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Risk of Recurrent Stroke in Patients with Symptomatic Mild (20–49% NASCET) Carotid Artery Stenosis

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WHAT THIS PAPER ADDS

This paper adds contemporary information on the risk of recurrent ipsilateral stroke in patients with symptomatic mild carotid artery stenosis. Although the patients are older at the time of their first stroke, the risk of recurrence is still at a similar level to that seen in the now 20 year old large intervention studies (ECST and NASCET). The present findings indirectly suggest that the recurrent stroke rates in both moderate and severe symptomatic carotid artery stenosis remain at a level where the use of CEA is justified despite improved medication.

Objective: The objective of this study was to evaluate the risk of recurrent ischaemic stroke in patients with ultrasound assessed symptomatic mild carotid artery stenosis (20–49% NASCET) treated solely with modern medical treatment.

Method: This was a retrospective, observational register cohort study. Three groups of patients were recruited from a database of all carotid Doppler ultrasound examinations performed in the Gothenburg region between 2004 and 2009. Patients with symptomatic mild carotid artery stenosis ($n = 162$) were compared with patients with asymptomatic carotid artery stenosis ($n = 301$) of equal degree and a group of patients with surgically (CEA) treated symptomatic moderate or severe carotid artery stenosis ($n = 220$). Kaplan-Meier estimates and Cox proportional hazard models were used to compare the primary outcome (ipsilateral ischaemic stroke) between groups.

Results: After a 3 year follow up, the cumulative incidence of recurrent ipsilateral stroke in patients with symptomatic mild carotid artery stenosis was 7.4%. Patients with symptomatic mild carotid artery stenosis had a substantially increased risk of recurrent ipsilateral stroke compared with asymptomatic patients with equal degree of stenosis (HR 5.5. 95% CI 1.8–17.1; $p = .003$) as also compared with patients with CEA treated symptomatic moderate or severe stenosis (HR 7.8. 95% CI 1.62–37.8; $p = .011$).

Conclusions: The present study on patients with symptomatic mild carotid artery stenosis, as determined by Doppler ultrasound, shows that there is still a substantial risk of recurrent stroke in this group.

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Keywords: Mild, Symptomatic, Carotid artery stenosis, Recurrent stroke

INTRODUCTION

Patients with transient ischaemic attack (TIA), or stroke and carotid artery stenosis carry an increased risk of recurrent stroke and should therefore be investigated and treated without delay.[1] Two large randomised studies, NASCET[2] and ECST,[3] have reported the benefit of carotid endarterectomy (CEA), in patients with moderate and severe stenosis which was reconfirmed in a recent meta-analysis.[4]

In addition, results from the NASCET and ECST trials showed that the risk of recurrent stroke was proportional to

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the degree of stenosis, and also patients with mild stenosis (50–69% ECST, 20–49% NASCET) showed an increased risk of recurrent stroke but that risk did not balance the surgical risk.[5] Around 20 years have passed since these trials fulfilled their recruitment and there is reason to believe that advances in optimal medical treatment have influenced the risk of recurrent stroke.[6–8] We therefore hypothesised that mild symptomatic carotid stenosis, with medical treatment according to current guidelines, has an even lower risk of recurrent stroke than in the ECST and NASCET trials. This finding would indirectly suggest that the role of CEA in moderate and severe stenosis should be analysed carefully, and perhaps CEA used more conservatively with focus instead on optimal medical treatment.

In the Gothenburg region in Western Sweden, Doppler ultrasound with flow velocity assessment is used as the first line diagnostic investigation of carotid artery stenosis. The peak systolic velocity correlates well with degree of stenosis when using accurate angle correction, enabling grading of the stenosis.[9,10] Current guidelines in the region state that only patients with symptomatic carotid stenosis $\geq$50% (NASCET) should undergo CEA. The patients in the current study are therefore almost exclusively treated medically and the risk of selection bias from CEA is minimised.

In the current study the risk of recurrent ipsilateral ischaemic stroke was evaluated in patients with ultrasound assessed mild symptomatic carotid artery stenosis (20–49% NASCET). Analyses were made to determine whether the stroke incidence was different from that seen in asymptomatic patients with an equal degree of stenosis and different from patients with symptomatic moderate or severe carotid artery stenosis ($\geq$50% NASCET) after CEA. The latter group resembles what might be considered the residual risk possible to achieve if surgical treatment of mild carotid artery stenosis had been performed.

