Gender Differences in Outcome of Conservatively Treated Patients With Asymptomatic High Grade Carotid Stenosis

Petra Dick, MD; Camillo Sherif, MD; Schila Sabeti, MD; Jasmin Amighi, MD; Erich Minar, MD; Martin Schillinger, MD

Background and Purpose—Gender differences are currently becoming increasingly recognized as an important prognostic factor in patients with atherosclerotic disease. We investigated gender-related differences in vascular outcome and mortality of asymptomatic patients with high-grade internal carotid artery (ICA) stenosis.

Methods—We enrolled 525 consecutive patients (325 males with a median age of 72 years and 200 females with a median age of 75 years) from a single center registry who were initially treated conservatively with respect to a neurologically asymptomatic ≥70% ICA stenosis. Patients were followed-up for a median of 38 months (interquartile range, 18 to 65) for major adverse cardiovascular, cerebral, and peripheral vascular events (MACE: combined end point including myocardial infarction, stroke, [partial] limb amputation, and death), vascular mortality, and all-cause mortality.

Results—Cumulative MACE-free survival rates in males and females at 1, 3, and 5 years were 83%, 65%, 48% versus 85%, 73%, and 67% (P = 0.004), respectively. Adjusted hazard ratios for MACE, vascular mortality, and all-cause mortality for males were 1.96 (P = 0.016), 2.48 (P < 0.001), and 1.70 (P = 0.007) as compared with females, irrespective of age, vascular risk factors, comorbidities, and the individual risk status estimated by the American Society of Anesthesiologists (ASA) score.

Conclusion—Male patients with high-grade carotid artery stenosis are at a considerably higher risk for poor outcome than their female counterparts. In particular, the risk for fatal vascular events is substantially increased in males. (Stroke. 2005;36:1178-1183.)

Key Words: atherosclerosis ■ carotid arteries ■ gender ■ outcome

Gender-related differences are becoming increasingly recognized as potentially important prognostic factors in atherosclerotic disease. It is well-known that the incidence of cardiovascular disease is higher in men than in women, in part because of differences in risk factors and hormones. Although recent clinical trials did not show protective effects of combination hormone replacement therapy with estrogens and progestins on vascular events, much experimental and epidemiological evidence suggests beneficial effects of estrogens on the endothelium and on atherosclerosis. However, during the past decade cardiovascular mortality has appreciably decreased among men, whereas women have experienced a continuous increase in the rates of cardiovascular death. This partly may be attributed to a rather sparing use of diagnostic tools and a tendency to less aggressive therapeutic interventions in women compared with their male counterparts. Nevertheless, women are still 3-times as likely to survive to the age of 90 years compared with men.

Beyond differences in the incidence of atherosclerosis, it also seems that the nature and prognosis of the disease differs in men and women. Recently, gender-related differences in carotid plaque distribution and degree of carotid stenosis have been reported. Men had less carotid stenosis but a greater carotid plaque area than women at equal ages. Otherwise, at the same degree of carotid stenosis, women had a lesser extent of plaque burden than men, and the latter was identified as a powerful predictor of poor cardiovascular outcome. Therefore, we hypothesized that in patients with high-grade carotid artery stenosis, women may exhibit a better vascular and overall prognosis than men. We thus investigated gender-related differences in major adverse cardiovascular, cerebral, and peripheral vascular events (MACE: combined end point including myocardial infarction, stroke, [partial] limb amputation, and death), vascular mortality, and all-cause mortality of patients with a >70% internal carotid artery stenosis, who were initially asymptomatic without a history of ischemic neurological symptoms in the carotid territory and were initially treated conservatively with respect to carotid disease.

Materials and Methods

Study Design and Patients
We enrolled 525 consecutive patients with ≥70% asymptomatic carotid artery stenosis in the present study. Patients were identified...
Hyperlipidemia was defined as hypercholesterolemia with cholester-
diabetes in patients using antidiabetic medication or insulin therapy.
Acceptance as indicative of diabetes mellitus, as was a history of
Diabetes mellitus was defined as a fasting blood glucose level of
Hypertension was defined as blood pressure of
Survillence Protocol
Patients were identified in the ultrasound laboratory of the Depart-
ment of Angiology. For verification of the inclusion and exclusion
criteria, results from the patients’ charts were reviewed. Baseline
data included patients’ medical history and physical examination,
and laboratory data for assessment of traditional vascular risk
factors. Patients’ histories were recorded with special attention to
vascular risk factors, past vascular events, current symptoms of
concomitant vascular disease, current medication, family history of
vascular events, and concomitant malignancies. The American So-
ciety of Anesthesiologists (ASA) classification was used to define
the level of comorbidity (ASA I to IV).
Study End Points
Patients were followed-up for MACE, vascular mortality, and
all-cause mortality. The incidence of these events was investigated
until December 31, 2002.

