Original Contribution

Symptomatic Patients Remain at Substantial Risk of Arterial Disease Complications Before and After Endarterectomy or Stenting

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Background and Purpose—After carotid endarterectomy (CEA) or carotid artery stenting (CAS) in patients with transient ischemic attack or minor ischemic stroke, recurrent stroke risk falls to a low rate on modern medical treatment.

Methods—We used data from 4583 patients with recent transient ischemic attack or minor stroke enrolled in the TIAregistry.org to perform a nested case–control analysis to evaluate pre- and post-CEA/CAS risk. Cases were defined as patients with a CEA/CAS during the 1-year follow-up period. For each case, 2 controls with a follow-up time greater than the time from qualifying event to CEA/CAS were randomly selected, matched by age and sex. Primary outcome was defined as major vascular events (MVE, including stroke, cardiovascular death, and myocardial infarction).

Results—The median delay from symptom onset of qualifying event to CEA/CAS was 11 days (interquartile range, 6–23). Overall, patients with CEA/CAS had a higher 1-year risk of MVE than other patients (14.8% versus 5.8%; adjusted hazard ratio, 2.40; 95% confidence interval, 1.61–3.60; $P<0.001$). During the matched preprocedural period, MVE occurred in 14 (7.5%) cases and in 13 (3.5%) controls, with an adjusted odds ratio =2.46 (95% confidence interval, 1.07–5.64; $P=0.03$). In the postprocedural period, the risk of MVE was also higher in cases than in controls (adjusted $P<0.03$).

Conclusions—Patients with CEA/CAS had a higher 12-month risk of MVE, as well as during pre- and postprocedural periods. These results suggest that patients in whom CEA/CAS is anticipated are likely to be an informative population for inclusion in studies testing new antithrombotic strategies started soon after symptom onset. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.015171.)**

Key Words: carotid arteries ■ carotid endarterectomy ■ myocardial infarction ■ prevention ■ transient ischemic attack

Stroke

About 20% of all ischemic strokes is associated with large-artery atherosclerosis, specifically internal carotid artery stenosis.[1–3] The risk of ipsilateral stroke varies from 4.4% and 13% per year in patients with symptomatic carotid artery stenosis to 50% to 69% and >70%, respectively.[4]

The purpose of surgical and medical management of carotid artery stenosis is to reduce the risk of ipsilateral stroke and also to decrease the rate of atherosclerotic events in other vascular beds. In spite of this, there remains a substantial risk of major vascular events (MVE, including stroke, myocardial

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infarction, and vascular death) that should be addressed by new treatment strategies.

In randomized controlled trials testing new antiplatelet treatment strategies after transient ischemic attack (TIA) or minor ischemic stroke, patients scheduled for carotid endarterectomy/carotid artery stenting (CEA/CAS) are usually excluded from enrollment on the premise that the risk of stroke after CEA/CAS procedure falls to such a low rate that their inclusion may not be informative, particularly with modern medical treatment.[5–8] We hypothesized that this assumption could be untrue and also that these patients are at a high risk of recurrence before the procedure.

The aim of the study was to determine the 365-day risk of MVEs in patients undergoing CEA/CAS while on best medical treatment as recommended in current guidelines, as well as pre- and postprocedural risks.[9,10]

Methods

Patients Studied

We analyzed data from the TIAregistry.org, an international, prospective, observational registry of patients with recent TIA or minor stroke designed to provide a 3-month, 1-year, and 5-year of clinical follow-up.[11] Four thousand seven hundred and eighty-nine patients from 21 countries were enrolled. Patients were eligible for enrollment if aged ≥18 years and if they presented with a TIA or minor stroke within 7 days of evaluation by a stroke specialist.

Data Collection

Patients were evaluated by a stroke specialist at baseline, 1, 3, and 12 months after baseline, and every 12 months for a 5-year period. Qualifying event was defined as the event (either TIA or minor ischemic stroke defined by producing no significant handicap with a Rankin scale score 0 or 1) leading patient to seek for first medical care. In cases of repetitive TIA, the last event before first medical contact was taken into account.