METHODS

Patient population

The study was a retrospective register study on patients having Doppler ultrasound examination of their carotid arteries at the vascular diagnostic unit at Sahlgrenska University Hospital between the years 2004 and 2009 (n = 9,697) and with a home address in the Gothenburg area. Sahlgrenska University Hospital is the sole supplier of vascular ultrasound diagnostics in the Gothenburg region with approximately 650,000 inhabitants. Ultrasound is the recommended first line investigation of carotid arteries after TIA and minor stroke according to strict local guidelines. The study thus included all patients in this geographical area, who were referred for evaluation of carotid atherosclerotic disease. Most of the patients had symptoms resembling minor stroke or TIA, with the remaining patients examined for other reasons, e.g. carotid bruits. All ultrasound investigations routinely included bilateral carotid artery examination and were documented in the Western Region Initiative to Gather Information on Atherosclerosis database (WINGA). In the database, carotid artery stenoses were graded using the ECST criteria adapted for Doppler ultrasound according to Jogestrand and Nowak.[9,10] The sonographer documented peak systolic velocity in the stenotic segment and the Doppler angle. The degree of stenosis was expressed as percentage reduction of lumen diameter according to ECST and was in this study converted to NASCET grading using the formula published by Rothwell et al.[11] Three groups of patients were identified in the database.

Group 1/symptomatic and: Group 2/asymptomatic patients with mild carotid artery stenosis (20–49% NASCET)

Records from all patients with a reported mild (20–49% NASCET) internal carotid artery stenosis were retrieved and carefully scrutinized for inclusion in the study. A 20–49% stenosis was defined from the velocity criteria:[9,10] peak systolic velocity being either 1.3–2.2 m/s within a 55–60° correction of the Doppler angle or 1.1–1.6 m/s with $<$45° angle correction. Patients fulfilling the criteria of a mild stenosis were divided into a symptomatic group and an asymptomatic group. Symptomatic carotid artery stenosis was defined as patients with neurological symptoms (stroke, minor stroke, TIA, retinal ischaemia) corresponding to the side of the mild stenosis and within 6 months of the ultrasound examination. The asymptomatic group was defined as patients either without neurological symptoms or symptoms corresponding to the contralateral (non-stenotic) carotid circulation, or the posterior circulation territory. Six months was chosen as the cut off point between symptomatic and asymptomatic patients according to American Guidelines and previously published studies.[2,3,12] Records of neurological symptoms were evaluated by certified physicians in clinical physiology (GB, JFL), and a certified neurologist (AN) scrutinized all uncertain classifications. Patients with insufficient records to decide which vascular territory caused the neurological symptoms, were excluded from the study (Fig. 1). All patients included in the study had to be eligible for CEA which was evaluated by certified physicians in clinical physiology (GB, JFL) and when in doubt by a certified vascular surgeon (SS).

Patients with bilateral carotid artery stenosis and lateralised symptoms were included in the symptomatic group. In patients with bilateral asymptomatic stenosis, one of the sides was randomly selected to be included in the follow up of ipsilateral stroke.

Exclusion criteria for both groups were: insufficient patient or examination records, causes of stenosis other than atherosclerotic disease (restenosis after previous CEA, dissection or tumour), peak systolic velocity and/or angle correction outside the specified range (Fig. 1).

Group 3/patients with symptomatic, moderate, or severe carotid artery stenosis ($\geq$50% NASCET) treated with CEA (CEA group)

To assess the cumulative risk of recurrent stroke after CEA in the study region, the WINGA database was cross

