Management of carotid stenosis in women

Consensus document

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ABSTRACT

Objective: Specific guidelines for management of cerebrovascular risk in women are currently lacking. This study aims to provide a consensus expert opinion to help make clinical decisions in women with carotid stenosis.

Methods: Proposals for the use of carotid endarterectomy (CEA), carotid stenting (CAS), and medical therapy for stroke prevention in women with carotid stenosis were provided by a group of 9 international experts with consensus method.

Results: Symptomatic women with severe carotid stenosis can be managed by CEA provided that the perioperative risk of the operators is low (<4%). Periprocedural stroke risks may be increased in symptomatic women if revascularization is performed by CAS; however, the choice of CAS vs CEA can be tailored in subgroups best fit for each procedure (e.g., women with restenosis or severe coronary disease, best suited for CAS; women with tortuous vessels or old age, best suited for CEA). There is currently limited evidence to consider medical therapy alone as the best choice for women with neurologically severe asymptomatic carotid stenosis, who should be best managed within randomized trials including a medical arm. Medical management and cardiovascular risk factor control must be implemented in all women with carotid stenosis in periprocedural period and lifelong regardless of whether or not intervention is planned.

Conclusions: The suggestions provided in this article may constitute a decision-making basis for planning treatment of carotid stenosis in women. Most recommendations are of limited strength; however, it is unlikely that new robust data will emerge soon to induce relevant changes.

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GLOSSARY

ACAS = Asymptomatic Carotid Atherosclerosis Study; **ACST1** = Asymptomatic Carotid Surgery 1 Trial; **ARR** = absolute risk reduction; **CAS** = carotid stenting; **CEA** = carotid endarterectomy; **CHD** = coronary heart disease; **CI** = confidence interval; **CREST** = Carotid Revascularization Endarterectomy vs Stenting Trial; **CSTC** = Carotid Stenting Trialists' Collaboration; **DM** = diabetes mellitus; **ECST** = European Carotid Surgery Trial; **EVA-3S** = Endarterectomy vs Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; **GRADE** = Grades of Recommendation Assessment, Development and Evaluation; **HR** = hazard ratio; **ICSS** = International Carotid Stenting Study; **MI** = myocardial infarction; **NASCET** = North American Symptomatic Carotid Endarterectomy; **OR** = odds ratio; **RCT** = randomized controlled trial; **RRR** = relative risk reduction; **SAPPHIRE** = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; **SPACE** = Stent-Protected Angioplasty vs Carotid Endarterectomy.

Women have a higher prevalence of stroke than men, with outcomes generally worse than those of men.¹ Stroke accounts for a higher proportion of cardiovascular than coronary heart disease (CHD) in women (while the ratio is opposite for men). Results from previous randomized controlled trials (RCTs) on carotid disease suggested possible differences in the potential benefits and risks of preventive interventions for carotid stenosis between the sexes. However, detailed guidelines and recommendations for stroke prevention and management of carotid stenosis in women are lacking.

This article represents proposals from a multidisciplinary consensus of experts after a thorough review of current scientific evidence and is intended to improve the clinical management of women with carotid stenosis.

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METHODS Literature regarding carotid endarterectomy (CEA), carotid stenting (CAS), and medical management for stroke risk reduction in women with carotid stenosis was formally reviewed (details in appendix e-1 on the *Neurology*[®] Web site at www.neurology.org) and a list of recommendations for treatment incorporating evaluations of evidence strength was provided. Using a score system adopted by other organizations,² recommendations were rated as Grades of Recommendation Assessment, Development and Evaluation (GRADE) 1 (strong: when benefit clearly outweighs risk and can be accepted with a high degree of confidence) or GRADE 2 (weak: when the benefits and risks are more closely matched and are more dependent on specific clinical scenarios) and divided into 3 level categories: A (high quality), B (moderate quality), and C (low quality). Statements for issues where there was limited evidence were rated as good clinical practice.

The expert panel in carotid stenosis was convened by e-mail contacting experts from the multidisciplinary fields of neurology, stroke services, interventional cardiology, stroke epidemiology, and vascular specialties. Experts have been selected according to demonstrated experience in the subjects under consideration (CEA, CAS, medical management, epidemiology of carotid stenosis) and availability to participate. Using Delphi method, the members of the panel were required to provide agreement for those treatments that have been shown to have sufficient evidence of clinical benefit for treatment of carotid stenosis in women. Recommendations were drafted when agreement among the majority of panelists was reached in accordance with the best-published and most recent evidence. In case of disagreement, issues were reanalyzed and a new version of the document based on most approved suggestions was e-mailed to all panelists. This consensus document (appendix e-2) was done with the understanding that most recommendations are based on limited strength and quality of evidence; nevertheless, these are the experts' opinions for optimal management of carotid stenosis in women after thorough literature review to provide clinicians with a comprehensive set of data. It is clear that such recommendations can change in the future, even though it is unlikely that new data will emerge soon.

This document is divided into 3 major sections:

1. Indications for invasive treatment of carotid stenosis in women
2. Risk factor modifications, including management of peri-intervention period
3. Medical therapy, including management of peri-intervention period

RESULTS **Indications for invasive treatment of carotid stenosis in women.** Current indications for CEA and CAS in patients with carotid stenosis are based on guidelines supported by multiple RCTs and large series comparing CEA vs medical therapy^{3–11} or CEA vs CAS.^{12–22}

However, many major carotid RCTs have not been powered to specifically assess outcome in women vs men, mainly because the former were underrepresented.^{4–14,17} Meta-analyses of RCT data comparing CAS and CEA by sex were carried out to overcome these limitations but results were still constrained by large heterogeneity among combined studies. Furthermore, there has never been an RCT comparing modern medical therapy alone to medical therapy + CAS or CEA for symptomatic carotid stenosis and RCTs evaluating current medical therapy for asymptomatic carotid stenosis are ongoing.

