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# Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)

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## Abstract

**Background—**In the randomised Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the primary endpoint did not differ between carotid artery stenting and carotid



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*By convention, when we refer to CAS results, we are referring to those “allocated to CAS” and similar for CEA.

**Contributors**
VJH wrote the first version of the manuscript. JHV did the statistical analysis. TGB contributed to the writing of the manuscript. All authors commented on and helped with revisions to the manuscript.

**Conflicts of interest**
We declare that we have no conflicts of interest.

endarterectomy in patients with symptomatic and asymptomatic stenosis. A prespecified secondary aim was to examine differences by sex.

**Methods—**Patients who were asymptomatic or had had a stroke or transient ischaemic attack within 180 days before random allocation were enrolled in CREST at 117 clinical centres in the USA and Canada. The primary outcome was the composite of stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years. We used standard survival methods including Kaplan- Meier survival curves and sex-by-treatment interaction term to assess the relation between patient factors and risk of reaching the primary outcome. Analyses were by intention to treat. CREST is registered with ClinicalTrials.gov, NCT00004732.

**Findings—**Between Dec 21, 2000, and July 18, 2008, 2502 patients were randomly assigned to carotid endarterectomy (n=1240) or carotid artery stenting (n=1262), 872 (34•9%) of whom were women. Rates of the primary endpoint for carotid artery stenting compared with carotid endarterectomy were 6•2% versus 6•8% in men (hazard ratio [HR] 0•99, 95% CI 0•66–1•46) and 8•9% versus 6•7% in women (1•35, 0•82–2•23). There was no significant interaction in the primary endpoint between sexes (interaction p=0•34). Periprocedural events occurred in 35 (4•3%) of 807 men assigned to carotid artery stenting compared with 40 (4•9%) of 823 assigned to carotid endarterectomy (HR 0•90, 95% CI 0•57–1•41) and 31 (6•8%) of 455 women assigned to carotid artery stenting compared with 16 (3•8%) of 417 assigned to carotid endarterectomy (1•84, 1•01–3•37; interaction p=0•064).

**Interpretation—**Periprocedural risk of events seems to be higher in women who have carotid artery stenting than those who have carotid endarterectomy whereas there is little difference in men. Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women.

## Introduction

The 2010 US guidelines for management of symptomatic carotid atherosclerosis recommend carotid endarterectomy under class I, level A evidence.[1] The guidelines take into account patient-specific factors such as age, sex, comorbidities, and severity of symptoms.[1] For asymptomatic disease, guidelines also recommend carotid endarterectomy under class I, level A evidence for highly selected patients, on the basis of assessment of comorbid conditions, life expectancy, and individual factors, and take sex into account.[2] Both guidelines suggest that higher perioperative event rates in women than in men might result in smaller gains from carotid endarterectomy for women.[1,2] These guidelines support the use of carotid artery stenting as an alternative to carotid endarterectomy for patients for whom surgery is contraindicated with class IIb, level B evidence, but no recommendations are made about potential sex differences. By contrast, the 2008 guidelines of the European Stroke Organisation do not recommend carotid endarterectomy or carotid artery stenting for asymptomatic individuals and suggest no benefit from carotid endarterectomy for women.[3] For symptomatic patients, the European recommendations for carotid endarterectomy are similar to the US guidelines and take into account sex differences, but angioplasty, carotid artery stenting, or both are only recommended for selected subgroups of patients with severe stenosis with class I, level A evidence.

The statement in the US guidelines that women have a higher perioperative rate of stroke or death than men was based on a post hoc finding from the multicentre US Asymptomatic Carotid Atherosclerosis Study (ACAS).[4,5] Similar results were reported in a prespecified secondary analysis of the multicentre European Asymptomatic Carotid Surgery Trial (ACST),[6] but the results regarding sex were not statistically significant for either trial. Potential sex differences were assessed post hoc in multicentre symptomatic carotid endarterectomy trials;[7,8] however, only the European Carotid Surgery Trial (ECST)[8]

detected a significant increase in perioperative stroke and death in women compared with men.

Although women bear the greater burden from stroke mortality,[9] they have been under-represented in revascularisation trials. Women made up 34% of participants in ACAS,[4] 34% in ACST,[6] 30% in the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[10,11] 30% in ECST,[8] and 30% in the Aspirin and Carotid Endarterectomy (ACE) trial.[12] Similar underrepresentation of women also occurred in randomized trials of carotid artery stenting versus carotid endarterectomy: the percentage of women enrolled in the Stent-Protected Angioplasty versus Carotid Endarterectomy in Symptomatic Patients (SPACE) trial[13] was 28% of 1186 participants and in the International Carotid Stenting Study (ICSS)[14] it was 30% of 1710. Other trials enrolled less than 100 women.[15] Thus, there is a paucity of information available to guide the use of carotid revascularisation in women—the group with the largest absolute burden from stroke.[9]

In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the risk of the primary endpoint (the composite of stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years) did not differ between carotid artery stenting and carotid endarterectomy in patients with asymptomatic and symptomatic carotid artery stenosis.[16] When CREST was designed in the late 1990s, prespecified plans for sex-specific subgroup analyses were included, as were recruitment strategies targeted for women.[17] A recruitment goal of 40% women was set to provide reasonable power to detect potential treatment differences between sexes—ie, to assess whether the overall difference in risk between carotid artery stenting and carotid endarterectomy is shared equally by men and women. We present the results of this *a-priori* plan.