Being aware of the potential confounding effect of revasculariza-
procedure, which may be performed in the absence of clinical
events, we included as a sensitivity analysis the performance of
percutaneous coronary interventions (PCI), coronary artery bypass
graft (CABG), carotid artery stenting (CAS) or endarterectomy
(CEA), peripheral bypass graft, and peripheral percutaneous inter-
vention in a secondary combined end point with MACE as defined.

Surveillance Protocol
Patients were followed-up clinically and by duplex ultrasound at 6
and 12 months after initial presentation, and then annually at the
outpatient ward of our department until December 2002. A follow-up
questionnaire was sent to each patient during January 2003 re-
evaluating the occurrence of the study end points until December
2002. Information from the follow-up questionnaires was validated
by reviewing the original hospital discharge reports of corresponding
readmissions attributable to MACEs. If the follow-up questionnaire
was not returned, personal telephone contact to the patients, their
relatives, or the treating physicians was established. Additional
information was obtained by reviewing the hospital discharge reports
of any other readmission during the follow-up period. Outcome was
assessed by 2 independent observers who were blinded with respect
to patients’ baseline clinical and laboratory data. Additionally,
mortality data were obtained from the „Österreichisches Statistisches
Zentralamt“ (Austrian Central Statistical Office), providing day and
cause of death of all patients.

Definitions
Hypertension was defined as blood pressure of >140/90 mmHg
examined repeatedly and was assumed to be present in all patients
with a history of hypertension using antihypertensive therapy.
Diabetes mellitus was defined as a fasting blood glucose level of
>126 mg/dL (7.0 mmol/L). Furthermore, an HbA1c >6.5% was
accepted as indicative of diabetes mellitus, as was a history of
diabetes in patients using anti diabetic medication or insulin therapy.
Hyperlipidemia was defined as hypercholesterolemia with cholesterol
>200 mg/dL (5.2 mmol/L) or low-density lipoprotein cholesterol
>130 mg/dL (3.4 mmol/L) and was assumed to be present in all
patients taking cholesterol synthesis inhibitor-inhibitors or other lipid
lowering medications. Coronary artery disease, according to the
Canadian Cardiovascular Society classification, was evaluated by
treadmill exercise testing, dobutamine echocardiography, myocar-
dial scintigraphy, and coronary angiography in selected cases. The
New York Heart Association categories were used to classify the
severity of congestive heart failure. Myocardial infarction was
defined according to the consensus document of The Joint European
Society of Cardiology/American College of Cardiology Committee
for the redefinition of myocardial infarction.14 Stroke was defined as
a neurological deficit that persisted >24 hours, evaluated by a
neurologist according to the modified Rankin stroke scale.15 Man-
datory cranial computed tomography or, if available, MRI was used
for confirmation of the diagnosis. Peripheral arterial disease was
classified according to the Fontaine stages.16

Statistical Analysis
Continuous data are given as median and interquartile range (range
from the 25th to the 75th percentile). Discrete data are given as counts
and percentages. χ² Tests and Mann–Whitney U test were used for
univariate analysis, as adequate. Survival and event-free survival
rates until the occurrence of a first MACE comparing males and
females are presented as Kaplan–Meier curves and compared by
means of the log rank test. Multivariate Cox proportional hazards
models were applied to assess the effect gender on the occurrence of
a first MACE. Variables that were unbalanced between males and
females (indicated by a P<0.20), as well as established risk factors
for MACE, were considered as potential confounders. We tested for
interactions between baseline variables by multiplicative interaction
terms and log likelihood χ² tests. We assessed the overall model fit
using the Cox–Snell residuals. We tested the proportional hazard
assumption for all covariates using Schoenfeld residuals (overall
test) and the scaled Schoenfeld residuals (variable-by-variable test-
ing). According to the tests, the proportional hazards assumption was
not violated. Results of the Cox proportional hazards model are
presented as the hazard ratio (HR) and the 95% confidence interval
(95% CI). A 2-sided P<0.05 was considered as statistically signif-
icant. Calculations were performed with Stata (release 8.0).