Carotid surgery (CEA) for symptomatic carotid stenosis in women according to RCTs. The most recent and largest to date RCT comparing CAS and CEA in patients with >50%–99% carotid stenosis, the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST),^{18–20} was designed with prespecified 90% power to detect effect modification by sex in primary endpoint (stroke, death, myocardial infarction [MI]) differences. In CREST, perioperative stroke/death rate after CEA for symptomatic patients was 3.2%.¹⁸ This rate was accepted in this document as the reference for current operative risk and threshold for acceptable perioperative stroke/death rate of carotid revascularization procedures for patients with symptomatic carotid stenosis, stated at <4% (instead of <6% as in previous guidelines). In the CEA arm of the CREST, there were no increased periprocedural risks in symptomatic women: composite of stroke/death/MI, 4.0% and 6.1%; stroke, 2.7% and 3.5%; MI, 1.3% and 2.8% for women and men, respectively.²⁰

Nevertheless, female sex was recognized as a surgical risk factor for symptomatic women undergoing CEA in post hoc subgroup analyses from other previous carotid RCTs comparing CEA to best medical treatment.^{23–26} Combined data from European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy (NASCET) trials showed that, among 3,157 patients undergoing surgery, the risk of perioperative stroke/death was 8.7% (95% confidence interval [CI] 6.1–11.3) in women vs 6.8% (95% CI 5.3–8.4) in men, resulting in a significantly increased hazard ratio (HR): 1.50 (95% CI 1.14–1.97; $p = 0.004$) when comparing women with men.²³ Furthermore, the absolute reduction with surgery in the 5-year cumulative risk of ipsilateral ischemic stroke and any perioperative stroke/death was greater in men (absolute risk reduction [ARR] 11%) and less evident in women (ARR 2.8%).²³

Timing of surgery for carotid stenosis after a TIA or minor stroke seems to be more relevant in women than in men in preventing recurrent stroke.²⁵ According to post hoc subgroup analyses of pooled data from ECST and NASCET, the benefit from CEA significantly diminished with increasing time from the most recent symptomatic event to randomization and differed by sex ($p < 0.001$); there was significantly less benefit in women and no change in men with increasing time. This decline in benefit for women occurred irrespective of carotid stenosis severity: even with 70%–99% symptomatic stenosis, there was no benefit if CEA was delayed >2 weeks since randomization.²⁵ The main determinant of this sex difference was a more rapid decline in the risk of stroke + death over time from the last event for women in the medical group ($p < 0.001$).²⁵

Combined data from NASCET and the Aspirin and Carotid Endarterectomy trials showed lack of any benefit of delayed (>2 weeks) CEA compared to medical therapy alone for women with moderate (50%–69%) carotid stenosis (ARR 3.0%, $p = 0.94$), contrary to men (ARR 10.0%, $p = 0.02$).²⁶

Although a number of major RCTs on CEA and pooled analyses of these may suggest that women with symptomatic carotid stenosis do not benefit from CEA as much as men, these results are mainly based on studies performed about 20 years ago. More recent data from CREST^{18–20} as well as data from many nonrandomized studies are not concordant in reporting a sex-related increased risk of stroke/death from CEA.^{27,28} Pooled analyses also suggested a decline in benefit with treatment delay for women.

Carotid stenting (CEA) for asymptomatic carotid stenosis in women according to RCTs. In CREST, perioperative stroke/death rate after CEA for overall asymptomatic patients was 1.4%. This rate was accepted in this document as the reference for current operative risk and threshold for acceptable perioperative stroke/death rate in carotid revascularization procedures for patients with asymptomatic carotid stenosis, stated at $\leq 2\%$ (instead of $< 3\%$ as in previous guidelines). In the CREST, asymptomatic women assigned to surgery showed outcomes similar to men: 3.7% composite of stroke/death/MI (vs 3.5% in men), 1.6% stroke (vs 1.3% in men), and 2.1% MI (vs 2.3% in men) during the periprocedural period. No disadvantages in women vs men were found at 4 years. However, statistical power for the subgroups of sex by symptoms and type of treatment might be small to detect differences.²⁰ Furthermore, the trial, as well as any published carotid RCT, did not have a concurrent medical arm to assess equipoise between revascularization of any type and modern medical therapy for asymptomatic carotid stenosis in women. Previous RCTs investigating the role of CEA for asymptomatic carotid stenosis vs medical therapy alone suggested considerable uncertainty in the benefit from CEA in asymptomatic women, especially in old age.^{8,9,29} A post hoc subgroup analysis of the Asymptomatic Carotid Atherosclerosis Study (ACAS) showed that sex differences in CEA outcomes were mainly related to higher operative stroke/death risk in women (3.6% women vs 1.7% men), resulting in an inferior relative risk reduction (RRR) in the overall benefit gain from surgery (compared to medical therapy alone) over time with respect to men: 66% RRR 5-year risk of fatal and nonfatal ipsilateral carotid stroke with CEA in men vs 17% RRR in women.⁸ However, ACAS was performed in 1994 and the trial had not prespecified sex subgroups for trial analysis, as was indeed preplanned in the Asymptomatic Carotid Surgery 1 Trial (ACST1). In the ACST1, the benefit gain

from surgery in women was half (ARR 4.08%) of that achieved in men (ARR 8.21%) at 5 years.⁹ At 10 years, a benefit gain from CEA was shown in women up to 75 years of age for nonoperative stroke (8.2%; 95% CI 2.9–13.6), but it was still inferior to that provided by CEA in asymptomatic men of similar ages.¹⁰ A meta-analysis of ACAS and ACST1 data showed a surgical benefit significant in men (odds ratio [OR] 0.49; 95% CI 0.36–0.66) but not in women (OR 0.96; 95% CI 0.63–1.45; pooled interaction $p = 0.01$).²⁹ Data on the overall benefit from CEA in asymptomatic women seem limited, and some guidelines only recommend CEA in asymptomatic women aged 75 years or less.³⁰ Therefore, asymptomatic women >75 years are least likely to benefit.