## Methods

### Study Design

Details of the design and primary results of CREST have been reported previously.[16,17] Patients were enrolled at 117 clinical centres in the USA and Canada. Patients who had had a stroke or transient ischaemic attack within 180 days before random allocation were deemed to have a symptomatic artery and were eligible if they had ipsilateral stenosis of at least 50% by angiography, at least 70% by ultrasound, or at least 70% by computed tomographic angiography or magnetic resonance angiography if ultrasound was 50–69%. Patients who had not had a stroke or transient ischaemic attack associated with the study artery within the previous 180 days were judged to have an asymptomatic artery and were eligible if the ipsilateral stenosis was at least 60% by angiography, at least 70% by ultrasound, or at least 80% by computed tomographic angiography or magnetic resonance angiography if ultrasound was 50–69%. Further details on inclusion and exclusion criteria are reported elsewhere.[16,17]

The protocol was approved by the institutional or ethics review boards at participating sites. All participants provided signed informed consent before enrolment.

### Randomisation and masking

Participants were randomly assigned by a web-based system to either carotid artery stenting or carotid endarterectomy. A permuted-block design with random block sizes of two, four, or six was used, and randomization was stratified by centre and symptomatic status. Stroke and myocardial infarction were adjudicated by specialty committees masked to treatment assignment. All other outcomes were unmasked. Investigators and patients were unmasked to treatment allocation.

## Procedure

Procedures were done by CREST-certified interventionalists and surgeons.[18] Patients who had carotid artery stenting were treated with aspirin and clopidogrel 48 h before and for 30 days after the procedure. Patients were treated with the RX Acculink stent (Abbott Vascular Solutions, Santa Clara, CA, USA) and, whenever feasible, the RX Accunet embolic-protection device. Patients who had carotid endarterectomy received aspirin at least 48 h before and for 1 year or more after the procedure. Patients' risk factors were managed in accordance with present standard of care. Full details of the procedures are provided elsewhere.[16,17]

Patients had neurological assessments at 18–54 h, 1 month, and every 6 months after the procedure. For myocardial infarction assessment, cardiac enzymes were obtained 6–8 h after the procedure and electrocardiography (ECG) was done at 6–48 h and 1 month after the procedure.

The primary endpoint for this analysis was the same as for the primary analysis: the composite of any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years after randomisation. Stroke was defined as an acute neurological event with focal symptoms and signs that lasted 24 h or more and was consistent with focal cerebral ischaemia. Myocardial infarction was defined by a creatinine kinase MB or troponin concentration at least twice the upper limit of normal according to the site's laboratory plus either chest pain or symptoms consistent with ischaemia or ECG evidence of ischaemia, including an increase of more than 1 mm in two or more contiguous leads according to the core laboratory or ST-segment depression. The periprocedural period was defined as the period from randomisation to 30 days after the procedure; if the procedure was not done within 30 days after randomisation, the periprocedural period was defined as the period from randomisation to 36 days after randomisation.

## Statistical analysis

We used similar analytical approaches to those for the CREST primary results.[16] In addition to the assessment of the primary endpoint, we also assessed components of the primary endpoint, which was preplanned but not explicitly detailed in the protocol. All analyses were by intention to treat. We used standard survival methods to assess the relation between patient factors (treatment, sex, and covariates of age and symptomatic status) and risk of events (the primary composite endpoint and the individual components). We calculated Kaplan-Meier survival curves of treatment and sex differences in risk. We used proportional hazards analysis to estimate the relative risk of treatment groups and sex strata, with interaction terms to test for potential effect modification by sex. Evidence of potential effect modification was assessed with an a-priori decided α level of 0•10. We classed the relative difference in risk as important if the associated interaction p value was below 0•10 (versus the standard 0•05 used for treatment main effects).

CREST was designed to provide 90% power to detect effect modification by sex if the treatment hazard ratio (HR) in one sex was 1•49 and the treatment HR in the other sex was either greater than 2•22 or less than 0•45. We anticipated that the power would be lower to detect differences for the individual components of the primary endpoint. We also assessed whether either symptomatic status or age affected any reported differences in risk according to sex by the introduction of three-way interactions (along with hierarchical two-way interactions); we anticipated that statistical power to detect these differences would be even lower.

CREST is registered with ClinicalTrials.gov, NCT00004732.

