A comparative analysis of the outcomes of carotid stenting and carotid endarterectomy in women

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Objective: Randomized controlled trials (RCTs) of carotid endarterectomy (CEA) advised little benefit from surgery in women because of high operative risk. Whether these findings are also applicable to carotid angioplasty and stenting (CAS) is subject of investigation. Our aim was to determine the risk of perioperative and late complications related to CAS and CEA in women.

Methods: Data from a single-center carotid surgery database including 1065 individuals with CAS (306 women and 759 men) and 1131 with CEA (325 women and 806 men) were analyzed in a consecutive series of patients. Perioperative risks of death, stroke, and local complications in women undergoing CAS and CEA were compared. Rates of restenosis >50% and stroke at 5 years in symptomatic and asymptomatic women were also assessed.

Results: The perioperative risks of stroke or death were no different in women who underwent CAS and CEA women (1.9% vs 3.0%; odds ratio [OR] = 0.63; 95% confidence interval [CI], 0.20-1.7; P = .45) whether they were symptomatic or not. Other perioperative complications were also similarly distributed between the two groups of women. Life-table estimates of any periprocedural stroke/death and ipsilateral stroke at 5 years after the procedure did not differ between women with CAS and CEA (4.1% vs 8.1%; P = .18). Five-year rates of restenosis >50% were nonsignificantly higher in women after CEA than after CAS (1.8% vs 8.1%; P = .058).

Conclusion: Women with carotid stenosis might have favorable early and late outcomes from CAS with complication rates similar and even lower than those attained with CEA. CAS, performed by trained operators, may be a valid primary choice for treatment of carotid stenosis, particularly in asymptomatic women for whom the risk of surgery seems to be higher. However, before claiming CAS for women, these results need to be confirmed by large RCTs.

The clinical and public health impact of stroke on women has gained increasing relevance during recent years in terms of worse outcomes (higher lethality, disability, and poor quality of life in women after a stroke) and larger prevalence due to the increased life expectancy of female gender.

In addition, benefit of preventive treatments may be consistently poorer in women than in men. Female gender has been identified as a potential factor affecting poor perioperative stroke and death rates associated with carotid endarterectomy (CEA), the “gold standard” treatment for patients with severe carotid disease. In patients with carotid stenosis, gender differences in treatment outcome have been reported in all large randomized controlled trials (RCT) comparing best medical therapy to CEA. Women with symptomatic or asymptomatic carotid stenosis were shown to have a high operative risk during CEA but a low risk of neurologic events when treated with medical therapy alone. Therefore, the benefit from CEA (highly effective in preventing strokes in male patients) is still questionable in females, and doubts about advantages of carotid revascularization have been raised.

Carotid angioplasty stenting (CAS) was developed to be a less invasive alternative for carotid artery revascularization in “high-risk” surgery patients. Recently published RCTs questioned the benefit of CAS mainly in patients with symptomatic carotid stenosis. Nevertheless, the benefit of CAS in specific subgroups of patients with carotid stenosis, particularly females and asymptomatics, is still unclear.

While based on CEA RCT data, most women might be assumed to be “high-risk” surgery patients, mainly for the high perioperative hazard; whether similar concerns regarding the unfavorable risk-to-benefit stroke ratio in women after CEA are also applicable to CAS remains a subject of investigation.

Therefore, the aim of this study was to analyze periprocedural risks and long-term durability of carotid revascularization in women after CAS and CEA procedures.

MATERIALS AND METHODS

Patients in a prospectively compiled computerized database of all primary extracranial carotid revascularizations (CAS and CEA) performed at a single center from January 1, 2004, to January 1, 2009, with >60% symptomatic or >70% asymptomatic carotid stenosis were reviewed. The revascularization treatment choice (CAS/CEA) was left to the discretion of the treating surgeon according to periprocedural risk evaluation, such as plaque and vessel morphology, neurologic status, and comorbidities. Although, after the learning curve phase, CAS was more widely applied also
to the common “standard-risk” population, sharing indications similar to CEA, there was a higher preference for CAS in patients with comorbidities such as coronary or respiratory disease or contralateral occlusion. Conversely, lessons from the learning curve experience of CAS allowed us to favor CEA in the elderly and in patients with hypoechoic or strongly calcified carotid plaque at ultrasound scan evaluation or difficult access (peripheral artery disease). For the purpose of the study, patients who underwent revascularization for recurrent carotid stenosis and bypass grafts were excluded.