Patient demographics, baseline characteristics, clinical information, examination findings, final vascular diagnosis, medication, and follow-up information were collected. Hypertension, diabetes mellitus, and dyslipidemia were defined as the use of medications for these conditions at any time before qualifying event. Smoking history was classified as current, former (smoking cessation >3 months ago), or never smokers.

All patients had a cerebral imaging (magnetic resonance imaging or computed tomography scan) and vascular imaging of extra- and intracranial arteries (supra aortic trunks and transcranial Doppler, magnetic resonance angiography, or computed tomography angiography). They were evaluated at follow-up for occurrence of any clinical event, new atrial fibrillation detection, medical treatment, and risk factor evaluation.

Large-Artery Atherosclerosis Subgroup

TOAST classification (Trial of Org 10172 in Acute Stroke Treatment)[12] was performed at baseline evaluation and at the 3-month follow-up visit. A revised classification on stroke subtypes was performed at 3 months using the ASCOD classification (Atherosclerosis, Small-Vessel Disease, Cardiac Pathology, Other Causes, Dissection).[13]

Case–Control Study

We performed a case–control study nested in the TIAregistry.org entire cohort[11] to compare the risk of MVE before and after CEA/CAS. Cases were defined as patients with a CEA/CAS with carotid stenosis ≥50% to 99% during a 365-day follow-up period. One hundred and eighty-seven patients underwent CEA/CAS during the 1-year follow-up. The date of the CEA/CAS procedure was considered as the index date. For each case, 2 controls were randomly selected, matched by age and sex. To be selected, controls had to have a follow-up period greater than the time from qualifying event to CEA/CAS procedure of their matched case. The index date of controls was defined as the date of the CEA/CAS of their matched cases.

As a sensitivity analysis, we performed a second nested case–control study by selected controls only among patients with large-artery atherosclerosis at baseline, according to ASCOD A1 or A2 phenotype (ie, patients with potentially symptomatic stenosis of an ipsilateral extra- or intracranial artery).[13]

Outcome

The main outcome was defined as first occurrence of MVE, including cardiovascular death, nonfatal stroke (either ischemic or hemorrhagic), and nonfatal myocardial infarction. The risk of new vascular event was estimated and compared between the 2 groups during a 365-day follow-up after the qualifying symptom onset and then before and after CEA/CAS procedure. We defined the pre- and postprocedural MVE risk by differentiating 2 separate periods: the preprocedural period defined as the time from symptom onset to date of CEA/CAS and the postprocedural period defined as the time from date of CEA/CAS to day 365 after symptom onset.

Statistical Analysis

Data were expressed as means (±standard deviation) or median (interquartile range for continuous variables and counts (percentage) for qualitative variables. Baseline characteristics were described and compared between the cases and matched controls by logistic regression models stratified by matched sets. Characteristics associated with cases ($P<0.10$) were included in a backward-selection multivariable logistic regression model using a value of $P>0.10$ as cutoff for retention in the model. Variable that remained in the stepwise regression model were subsequently used to adjust the comparisons in pre- and postprocedural risk.

We compared the preprocedural risk of MVE between cases and matched controls using a logistic regression model stratified by matched sets; odds ratio and its 95% confidence interval (CI) was derived from this model as effect size.

We estimated and compared the postprocedural risk of MVE using Kaplan–Meier methods and Log-rank test. Death from causes other than cardiovascular disease were treated as censoring cases, and patients lost to follow-up were treated as censored cases on the basis of the last follow-up. Between-groups comparisons of postprocedural risk of MVE were done using a Cox proportional hazard regression model stratified on the matched sets. The proportional hazards assumption was verified by using Schœnfeld residuals.

Statistical testing was done with a 2-tailed α-level of 0.05 considered significant. Data were analyzed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Four thousand seven hundred and eighty-nine patients were enrolled in the TIAregistry.org between June 2009 and December 2011. Of these, 173 did not meet inclusion criteria and 33 had no follow-up information after the qualifying event, leaving 4583 patients for analysis (Figure I in the online-only Data Supplement). Among these, 187 had CEA/CAS for a 50% to 99% symptomatic carotid stenosis and 23 had an intracranial revascularization procedure. Baseline characteristics of the 2 groups are presented in Table 1. One hundred and eighty-seven cases and 374 matched controls were identified. Median time from symptom onset to date of CEA/CAS procedure in cases was 11 days (interquartile range 7–22). All patients except 1 had the recommended medical