### Role of the funding source

Representatives of the study sponsors were involved in the review of the manuscript and review of the study design, but were not directly involved in the collection, management, analysis, or interpretation of the data, the writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Dec 21, 2000, and July 18, 2008, 2502 patients were randomly assigned to carotid endarterectomy (n=1240) or carotid artery stenting (n=1262),[16] 872 (34•9%) of whom were women. Fewer women than men were white, and women had higher prevalence of hypertension, higher mean systolic blood pressure, lower mean diastolic blood pressure, and shorter lesion length than men (table 1). 466 women and 855 men had symptomatic stenosis and 406 women and 775 men had asymptomatic stenosis.

As reported in the primary paper,[16] there was no difference between carotid artery stenting and carotid endarterectomy in the estimated 4-year rates of the primary outcome (7•2% and 6•8%, respectively; HR 1•11, 95% CI 0•81–1•51; p=0•51). Table 2 and the figure provide details of sex-specific event rates. After adjustment for age and symptomatic status, the HR for the primary outcome in women assigned to carotid artery stenting compared with those assigned to carotid endarterectomy was 1•35 (95% CI 0•82 – 2•23; p=0•24). The HR for the primary outcome in men assigned to carotid artery stenting compared with those assigned to carotid endarterectomy was 0•99 (0•66–1•46; p=0•94). There was no evidence of a difference between sexes in the 4-year primary composite outcome (p=0•34).

The primary results paper reported higher 4-year stroke rates (p=0•049) and higher 4-year stroke and death rates (p=0•03) for patients assigned to carotid artery stenting than those assigned to carotid endarterectomy.[16] There was no evidence of a difference between sexes in 4-year rate of stroke (interaction p=0•65) or of stroke or death (0•79; table 2).

There was evidence of a sex-specific difference in the periprocedural component of the primary outcome (interaction p=0•064; table 2). Women assigned to carotid artery stenting had higher rates of periprocedural events than those assigned to carotid endarterectomy (HR 1•84, 95% CI 1•01–3•37; p=0•047). By contrast, there was no evidence of a difference in the periprocedural component of the primary outcome between groups for men (HR 0•90, 95% CI 0•57–1•41; p=0•64). This sex-specific difference in periprocedural event rates seems to be driven by sex-specific differences in periprocedural stroke rates. Women assigned to carotid artery stenting had higher stroke rates in the periprocedural period than did those assigned to carotid endarterectomy (HR 2•63, 95% CI 1•23–5•65; p=0•013) but there was no difference between groups for men (1•39, 0•78–2•48; p=0•26; table 2). Results were similar for rates of periprocedural stroke or death; however, because there were few deaths (13) in the periprocedural period, the stroke or death category is largely comprised of stroke events. Men had a significantly lower periprocedural myocardial infarction event rate after carotid artery stenting compared with carotid endarterectomy (HR 0•34, 95% CI 0•15–0•81; p=0•015) whereas there was no difference between the groups for women (0•92, 0•32–2•62; p=0•87; table 2).

In the assessment of whether sex-specific differences were affected by symptomatic status or age, no interaction reached significance, either for the periprocedural period (interaction p=0•33 for symptomatic status and 0•52 for age) or at 4 years (interaction p=0•35 for symptomatic status and 0•45 for age; data not shown). Table 3 provides results by symptomatic groups, adjusted for age.

## Discussion

No difference between carotid artery stenting and carotid endarterectomy was detected for women or men in the primary endpoint of CREST. However, we did identify a sex difference in the periprocedural rates of stroke, myocardial infarction, or death after carotid artery stenting and carotid endarterectomy. This sex difference was driven by a higher risk of periprocedural stroke after carotid artery stenting in women; the risk of periprocedural stroke did not differ by procedure for men. These results suggest that the possibility of an increased periprocedural risk of stroke in women after carotid artery stenting should be taken into account when selecting treatment for carotid artery disease.

That women have an increased risk of stroke in the 30 days after carotid endarterectomy was first suggested by results from ACAS, clinical reviews, and retrospective series.[4,19–21] Because this increased risk could lessen the long-term benefit of carotid endarterectomy in women, subsequent trials of carotid revascularisation appropriately included subgroup analyses of the primary endpoint by sex. In ECST,[8] women were 29% less likely than men to have a major stroke or die. By contrast, in ACST,[6] NASCET,[10] and the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS),[22] there was no difference by sex detected in the primary endpoint of the trials. For the three large randomised trials of carotid artery stenting versus carotid endarterectomy that preceded CREST—SPACE,[13] the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, and ICSS[14]—the safety results up to 120 days were recently reported in a meta-analysis of individual patient data.[23] Although the investigators did not detect a significant interaction for sex among the 2462 men and 971 women (p=0•24), the relative risk of any stroke or death in patients assigned to carotid artery stenting compared with those assigned to carotid endarterectomy seemed to be higher in men (1•68, 95% CI 1•25–2•25) than in women (1•22, 0•79–1•89).[23] Because of differences in definitions of the primary endpoints (increased assessment of myocardial infarction events in CREST than in the studies in the meta-analysis) and the length of exposure (a periprocedural period of 30–60 days depending on the timing of the procedure in CREST vs 120 days in the meta-analysis), direct comparisons are difficult (panel). However, the results from the meta-analysis are likely to be most similar to the CREST periprocedural stroke or death endpoint for symptomatic patients; although there was no significant evidence of effect modification (interaction p=0•25), the relative risk seemed to be higher in women than in men. Conclusions regarding the comparison of these results with the meta-analysis are not definitive. Results from CREST and the meta-analysis might be concordant because neither reported significant effect modification by sex. Alternatively, the results might be discordant because in CREST there was a higher risk of stroke and death in women than men, whereas in the meta-analysis a higher risk was reported in men than in women. Additional studies are needed before a definitive answer can be reached, but additional pooled analyses including CREST data might provide a partial answer to the question of whether the patient's sex is an important factor in the selection of revascularisation techniques.