To avoid bias due to the learning curve effect of the operators, patients with CAS performed within the training phase (2001-2003 interval) were excluded. According to our experience, the caseload necessary to perform safe CAS (assuming 2% as the safety threshold/year for major peri-procedural complication rate) included the first 195 procedures. It was after this training (collected in the same group of operators who also performed procedures in the following years) that the rate of disabling strokes (mainly occurring during the most challenging phases of the CAS procedure such as catheterization, requiring expert skills) significantly decreased and remained stable at <2% for each of the following years (>2004). These data have been published in previous reports.10,11

CAS was carried out following a standardized protocol in an endovascular room equipped with a high-quality fixed imaging system (Axiom Artis FA; Siemens, Erlangen, Germany). On-table rotational angiography was used in selected cases to better visualize the stenosis and to select the optimal working projection.

Percutaneous transfemoral or transbrachial approaches under local anesthesia were used. Neurologic status was continuously monitored, and transcranial Doppler (TCD 4040 Pyoneer EME) monitoring was used when possible. Intravenous heparin (100 U/kg) was given routinely before selective catheterization of the common carotid artery (CCA) and not reversed at the end of the procedure.

All procedures were performed with cerebral protection devices (CPD) and different stent models (open cell, close cell, or hybrid configuration [tapered or straight]). The choice of specific material depended on vessel anatomy and lesion characteristics. CPDs were proximal occlusion devices: (n = 16, 5.2%) MO.MA System (Invatec, Roncadelle, Italy) or distal filters: (n = 290) FilterWire EZ system (Boston Scientific, Natick, Mass) (n = 225, 73.5%); Angioguard RX Filter (Johnson and Johnson-Cordis, Warren, NJ) (n = 27, 8.8%); Emboshield Filter (Abbott Laboratories, Abbott Park, Ill) (n = 27, 8.8%); Rx Accunet Filter (Guidant; Santa Clara, Calif) (n = 4, 1.3%); Rubicon Filter (Rubicon Medical Inc, Salt Lake City, Utah) (n = 1, 0.3%); SpideRX Filter (EV3, Plymouth, Minn) (n = 6, 1.9%).

Self-expandable stents were close-cell design/elgiloy fabric in 180 cases (58.8%) (n = 157 Carotid Wallstents, Boston Scientific Corp, Natick, Mass); (n = 23) Xact (Abbott Vascular Devices, Redwood City, Calif) and open cell/nitinol made in 126 (41.2%; n = 91) Precise stents (Johnson and Johnson-Cordis) (n = 11) PROTEGE Rx Stent System (EV3), (n = 8) Acculink (Guidant); and (n = 16) multidesigned Cristallo Ideale (Invatec).

Stent size and length were chosen according to preoperative measurements of the target vessel by Doppler ultrasound scan examination. Closure devices for the access control have been used since 2006.

Consecutive primary CEAs performed from January 2001 to August 2007 were included in the analysis. CEAs performed in the last 2 years (2007-2008) were excluded to avoid possible selection bias because of the increasing trend to perform CAS as a primary choice in most patients, restricting CEA to a minority and most hazardous cases in the more recent period.

CEA was performed under local or general anesthesia. A shunt was used selectively according to clamping intolerance. Eversion or patch and occasionally direct closure were used. Patient monitoring followed the same modality as CAS in awake patients; TCD flow velocity or stump pressure measurements were used when general anesthesia was employed. Systemic heparinization was used at the same dosage as CAS and then reversed after carotid declamping.

**Patient evaluation.** Features and time of preoperative symptoms were evaluated by external neurologic audit. Patients were defined symptomatic when ipsilateral hemispheric or retinal symptoms occurred within 6 months from the procedure.

The degree and characteristics of carotid stenosis at baseline and during follow-up were assessed with duplex ultrasound scan by experienced operators who defined site, degree, length of stenosis, plaque characteristics, and vessel measurements previously validated against angiography as a gold standard technique. Two carotid measurements were additionally recorded by ultrasound scan before CAS: CCA (2 cm below the bulb) and internal carotid diameter (ICA 2 cm above the carotid bulb, or in case of longer plaques distal to the plaque end). In the group of patients with CEA, we did not take specific carotid vessel diameter measurements. Carotid plaque was defined as “complex plaque” according to the duplex ultrasound scan appearance of prevalence of hypoechoic pattern (suggesting for presence of hemorrhage, thrombus, and fatty tissues). However, in CEA, morphologic assessment was confirmed by intraoperative macroscopic evaluation.