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Table 1. Baseline Characteristics of Case and Controls

	Cases (n=187)	Controls (n=374)	*P* Value
Demographic			
Age, means (SD), y	71 (10)	70 (10)	0.28
Men	142 (75.9)	284 (75.9)	1.00
Medical history			
Hypertension	136 (72.7)	242 (64.9)	0.003
Diabetes mellitus	42 (22.5)	81 (21.7)	0.46
Dyslipidemia	88 (50.3)	136 (40.5)	0.006
Current smokers	52 (28.0)	78 (21.2)	0.03
Regular alcohol	47 (25.5)	97 (26.3)	0.72
Coronary heart disease	41 (21.9)	55 (14.8)	0.006
Congestive heart failure	5 (2.7)	11 (3.0)	0.86
Atrial fibrillation or flutter	16 (8.6)	39 (10.5)	0.83
Pace maker	2 (1.1)	12 (3.2)	0.30
Significant valvular disease	4 (2.1)	10 (2.7)	1.00
Prosthetic valve disease	0 (0.0)	7 (1.9)	…
Number of previous recent TIA			0.003
0	134 (73.2)	329 (89.2)	
<5	42 (22.9)	36 (9.8)	
≥5	7 (3.8)	4 (1.1)	
Examinations			
BMI, mean (SD), kg/m2	26.5 (4.1)	26.1 (4.4)	0.12
Systolic BP, mean (SD), mm Hg	149 (22)	146 (24)	0.64
Diastolic BP, mean (SD), mm Hg	79 (13)	81 (14)	0.23
Glucose, median (IQR), mg/dL	105 (92–136)	106 (93–130)	0.81
Total cholesterol, mean (SD), mg/dL	192 (50)	190 (44)	0.72
LDL cholesterol, mean (SD), mg/dL	116 (44)	116 (37)	0.42
HDL cholesterol, mean (SD), mg/dL	48 (15)	49 (14)	0.68
Triglyceride, median (IQR), mg/dL	133 (98–184)	120 (84–162)	0.35

Data are number (percentage) unless otherwise indicated. Cases were defined as patients with a planned CEA/CAS during the 1-year follow-up, and controls were defined as patients with a follow-up time greater than the time from qualifying event CEA/CAS; they were randomly selected and matched by age and sex. BMI indicates body mass index; BP, blood pressure, CAS carotid artery stenting; CEA, carotid endarterectomy; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; and TIA, transient ischemic attack.

management, including antiplatelet therapy, statin treatment, and antihypertensive treatment.[9–11]

Over 365 days after symptom onset, 27 (14.8%) patients with a CEA/CAS procedure had an MVE versus 247/4396 (5.8%) patients without CEA/CAS (adjusted hazard ratio, 2.40; 95% CI, 1.61–3.60; *P*<0.001; Figure II in the online-only Data Supplement). Events occurred before or after CEA/CAS.

Preprocedural Risk

Overall 365-day risk is shown in Figure A. As shown in Figure B and Table 2, patients with a CEA/CAS had a higher preprocedural risk of MVE than those without (7.5% versus 3.5%; odds ratio, 2.23; 95% CI, 1.03–4.85; *P*=0.04). This result remained significant after adjustments on potential confounding factors (Table 2). In sensitivity analysis comparing cases to matched controls selected among patients with large-artery atherosclerosis at baseline (Tables I and II in the online-only Data Supplement), the difference remained significant (7.5% versus 3.2%, adjusted odds ratio, 2.87; 95% CI, 1.22–6.78; *P*=0.02).

Postprocedural Risk

As shown in Figure C and Table 3, the postprocedural MVE risk was higher in cases than that in their matched controls (Kaplan–Meier estimates, 7.0% versus 2.4%; log-rank, *P*=0.01). In multivariate analysis including potential confounding factors, this difference remained significant (adjusted hazard ratio, 2.64; 95% CI, 1.11–6.30; *P*=0.03). In sensitivity analysis, postprocedural MVE risk in patients with a CEA/CAS remained higher than that in their matched controls with large-artery atherosclerosis, without reaching statistical significance (adjusted hazard ratio, 1.69; 95% CI, 0.82–3.50; *P*=0.15; Table II in the online-only Data Supplement).