Women might be at higher risk of periprocedural stroke and death because of technical difficulties related to the fact that they have smaller internal carotid arteries than men:[21] women, on average, have 40% smaller internal carotid arteries than men.[19] In a post-hoc analysis from ECST, investigators reported no differences between women and men in the amount of stenosis or use of a patch but did note that women had significantly lower height, weight, and body surface area and were older.[24] In CREST, women were more likely than men to be hypertensive and they also had a higher mean systolic blood pressure, lower mean diastolic blood pressure, and lower weight than men. For patients assigned to carotid artery stenting who received a procedural angiogram, the lesion length was significantly shorter for women than for men. Further analyses of procedural angiograms are underway.

Women might be at increased risk of periprocedural stroke from carotid endarterectomy because they have a higher number of postoperative embolic signals than men.[25,26] Also, reduced or impaired cerebrovascular reactivity might be a marker of increased risk, and there might be differences in cerebrovascular reactivity between men and women.[27,28]

Subgroup analyses can lead to spurious findings and should be interpreted with caution; however, to protect against spurious findings, we followed published criteria.[29,30] Specifically, the primary analysis by sex was prespecified and was guided by an a-priori hypothesis, the statistical methods were prespecified, the subgroup was defined by baseline characteristics, and the number of subgroup analyses in CREST was limited.[16,17]

CREST included a targeted recruitment goal for women to provide sufficient statistical power to test for interaction. However, the sample sizes were too small to further subdivide by symptomatic status, age, and other important clinical predictors. Because of the burden of stroke in women and the evidence of a higher periprocedural risk of complications in women than in men, future clinical trials of revascularisation for the management of carotid atherosclerosis should aim to enroll a larger number of women. Indeed, the National Institutes of Health now mandates that clinical trials be designed and undertaken to provide for valid analyses to test for sex interaction.[31]

The findings we report might also be a result of spurious relations introduced as a natural product of the large number of associations that were assessed. For several reasons (eg, complexities of the effect of the association between tests, and challenges in defining whether adjustments need to be made for comparisons in this paper or a series of papers), we did not make a formal adjustment to the p values, but rather urge caution in the interpretation of these results.

Panel: Research in context

Systematic review

Members of our team were among the investigators in the Asymptomatic Carotid Atherosclerosis Study (ACAS), which was the first carotid endarterectomy trial to report the post-hoc finding that women had a higher perioperative stroke and death rate than men; however, this finding was not statistically significant. Accordingly, we have done previous literature searches for publications on this topic.[15] Additionally, we searched PubMed for articles published in English, from 1991 to November, 2010, with the terms “clinical trials”, “carotid endarterectomy”, and “carotid stenting.” References within these papers were also checked for additional related citations. The papers were manually reviewed and were restricted to multicentre randomised trials and available information on enrolment and outcomes of women. The meta-analysis of the Carotid Stenting Trialists’ Collaboration,[23] in which the individual patient data from three trials were analysed, is the most comparable to the symptomatic patients in this study, although the periprocedural periods differ.

Interpretation

Based on ACAS and other studies, we did this a-priori subgroup analysis with the hypothesis that carotid artery stenting would pose lower risk than carotid endarterectomy in women. Although there was no evidence of a relative difference in the 4-year primary composite outcome by sex, the periprocedural stroke risk for women in the carotid artery stenting group was more than twice the risk in those in the carotid endarterectomy group, whereas there was little difference in men. The meta-analysis also did not detect a sex difference,[23] but failure to detect a difference does not establish the absence of a sex difference. This study adds to previous findings by showing a higher periprocedural risk

from carotid artery stenting in women, providing evidence that our hypothesised benefit for women treated with carotid artery stenting is not present. This additional information supports that the sex of the patients should be taken into account in decisions for treatment of carotid disease. Additional pooled analyses of data including CREST might provide a partial answer to the question of whether the patient's sex is an important consideration in selecting revascularisation technique.