Contrast-enhanced computed tomography (CTA) was performed selectively, in case of uncertainty at ultrasound scan examination. The degree of stenosis was always confirmed by visual evaluation with angiography during CAS. Cerebral CT scan was used in symptomatic patients to assess the extent of recent lesions if any.

Patients scheduled for CAS received antiplatelet therapy consisting of acetylsalicylic acid (mean dosage 125 mg/die) and clopidogrel (75 mg/die) for at least 30 days after a 300-mg leading dose administered 12 hours before CAS. In patients who underwent CEA, single antiplatelet medication was not discontinued for surgery. Written consent was obtained from all patients before revascularization.
Clinical and ultrasound scan examinations were scheduled at 6 months, 12 months, and yearly thereafter. Carotid restenosis was set at >50%. Patients were instructed to report any new neurologic symptoms occurring after hospital discharge. When neurologic symptoms or uncertainty occurred anytime after the procedure, patients were evaluated by a certified neurologist expert in vascular disease.

**Outcome measures.** Stroke was defined as any new hemispheric or retinal neurologic event persisting >24 hours and classified as fatal, disabling (modified Rankin Score ≥3), or nondisabling (modified Rankin Score <3). Myocardial infarction (MI) was diagnosed by the cardiologist in the occurrence of persistent ST segment changes on electrocardiogram and/or new Q wave in two leads or the presence of elevated enzymes (including troponin >0.1 ng/mL).

Primary outcome was the combined risk of any stroke or death within 30 days. Secondary outcomes were any stroke, disabling stroke, transient ischemic attack (TIA), MI, and local complications (hematoma or nerve palsy) occurring within 30 days. Late outcomes included the combined endpoint of ipsilateral stroke after the procedure plus any periprocedural stroke or death, and the rate of any stroke, death, and restenosis after the procedure.

**Statistical analysis.** In assessing outcome, patients were analyzed according to the treatment they received (on-treatment analysis). Patients who were scheduled for CAS, and eventually converted to CEA because of CAS failure, were analyzed according to the treatment they actually received.

Tests of statistical significance comparing women and men were conducted using $\chi^2$ and Fisher’s exact test for categoric variables, analysis of variance (ANOVA), and $t$ test for continuous variables. Unadjusted and adjusted odds ratios (ORs) with correspondent 95% confidence intervals (CIs) were used to compare outcomes between genders.

The association between demographic, clinical, and procedural characteristics, and the combined periprocedural (within 30 days) risk of any stroke or death was first assessed by univariate logistic method. Analyses were stratified by preoperative symptoms to compensate for evident differences in symptomatic and asymptomatic distribution of patients.

Multivariable logistic regression analyses using backward elimination methods were performed to adjust for potential confounders including age, CAS vs CEA procedure, preoperative symptoms, contralateral occlusion, coronary disease, peripheral artery disease, diabetes, hypertension, history of hyperlipidemia requiring statin therapy, and “complex” carotid plaque. Sensitivity analyses were performed to adjust for technical details used in each CAS or CEA group. Interactions among the covariates and female gender were assessed in models stratified by CAS or CEA in which procedure-specific technical factors were tested (in CEA analysis: anesthesia, shunt, primary closure; in CAS analysis: open vs close cell design of the stent, occlusion vs filter cerebral protection device model). Results from multivariable analysis are presented as hazard ratios (HRs) with 95% CIs.

The rates of endpoints at 5 years were estimated with the Kaplan-Meier method to compensate for patient dropouts, and the level of significance was calculated with log-rank test and its SE. The Kaplan-Meier curves were computed for symptomatic and asymptomatic patients using stroke as an endpoint (late ipsilateral stroke and any periprocedural stroke/death). Curves were displayed up to a value of SE <0.10%. For all tests, a probability value of $P < .05$ was considered statistically significant. StatCalc-EPINFO 6.0/PC v 3.5.1 and SPSS/PC v 13.00 Win package (SPSS for Windows, Chicago, Ill, 2003) were used for all data analyses.

**RESULTS**

Over the study period, a total of 2196 interventions for primary carotid stenosis were performed in 1951 patients: 1065 CAS (in 971 patients) and 1131 CEA (in 980 patients).