Discussion

Patients with ischemic stroke/TIA and symptomatic large-artery atherosclerosis have the highest risk of stroke recurrence in the TIAregistry.org.[11] Patients with 50% to 99% carotid stenosis who benefit from early CEA/CAS procedure have an important reduction of risk recurrence.[4,14,15] Despite this, among consecutive patients enrolled in the TIAregistry.org, patients with CEA/CAS, performed with a median delay of 11 days after symptom onset, had a much higher 365-day risk of MVE (14.8%) than patients who did not have CEA/CAS (5.8%). We also found that MVE risk was higher before the CEA/CAS procedure than in controls. Of the 14 MVE that occurred before the CEA/CAS procedure, 13 were a stroke, with a median delay from symptom onset to MVE of 5 days. Thus, although the CEA/CAS procedure occurred within 14 days as currently recommended,[16–18] these patients had a high early risk of recurrence. Our results are in accordance with previous studies.

A 2002 to 2004 population-based study showed a before-procedure stroke recurrence rate of 21% at 2 weeks and 31% at 12 weeks in 49 patients who had CEA with a median delay of 100 days.[19] In a more recent, smaller population-based study that included 314 anterior circulation ischemic strokes, 3/36 patients with carotid stenosis eligible for CEA had a stroke recurrence at 14 days and before the procedure (8.3%) as compared with 5/278 (1.8%) patients not eligible for CEA.[20] Another 2007 to 2009 cohort study showed a risk of early stroke recurrence of 11.2% in the first 2 weeks after the presenting event, while median delay for CEA was 29 days.[21]

Another study that aimed to identify the risk of ipsilateral ischemic stroke in 377 patients with symptomatic carotid stenosis awaiting revascularization found a risk of 6.6% at 3 days, 11.5% at 14 days, and 18.8% at 90 days.[22]