Carotid stenting for symptomatic and asymptomatic carotid stenosis in women. CAS was developed as a potential alternative treatment to CEA in patients with severe carotid stenosis at increased operative risk.^{2,31} Conflicting results on the overall risks of CAS in women have been published in RCTs,^{12–20,32–34} while large RCTs on asymptomatic carotid stenosis are ongoing. In the CREST, rates of primary periprocedural endpoints for combined symptomatic/asymptomatic patients (stroke/death/MI) after CAS were higher in 455 women (6.8%) than in 807 men (4.3%), although statistical testing was not performed.²⁰ The rate in CAS women was significantly higher than that achieved in CEA women (HR 1.84, 95% CI 1.01–3.37; $p = 0.047$). This sex-specific difference was driven by a higher periprocedural stroke risk in women for CAS than for CEA (5.5% vs 2.2%; HR 2.63; $p = 0.013$), while there were no significant differences in men (3.3% vs 2.4%; HR 1.39; $p = 0.26$). Sex-specific differences in periprocedural stroke were consistent by symptomatic status. However, the CREST did not find significant sex-related difference by treatment in primary endpoint rates at 4 years ($p = 0.34$).^{18,20}

The Stent-Protected Angioplasty vs Carotid Endarterectomy (SPACE) trial including 28% symptomatic women (171 women and 436 men in the CAS group; 167 women and 422 men in the CEA group) showed a nonsignificant increase in the outcome of periprocedural ipsilateral stroke/death for symptomatic women after CAS in subgroup analyses stratified by sex: 8.2% vs 6.4% in women vs men respectively, $p = 0.48$, in the CAS arm and 6.0% vs 6.6% in women vs men respectively, $p = 0.85$, in the CEA arm.¹⁵ The combined rate of ipsilateral stroke within 2 years plus periprocedural stroke and death was lower in women than in men after either CAS (8.3% vs 9.9%) or CEA (6.7% vs 9.6%). Nevertheless, none of these differences was significant.¹⁴

Limited data are available from the small number of women included in 3 other CAS vs CEA

randomized trials: the Endarterectomy vs Angioplasty in Patients With Severe Symptomatic Carotid Stenosis ([EVA-3S], women $n = 72$ [28%]); the International Carotid Stenting Study ([ICSS], women $n = 503$ [29%]); and the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy ([SAPPHIRE], women $n = 55$ [33%]).^{12,17,21} Exploratory analyses of composite outcome (stroke/death/MI) from ICSS suggested that CAS might have similar risks for both sexes (8.0% in women vs 8.8% in men) but that CEA might be more hazardous in women (7.6% vs 4.2% in women vs men); however, the difference did not reach significance (interaction $p = 0.071$).¹⁷

A combined sex-stratified analysis of patient data at 120 days after treatment from the 3 major European RCTs on carotid stenting in symptomatic patients performed by the Carotid Stenting Trialists' Collaboration (CSTC) found that surgical risk was higher in women than in men, whereas risk of stenting was virtually unaffected by sex.³²

A meta-analysis focusing on sex differences in outcomes of CAS vs CEA and including data from the CSTC study, CAVATAS,³³ and CREST for a total of 6,439 patients (1,995 women and 4,444 men) showed that there was no real significant effect of sex on the risks of either CAS or CEA treatment.³⁴ The pooled risk ratio in women vs men was 1.11 (95% CI 0.87–1.41) after CAS and 1.04 (95% CI 0.77–1.41) after CEA.³⁴ However, the meta-analysis was weakened by pooling together evaluation of symptomatic and asymptomatic patients and combining periprocedural with 120-day outcomes assessment.

Individual RCTs and meta-analyses of these provided limited and conflicting data for women with carotid stenosis (tables 1 and 2). One of the reasons could be that women have been underrepresented, constituting about 30% of patients in symptomatic trials and about 35% of patients in asymptomatic trials. Indeed, there are data to support the availability of more women to be potentially included in trials than have been: 42.3% of 54,658 carotid procedures (mainly

Table 1 Results by sex in carotid revascularization trials: CEA vs medical treatment

		Reduction in the 5-year risk of ipsilateral stroke and any operative stroke or death with surgery		
			Results by sex	
Setting	Women, % (n)	Total results	Men	Women
CEA vs medical therapy				
Primary prevention				
ACAS and ACST meta-analysis ²⁶	34 (1,644/4,779)	ARR 5.5%	ARR 4.1%; 3 y	ARR 2.0%; 3 y
ACAS ⁸	34 (568/1,659)	ARR 5.1% (RRR 53%)	ARR 8% (RRR 66%)	ARR 1.4% (RRR 17%)
ACST ^{9,10}	34 (1,076/3,120)	ARR 5.3% 5-y; ARR 4.5% 10-y	ARR 8.21% 5-y; ARR 5.5% in <75 y at 10-y	ARR 4.1% 5-y; ARR 2.5% in <75 y at 10-y
Secondary prevention				
VA ^{e5}	0 (0/189)	ARR 17% in >70% stenosis at 11.9 mo		—
NASCET and ECST pooled data ^{23–25}	29 (1,718/5,893); NASCET 30; ECST 28		ARR 6.0%	ARR −0.4%
Stenosis >70%–99%; n = 692			ARR 15%	ARR 9.9%
Within 2 wk		NNT 3; ARR 30.2%; <i>p</i> < 0.00001	ARR 23.0%	ARR 41.7%
Within 2–4 wk		NNT 6; ARR 17.6%; <i>p</i> = 0.015	ARR 23.8%	ARR 6.6%
4–12 wk		NNT 9; ARR 11.4%; <i>p</i> = 0.01	ARR 18.3%	ARR −2.2%
After 12 wk		NNT 8; ARR 12.9%; <i>p</i> = 0.06	ARR 20.4%	ARR −2.4%
Stenosis 50%–69%; n = 1,502			ARR 8.0%	ARR −2.7%
Within 2 wk		NNT 7; ARR 14.8%, <i>p</i> = 0.001	ARR 15.2%	ARR 13.8%
Within 2–4 wk		NNT 29; ARR 3.4%, <i>p</i> = 0.6	ARR 6.8%	ARR −5.7%
4–12 wk		NNT 24; ARR 4.1%, <i>p</i> = 0.3	ARR 5.0%	ARR −2% to 2%
After 12 wk		ARR −2.5%, <i>p</i> = 0.7	ARR 6.3%	ARR −21.7%