A total of 306 CAS were performed in 282 women and 759 CAS were performed in 689 men. Three hundred twenty-five CEAs were performed in 285 woman and 806 in 695 men.

**Comparison between women who underwent CAS and CEA.** Demographic and baseline data for the CAS and CEA groups are displayed in Table 1. A greater number of asymptomatic women were treated with CAS (78.8% vs 67.7%, in CAS and CEA, respectively; $P = .002$) due to a higher preference to perform CEA in the presence of “complex”/hypoechoic carotid plaque (34.5% vs 26.8% in CAS and CEA, respectively; $P = .04$). CAS was less likely in women with difficult endoluminal access to carotid vessels for the presence of peripheral vascular disease (7.4% vs 12.6% in CAS and CEA, respectively; $P = .035$). Women who underwent CEA compared to those who underwent CAS were less likely to present contralateral carotid occlusion (2.8% vs 6.4%; $P = .002$), history of hyperlipidemia (54.7% vs 64%; $P = .02$) and coronary disease (22.8% vs 31.6%; $P = .02$).

**Periprocedural outcomes.** Six women failed CAS (procedure success rate 98%) because of impossibility to approach or cross the carotid lesion (n = 5) or because of acute stent thrombosis (n = 1) and were converted to CEA. In one of these women, a mild arm and leg deficit developed after CAS due to incomplete carotid plaque coverage by stenting (plaque protrusion through stent struts). Neurologic deficit resolved completely after conversion to CEA. No other complications occurred among women converted to CEA with the exception of one neck hematoma. There was no technical failure in the CAS group of women who underwent CEA.

There were no significant overall differences in periprocedural outcomes between women who underwent CAS and CEA. No deaths occurred in the CAS group, while 2 women died after CEA, 1; one patient died from cardiac complications and the other for fatal stroke. The risk of periprocedural stroke or death was slightly lower in the
CAS group compared to those who underwent CEA (1.9% vs 3.0%; \(P = .45\); \text{Table II}). The tendency toward a lower risk in CAS women who underwent CAS was more evident in the asymptomatic subgroup (1.2% vs 3.2%; \(P = .2\)). In the symptomatic subgroup of women, stroke risk was non-significantly higher in CAS: 4.6% vs 1.9%; \(P = .37\). Other outcome measures in the CAS group compared to women who underwent CEA are reported in \text{Table II}. Distribution of minor neurologic events (3.2% vs 1.2%; \(P = .1\)) and local hematoma (1.6% vs 2.8%; \(P = .8\)) were higher in women who underwent CAS, even though not significantly different from those in the CEA group. There was a higher rate of major adverse cardiac events (MACEs) (2.3% vs 3.7% in CAS vs CEA; \(P = .35\)) and nerve palsy in CEA women population (0.5% vs 1.9% in CAS vs CEA, respectively; \(P = .25\)).

Univariate analysis demonstrated that the only factor significantly associated with a periprocedural stroke or death risk in women was history of hyperlipemia requiring statin therapy (OR, 0.30; 95% CI, 0.10-0.88; \(P = .036\)). In multivariable logistic regression analysis after adjusting for confounding factors, the history of hyperlipemia requiring use of statins (HR, 0.3; 95% CI, 0.10-0.88; \(P = .028\)) was confirmed as the only negative predictor for the primary outcome. Multivariable analyses stratified by procedure and adjusting also for technical details (anesthesia, shunt, patch in CEA, open cell stent, occlusion vs filter protection device for CAS) failed to show any significant predictor in both the subgroup of females who underwent CAS and CEA.

Late outcomes. Mean follow-up was 22.8 ± 19 months (range, 1-60 months) in the CAS group and 24.5 ± 19 (range, 1-74 months) in the CEA group of women. During the observation period, 27 females died, n = 17 after CAS, n = 10 after CEA. In the CAS group, two fatal strokes (one hemorrhagic), seven cancer, and eight cardiac deaths occurred; in the CEA group, there were three fatal strokes (one hemorrhagic), two cancer, and five cardiac deaths. Kaplan-Meier survival analysis showed no difference in 5-year survival between the CAS and CEA groups (86.4% vs 91.2%; \(P = .11\); \text{Fig 1}). The incidence of

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### Table I. Baseline characteristics of 631 women in CAS vs CEA