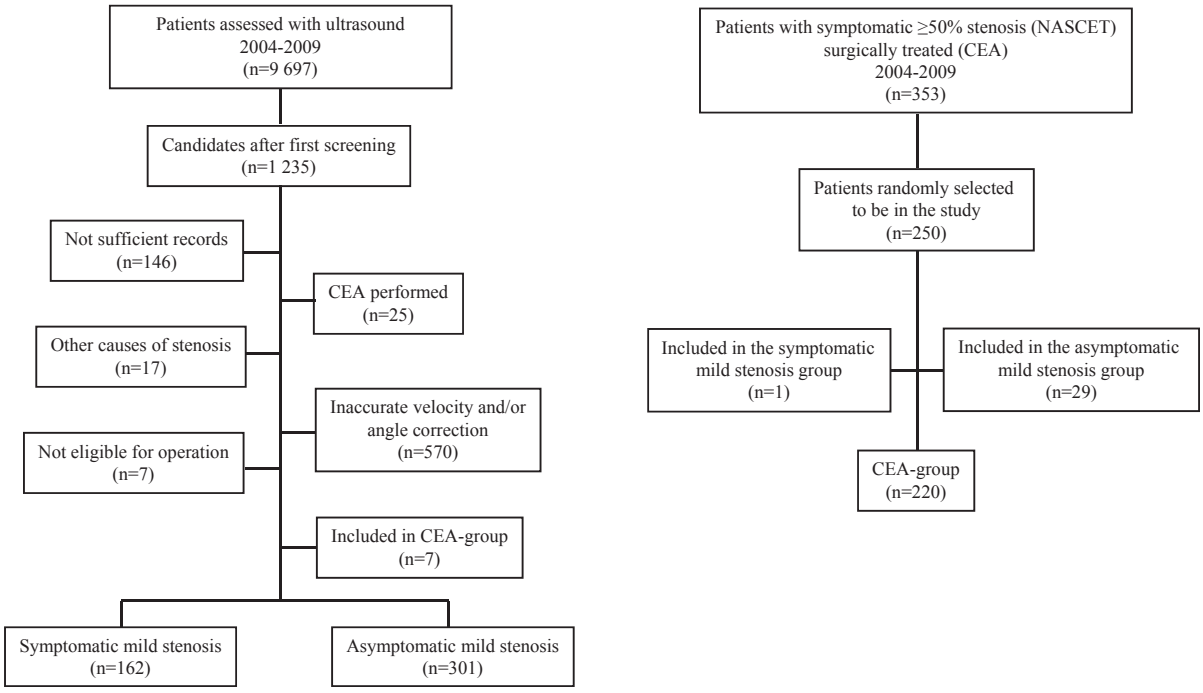

Figure 1. Distribution of included and excluded patients in symptomatic, asymptomatic, and CEA groups. "Not sufficient records" includes, for example, no records, other cause of symptoms, and unclear symptoms. "CEA performed" includes patients for whom CEA was performed even though the stenosis was mild. "Other causes of carotid stenosis" were, for example, a tumour.

checked against the Swedish Vascular Register (SWEDVASC) to identify individuals with a CEA treated symptomatic, moderate, or severe (≥50% NASCET) stenosis ($n = 353$). From these patients the statistical package was used to randomly select 250 patients to be included as a "control group" in the current study. The patients were included at the time of surgery. The only exclusions were patients who had already been included in any of the other groups of mild stenosis at the time of CEA. The timing of CEA in relation to the referring event changed during the study period. In the first time period (2004–2006) it was 36 days, whereas at the end of the study it was close to 7 days.[13]

Patient characteristics and comorbidity

Data on comorbidity were retrieved from a search of the National Inpatient Register at the National Board of Health and Welfare, Sweden from January 1, 1987 to the date of ultrasound examination. Data on hospitalisation for myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), congestive heart failure (CHF), peripheral artery disease (PAD), atrial fibrillation (AF), and diabetes mellitus (DM) were retrieved (ICD codes are presented in the supplementary material).

Data on hypertension and smoking status were collected manually by reading all patient records 6 months prior to inclusion into the study. A patient was registered as a non-smoker if smoking was stopped 6 months prior to inclusion in the study.

Medication

Information on prescribed medication before and after inclusion in the study was retrieved from the Swedish Prescribed Drug Register on anti-platelet (ATC B01AC) and lipid lowering medication (ATC C10*). The Swedish Prescribed Drug Register dates back to 2005, which allowed for inclusion of medication data on patients included in the study after January 1, 2006 ($n = 480$). A patient was considered to be on medication if three prescriptions had been administered from a pharmacy in the 12 month period before or after inclusion respectively.

Follow up and outcome events

Patients were followed up for a maximum of 3 years after inclusion. The primary endpoint of the study was recurrent ischaemic ipsilateral stroke. The secondary endpoint was ischaemic stroke in any vascular territory. Recurrent TIA and retinal ischaemia were not included in the analysis. Recurrent stroke was defined as a stroke with neurological symptoms lasting more than 24 h or being fatal.[14] Patients with minor stroke as a neurological symptom preceding the ultrasound were considered to have recurrent stroke if clinical worsening of symptoms was clearly described in their medical records. In the CEA group (Group 3), stroke within 30 days of surgery was considered to be a peri-operative complication, and these patients were not excluded in the follow up. Death from other causes than stroke or CEA caused by new neurological symptoms during follow up, resulted in censoring.