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Stroke

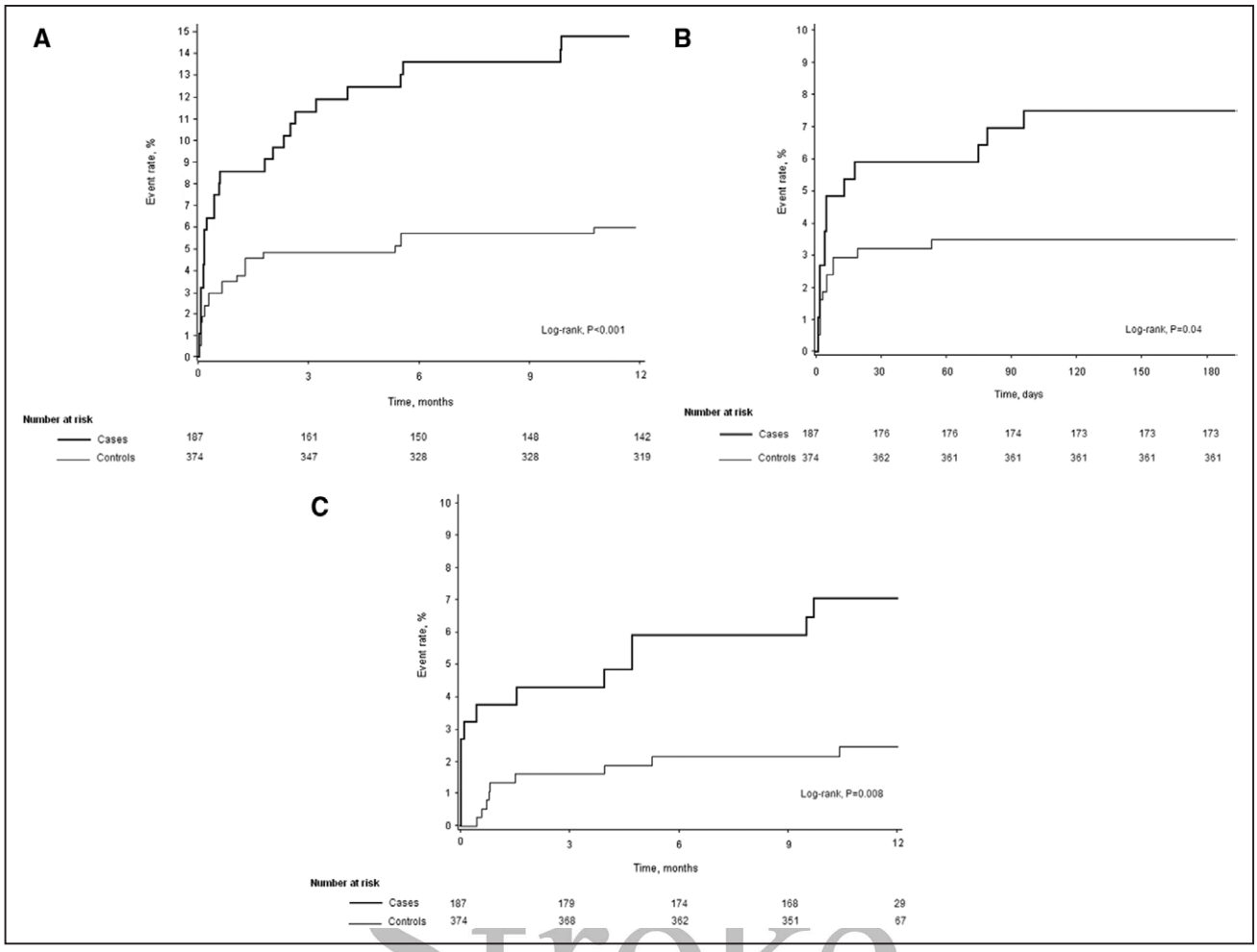

Figure. Patients with transient ischemic attack (TIA) and minor stroke in the TIAregistry.org with carotid endarterectomy (CEA)/carotid endarterectomy (CAS; cases) and age- and sex-matched controls selected among all other patients in the TIAregistry.org without CEA/CAS: Kaplan–Meier incidence of major vascular event during 365 days (**A**), during preprocedural period (**B**), and during postprocedural period (**C**).

Hence, studies show that despite contemporary early, urgent management of TIA and minor ischemic stroke with a much shorter delay of CEA, patients eligible for CEA still have a high rate of recurrence before and after the procedure. Hence, the preprocedural period is a period at high risk of recurrence, even if the CEA/CAS procedure is performed within the recommended 15-day period. The few days after stroke onset is likely the time where plaque instability involves inflammation and superimposed thrombus. This suggests that we should try to even shorten the delay of CEA/CAS and that more effective antithrombotic treatments should be trialed in preprocedural period in these patients, as in the CHANCE trial, dual antiplatelet therapy reduced the risk during the first days as compared with aspirin only.[23] But other agents capable to reduce inflammation or other biomarkers such as Lp(a) (lipoprotein[a]) should also be trialed (eg, early statin therapy, PCK9 [proprotein convertase subtilisin/hexin type 9] inhibition, methotrexate).

Table 2. Preprocedural Risk of Major Vascular Event According to CEA/CAS (Cases) or Not (Controls)

	Cases (N=187)	Controls (N=374)	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)*	*P* Value
MVE	14 (7.5)	13 (3.5)	2.23 (1.03–4.85)	0.04	2.46 (1.07–5.64)	0.03
Nonfatal stroke	13 (6.9)	13 (3.5)	2.07 (0.94–4.55)	0.07	2.20 (0.94–5.16)	0.07
Cardiovascular death	0 (0.0)	0 (0.0)	…	…	…	…
Nonfatal myocardial infarction	2 (1.1)	0 (0.0)	NC	NC	NC	NC

Values are number (%) unless otherwise indicated. Cases were defined as patients with a CEA/CAS during the 1-year follow-up, and controls are defined as patient with a follow-up time greater than the time from qualifying event to CEA/CAS procedure; they were randomly selected and matched by age and sex. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; MVE, major vascular events (stroke, cardiovascular death, and myocardial infarction); NC, noncalculable; and OR, odds ratio.

*Adjusted on hypertension and number of TIA episode.