<table>
<thead>
<tr>
<th></th>
<th>CAS group ((n = 306)) n (%)</th>
<th>CEA group ((n = 325)) n (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>characteristics</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age (mean [range])</td>
<td>71.18 ± 7.6 (46-87)</td>
<td>71.23 ± 7.6 (48-87)</td>
<td>1.00</td>
<td>0.89-1.2</td>
<td>.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>264 (86.2)</td>
<td>271 (83.3)</td>
<td>1.25</td>
<td>0.90-1.8</td>
<td>.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>87 (28.4)</td>
<td>94 (28.9)</td>
<td>1.02</td>
<td>0.79-1.4</td>
<td>.93</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>23 (7.4)</td>
<td>41 (12.6)</td>
<td>0.56</td>
<td>0.32-0.96</td>
<td>.035</td>
</tr>
<tr>
<td>History of hyperlipemia</td>
<td>196 (64.0)</td>
<td>178 (54.7)</td>
<td>1.47</td>
<td>1.07-2.0</td>
<td>.019</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>97 (31.6)</td>
<td>74 (22.8)</td>
<td>1.57</td>
<td>1.10-2.03</td>
<td>.015</td>
</tr>
<tr>
<td>Contralateral occlusion</td>
<td>21 (6.4)</td>
<td>9 (2.8)</td>
<td>2.58</td>
<td>1.16-5.7</td>
<td>.023</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>65 (21.2)</td>
<td>105 (32.3)</td>
<td>0.56</td>
<td>0.39-0.8</td>
<td>.002</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>34</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>31</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex plaque*</td>
<td>82 (26.8)</td>
<td>112 (34.5)</td>
<td>0.69</td>
<td>0.49-0.9</td>
<td>.04</td>
</tr>
<tr>
<td>Bilateral procedure</td>
<td>24 (7.8)</td>
<td>40 (12.3)</td>
<td>0.58</td>
<td>0.33-1.0</td>
<td>.06</td>
</tr>
</tbody>
</table>

\*Complex plaque was defined macroscopically at intraoperative evaluation in CEA and according with duplex scan in CAS.

### Table II. Outcomes at 30 days in 631 women after CAS vs CEA

<table>
<thead>
<tr>
<th></th>
<th>CAS group ((n = 306)) n (%)</th>
<th>CEA group ((n = 325)) n (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or stroke</td>
<td>6 (1.9)</td>
<td>10 (3)</td>
<td>0.63</td>
<td>0.2-1.7</td>
<td>.45</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (1.9)</td>
<td>9 (2.7)</td>
<td>0.7</td>
<td>0.2-1.9</td>
<td>.6</td>
</tr>
<tr>
<td>Stroke in asymptomatic</td>
<td>3/241 (1.2)</td>
<td>7/220 (3.2)</td>
<td>0.38</td>
<td>0.09-1.5</td>
<td>.2</td>
</tr>
<tr>
<td>Disabling stroke in asymptomatic</td>
<td>0/241</td>
<td>1/220 (0.5)</td>
<td>0.0-35.6</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>Stroke in symptomatic</td>
<td>5/65 (4.6)</td>
<td>2/105 (1.9)</td>
<td>2.49</td>
<td>0.28-30.43</td>
<td>.37</td>
</tr>
<tr>
<td>Disabling stroke in symptomatic</td>
<td>2/65 (3.0)</td>
<td>5/105 (4.8)</td>
<td>1.08</td>
<td>0.12-8.2</td>
<td>1</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>2 (0.65)</td>
<td>3 (0.9)</td>
<td>0.7</td>
<td>0.11-4.2</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>—</td>
<td>2 (0.6)</td>
<td></td>
<td>0.84-8.7</td>
<td>.1</td>
</tr>
<tr>
<td>TIA</td>
<td>10 (3.2)</td>
<td>4 (1.23)</td>
<td>2.7</td>
<td>0.11-4.25</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.65)</td>
<td>3 (0.9)</td>
<td>0.7</td>
<td>0.11-4.25</td>
<td>1</td>
</tr>
<tr>
<td>MACE</td>
<td>7 (2.3)</td>
<td>12 (3.7)</td>
<td>0.61</td>
<td>0.24-1.57</td>
<td>.35</td>
</tr>
<tr>
<td>Hematoma</td>
<td>5 (1.6)</td>
<td>9 (2.8)</td>
<td>0.76</td>
<td>0.23-2.54</td>
<td>.8</td>
</tr>
</tbody>
</table>