Abbreviations: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ARR = absolute risk reduction; CEA = carotid endarterectomy; ECST = European Carotid Surgery Trial; NASCET = North American Symptomatic Carotid Endarterectomy; NNT = number needed to treat; RRR = relative risk reduction; VA = Veterans Administration.

Table 2 Results by sex in carotid revascularization trials: CAS vs CEA

		Reduction in the risk of stroke and death		
			Results by sex	
Setting	Women, % (n)	Total results	Men	Women
CEA vs CAS				
Primary prevention (asymptomatic)				
CREST (asymptomatic) ^{18,20}	34% (406/1,181)	Periprocedural stroke or death at 30 days: 2.5% in CAS vs 1.4% in CEA; <i>p</i> = 0.15	Periprocedural stroke or death at 30 days: 2.1% in CAS vs 1.3% in CEA; <i>p</i> = 0.33; treatment by sex interaction; <i>p</i> = 0.82	Periprocedural stroke or death at 30 days: 3.3% in CAS vs 1.6% in CEA; <i>p</i> = 0.28
Secondary prevention (symptomatic)				
Carotid Stenting Trialists' Collaboration (pooled analysis of EVA-3S, SPACE, and ICSS) ³²	28% (971/3,433)	Risk of any stroke or death at 120 days: 8.9% with CAS vs 5.8% with CEA; <i>p</i> = 0.0006	Any stroke or death at 120 days: 9.0% in CAS vs 5.4% in CEA; <i>p</i> = 0.24	Any stroke or death at 120 days: 8.5% in CAS vs 6.9% in CEA
CREST (symptomatic) ^{18,20}	35% (466/1,321)	Periprocedural stroke or death at 30 days: 6.0% in CAS vs 3.2% in CEA; <i>p</i> = 0.02	Periprocedural stroke or death at 30 days: 5.1% in CAS vs 3.5% in CEA; <i>p</i> = 0.23; treatment by sex interaction; <i>p</i> = 0.25	Periprocedural stroke or death at 30 days: 7.5% in CAS vs 2.7% in CEA; <i>p</i> = 0.030
Primary + secondary prevention (asymptomatic + symptomatic)				
CREST, CAVATAS, and CSTC meta-analysis data ³⁴	31% (1,995/6,439)	Risk of any stroke or death at 120 days: 8.27% with CAS vs 5.6% with CEA	Any stroke or death at 120 days: overall (CAS + CEA) 6.9%; 8% in CAS vs 5.6% in CEA; <i>p</i> = NS	Any stroke or death at 120 days: overall (CAS + CEA) 7.1%; 8.6% in CAS vs 5.6% in CEA; <i>p</i> = NS

Abbreviations: CAS = carotid stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy vs Stenting Trial; CSTC = Carotid Stenting Trialists' Collaboration; EVA-3S = Endarterectomy vs Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; ICSS = International Carotid Stenting Study; NS = not significant; SPACE = Stent-Protected Angioplasty vs Carotid Endarterectomy.

CEA)³⁵ and 42.5% of 249,592 carotid procedures (mainly CAS)³⁶ were performed in women in non-randomized population studies. The overall low number of enrolled women in carotid trials might be a consequence of low prevalence of carotid stenosis in women, but it is also likely related to delay in diagnosis and withholding treatment. A retrospective study of patients diagnosed with TIA and severe carotid stenosis found that women were less likely to undergo CEA (36.4% vs 53.8% men; $p = 0.004$) and treatment was more delayed ($p = 0.004$).³⁷

Nonrandomized studies on women undergoing CEA, CAS, or medical therapy. Variable sex-related effects on CAS and CEA outcomes have been shown according to nonrandomized evidence. Female patients with high-grade asymptomatic carotid artery stenosis might benefit more than male patients when left under medical therapy alone.^{38,39}

A retrospective study based on a national database of carotid revascularizations in the United States found that women and men had equivalent rates of periprocedural stroke when undergoing CEA (1.0% vs 1.0%) and CAS (2.7% vs 2.0%).³⁵ Nevertheless, symptomatic women had a significantly higher rate of periprocedural stroke than symptomatic men (3.8% vs 2.3%; $p = 0.03$). In asymptomatic women, rates of periprocedural strokes were significantly higher after CAS than after CEA ($p < 0.001$).³⁵

Nationwide US practice with CAS ($n = 31,197$) and CEA ($n = 218,395$) showed that CAS (OR 1.28;

95% CI 1.03–1.58) and female sex (OR 1.23; 95% CI 1.04–1.45) were independently associated with in-hospital stroke or death following asymptomatic carotid revascularization.³⁶ Similarly, a large US analysis using New York and Florida statewide hospital discharge databases showed perioperative CEA advantages over CAS in both symptomatic and asymptomatic women.²² Compared with CAS, CEA rates in asymptomatic vs symptomatic women were significantly lower for in-hospital mortality (0.3% vs 0.8% and 0.4% vs 3.4%), stroke (1.5% vs 2.6% and 3.5% vs 9.4%), and combined stroke/mortality (1.7% vs 3.1% and 3.8% vs 10.9%).²²

Nevertheless, there are also multiple studies, mainly case series, showing no difference in outcomes between sexes from CEA or CAS, as summarized in table e-1. Recommendations for this section are shown in table 3.