Data on recurrent stroke and new CEA were retrieved from the date of inclusion until December 31, 2010 using a search of the National Inpatient Register and the causes of death register at the National Board of Health and Welfare. The following ICD codes were used (ICD-10: I63, I64) and CEA (ICD-9: 3092; ICD-10: PAF20, PAF21). Patient records on recurrent stroke were evaluated and classified by a certified physician (MR), blinded to the inclusion group, and a certified neurologist (AN) scrutinised all uncertain classifications.

Ethics

The local ethics committee at Gothenburg University approved study procedures.

Statistical analysis

Comparisons were made between Group 1/symptomatic low grade stenosis and the two control groups: Group 2/asymptomatic low grade carotid artery stenosis and Group 3/symptomatic moderate and high grade carotid artery stenosis after CEA. The Mann-Whitney *U* test was used for continuous variables and the chi-square test was used for categorical variables when appropriate. Kaplan-Meier estimates were constructed and Cox regression was used to compare groups, always including sex and age as covariates.

Other covariates were included based on significant differences of baseline characteristics between groups in combination with a biologically plausible association with outcome. Hazard ratios (HR) were calculated with 95% confidence intervals. Statistical significance was considered at $p < 0.05$ (two sided). SPSS statistical software (22.0) was used.

RESULTS

Patient population

A flow chart describing inclusion into the study is given in Fig. 1. A total of 162 patients fulfilled the criteria for the 20–49% symptomatic carotid stenosis (Group 1) and there were 301 patients with 20–49% in the asymptomatic carotid stenosis (Group 2). Two hundred and twenty patients met the study inclusion criteria for CEA treated symptomatic moderate or severe stenosis (Group 3). In Group 2, 20 patients (7%) had neurological symptoms from the posterior circulation and 106 patients (35%) had symptoms from the contralateral (non-stenotic) carotid territory while the remaining 175 (58%) had no neurological symptoms within the preceding 6 months.

Patient characteristics

Baseline characteristics of the three groups are given in Table 1. When comparing the symptomatic group with the

Table 1. Baseline characteristics, stroke events during follow up, risk factors, and medication before and after inclusion.

	Group 1 Symptomatic ($n = 162$)	Group 2 Asymptomatic ($n = 301$)	Group 3 CEA ($n = 220$)	Statistics Symptomatic vs. asymptomatic *p*-value	Symptomatic vs. CEA *p*-value
Ipsilateral stroke in follow up (%)	12 (7.4)	4 (1.3)	3 (1.4)	.001	.003
Any stroke in follow up (%)	19 (12)	21 (7.0)	7 (3.2)	.083	.001
Median age in years (IQR)	75 (12)	73 (14)	71 (14)	.057	<.001
Sex (%)				.007	<.001
Male	93 (57)	133 (44)	149 (68)		
Female	69 (43)	168 (56)	71 (32)		
History/risk factors (%)					
Hypertension	109 (67)	212 (70)	154 (70)	.484	.571
Smoking	38 (24)	71 (24)	76 (35)	.975	.019
MI, PCI, CABG	33 (24)	59 (20)	57 (26)	.843	.207
Myocardial infarction (MI)	24 (15)	40 (13)	33 (1)	.650	.960
PCI	8 (4.9)	24 (8.0)	26 (12)	.219	.020
CABG	12 (7.4)	32 (11)	28 (13)	.259	.093
Congestive heart failure	19 (12)	34 (11)	24 (11)	.889	.802
PAD	5 (3.1)	26 (8.6)	23 (11)	.023	.006
Atrial fibrillation	24 (15)	37 (12)	29 (13)	.444	.648
Diabetes mellitus	31 (19)	62 (21)	49 (22)	.708	.456
Medication (%) 2006–2010	($n = 124$)	($n = 214$)	($n = 142$)		
Antiplatelet before inclusion	51 (41)	94 (44)	60 (42)	.617	.853
Antiplatelet after inclusion	102 (82)	161 (75)	129 (91)	.134	.039
Lipid lowering before inclusion	33 (27)	71 (33)	41 (29)	.208	.682
Lipid lowering after inclusion	78 (63)	141 (67)	101 (71)	.580	.154

Group 1: symptomatic mild stenosis; Group 2: asymptomatic mild stenosis; Group 3: CEA treated symptomatic moderate or severe stenosis.