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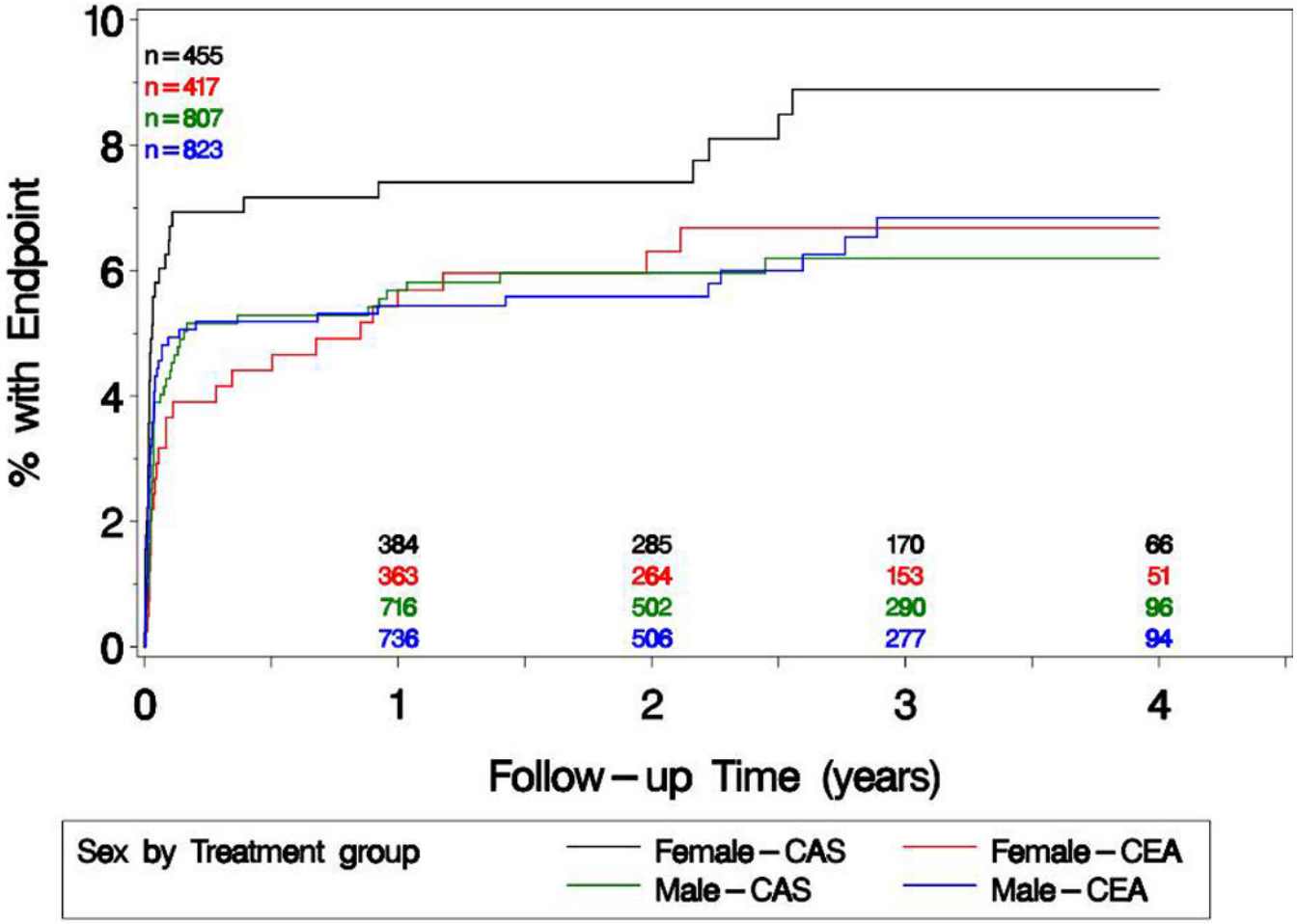


**Figure.**

Percent of patients with primary endpoint according to sex and treatment group, by follow-up year using Kaplan-Meier curves. The primary endpoint was a composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization. The number of patients at risk at each year of follow-up is provided. Black is for females in the CAS group, red is for females in the CEA group, green is for males in the CAS group, and blue is for males in the CEA group.