Risk factor modification, including management over the peri-intervention period. The reasons for the periprocedural risk differences between women and men remain speculative. Vascular diseases are more difficult to treat in women, possibly because there are distinct anatomic and pathophysiologic differences in carotid vessels: women have smaller and less compliant arteries than men and carotid plaque texture is different, leading to increased thrombotic risks.⁴⁰ Histologic analyses of CEA samples revealed that women were more likely to have more stable plaques, which are less prone to rupture. Moreover, although women

Table 3 Recommendations for indications for invasive treatment of carotid stenosis in women

Point 1	Periprocedural risks in women with carotid stenosis <ul style="list-style-type: none">• Periprocedural outcome of carotid revascularization in women is affected by comorbid risk profile at the time of operation, inadequate risk factor management, as well as delay of treatment. Grade 1, Level A.• To improve periprocedural care, reduce periprocedural risks, and provide benefit in women, carotid procedures (CEA and CAS) need to be applied in association with better risk factor modification and medical therapy implementation in all women with carotid stenosis. Grade 1, Level A.
Point 2	Symptomatic carotid stenosis in women: CAS vs CEA <ul style="list-style-type: none">• There has never been an RCT comparing modern medical therapy alone to medical therapy and CAS or CEA for symptomatic patients with carotid stenosis. CEA is preferred over CAS or medical therapy alone in symptomatic women >70 years with 50%-99% carotid stenosis (NASCET criterion) or lipid-rich plaques that can be completely and safely removed by cervical incision in women who have virgin, nonradiated necks, provided that surgery is performed by experienced surgeons (i.e., with <4% periprocedural stroke/death risk according to rates of the most recent RCT, CREST). The risks with CAS might overcome those of surgery in these women. Grade 2, Level B.
Point 3	Symptomatic carotid stenosis in women: CAS vs CEA <ul style="list-style-type: none">• CAS is preferred over CEA or medical therapy alone in symptomatic women with 50%-99% carotid stenosis (NASCET criterion) having prior recent ipsilateral operation, tracheal stoma, external beam irradiation resulting in fibrosis of the tissues of the ipsilateral neck, or prior cranial nerve injury and lesions that extend either proximal to the clavicle or distal to the C2 vertebral body, provided that the procedure is performed by experienced operators (<4% periprocedural stroke/death risk). Grade 2, Level B.
Point 4	Timing for intervention in symptomatic carotid stenosis in women <ul style="list-style-type: none">• In recent neurologically symptomatic women with 50%-99% carotid stenosis, CEA should be applied early, ideally within the first 2-week window since the index event, to provide the highest benefit in stroke prevention. The role of CAS in neurologically acute carotid stenosis in women needs to be established. Grade 1, Level B.
Point 5	Contraindications for revascularization in women with carotid stenosis <ul style="list-style-type: none">• For neurologically symptomatic women with stenosis <50% or asymptomatic ones with stenosis <60% diameter reduction, optimal medical therapy is indicated. There are no data to support either CAS or CEA in this patient group. Grade 1, Level A.
Point 6	Carotid stenosis in women with high comorbidity profile <ul style="list-style-type: none">• In recent symptomatic women at high surgical risk due to comorbidities, especially cardiac (such as severe uncorrectable CAD, CHF, or COPD) and severe carotid stenosis, CAS (provided in centers with low peri-CAS stroke/death rates) is preferred over CEA. Grade 2, Level C.• However, the overall periprocedural risks need to be taken into consideration in order to selectively apply CEA in subgroups of women at higher risks from CAS (advanced age, tortuous vessels). Regardless of revascularization, optimal medical management should be implemented in all recent symptomatic women with 50%-99% carotid stenosis at high surgical risk. Grade 1, Level B.• The overall benefit in stroke prevention in women with recent symptomatic 50%-99% carotid stenosis may be lower than men and risk comorbidity risk stratification needs to be balanced with stroke risk. Grade 2, Level B.
Point 7	Asymptomatic carotid stenosis in women <ul style="list-style-type: none">• Equipose between carotid revascularization (CAS or CEA) and modern medical therapy for asymptomatic carotid stenosis might be likely, but there is limited evidence to consider current medical therapy alone as the best choice for neurologically asymptomatic women with severe carotid stenosis. Grade 2, Level B.• Neurologically asymptomatic women with 60%-99% carotid stenosis can be considered for CEA for reduction of long-term risk of stroke provided the patient has a 5- to 10-year life expectancy and the center perioperative stroke/death rates are low (i.e., with ≤2.0% periprocedural stroke/death risk according to rates of the most recent RCT, CREST). Grade 1, Level B.• CAS in asymptomatic women with 60%-99% diameter stenosis should be mainly performed within randomized trials including a medical arm with or without a CEA arm. Good clinical practice.• However, the overall risks need to be taken into consideration in order to selectively apply CAS or medical therapy alone in neurologically asymptomatic subgroups at higher risks from CEA (severe CAD, high neck lesions) and at supposed higher stroke risk under medical therapy alone (e.g., stroke familiarity, stenosis progression). Good clinical practice.• The overall benefit in stroke prevention of carotid revascularization in women with asymptomatic carotid stenosis is expected to be lower than in men. Grade 2, Level B.