Results
Patients
We included 525 consecutive patients in the final analysis
(325 males with a median age of 72 years and 200 females
with a median age of 75 years; Table 1). Hormone replace-
ment therapy was recorded in 16 females (8%) at study entry.
Males had a higher ASA score and were more frequently
receiving clopidogrel. Furthermore, there was a trend toward
a higher body mass index in males, and males tended to be
less frequently smokers. Females, however, were signifi-
cantly older and tended to have more frequently concomitant
symptomatic coronary artery disease.

Follow-Up
During the median follow-up period of 38 months (interquar-
tile range, 18 to 65), 203 MACEs occurred in 184 patients
(35%), including 13 myocardial infarctions, 44 strokes (35
ipsilateral, 7 contralateral, 2 posterior circulation), and 7
amputations, and 139 patients (27%) died. The majority of
deaths were caused by fatal vascular events (n=114, 82%;
including 4 deaths after emergency coronary revasculariza-
tion procedures: 2 deaths after urgent CABG caused by
unstable angina, 2 death after emergency PCI caused by
evolving myocardial infarction), and the remaining patients
died of malignancies, respiratory failure, infection with sepsis, pulmonary embolism, multi-organ failure after major surgery, and unknown causes.

During the follow-up period, 157 revascularization procedures were performed, including 20 PCIs, 19 CABGs, 88 carotid revascularization procedures (CAS or CEA), 8 peripheral bypass operations, and 22 peripheral percutaneous interventions. The 88 carotid revascularization procedures were performed in 44 patients with neurological events (40 CAS and 4 CEAs within 6 weeks after the events) and in 44 patients (all CAS) with rapidly progressive carotid stenoses during a 6-month interval to a degree of stenosis \( \geq 90\% \) by duplex ultrasound, and confirmed by angiography in all 44 patients. Overall, the calculated annual percentage of increase of the degree of stenosis was a median of 9\% in these 44 patients who underwent CAS and a median of 1\% in the remaining subjects. Complications of carotid revascularization included 2 strokes and no deaths, and both postintervention strokes occurred in male patients with a de novo symptomatic carotid stenosis and minor strokes as the cause to perform the procedure.

For all subsequent analyses, the time interval until the first MACE has been considered. Cumulative rates of MACE-free, vascular death-free, and overall survival in males and females at 1, 3, and 5 years were 83\%, 65\%, 48\% versus 85\%, 73\%, 67\% \( (P=0.004) \), 90\%, 79\%, 67\% versus 93\%, 87\%, 85\% \( (P<0.001) \), and 89\%, 77\%, 63\% versus 90\%, 81\%, and 78\% \( P=0.013 \), respectively. Males had MACE, vascular death, or death of any cause during the follow-up period significantly more often compared with females (Figure 1). Being aware of several potential confounding factors, we then applied a multivariate Cox proportional hazards model and adjusted the hazard ratios for age, body mass index, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease (Canadian Cardiovascular Society stage), congestive heart failure (New York Heart Association