CAS, Carotid angioplasty and stenting; CEA, carotid endarterectomy; OR, odds ratio; CI, confidence interval; TIA, transient ischemic attack; MACE, major adverse clinical event (stroke/death/myocardial infarction).
late stroke after the procedures was low (n = 10) and equally distributed in CAS and CEA populations. Six of these strokes were ipsilateral to the treated carotid (one in CAS and five in CEA). There were no differences at 5 years after the procedure in Kaplan-Meier estimates of ipsilateral stroke and any periprocedural stroke or death between the CAS and CEA groups (4.1% vs 8.1%; \( P = .18 \); Fig 2). In both the symptomatic and asymptomatic patients, estimates were similar between women who underwent CAS and CEA (for symptomatic females: 5.2% vs 7.9%; \( P = .57 \); for asymptomatic females 2.8% vs 3.8% in the CAS and CEA groups, respectively; \( P = .44 \)). During follow-up, recurrent stenosis of 50% or more was detected in 17 female patients (5 after CAS and 12 after CEA). Kaplan-Meier analysis revealed no significant difference between women in the CAS and CEA groups in the restenosis rate at 5 years (1.8% vs 8.1% for CAS and CEA, respectively; \( P = .058 \); Fig 3).

Only four recurrent stenosis (three in the CAS group and one in women who underwent CEA) led to neurologic symptoms. Overall, nine reinterventions were performed, four after CAS, and five after CEA due to symptoms or high-grade asymptomatic restenosis.

**DISCUSSION**

In this study, the initial hypothesis of CAS as a more hazardous procedure for women was not confirmed: periprocedural stroke and death rate in women who underwent CAS (1.9%) was low and below the recommended standard threshold of perioperative risk for carotid revascularization (3%). Although women who underwent CAS were a higher risk population (high frequency of coronary disease, hyperlipemia, and contralateral occlusion), perioperative and late risks were comparable and even lower than those of women who underwent CEA. The lack of effect of gender on CAS outcome of this study was strengthened by logistic regression analysis providing estimates of the effect of the procedure on perioperative stroke/death risk in the presence of potential confounding factors not equally distributed between women who underwent CAS and CEA. However, the data may still be unbalanced and underpowered to prove equipoise between treatments and should be interpreted with caution. This concern is raised by the low primary outcome rates observed in this series for women in both the CAS and CEA groups. Specifically, 16 periprocedural stroke/death events occurred in 306 women who underwent CAS and 325 who underwent CEA.

CAS was associated with low risks of periprocedural stroke especially in asymptomatic females, in whom the periprocedural stroke rate of CAS was less than half compared to that of CEA (1.2% vs 3.2%; \( OR = 0.38 \); 95% CI, 0.09-1.5; \( P = .2 \)), and the risk of disabling stroke was 0. We stratified the analysis of outcomes by symptoms, because symptomatic and asymptomatic patients were not equally distributed between the two female groups. Indeed, the preference to avoid hypoechoic/complex carotid plaque during CAS allowed to a higher frequency of symptomatic
plaques (34.5% vs 26.8%) and symptomatic patients (32.3% vs 21.2%) into the group of women who underwent CEA. Although the differences in outcomes between women who underwent CAS and CEA did not reach statistical significance, and selection biases could have affected the results, the overall absolute findings may be consistent with a safe and favorable outcome for women treated with CAS, particularly when asymptomatic.

Other reports have suggested that the perioperative risk related to carotid surgery (CEA) might be much higher specifically in asymptomatic women. Such increased risk was not assessed for the women in our CAS group, suggesting a potential benefit of CAS particularly in asymptomatic women in whom the risk of CEA seems to be higher.

Conversely, our data might suggest a higher risk of CAS with respect to CEA for symptomatic patients, although no significant differences in outcomes were found. However, we cannot provide any reliable suggestions for symptomatic women because the numbers were small especially for CAS (n = 65). Only one-fourth of the overall female population was symptomatic (n = 170), and the power of our study was particularly low to detect the differences between symptomatic subgroups of women who underwent CAS and CEA.

Published RCTs on CAS in symptomatic patients agreed on an increased risk from CAS vs CEA in symptomatic populations, regardless of the gender. Today, the efficacy of CAS for “all-comers” is still not proven (also, the latest International Carotid Stenting Study [ICSS] confirmed a two-time perioperative risk of stroke in CAS vs CEA, 7.6% vs 3.9%, online publication), but other RCTs are still ongoing (Carotid Revascularization Endarterectomy versus Stenting Trial [CREST], Asymptomatic Carotid Surgery Trial [ACST2]) to confirm these data. In the meantime, CAS is commonly accepted for some subgroups of patients considered at high risk for surgery. Women, at least some of them, may represent one of these subgroups because of a higher risk of CEA (eg, asymptomatic females). However, before claiming CAS as the treatment of choice for women with carotid stenosis, these hypotheses need to be confirmed by ongoing RCTs.