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Table 3. Postprocedural Risk of Major Vascular Events According to CEA/CAS (Cases) or Not (Controls)

	No of Event, %*					
	Cases (N=187)	Controls (N=374)	Crude HR (95% CI)	*P* Value	Adjusted† HR (95% CI)	*P* Value
MVE	13 (7.0)	9 (2.4)	2.96 (1.27–6.93)	0.01	2.64 (1.11–6.30)	0.03
Nonfatal stroke	9 (5.0)	6 (1.6)	3.11 (1.11–8.73)	0.03	2.54 (0.88–7.35)	0.08
Cardiovascular death	3 (0.6)	1 (0.8)	NC	NC	NC	NC
Nonfatal acute myocardial infarction	2 (1.1)	2 (0.5)	2.00 (0.28–14.21)	0.49	NC	NC

Cases were defined as patients with a CEA/CAS during the 1-year follow-up, and controls are defined as patient with a follow-up time greater than the time from qualifying event to CEA/CAS procedure; they were randomly selected and matched by age and sex. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio; MVE, major vascular events (stroke, cardiovascular death, and myocardial infarction); NC, noncalculable; and TIA, transient ischemic attack.

*Values are number (%) Kaplan–Meier estimates.

†Adjusted on hypertension and number of TIA episode.

Beside this high risk of recurrence before the CEA/CAS procedure, our data showed that patients with symptomatic carotid stenosis also have a higher postprocedural risk up to day 365 as compared with control patients in the TIAregistry.org, with no indication to CEA/CAS procedure (14.4% versus 5.6%), probably because of a higher prevalence of risk factors and atherosclerotic disease burden that is usually not restricted to carotid and cerebral arteries.[24]

Hence, patients with large-artery atherosclerosis, particularly those with symptomatic carotid stenosis with CEA/CAS indication, represent a high-risk population both in the preprocedural and in the postprocedural period. However, little progress has been made in the antithrombotic treatment in the preprocedural period.

Strength and Limitations

The strength of our study is the large sample size and multicenter design, with inclusion within 24 hours of symptom onset in 85% of patients, based on TIA clinic, ensuring the quality of data collection, stroke subtyping, likely reflecting the reality in these settings. Our study also had limitations. First, this is a post hoc analysis of a registry, and certain data were not available, such as the exact time of recurrent event occurring the same day of the procedure. No separate analysis was done regarding the patients with endarterectomy versus stenting. We also could not perform an analysis by degree of stenosis or plaque characteristics (ulcerative versus nonulcerative). Four patients were planned for CEA/CAS procedure but did not undergo the procedure mainly because of recurrence. Inclusion of these patients in the group of patients who actually had CEA/CAS did not change the results.

In conclusion, in the TIAregistry.org, we found that patients who underwent CEA/CAS had a higher 365-day risk of MVE after a qualifying event compared with patients with no indication for CEA/CAS. The risk was high before the procedure, despite recommended optimal medical treatment and optimal median delay of revascularization. Considering that these patients have a higher prevalence of hypertension, diabetes mellitus, coronary heart disease, dyslipidemia, and smoking, targeted treatment strategies should be considered to reduce the risk in both pre- and postprocedural period. Although continued effort to shorten the delay of carotid revascularization should be made, we also think that these results suggest that patients in whom early CEA/CAS is anticipated are likely to be an informative population for inclusion in studies testing new antithrombotic strategies started within 24 hours of symptom onset.

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Symptomatic Patients Remain at Substantial Risk of Arterial Disease Complications Before and After Endarterectomy or Stenting

Cristina Hobeanu, Philippa C. Lavallée, Peter M. Rothwell, Leila Sissani, Gregory W. Albers, Natan M. Bornstein, Louis R. Caplan, Geoffrey A. Donnan, José M. Ferro, Michael G. Hennerici, Julien Labreuche, Carlos Molina, Philippe Gabriel Steg, Pierre-Jean Touboul, Shinichiro Uchiyama, Éric Vicaut, Lawrence K.S. Wong and Pierre Amarenco