**Table 1**

Demographics and clinical characteristics

| | Overall | | | Women | | Men | |
|---|---|---|---|---|---|---|---|
| | **Women (n=872)** | **Men (n=1630)** | **p value** | **CAS (n=455)** | **CEA (n=417)** | **CAS (n=807)** | **CEA (n=823)** |
| Age (years) | 69.2 (9.2) | 69.0 (8.6) | 0.66 | 69.4 (9.3) | 68.9 (9.4) | 68.6 (8.7) | 69.3 (8.4) |
| White | 801/872 (91.9%) | 1531/1630 (93.9%) | 0.05 | 415/455 (91.2%) | 386/417 (92.6%) | 757/807 (93.8%) | 774/823 (94.1%) |
| Asymptomatic | 406/872 (46.6%) | 775/1630 (47.5%) | 0.64 | 215/455 (47.3%) | 191/417 (45.8%) | 379/807 (47.0%) | 396/823 (48.1%) |
| Hypertension | 766/868 (88.3%) | 1375/1624 (84.7%) | 0.014 | 409/454 (90.1%) | 357/414 (86.2%) | 671/805 (83.4)% | 704/819 (86.0%) |
| Diabetes | 274/868 (31.6%) | 485/1621 (29.9%) | 0.40 | 146/453 (32.2%) | 128/415 (30.8%) | 238/804 (29.6%) | 247/817 (30.2%) |
| Dyslipidaemia | 729/864 (84.4%) | 1364/1617 (84.4%) | 0.99 | 375/454 (82.6%) | 354/410 (86.3%) | 665/800 (83.1%) | 699/817 (85.6%) |
| Present smoker | 236/852 (27.7%) | 410/1608 (25.5%) | 0.24 | 127/446 (28.5%) | 109/406 (26.9%) | 202/798 (25.3%) | 208/810 (25.7%) |
| Left lesion | 461/872 (52.9%) | 826/1630 (50.7%) | 0.30 | 227/455 (49.9%) | 234/417 (56.1%) | 412/807 (51.1%) | 414/823 (50.3%) |
| Systolic blood pressure (mm Hg)* | 142.9 (21.5) | 140.7 (19.7) | 0.01 | 143.1 (22.1) | 142.6 (21.0) | 140.8 (19.0) | 140.5 (20.3) |
| Diastolic blood pressure (mm Hg)† | 72.6 (12.1) | 74.7 (11.1) | <0.0001 | 72.5 (12.4) | 72.8 (11.9) | 74.8 (11.0) | 74.5 (11.2) |
| Weight (lbs)‡ | 163.2 (62.6) | 189.3 (35.5) | <0.0001 | 161.2 (35.5) | 165.4 (82.4) | 190.3 (34.2) | 188.3 (36.6) |
| Minimal lumen§¶ | 1.3 (1.1) | 1.3 (2.1) | 0.83 | 1.3 (1.1) | --- | 1.3 (2.1) | --- |
| Lesion length¶// | 16.4 (8.2) | 18.2 (8.8) | 0.0002 | 16.4 (8.2) | --- | 18.2 (8.8) | --- |

Data are mean (SD) or n/N (%). There were no significant differences by treatment between sexes. CAS=carotid artery stenting. CEA=carotid endarterectomy.

*Data available for 855 women (445 CAS and 410 CEA) and 1614 men (802 CAS and 812 CEA).

†Data available for 857 women (447 CAS and 410 CEA) and 1612 men (800 CAS and 812 CEA).

‡Data available for 854 women (443 CAS and 411 CEA) and 1606 men (799 CAS and 807 CEA).

§Data available for 414 women and 743 men.

¶Values taken from the procedural angiogram so only available on patients randomly assigned to CAS who had a procedural angiogram.

//Data available for 426 women and 763 men.

**Table 2**

Primary endpoint and components of the primary endpoint

| | Periprocedural period | | | | | | 4-year period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CAS group: number of events (% [SE])* | CEA group: number of events (% [SE])* | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value | CAS group: number of events (% [SE])‡ | CEA group: number of events (% [SE])‡ | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value |
| **Primary endpoint§** | | | | | | | | | | | | |
| Men | 35 (4·3% [0·7]) | 40 (4·9% [0·7]) | −0·5% (−2·6 to 1·5) | 0·90 (0·57 to 1·41) | 0·64 | 0·064 | 48 (6·2% [0·9]) | 50 (6·8% [1·0]) | −0·6% (−3·2 to 1·9) | 0·99 (0·66 to 1·46) | 0·94 | 0·34 |
| Women | 31 (6·8% [1·2]) | 16 (3·8% [0·9]) | 3·0% (0·0 to 5·9) | 1·84 (1·01 to 3·37) | 0·047 | .. | 37 (8·9% [1·4]) | 26 (6·7% [1·3]) | 2·2% (−1·6 to 6·0) | 1·35 (0·82 to 2·23) | 0·24 | .. |
| **Myocardial infarction** | | | | | | | | | | | | |
| Men | 7 (0·9% [0·4]) | 21 (2·6% [0·3]) | −1·7% (−2·9 to −0·4) | 0·34 (0·15 to 0·81) | 0·015 | 0·16 | .. | .. | .. | .. | .. | .. |
| Women | 7 (1·5% [0·6]) | 7 (1·7% [0·6]) | −0·1% (−1·8 to 1·5) | 0·92 (0·32 to 2·62) | 0·87 | .. | .. | .. | .. | .. | .. | .. |
| **Stroke¶** | | | | | | | | | | | | |
| Men | 27 (3·3% [0·6]) | 20 (2·4% [0·5]) | 0·9% (−0·7 to 2·5) | 1·39 (0·78 to 2·48) | 0·26 | 0·19 | 40 (5·2% [0·8]) | 31 (4·5% [0·8]) | 0·7% (−1·6 to 3·0) | 1·34 (0·84 to 2·15) | 0·22 | 0·65 |
| Women | 25 (5·5% [1·1]) | 9 (2·2% [0·7]) | 3·3% (0·8 to 5·9) | 2·63 (1·23 to 5·65) | 0·013 | .. | 32 (7·8% [1·4]) | 19 (5·0% [1·1]) | 2·8% (−0·7 to 6·3) | 1·60 (0·9 to 2·82) | 0·11 | .. |
| **Stroke or death‖** | | | | | | | | | | | | |
| Men | 30 (3·7% [0·7]) | 20 (2·4% [0·5]) | 1·3% (−0·4 to 3·0) | 1·55 (0·88 to 2·73) | 0·13 | 0·28 | 43 (5·6% [0·8]) | 31 (4·5% [0·8]) | 1·1% (−1·3 to 3·4) | 1·44 (0·91 to 2·29) | 0·12 | 0·79 |
| Women | 25 (5·5% [1·1]) | 9 (2·2% [0·7]) | 3·3% (0·8 to 5·9) | 2·63 (1·23 to 5·65) | 0·013 | .. | 32 (7·8% [1·4]) | 19 (5·0% [1·1]) | 2·8% (−0·7 to 6·3) | 1·60 (0·90 to 2·82) | 0·11 | .. |