Recent literature showed that CAS may be performed with low complication rates in women, but there is no strong evidence, also supported by RCTs, to this regard, as the overall populations of women is limited. The CREST lead-in study is, at present, the largest experience analyzing gender-related outcomes of CAS (1564 patients, 576 women and 985 men) and found similar perioperative stroke and death rates in women vs men (4.5% vs 4.2%). Despite the large number of patients, the overall number of events was low (n = 67 in the total population). Authors raised concerns on the study power and calculated that the actual power of their study to detect such small differences was marginal (about 6%). An increase of up to 7.5% (event rate females/males difference = 3.0) in the event rates in women could have been needed to provide 80% power. However, it appears somewhat unlikely that such gender-related differences could exist as shown in recent literature. Goldstein et al in 238 CAS reported a combined 30-day stroke, death, and MI rate of 5.7% vs 5.4% in males and females, respectively. In addition, no differences were observed in long-term survival, stroke-free survival, and restenosis rates. Park et al showed very low perioperative stroke and death rates in women who underwent both CAS (2%) and CEA (0%) procedures. Nevertheless, their sample of 100 female patients for both CAS and CEA was too small to detect a difference.

Even more insubstantial and also conflicting information on the risks of CAS in women is available from published RCTs. The stent-protected angioplasty vs carotid endarterectomy in symptomatic patients (SPACE) trial, including 171 symptomatic women and 436 symptomatic men in the CAS group, was the only RCT that specifically analyzed the outcome in women and showed a slightly nonsignificant increase in the primary endpoint (ipsilateral stroke or death within 30 days) rate for symptomatic women in a subgroup analysis stratified by gender (8.2% vs 6.4%). The rate of ipsilateral stroke within 2 years plus periprocedural stroke and death was indeed lower in women (8.3% vs 9.9%). Nevertheless, none of these differences were significant. Very limited information, if any, is available from the small number of women included in all other large CAS trials (n = 72; 28%) in the endarterectomy vs angioplasty in patients with symptomatic severe carotid stenosis (EVA3S) and n = 55 (33%) in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial.

In reality, women are severely under-represented in all carotid trials (CEA and CAS trials) and it remains to be seen whether sufficient enrollment of women will play a decisive role in the ongoing trials analyzing CAS.

The causes of perioperative gender risk difference in CEA are not known. Due to the carotid small size and women’s vessel anatomy, the surgical procedure may be more problematic, and consequently, the incidence of carotid thrombosis and surgery-related complications in women increases. CAS has the potential to avoid these complications by using a completely different approach for treating carotid stenosis. The carotid artery is not opened and sutured, but the carotid flow is restored by using appropriately sized stents.

In our study, although women in the CAS group had small vessels, these did not increase the stroke risk or the restenosis rate (1.8%) at 5 years. Conversely, in the CEA group, the restenosis risk was higher (8.1%), although there was a borderline difference when compared to CAS (P = .058). In contrast with our data, the SPACE trial raised concerns that the risk of restenosis might be two times higher after CAS than after CEA, although the analysis was not stratified by gender. However, today there is still large variability and lack of standards to assess restenosis rates. Criteria for measurements not uniform in stent vs no-stent arteries, different thresholds, and ultrasound scan-subjective assessments make comparisons in restenosis rates poorly reliable, and “restenosis” should be considered as a
secondary minor endpoint. Of relevance, even CAS trials showing restenosis rates higher after CAS than after CEA failed to show any increased late stroke risk after CAS confirming an efficacy from CAS in stroke prevention, which our study confirmed in women (low stroke rate after CAS in the women in our study). This study focused primarily on periprocedural risks, since this has been recognized as the most hazardous period of CEA for women with carotid stenosis. In the long term, women, especially when asymptomatic, are believed to have a very low stroke risk defeating any benefit provided from early revascularization. However, the apparent small risk is compensated by the higher survival of women. Stroke rate increases with age in both genders; the longer the survival times, the higher the risk of stroke. Late unpublished data from the ACST study found that the risk of stroke for women allocated to best medical treatment increased at 10 years to 16% vs 10% in the surgical arm (CEA) making the difference statistically relevant \((P = .05)\) in favor of surgery for women. For asymptomatic women undergoing CAS, in whom the initial periprocedural risk appears to be decreased, the long-term benefit might be even higher.