Hospitalisation for myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), congestive heart failure (CHF), peripheral artery disease (PAD), atrial fibrillation (AF) and diabetes mellitus (DM) were retrieved (ICD codes are presented in the supplementary material).

asymptomatic group the former had significantly more recurrent ipsilateral stroke events, were more likely to be male, and had a lower frequency of hospitalisation for PAD.

When comparing the symptomatic group with the CEA group, the former had significantly more recurrent ipsilateral stroke events, were older, were more likely to be male, smoked less, had fewer previous PCI, and a higher frequency of PAD. In addition, treatment with anti-platelet medication and statins after inclusion was more common in the CEA group compared with the group with symptomatic mild stenosis.

Baseline characteristics for recurrent ipsilateral stroke, independent of group at inclusion, are given in Table 2. When comparing all patients with recurrent ipsilateral stroke with patients with no recurrence, older age and hypertension were more common among those who developed an ipsilateral stroke during follow up whereas the frequency of smoking was lower.

Table 2. Characteristics, risk factors, and medication in relation to ipsilateral ischaemic stroke and no ipsilateral ischaemic stroke during follow up.

	Ipsilateral stroke (%) ($n = 19$)	No ipsilateral stroke (%) ($n = 664$)	Statistics p-value
Group			<.001
Symptomatic	12 (63)	150 (23)	
Asymptomatic	4 (21)	297 (45)	
CEA	3 (16)	217 (33)	
Median age in years (IQR)	79 (15)	73 (13)	.004
Sex			.970
Male	11 (58)	364 (55)	
Female	8 (42)	300 (45)	
History/risk factors			
Hypertension	18 (95)	457 (69)	.016
Smoking	1 (5.2)	184 (28)	.030
MI, PCI, CABG	7 (37)	142 (21)	.153
Myocardial infarction	5 (26)	92 (14)	.171
PCI	2 (11)	56 (8.4)	.627
CABG	2 (11)	70 (11)	1.000
Congestive heart failure	4 (21)	73 (11)	.256
PAD	2 (11)	52 (7.8)	.656
Atrial fibrillation	5 (26)	85 (13)	.092
Diabetes mellitus	5 (26)	137 (21)	.567
Medication (%) 2006–2010	(n = 15)	(n = 465)	
Antiplatelet before inclusion	11 (73)	194 (42)	.015
Antiplatelet after inclusion	11 (73)	381 (82)	.493
Lipid-lowering before inclusion	7 (47)	138 (30)	.164
Lipid-lowering after inclusion	10 (67)	310 (67)	1.000

Hospitalisation for myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), congestive heart failure (CHF), peripheral artery disease (PAD), atrial fibrillation (AF), and diabetes mellitus (DM) were retrieved (ICD codes are presented in the supplementary material).

Ipsilateral recurrent stroke is more common in patients with symptomatic mild stenosis

The median follow up was 3 years (mean 2.47 years, IQR 2.04–3). In the symptomatic group, 12 patients (7.4%) developed an ipsilateral stroke, resulting in an annual risk of 2.5% and an incidence rate of 30 strokes/1,000 patient years. Seven of 12 strokes occurred during the first 3 months of follow up and two cases occurred during the first 2 weeks. In the asymptomatic group, four patients (1.3%) developed an ipsilateral stroke, resulting in an annual risk of 0.4% (incidence rate = 5.4 strokes/1,000 patient years). In the CEA group the complication frequency 30 days after surgery was 3.1% and included two strokes (day 1 and 7). During follow up beyond 30 days, three patients (1.4%) in the CEA group developed an ipsilateral stroke, resulting in an annual risk of 0.5% (incidence rate = 5.3 strokes/1,000 patient years).

Kaplan-Meier curves for the proportion without ipsilateral stroke are shown in Fig. 2. When the symptomatic group was compared with the asymptomatic group using Cox regression, there was a 5.5 times increased risk of having a recurrent ipsilateral stroke for the symptomatic group (95% CI 1.8–17.1; $p = .003$) and an increased risk of recurrent ipsilateral stroke with age, HR 1.1 (95% CI 1.0–1.2; $p = .007$). In addition, when two more potential confounders, hypertension and PAD, were introduced into the model, there was a 6.0 times increased risk of recurrent ipsilateral stroke for the symptomatic group (95% CI 1.9–18.7; $p = .002$) and still an increased risk of recurrent stroke with age, HR 1.1 (95% CI 1.0–1.2; $p = .007$). Hypertension was associated with a borderline significant increase in risk, HR 6.8 (95% CI 0.9–51.9; $p = .063$). The hazard ratio was not affected if medication in the first year of follow up was introduced into the model.