For death, stroke, and myocardial infarction outcomes, patients might have had more than one event (eg, fatal stroke events are included in both death and stroke outcomes, individuals might have both an ipsilateral and a subsequent non-ipsilateral stroke). CAS=carotid artery stenting. SE=standard error. CEA=carotid endarterectomy. HR=hazard ratio.

*Because of the short periprocedural period that minimises censoring, event rates and absolute differences in event rates were calculated as a proportion of patients with events.

†Adjusted for age and symptomatic status. For the periprocedural period, all patients were censored at the end of their periprocedural period.

[‡] Kaplan-Meier survival estimates.

[§] Defined as any stroke, myocardial infarction, or death for the periprocedural period and any stroke, death, or myocardial infarction within the periprocedural period plus postprocedural ipsilateral stroke for the 4-year period.

[¶] Defined as any stroke for the periprocedural period and any stroke within the periprocedural period plus postprocedural ipsilateral stroke for the 4-year period.

[//] For the periprocedural period includes any stroke or death and for the 4-year period includes any stroke or death in the periprocedural period plus postprocedural ipsilateral stroke.

## Table 3

Primary endpoint and components of the primary endpoint by symptomatic groups

| | Periprocedural period | | | | | | 4-year period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CAS group: number of events (% [SE])* | CEA group: number of events (% [SE])* | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value | CAS group: number of events (% [SE])‡ | CEA group: number of events (% [SE])‡ | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value |
| **Symptomatic patients** | | | | | | | | | | | | |
| Primary endpoint§ | | | | | | | | | | | | |
| Men | 23 (5·4% [1·1]) | 26 (6·1% [1·2]) | −0·7 (−3·8 to 2·4) | 0·88 (0·50 to 1·55) | 0·66 | 0·04 | 29 (6·9% [1·2]) | 33 (8·5% [1·5]) | −1·7 (−5·4 to 2·1) | 0·87 (0·53 to 1·44) | 0·59 | 0·19 |
| Women | 22 (9·2% [1·9]) | 9 (4·0% [1·3]) | 5·2 (0·7 to 9·6) | 2·33 (1·07 to 5·07) | 0·033 | .. | 26 (11·7% [2·2]) | 17 (8·2% [1·9]) | 3·5 (−2·2 to 9·2) | 1·49 (0·81 to 2·74) | 0·20 | .. |
| Myocardial infarction | | | | | | | | | | | | |
| Men | 3 (0·7% [0·4]) | 12 (2·8% [0·8]) | −2·1 (−3·9 to −0·4) | 0·25 (0·07 to 0·88) | 0·030 | 0·11 | .. | | .. | | .. | .. |
| Women | 4 (1·7% [0·8]) | 3 (1·3% [0·8]) | 0·3 (−1·9 to 2·5) | 1·26 (0·28 to 5·63) | 0·76 | .. | .. | | .. | | .. | .. |
| Stroke ¶ | | | | | | | | | | | | |
| Men | 19 (4·4% [1·0]) | 15 (3·5% [0·9]) | 0·9 (−1·7 to 3·5) | 1·28 (0·65 to 2·52) | 0·47 | 0·17 | 25 (6·0% [1·2]) | 23 (6·2% [1·3]) | −0·2 (−3·7 to 3·2) | 1·10 (0·62 to 1·94) | 0·74 | 0·41 |
| Women | 18 (7·5% [1·7]) | 6 (2·7% [1·1]) | 4·8 (0·9 to 8·8) | 2·80 (1·11 to 7·07) | 0·030 | .. | 23 (10·4% [2·1]) | 14 (6·9% [1·8]) | 3·6 (−1·8 to 9·0) | 1·58 (0·81 to 3·08) | 0·18 | .. |
| Stroke or death // | | | | | | | | | | | | |
| Men | 22 (5·1% [1·1]) | 15 (3·5% [0·9]) | 1·6 (−1·1 to 4·4) | 1·49 (0·77 to 2·87) | 0·23 | 0·25 | 28 (6·7% [1·2]) | 23 (6·2% [1·3]) | 0·5 (−3·0 to 3·9) | 1·23 (0·71 to 2·14) | 0·46 | 0·56 |
| Women | 18 (7·5% [1·7]) | 6 (2·7% [1·1]) | 4·8 (0·9 to 8·8) | 2·80 (1·11 to 7·07) | 0·030 | .. | 23 (10·4% [2·1]) | 14 (6·9% [1·8]) | 3·6 (−1·8 to 9·0) | 1·58 (0·81 to 3·08) | 0·18 | .. |
| **Asymptomatic patients** | | | | | | | | | | | | |
| Primary endpoint§ | | | | | | | | | | | | |
| Men | 12 (3·2% [0·9]) | 14 (3·5% [0·9]) | −0·4 (−2·9 to 2·2) | 0·93 (0·43 to 2·01) | 0·85 | 0·72 | 19 (5·5% [1·3]) | 17 (5·0% [1·2]) | 0·5 (−2·9 to 4·0) | 1·24 (0·65 to 2·39) | 0·52 | 0·83 |
| Women | 9 (4·2% [1·4]) | 7 (3·7% [1·4]) | 0·5 (−3·3 to 4·3) | 1·18 (0·44 to 3·16) | 0·75 | .. | 11 (5·7% [1·7]) | 9 (4·8% [1·6]) | 0·9 (−3·7 to 5·4) | 1·08 (0·45 to 2·62) | 0·86 | .. |