| TABLE 1. Demographic Data and Clinical Characteristics of Male and Female Patients With Asymptomatic High-Grade Internal Carotid Artery Stenosis |
|-----------------|-----------------|----------|
|                              | Males (n=325)   | Females (n=200) | \( P \)   |
| Age, y                      | 72 (65 to 77)   | 75 (68 to 80)   | <0.001    |
| Body mass index, kg/m\(^2\) | 26.5 (24.2 to 29.4) | 25.5 (22.6 to 28.8) | 0.057     |
| Current smoking             | 55 (17\%)       | 47 (24\%)       | 0.064     |
| Hyperlipidemia              | 240 (74\%)      | 159 (80\%)      | 0.14      |
| Arterial hypertension       | 241 (74\%)      | 154 (77\%)      | 0.46      |
| Diabetes mellitus           | 111 (34\%)      | 68 (34\%)       | 0.97      |
| Coronary artery disease, CCS| 108 (33\%)      | 52 (26\%)       | 0.090     |
| CCS I                       | 28 (9\%)        | 31 (16\%)       |           |
| CCS II                      | 4 (1\%)         | 3 (2\%)         |           |
| CCS III                     | 1 (0.2\%)       | ...             |           |
| History of myocardial infarction | 70 (22\%)    | 42 (21\%)       | 0.88      |
| Congestive heart failure, NYHA | 42 (13\%)      | 14 (7\%)        | 0.18      |
| NYHA I                      | 42 (13\%)       | 14 (7\%)        |           |
| NYHA II                     | 27 (8\%)        | 16 (8\%)        |           |
| NYHA III                    | 6 (2\%)         | 3 (2\%)         |           |
| NYHA IV                     | ...             | ...             |           |
| Peripheral artery disease [Fontaine] | 33 (10\%)      | 20 (10\%)       | 0.18      |
| Stage I                     | 94 (29\%)       | 49 (25\%)       |           |
| Stage II                    | 11 (3\%)        | 2 (1\%)         |           |
| Stage III                   | 4 (1\%)         | ...             |           |
| Malignancy                  | 5 (2\%)         | 3 (2\%)         | 0.97      |
| Statin therapy              | 205 (63\%)      | 118 (59\%)      | 0.35      |
| Clopidogrel therapy         | 129 (40\%)      | 60 (30\%)       | 0.025     |
| ASA score                   | 0.037           |                |           |
| I                           | 87 (27\%)       | 65 (33\%)       |           |
| II                          | 156 (48\%)      | 105 (53\%)      |           |
| III                         | 75 (23\%)       | 26 (13\%)       |           |
| IV                          | 7 (2\%)         | 4 (2\%)         |           |

ASA indicates American Society of Anesthesiologists; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association.

Data are given as median (interquartile range) or as counts (%).
stage), peripheral artery disease (Fontaine stage), presence of a malignancy, ASA score (I to IV), and use of statins and clopidogrel. Adjusted hazard ratios for MACE, vascular mortality, and all-cause mortality for males were 1.96 (95% CI, 1.13 to 3.38), 2.48 (95% CI, 1.57 to 3.93), and 1.70 (95% CI, 1.15 to 2.49) compared with females, irrespective of age, vascular risk factors, comorbidities, and ASA score (Table 2, Figure 2).

Including the performance of revascularization procedures in a secondary combined end point (myocardial infarction, stroke, amputation, death, PCI, CABG, CAS, CEA, peripheral bypass graft, and peripheral percutaneous intervention) confirmed a significantly higher risk for poor outcome in males compared with females (adjusted hazard ratio, 1.51; 95% CI, 1.02 to 2.23; P=0.041).

**Discussion**

We found that male patients with an asymptomatic high-grade carotid artery stenosis were at a significantly higher risk for future MACE, vascular mortality, and all-cause mortality than their female counterparts, irrespective of age, traditional vascular risk factors, and comorbidities. This difference was most pronounced for fatal vascular events, with a 2.5-fold increased risk in men. Recognizing these gender-related differences may have some implications for monitoring and treatment strategies in these patients.
Fatal and nonfatal vascular and cardiac events are frequently encountered in patients with carotid stenosis. Widely comparable to our findings, Norris et al reported an annual cardiac event rate of 8.3% and an annual death rate of 6.5%, also including patients with a less severe degree of carotid stenosis. The event rates described previously for patients in the control groups of the ACST and ACAS trials were 16% at 3.4 years and 11% at 2.7 years, respectively, lower than the 20% death rate at 3 years in the present study. These differences in outcome likely arise from different clinical settings (randomized controlled trials versus consecutive patient series). More specific event rates discriminating cardiac, cerebrovascular, and peripheral outcomes in males and females with asymptomatic high-grade carotid stenosis were not described in the literature as yet.

It has been demonstrated unequivocally that at the same degree of carotid stenosis, men had a higher plaque burden than women. This held true both for ultrasound and angiographic measurements. Differences of carotid bifurcation plaque load likely translate into a differential risk for ipsilateral stroke, and a close association between carotid plaque area and the risk for vascular adverse events such as myocardial infarction, cerebrovascular accidents, and death has been reported. Our present observation supports the view that in the presence of a high-grade carotid stenosis, males are at a higher vascular risk than females. Unfortunately, we were unable to obtain the carotid plaque area, to assess whether the increase in vascular risk may be (partially) attributed to this fact, or, otherwise, whether males exhibit an increased risk irrespective of the plaque area.