When the group with symptomatic mild stenosis was compared with the CEA group using Cox regression, there was a 7.8 times higher risk of recurrent ipsilateral stroke in the symptomatic group (95% CI 1.62–37.8; $p = 0.011$). The hazard ratio was not affected if medication in the first year of follow up was introduced into the model.

Follow up of ischaemic stroke in any territory

The risk of any ischaemic stroke (stroke in all territories) was analysed as a measure of the patient's general risk of suffering a stroke. The median follow up was 3 years (mean 2.28 years, IQR 1.59–3). During follow up in the group with symptomatic mild stenosis, 19 patients (12%) developed a stroke, resulting in an annual risk of 4.0%. In the group with asymptomatic mild stenosis, 21 patients (7.0%) developed a stroke, resulting in an annual risk of 2.3%, and in the CEA group seven patients (3.2%) developed a stroke, resulting in an annual risk of 1.1%. Kaplan-Meier curves on the proportion without any stroke are shown in Fig. 3. There were no significant differences between the symptomatic group and the asymptomatic group when compared using Cox regression. However, the HR for stroke was significantly increased with age (HR 1.2. 95% CI 1.04–1.13; $p = 0.000$).

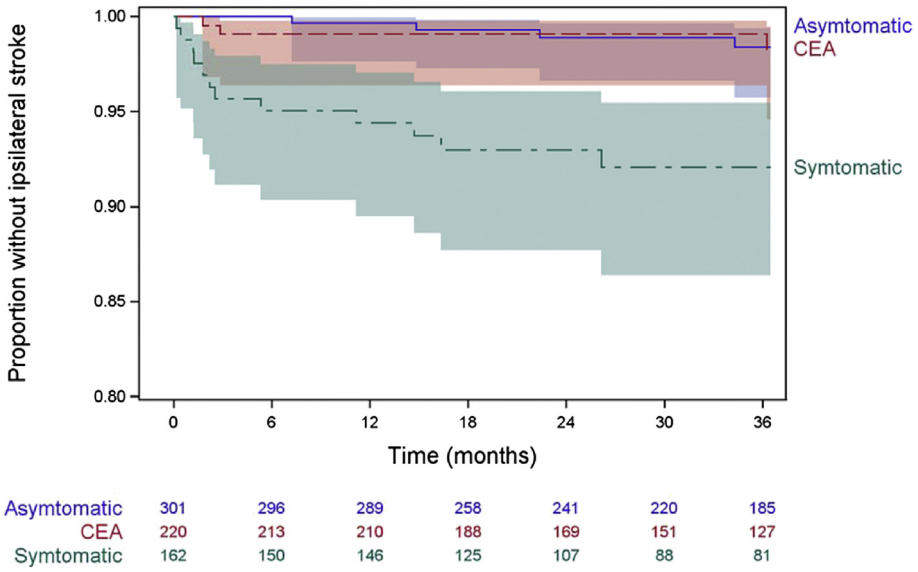

Figure 2. Kaplan-Meier curves for proportions without ipsilateral stroke. The numbers below show the number of patients remaining in the study at that time. Symptomatic mild stenosis (Group 1). Asymptomatic mild stenosis (Group 2). Symptomatic moderate or severe stenosis after CEA (Group 3). Death from other causes than ipsilateral stroke or ipsilateral CEA during follow up resulted in censoring. Peri-operative stroke in the CEA group, (two events on days 1 and 7, respectively) is not shown in the graph and was not censored to follow up.