Abbreviations: CAD = coronary artery disease; CAS = carotid stenting; CEA = carotid endarterectomy; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CREST = Carotid Revascularization Endarterectomy vs Stenting Trial; NASCET = North American Symptomatic Carotid Endarterectomy; RCT = randomized controlled trial.

have significantly narrower carotid stenoses, men have larger plaque areas.^{40,41}

Due to these anatomic differences, carotid technical procedures need to be tailored to arterial anatomy and physiology (patch for CEA, tailored stenting for CAS).^{2,31}

Another influencing factor for higher periprocedural risk in women relies on the different risk profiles between women and men. Women undergoing carotid/vascular procedures are usually older, are more often obese, more often have hyperlipidemia, hypertension, or advanced peripheral artery disease,

and are less likely to smoke or have coronary disease or diabetes when compared to men.^{37,42–49} Additionally, a different risk profile in women vs men is likely to be related to a less aggressive approach for vascular disease in women leading to underuse of therapies and delay of diagnosis and surgical treatment.³⁷

Ideal cardiovascular health goals have been recently endorsed by the American Heart Association cardiovascular health and cardiovascular disease guidelines in women.¹ There was consensus among the panelists to retain the same goals for stroke prevention in adult women (>20 years) with carotid stenosis and before the peri-interventional period in those undergoing invasive treatment for carotid stenosis. These include smoking, body mass index, physical activity, diet, cholesterol levels, fasting plasma glucose, and blood pressure management.^{1,50}

Recommendations for this section are shown in table 4.

Medical therapy, including medical management in the peri-intervention period. Improvements in medical treatment over the last 20 years allowed for decreased periprocedural stroke/death risks in patients undergoing carotid intervention. However, women are less likely to receive antiplatelet, lipid-lowering, and β -blocker therapy in the presence of either peripheral or cardiovascular disease,^{37,51} even if these treatments

have a Class I indication for patients with carotid stenosis according to the major guidelines.^{2,31,51,52}

Multiple trials verified the benefit of aspirin in the reduction of recurrent ischemic stroke in both symptomatic men and women. Acetylsalicylic acid (75–325 mg a day in high risk; 81–100 mg a day in lower risk) is recommended by multiple guidelines for stroke prevention in women.^{2,31,52} Women appear to benefit from aspirin for prevention of a first stroke, an effect not as striking in men.^{53–55} The Women's Health Study, a large randomized, double-blind trial, showed that in women low-dose aspirin (100 mg a day) had a protective effect against a first stroke, namely a 24% reduction in the risk of ischemic stroke (RR 0.76; 95% CI 0.63–0.93; $p = 0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (RR 1.24; 95% CI 0.82–1.87; $p = 0.31$).⁵³ A sex-specific meta-analysis of aspirin therapy found that aspirin therapy was associated with a 17% reduction of stroke (OR 0.83; 95% CI 0.70–0.97; $p = 0.02$).⁵⁴ The choice of antiplatelet therapy among aspirin, clopidogrel, and dipyridamole + aspirin is not clearly defined because data are uncertain.² Aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy in women with carotid stenosis during the periprocedural period.^{2,53–55}

Clopidogrel is recommended in addition to aspirin in all CAS procedures to avoid early thrombotic risks

Table 4 Recommendations for risk factor modification and ideal lifestyle goals in women with carotid stenosis, including management over the peri-intervention period

Point 8	Technical details for revascularization of carotid arteries in women
	<ul style="list-style-type: none"> Women commonly show smaller vessel anatomies, less compliant arteries, and more fragile carotid plaque textures than men. Tailored technical procedures such as patch for CEA (Grade 1, Level B) and sized stenting (good clinical practice) for CAS may be considered to improve periprocedural outcome of carotid intervention in women. In recent neurologically symptomatic women with 50%–99% carotid stenosis, patch angioplasty or eversion endarterectomy is preferable over primary closure to reduce the early and late complications of CEA. Grade 1, Level B.
Point 9	Risk factor management and medical therapy for women with carotid stenosis
	<ul style="list-style-type: none"> Medical management should be implemented in all women with 50%–99% carotid stenosis. Periprocedural medical management of women undergoing carotid revascularization should include blood pressure control (ideal <140/<80 mm Hg untreated), antiplatelets, and statin therapy (low-density lipoprotein <100 mg/dL, <2.6 mmol/L). Grade 1, Level A. In women with carotid artery stenosis, regardless of whether or not intervention is planned, treatment of hypertension, hypercholesterolemia, and efforts at smoking cessation are recommended to reduce overall cardiovascular risk. Targets are those defined by the AHA effectiveness guidelines for women with CVD.^a Grade 1, Level A. Use of existing guidelines for glycemic control and blood pressure targets in women with diabetes is recommended for women who have had a stroke or TIA, but the benefits of meeting these targets on reducing stroke risk or decreasing complication rates after CEA and CAS are uncertain. Grade 2, Level C. Statins should be routinely used in women undergoing carotid revascularization. Grade 1, Level B. Best medical therapy (antiplatelet, statins, antihypertensive) should be continued in women with carotid stenosis lifelong. Grade 1, Level B.

Abbreviations: AHA = American Heart Association; CAS = carotid stenting; CEA = carotid endarterectomy; CVD = cardiovascular disease.

^aMosca L, Benjamin EJ, Berra K, Bezanson JL, et al; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women: 2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011;57:1404–1423.