**Study limitations.** This study presents limitations. First, this was not a randomized trial and was based on a retrospective analysis of data leading to all well-known population selection bias. Evident differences between the entire CAS and CEA populations were adjusted using multivariable analyses, but inevitably, some variables, and especially procedural factors specific for each treatment group, could not be accounted for. However, sensitivity analyses were performed to adjust for these technical details, and a number of these technical confounders were specifically tested in multivariable models stratified for treatment group (CAS or CEA alone) showing an insignificant effect on outcome.

Secondly, the results might be underpowered because of no “a priori” power calculation. The relatively small numbers of women could not exclude type II errors. Caution should be taken in interpretation of specific OR from logistic regression analysis because the number of events compared with the number of parameters in the model may result in unstable estimates.

Thirdly, our results were obtained after a considerable number of CAS procedures that allowed operators to achieve a stable low complication rate. The same safe outcome in women could not be ensured in other settings with less experience in CAS.

Finally, patients were not compared to medically-treated patients with carotid stenosis; therefore, it was difficult to establish the superiority of gender-related CAS treatment.

**CONCLUSION**

At this time, there is no evidence of a gender effect on clinical outcome after CAS. The periprocedural risk of stroke or death in women who underwent CAS is low (1.9%), and the risk of further ipsilateral strokes after CAS is not more than 0.4% per year (5-year ipsilateral and any perioperative stroke/death rate, 4.1%). Asymptomatic women, in whom a poor periprocedural outcome is expected after CEA, might benefit the most from CAS. Differences in anatomy (eg, small vessel size) that increase the operative risk in women during CEA may be overcome by a CAS approach in the future. CAS might be a primary choice for treatment of asymptomatic carotid stenosis in women. However, further high-level and high-powered studies are needed to confirm this hypothesis.

**AUTHOR CONTRIBUTIONS**

Conception and design: PDR, GG, VC Analysis and interpretation: PDR, GP, PC Data collection: GP, EC, FV, GG Writing the article: PDR, VC, GP Critical revision of the article: FV, PC Final approval of the article: PC Statistical analysis: GP, PDR, EC Obtained funding: Not applicable Overall responsibility: PC, PDR

**REFERENCES**

DISCUSSION

Dr Marc Mitchell (Jackson, Miss). As I understand your data, it demonstrates good results with both carotid endarterectomy and carotid angioplasty and stenting in both men and women. I think the data makes a strong argument that women benefit from carotid interventions just as men do. On what basis do you conclude that carotid angioplasty and stenting is superior to endarterectomy in both men and women? I think it demonstrates good results with both carotid endarterectomy and carotid angioplasty with stenting and carotid endarterectomy.

Dr De Rango. Because there might be some women, as asymptomatic women, who benefit less from carotid endarterectomy and may better advantage from carotid angioplasty and stenting. We did not find any difference in outcome between genders after carotid endarterectomy when we analyzed women as a whole. We did a subgroup comparison between genders stratified by symptoms and, after carotid endarterectomy, and according to our data, the risk of stroke in asymptomatic women was higher than in asymptomatic men. On the contrary, there was no difference between genders in the perioperative and late stroke risk for either asymptomatic or symptomatic subgroups of patients after carotid angioplasty and stenting. Therefore, we believe there may be some subgroups of women who are still at high risk from surgery and from carotid endarterectomy and could benefit from stenting.

Dr Wei Zhou (Palo Alto, Calif). When we analyzed risk factors for microemboli during carotid stenting, peripheral vascular disease was shown to be an independent predictor for contralateral hemisphere subclinical microemboli. In your group, there were many more patients with peripheral vascular diseases in the male cohort than the female cohort. Would you please comment on how this variable affected your outcome?

Dr De Rango. We did not find that the difference in distribution of peripheral vascular disease affected outcome. Specifically, in our multivariate analysis, there was no influence (“confounding effect”) of peripheral disease on operative risks. We did not specifically analyze outcome in the subgroup of patients with peripheral disease who accounted for a small part of the overall population. Multivariate analysis, however, failed to show an association between the presence of peripheral disease and the outcome.