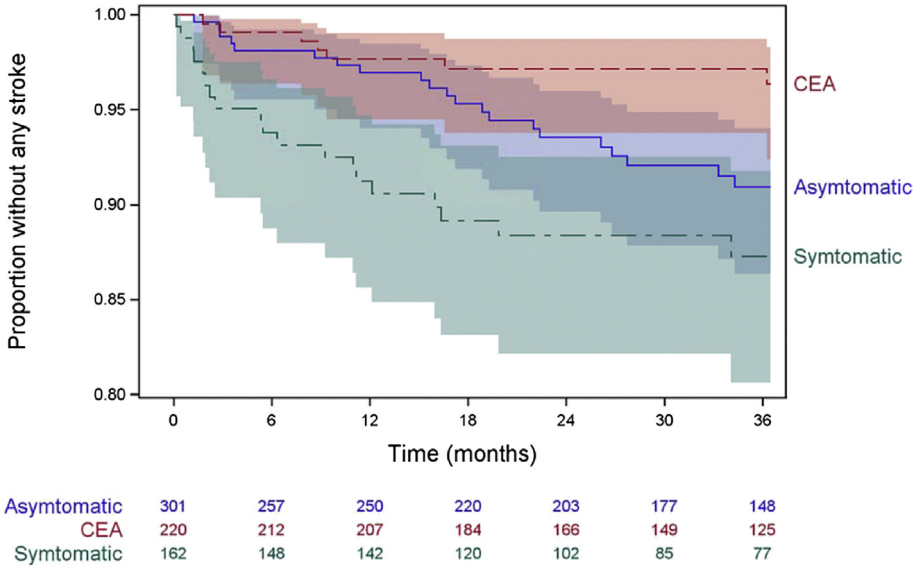

Figure 3. Kaplan-Meier curves for proportions without any stroke. The numbers below show the number of patients remaining in the study at that time. Symptomatic mild stenosis (Group 1). Asymptomatic mild stenosis (Group 2). Symptomatic moderate or severe stenosis after CEA (Group 3). Death from other causes than stroke or CEA on any side resulted in censoring.

The hazard ratio was not significantly affected if medication in the first year of follow up was introduced into the model.

When the symptomatic group was compared with the CEA group using Cox regression, there was a 3.1 times higher risk of recurrent stroke in the symptomatic group (95% CI 1.3—7.4; $p = .013$) and an increased risk of recurrent stroke with age, HR 1.1 (95% CI 1.0—1.1; $p = 0.005$). In addition to this analysis, the variables smoking and hypertension were also included in the model, which resulted in a 3.3 times higher risk of recurrent stroke in the symptomatic group (95% CI 1.37—7.99; $p = .008$). The hazard ratio for age was 1.1 (95% CI 1.02—1.14; $p = .007$) and for hypertension was 11.8 (95% CI 1.60—87.5; $p = .015$). The hazard ratio was not significantly affected if medication in the first year of follow up was introduced into the model.

DISCUSSION

The major finding in this study was a 7.4% cumulative incidence of recurrent ipsilateral stroke after 3 years follow up in patients with symptomatic mild carotid artery stenosis. Patients with symptomatic mild carotid artery stenosis also had a substantially increased risk of

recurrent ipsilateral stroke compared with asymptomatic patients with an equal degree of stenosis and also compared with patients with symptomatic moderate or severe stenosis after CEA. Seven of the 12 strokes in the symptomatic group occurred during the first 3 months of follow up. This finding is in line with previous studies confirming that the risk of recurrent stroke is highest in the early phase.[1]

The CEA group is also exposed to a peri-operative risk. In a recently published register study,[15] the risk of major complications after CEA is in the order of 3.6% if surgery is performed 3—7 days after the index event. In this cohort the peri-operative risk reached 3.1% and included two cases of stroke. So even when considering this risk, the patients with symptomatic mild stenosis seem to have a net increase in risk of recurrent stroke and might therefore benefit from carotid surgery.

The cohort in this study was retrospectively recruited from a database of all patients undergoing diagnostic carotid artery ultrasound examinations from 2004 to 2009 in the Gothenburg area. During this time period, ultrasound was the recommended first line investigation for carotid atherosclerotic disease. The examinations were performed in only three vascular laboratories. When identifying patients for this study, strict criteria for defining a carotid artery stenosis in the 20—49% (NASCET) range were applied, emphasizing the importance of insonation angle when measuring peak systolic velocities. However, the strict criteria led to a substantial loss of patients owing to missing data on the exact insonation angle and/or Doppler velocity (Fig. 1), the advantage being a homogenous sample of patients with a very similar degree of carotid stenosis. It is believed that the use of these strict criteria is critical as, so far, the degree of stenosis is the only established useful ultrasound derived predictor of recurrent ipsilateral stroke in patients with symptomatic carotid atherosclerosis.[5]