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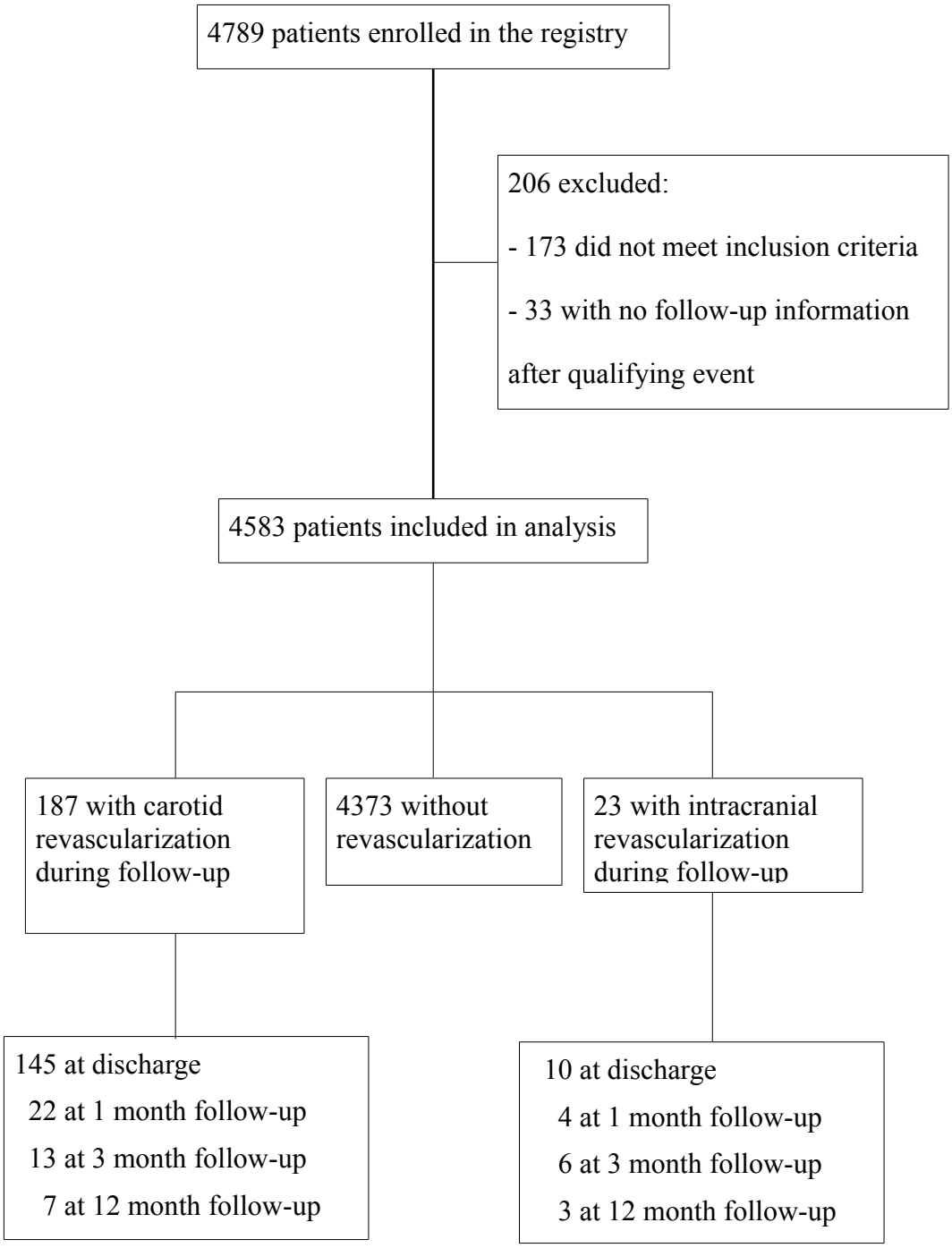
SYMPTOMATIC PATIENTS REMAIN AT SUBSTANTIAL RISK OF ARTERIAL DISEASE COMPLICATIONS BEFORE AND AFTER ENDARTERCTOMY OR STENTING

