eligible for reimbursement using current CMS guidelines. If CMS were to expand

its coverage and remove restrictions for treating high-risk symptomatic patients with moderate (50% to 69%) carotid stenosis and asymptomatic high-risk patients with >80% stenosis, a little over half (54%) of patients treated with CAS in CaRESS would have been reimbursable according to the CMS.

Limitations

The study had the major limitation inherent to any observational cohort study, namely, lack of randomization. Further, there is a potential for type II error with post hoc statistical comparisons between small subgroups with low expected event rates. These subanalyses are potentially underpowered to determine real differences, so caution should be advised regarding statements of observed differences in outcomes between CEA and CAS for the small subgroup comparisons. Further, most of the patients in the study were asymptomatic, but this is common among comparative carotid revascularization trials.^{1–6}

Conclusion

The 4-year results of the CaRESS trial suggested that the risk of death or stroke following CAS using distal protection is equivalent to endarterectomy in a broad-category population with carotid stenosis. There did not appear to be any differences in mortality between treatment arms when comparing high-risk with non-high-risk patients. After 4 years, carotid stenting had a 2-fold higher restenosis rate compared to CEA. It is expected that as further evidence is collected and published, the CMS guidelines will also be expanded to reflect a broader population.

Acknowledgment: The CaRESS Steering Committee would like to thank Christopher Kenwood, MS, at New England Research Institutes, Inc., for his assistance in the statistical analyses for this article.

APPENDIX

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