The study cohort of 162 patients with symptomatic mild stenosis can be compared with 377 individuals in the ECST trial, with an equal degree of stenosis (50—69% ECST), randomly assigned to the conservatively treated control group.[3] The follow up time in ECST in the control group was on average 6.1 years. If an even distribution of events over time is assumed in this subgroup of the ECST trial, the incidence rate, IR, would be 18 ipsilateral events/1,000 patient years, which can be compared with the results in the current study showing an IR of 30 events/1,000 patient years. However, there were several differences in patient characteristics; symptomatic patients in the current study were older (75 vs. 62 years) and included more women (43% vs. 28%), there was a higher incidence of diabetes (19% vs. 12%), and as expected, a lower frequency of smoking (26% vs. 50%). In the first year of follow up, lipid lowering medication was much more common in the present study cohort compared with ECST (63% vs. 8%), while treatments with platelet inhibitors were of similar magnitude (82% vs. 79%). Taken together, differences between the current study and the 20 year old ECST study reflect some anticipated changes in risk factor patterns such as older patients, less smoking, more diabetes, and improved medication.[16,17] Despite these differences, the risk of recurrent stroke was of the same magnitude in both studies, although occurring at a higher age. The main hypothesis of this study was that mild stenosis, with the optimal medical treatment available today, is associated with a lower risk than in the ECST and NASCET trials. However, support was not found for this hypothesis, and the study findings indirectly suggest that the recurrent stroke rates in more severe forms of symptomatic carotid artery stenosis remain at a level at which the use of CEA is well justified.

Two different “control groups” were introduced to the present analyses. As expected, the risk of recurrent ipsilateral stroke was significantly lower in patients with a similar atherosclerotic plaque burden but being asymptomatic at the time of the ultrasound. This confirms the importance of developing diagnostic tools to identify vulnerable types of atherosclerosis that carry an increased risk of developing symptomatic disease.[18] Another interesting finding in the current study was the low risk of recurrent ipsilateral stroke during follow up after CEA (5 events/1,000 patient years). The risk was comparable with that found in the group of asymptomatic patients with mild stenosis in the current study, and lower than the incidence rate found in the CEA arm of the ECST trial (9 events/1,000 patient years).[3] The CEA group was included in the current study to illustrate the potential residual risk achievable after surgical treatment in patients with a symptomatic plaque burden. The low risk of ipsilateral recurrent stroke in patients after CEA strongly supports the use of this intervention against symptomatic carotid artery stenosis.

Information on secondary prevention medication was collected from the national pharmacy register and a patient was considered to be on antiplatelet or lipid lowering drugs if three prescriptions had been administered from a pharmacy in the 12 month period before or after inclusion respectively. The results in Table 2 show that in patients with mild symptomatic stenosis, only 63% were on statin treatment and 82% on antiplatelet treatment after inclusion. This finding does not exclude the possibility of the drugs being prescribed, but the register data indicate that no such medication was dispensed from the pharmacy.

The risk of any stroke was included in the analysis to estimate the general risk of developing stroke in this cohort. The risk was similar in the symptomatic and asymptomatic groups suggesting that presence of carotid atherosclerosis signals an overall risk of developing stroke. Interestingly, the risk of any stroke was lowest in the CEA group. One explanation could be the structured follow up of these patients at the outpatient clinic resulting in better secondary medical prevention as reflected in the highest frequency of antiplatelet medication in this group. Having undergone surgery, these patients might also be more motivated to lifestyle changes. Another tempting speculation would be that there is a general protective effect of CEA on stroke recurrence;[19] however, the current study was not designed to address these issues.

Limitations

There are some limitations to this study, most significantly the retrospective design and the large group of patients excluded because of insufficient patient record data. Therefore, a prospective study is planned with the same design to prospectively follow patients with mild symptomatic carotid stenosis exclusively treated with medication. Another limitation is the limited size of the study and the resulting low stroke rates making confidence intervals large and allowing adjustment only for a limited number of confounding factors.

Conclusion

In conclusion, the present retrospective study on risk of recurrent ipsilateral ischaemic stroke in patients with symptomatic low grade carotid artery stenosis, as determined by Doppler ultrasound, shows that there is still a substantial risk of stroke recurrence in this group that seems to exceed the peri-operative risk in a 3 year perspective. However, a prospective study and a randomised controlled trial are needed before reconsidering current treatment strategies.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2016.05.014.

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