Men had a 1.96-fold higher risk for MACE and a 2.5-fold increased risk for fatal vascular events compared with women, which was adjusted for comorbidities as well as for patients’ ASA risk status, effect sizes that have to be considered clinically relevant. Gender differences in patients with cerebrovascular disease were recognized in several previous trials. Data from Framingham suggested that females had a better prognosis after cerebral ischemic events. The Canadian Aspirin trial in the 1970s remarked on the male/female treatment difference and eventually concluded that the differences were caused by a lower risk level for stroke in females. In the ACAS trial, carotid endarterectomy was more effective in men than in women, whereas other studies including the NASCET trial showed that gender was not associated with altered rates of stroke-free survival. Among all potential gender-related factors that may contribute to these differences in vascular outcome, the impact of

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted* risk for MACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>1.96</td>
<td>1.13 to 3.38</td>
<td>0.016</td>
</tr>
<tr>
<td>Adjusted* risk for vascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>2.48</td>
<td>1.57 to 3.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted* risk for mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>1.70</td>
<td>1.15 to 2.49</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Models were adjusted for age (in quartiles), body mass index, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease (CCS stage), congestive heart failure (NYHA), peripheral artery disease (Fontaine), presence of a malignancy, ASA score (I to IV), and use of statins and clopidogrel.

MACE indicates myocardial infarction, stroke, [partial] limb amputation, and death; ... reference group.

Fatal and nonfatal vascular and cardiac events are frequently encountered in patients with carotid stenosis. Widely comparable to our findings, Norris et al reported an annual cardiac event rate of 8.3% and an annual death rate of 6.5%, also including patients with a less severe degree of carotid stenosis <75%. The event rates described previously for patients in the control groups of the ACST and ACAS trials were 16% at 3.4 years and 11% at 2.7 years, respectively, lower than the 20% death rate at 3 years in the present study. These differences in outcome likely arise from different clinical settings (randomized controlled trials versus consecutive patient series). More specific event rates discriminating cardiac, cerebrovascular, and peripheral outcomes in males and females with asymptomatic high-grade carotid stenosis were not described in the literature as yet.

It has been demonstrated unequivocally that at the same degree of carotid stenosis, men had a higher plaque burden than women. This held true both for ultrasound and angiographic measurements. Differences of carotid bifurcation plaque load likely translate into a differential risk for ipsilateral stroke, and a close association between carotid plaque area and the risk for vascular adverse events such as myocardial infarction, cerebrovascular accidents, and death has been reported. Our present observation supports the view that in the presence of a high-grade carotid stenosis, males are at a higher vascular risk than females. Unfortunately, we were unable to obtain the carotid plaque area, to assess whether the increase in vascular risk may be (partially) attributed to this fact, or, otherwise, whether males exhibit an increased risk irrespective of the plaque area.

Men had a 1.96-fold higher risk for MACE and a 2.5-fold increased risk for fatal vascular events compared with women, which was adjusted for comorbidities as well as for patients’ ASA risk status, effect sizes that have to be considered clinically relevant. Gender differences in patients with cerebrovascular disease were recognized in several previous trials. Data from Framingham suggested that females had a better prognosis after cerebral ischemic events. The Canadian Aspirin trial in the 1970s remarked on the male/female treatment difference and eventually concluded that the differences were caused by a lower risk level for stroke in females. In the ACAS trial, carotid endarterectomy was more effective in men than in women, whereas other studies including the NASCET trial showed that gender was not associated with altered rates of stroke-free survival. Among all potential gender-related factors that may contribute to these differences in vascular outcome, the impact of

---

**TABLE 2. Multivariate Cox Proportional Hazards Models Assessing the Risk for MACE and Mortality in 325 Male vs 200 Female Conservatively Treated Patients With Asymptomatic High-Grade Internal Carotid Artery Stenosis**

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted* risk for MACE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>1.96</td>
<td>1.13 to 3.38</td>
<td>0.016</td>
</tr>
<tr>
<td>Adjusted* risk for vascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>2.48</td>
<td>1.57 to 3.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted* risk for mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>1.70</td>
<td>1.15 to 2.49</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Models were adjusted for age (in quartiles), body mass index, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease (CCS stage), congestive heart failure (NYHA), peripheral artery disease (Fontaine), presence of a malignancy, ASA score (I to IV), and use of statins and clopidogrel.