Table 5 Recommendations for medical therapy in the overall management of women with carotid stenosis, including medical management in the peri-intervention period

Point 10	Periprocedural and long-term antiplatelet therapy in women with carotid stenosis
	<ul style="list-style-type: none"> • Antiplatelet therapy in asymptomatic women patients with carotid atherosclerosis is suggested for reducing overall cardiovascular morbidity. Grade 1, Level A.
	<ul style="list-style-type: none"> • Antiplatelet medications in women receiving treatment for carotid stenosis should be continued throughout the periprocedural period. Grade 1, Level B.
	<ul style="list-style-type: none"> • One antiplatelet medication does need to be maintained during the perioperative period of CEA; typically aspirin, but clopidogrel or substitute (e.g., adenosine diphosphate receptor inhibitors, dipyridamole) can be considered as well. Grade 1, Level B.
	<ul style="list-style-type: none"> • Periprocedural antithrombotic management of CAS should include dual antiplatelet therapy with aspirin and either ticlopidine or clopidogrel (or other substitute). Dual antiplatelet therapy should be initiated at least 3 days prior to CAS and continued at least for 1 month, whereas aspirin or clopidogrel therapy should be continued indefinitely. Grade 1, Level B.
	<ul style="list-style-type: none"> • Women may be more often resistant to clopidogrel, but the clinical relevance of the increased resistance prevalence is uncertain. The use of clopidogrel in the postprocedural period should be decided on a case-by-case basis. Grade 2, Level C.

Abbreviations: CAS = carotid stenting; CEA = carotid endarterectomy.

in women and men.⁵⁶ Although women are suggested to have lower residual platelet reactivity after low-dose aspirin and to be at higher risk of developing resistance to clopidogrel,⁵⁶ the evidence to justify differential platelet reactivity and related differential antiplatelet dosing/drug among sexes is weak. Use of clopidogrel after CAS in women should be maintained for at least the first month after the procedure, while aspirin should be continued indefinitely.

Subgroup analyses from RCTs suggested that statin therapy is cost-effective in both women and men.^{57,58} A large meta-analysis composed of 18 RCTs analyzing statin efficacy on women (n = 40,275 women) has recently confirmed that cardiovascular event rate was lower among those randomized to statins compared to controls.⁵⁹ The benefit in women was higher in secondary prevention than in primary prevention trials (OR 0.78; 95% CI 0.70–0.88, *p* < 0.0001, and OR 0.85; 95% CI 0.75–0.98, *p* = 0.0209, respectively).⁵⁹ To achieve the highest benefit in women with carotid stenosis, statins should be initiated prior to any interventional treatment.

Blood pressure fluctuations, both above and below the normal range, are a significant source of morbidity and contribute to MI and postprocedural reperfusion syndrome. Adequate periprocedural blood pressure management in women is critical for obtaining optimal postoperative results.² Antihypertensive therapy aimed at reducing blood pressure to <140/90 mm Hg has been recommended in individuals (including women) with asymptomatic carotid stenosis and for patients who had an ischemic stroke or TIA and are beyond the hyperacute period.^{2,52,60}

The prevalence of diabetes mellitus (DM) is increasing dramatically over time in women, in parallel with the increases in prevalence of overweight and obesity.^{1,50} DM is a major risk factor for stroke and perioperative stroke, especially during CEA.^{60,e1} Cardiovascular risk

factors among women with DM are managed less aggressively than among men (table e-2).^{e2} Nevertheless, according to RCTs, treatment of diabetes with the goal of close glucose control has not been shown to reduce stroke risk or decrease complication rate.^{e3,e4}

Recommendations for this section are shown in table 5.

DISCUSSION The latest cardiovascular recommendations on sex-specific prevention treatment in cardiovascular disease for women as well as carotid guidelines provided no detailed indications regarding management of carotid disease in women.^{2,50} This specific multidisciplinary expert consensus offers evidence-based recommendations to help physicians in decision-making for the prevention of stroke in women with carotid stenosis. This document was done with the understanding that most proposals are based on limited strength and quality of evidence and that such recommendations can change in the future. However, it is unlikely that changes will occur soon. Time is ripe for a separate women's carotid trial since they were unrepresented in earlier trials contributing to current limited knowledge in the field.

AUTHOR CONTRIBUTIONS

Dr. Paola De Rango: study concept and design, acquisition of data, analysis and interpretation, drafting the article, critical revision of the manuscript for important intellectual content. Prof. Martin M. Brown: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Dr. Leys Didier: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Dr. Virginia J. Howard: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Dr. Wesley S. Moore: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Dr. Maurizio Paciaroni: analysis and interpretation, drafting the article, critical revision of the manuscript for important intellectual content. Dr. Peter Ringleb: analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Caron Rockman: analysis and interpretation, critical revision of the manuscript

for important intellectual content. Dr. Valeria Caso: analysis and interpretation, acquisition of data, drafting the article, critical revision of the manuscript for important intellectual content, study supervision.

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REFERENCES

- Go AS, Mozaffarian D, Roger VL, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics: 2013 update: a report from the American Heart Association. *Circulation* 2013;127:143–152.
- Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 2011;54:e1–e31.
- Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database Syst Rev* 2011;4:CD001081.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445–453.
- Barnett HJM, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes BR. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415–1425.
- European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379–1387.
- European Carotid Surgery Trialists' Collaborative Group (ECST). Endarterectomy for moderate symptomatic carotid stenosis: Interim results from the MRC European Carotid Surgery Trial. *Lancet* 1996;347:1591–1593.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–1428.
- Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in

- patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491–1502.
- Halliday A, Harrison M, Hayter E, et al; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;376:1074–1084.
- Mayberg MR, Winn HR. Endarterectomy for asymptomatic carotid artery stenosis. Resolving the controversy. *JAMA* 1995;273:1459–1461.
- Mas JL, Chatellier G, Beyssen B, et al; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;355:1660–1671.
- Mas JL, Trinquart L, Leys D, et al; EVA-3S investigators. Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008;7:885–892.
- Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;7:893–902.
- Stingele R, Berger J, Alfke K, et al; SPACE investigators. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. *Lancet Neurol* 2008;7:216–222.
- SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;368:1239–1247.
- International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010;375:985–997.
- Brott TG, Hobson RW, 2nd, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11–23.
- Silver FL, Mackey A, Clark WM, et al; CREST Investigators. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675–680.
- Howard VJ, Lutsep HL, Mackey A, et al; CREST investigators. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol* 2011;10:530–537.
- Gurm HS, Yadav JS, Fayad P, et al; SAPPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;358:1572–1579.
- Vouyouka AG, Egorova NN, Sosunov EA, et al. Analysis of Florida and New York state hospital discharges suggests that carotid stenting in symptomatic women is associated with significant increase in mortality and perioperative morbidity compared with carotid endarterectomy. *J Vasc Surg* 2012;56:334–342.
- Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis

- in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915–924.
24. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR; Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107–116.
25. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. *Stroke* 2004;35:2855–2861.
26. Alamowitch S, Eliasziw M, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial (NASCET); ASA Trial Group; Carotid Endarterectomy (ACE) Trial Group. The risk and benefit of endarterectomy in women with symptomatic internal carotid artery disease. *Stroke* 2005;36:27–31.
27. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. *Cerebrovasc Dis* 2005;20:69–77.
28. Kapral MK, Wang H, Austin PC, et al; Ontario Carotid Endarterectomy Registry. Sex differences in carotid endarterectomy outcomes: results from the Ontario Carotid Endarterectomy Registry. *Stroke* 2003;34:1120–1125.
29. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? *Lancet* 2004;364:1122–1123; author reply 1125–1126.
30. Chaturvedi S, Bruno A, Feasby T, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Carotid endarterectomy: an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65:794–801.
31. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2011;57:1002–1044.
32. Carotid Stenting Trialists' Collaboration; Bonati LH, Dobson J, Algra A, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 2010;376:1062–1073.
33. Ederle J, Bonati LH, Dobson J, et al; CAVATAS Investigators. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol* 2009;8:898–907.
34. Brown MM, Raine R. Should sex influence the choice between carotid stenting and carotid endarterectomy? *Lancet Neurol* 2011;10:494–497.
35. Rockman CB, Garg K, Jacobowitz GR, et al. Outcome of carotid artery interventions among female patients, 2004 to 2005. *J Vasc Surg* 2011;53:1457–1464.
36. Young KC, Jahromi BS. Does current practice in the United States of carotid artery stent placement benefit asymptomatic octogenarians? *AJNR Am J Neuroradiol* 2011;32:170–173.
37. Poisson SN, Johnston SC, Sidney S, Klingman JG, Nguyen-Huynh MN. Gender differences in treatment of severe carotid stenosis after transient ischemic attack. *Stroke* 2010;41:1891–1895.
38. Dick P, Sherif C, Sabeti S, Amighi J, Minar E, Schillinger M. Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. *Stroke* 2005;36:1178–1183.
39. Marquardt L, Fairhead JF, Rothwell PM. Lower rates of intervention for symptomatic carotid stenosis in women than in men reflect differences in disease incidence: a population-based study. *Stroke* 2010;41:16–20.
40. Schulz UG, Rothwell PM. Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque. *Stroke* 2001;32:1525–1531.
41. Hellings WE, Pasterkamp G, Vollebregt A, et al. Intra-observer and interobserver variability and spatial differences in histologic examination of carotid endarterectomy specimens. *J Vasc Surg* 2007;46:1147–1154.
42. Baracchini C, Mazzalai F, Gruppo M, Lorenzetti R, Ermani M, Ballotta E. Carotid endarterectomy protects elderly patients from cognitive decline: a prospective study. *Surgery* 2012;151:99–106.
43. Grootenboer N, Hunink MG, Hoeks S, Hendriks JM, van Sambeek MR, Poldermans D. The impact of gender on prognosis after non-cardiac vascular surgery. *Eur J Vasc Endovasc Surg* 2011;42:510–516.
44. Halm EA, Tuhim S, Wang JJ, Rockman C, Riles TS, Chassin MR. Risk factors for perioperative death and stroke after carotid endarterectomy: results of the New York Carotid Artery Surgery Study. *Stroke* 2009;40:221–229.
45. Sjölander M, Eriksson M, Glader EL. Few sex differences in the use of drugs for secondary prevention after stroke: a nationwide observational study. *Pharmacoepidemiol Drug Saf* 2012;21:911–919.
46. Vouyouka AG, Egorova NN, Salloum A, et al. Lessons learned from the analysis of gender effect on risk factors and procedural outcomes of lower extremity arterial disease. *J Vasc Surg* 2010;52:1196–1202.
47. Egorova N, Vouyouka AG, Quin J, et al. Analysis of gender-related differences in lower extremity peripheral arterial disease. *J Vasc Surg* 2010;51:372–379.
48. Akbari CM, Pulling MC, Pomposelli FB, Jr., Gibbons GW, Campbell DR, Leger FW. Gender and carotid endarterectomy: does it matter? *J Vasc Surg* 2000;31:1103–1109.
49. Yavas S, Mavioglu L, Kocabeyoglu S, et al. Is female gender really a risk factor for carotid endarterectomy? *Ann Vasc Surg* 2010;24:775–785.
50. Mosca L, Benjamin EJ, Berra K, Bezanson JL, et al; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011;57:1404–1423.
51. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic

- Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(suppl 2):e637S–e668S.
52. Furie KL, Kasner SE, Adams RJ, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227–276.
 53. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–1304.
 54. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;295:306–313.
 55. Dorresteyn JA, Visseren FL, Ridker PM, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. *Eur Heart J* 2011;32:2962–2969.
 56. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354–362.
 57. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation* 2010;121:1069–1077.
 58. Goldstein LB, Amarenco P, Lamonte M, et al; SPARCL Investigators. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. *Stroke* 2008;39:2444–2448.
 59. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol* 2012;59:572–582.
 60. Goldstein LB, Bushnell CD, Adams RJ, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:517–584.