| | Periprocedural period | | | | | | 4-year period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CAS group: number of events (% [SE])* | CEA group: number of events (% [SE])* | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value | CAS group: number of events (% [SE])‡ | CEA group: number of events (% [SE])‡ | Treatment effect (95% CI) | HR (95% CI)† | p value | Interaction p value |
| Myocardial infarction | | | | | | | | | | | | |
| Men | 4 (1·1% [0·5]) | 9 (2·3% [0·7]) | −1·2 (−3·0 to 0·6) | 0·48 (0·15 to 1·56) | 0·22 | 0·74 | .. | .. | .. | .. | .. | .. |
| Women | 3 (1·4% [0·8]) | 4 (2·1% [1·0]) | −0·7 (−3·3 to 1·9) | 0·67 (0·15 to 3·01) | 0·60 | .. | .. | .. | .. | .. | .. | .. |
| Stroke ¶ | | | | | | | | | | | | |
| Men | 8 (2·1% [0·7]) | 5 (1·3% [0·6]) | 0·8 (−1·0 to 2·7) | 1·75 (0·57 to 5·37) | 0·33 | 0·82 | 15 (4·4% [1·1]) | 8 (2·7% [1·0]) | 1·7 (−1·2 to 4·7) | 2·16 (0·91 to 5·10) | 0·08 | 0·71 |
| Women | 7 (3·3% [1·2]) | 3 (1·6% [0·9]) | 1·7 (−1·3 to 4·6) | 2·11 (0·55 to 8·15) | 0·28 | .. | 9 (4·8% [1·6]) | 5 (2·7% [1·2]) | 2·1 (−1·8 to 6·0) | 1·59 (0·53 to 4·75) | 0·40 | .. |
| Stroke or death // | | | | | | | | | | | | |
| Men | 8 (2·1% [0·7]) | 5 (1·3% [0·6]) | 0·8 (−1·0 to 2·7) | 1·75 (0·57 to 5·37) | 0·33 | 0·82 | 15 (4·4% [1·1]) | 8 (2·7% [1·0]) | 1·7 (−1·2 to 4·7) | 2·16 (0·91 to 5·10) | 0·08 | 0·71 |
| Women | 7 (3·3% [1·2]) | 3 (1·6% [0·9]) | 1·7 (−1·3 to 4·6) | 2·11 (0·55 to 8·15) | 0·28 | .. | 9 (4·8% [1·6]) | 5 (2·7% [1·2]) | 2·1 (−1·8 to 6·0) | 1·59 (0·53 to 4·75) | 0·40 | .. |

For death, stroke, and myocardial infarction outcomes, patients might have had more than one event (eg, fatal stroke events are included in both death and stroke outcomes, and individuals might have both an ipsilateral and a subsequent non-ipsilateral stroke). CAS=carotid artery stenting. SE=standard error. CEA=carotid endarterectomy. HR=hazard ratio.

*Because of the short periprocedural period that minimises censoring, event rates and absolute differences in event rates were calculated as a proportion of patients with events.

†Adjusted for age and symptomatic status. For the periprocedural period, all patients were censored at the end of their periprocedural period.

‡Kaplan-Meier survival estimates.

§Defined as any stroke, myocardial infarction, or death for the periprocedural period and any stroke, death, or myocardial infarction within the periprocedural period plus postprocedural ipsilateral stroke for the 4-year period.

¶Defined as any stroke for the periprocedural period and any stroke within the periprocedural period plus postprocedural ipsilateral stroke for the 4-year period.

//For the periprocedural period includes any stroke or death, and for the 4-year period includes any stroke or death in the periprocedural period plus postprocedural ipsilateral stroke.