MACE indicates myocardial infarction, stroke, [partial] limb amputation, and death; ... reference group.

Fatal and nonfatal vascular and cardiac events are frequently encountered in patients with carotid stenosis. Widely comparable to our findings, Norris et al reported an annual cardiac event rate of 8.3% and an annual death rate of 6.5%, also including patients with a less severe degree of carotid stenosis <75%. The event rates described previously for patients in the control groups of the ACST and ACAS trials were 16% at 3.4 years and 11% at 2.7 years, respectively, lower than the 20% death rate at 3 years in the present study. These differences in outcome likely arise from different clinical settings (randomized controlled trials versus consecutive patient series). More specific event rates discriminating cardiac, cerebrovascular, and peripheral outcomes in males and females with asymptomatic high-grade carotid stenosis were not described in the literature as yet.

It has been demonstrated unequivocally that at the same degree of carotid stenosis, men had a higher plaque burden than women. This held true both for ultrasound and angiographic measurements. Differences of carotid bifurcation plaque load likely translate into a differential risk for ipsilateral stroke, and a close association between carotid plaque area and the risk for vascular adverse events such as myocardial infarction, cerebrovascular accidents, and death has been reported. Our present observation supports the view that in the presence of a high-grade carotid stenosis, males are at a higher vascular risk than females. Unfortunately, we were unable to obtain the carotid plaque area, to assess whether the increase in vascular risk may be (partially) attributed to this fact, or, otherwise, whether males exhibit an increased risk irrespective of the plaque area.

Men had a 1.96-fold higher risk for MACE and a 2.5-fold increased risk for fatal vascular events compared with women, which was adjusted for comorbidities as well as for patients’ ASA risk status, effect sizes that have to be considered clinically relevant. Gender differences in patients with cerebrovascular disease were recognized in several previous trials. Data from Framingham suggested that females had a better prognosis after cerebral ischemic events. The Canadian Aspirin trial in the 1970s remarked on the male/female treatment difference and eventually concluded that the differences were caused by a lower risk level for stroke in females. In the ACAS trial, carotid endarterectomy was more effective in men than in women, whereas other studies including the NASCET trial showed that gender was not associated with altered rates of stroke-free survival. Among all potential gender-related factors that may contribute to these differences in vascular outcome, the impact of

---

**Figure 2. Adjusted hazard ratios for major adverse cardiovascular, cerebral, and peripheral vascular events (MACE), vascular mortality, and all-cause mortality in 525 patients with asymptomatic high-grade carotid artery stenosis undergoing conservative medical treatment.**
hormones has been studied most extensively. However, in the present cohort of elderly patients, hormone replacement therapy was used only in a minority of individuals (8% of female participants) and natural hormones at this age may not play a relevant role either.

Several studies elucidated gender-related differences in medical treatment of patients with cerebrovascular atherosclerosis and stroke. In particular, males were more likely to receive antithrombotic medication. Similarly, we observed that males were more likely to receive clopidogrel than females, although all patients were using any antithrombotic medication (clopidogrel or ASA). Nevertheless, similar to a previous observation in patients after stroke, this did not translate into a clinical benefit, and males, particularly of older age, had a worse prognosis than females.

Limitations
We are aware of some limitations of the present study. From the observational study design, we can only speculate about a causal relationship between gender and differences in outcome of these patients. In fact, unmeasured confounders may have influenced our findings. However, looking at the list of measured confounders, we are confident that the most important known confounders have been considered for adjustment of the multivariate analysis. Prospective interventional trials will be needed to assess whether males may benefit from more aggressive monitoring and treatment strategies.

Conclusion
Male patients with high-grade carotid artery stenosis are at a considerably higher risk for poor outcome than their female counterparts. In particular, the risk for fatal vascular events is substantially higher in males.

References
Gender Differences in Outcome of Conservatively Treated Patients With Asymptomatic High Grade Carotid Stenosis
Petra Dick, Camillo Sherif, Schila Sabeti, Jasmin Amighi, Erich Minar and Martin Schillinger

Stroke. 2005;36:1178-1183; originally published online May 12, 2005;
doi: 10.1161/01.STR.0000166056.04922.f2
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/6/1178

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/