Cristina Hobeanu et al

SUPPLEMENTARY MATERIAL

1

Supplementary Figurel. Flow chart of the TIA-REGISTRY



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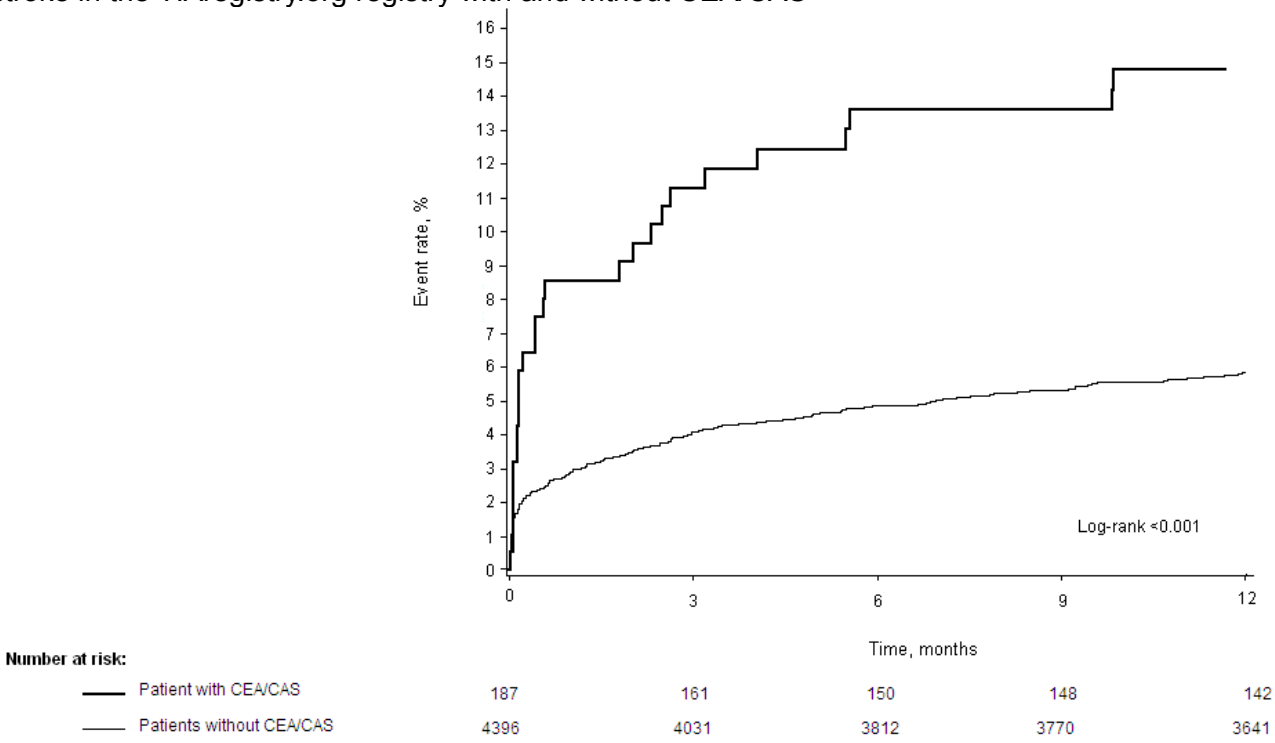
Supplementary Figure II.Kaplan-Meier incidence of MVE in patients with TIA and minor stroke in the TIAregistry.org registry with and without CEA/CAS



Supplementary table I. Baseline characteristic of patients among those with a Large artery atherosclerosis

	Carotid revascularization		P
	No n = 833	Yes n = 187	
Demographic			
Age, mean (SD), years	67 (11)	71 (10)	0.09
Men	559 (67.5)	142 (75.9)	0.02
Medical history			
Hypertension	539 (64.9)	136 (72.7)	0.04
Diabetes	177 (21.3)	42 (22.5)	0.73
Dyslipidemia	251 (34.4)	88 (50.3)	<0.001
Current smokers	219 (26.5)	52 (28.0)	0.68
Regular alcohol	184 (22.3)	47 (25.5)	0.35
Coronary heart disease	131 (15.7)	41 (21.9)	0.04
Congestive Heart Failure	24 (3.0)	5 (2.7)	0.87
Atrial Fibrillation or Flutter	20 (2.4)	16 (8.6)	<0.001
Pace Maker	13 (1.6)	2 (1.1)	0.61
Significant valvular disease	11 (1.3)	4 (2.1)	0.40
Prosthetic valve disease	8 (1.0)	0 (0.0)	-
Number of previous recent TIA			0.003
0	683 (83.0)	134 (73.2)	
<5	129 (15.7)	42 (23.0)	
≥5	11 (1.3)	7 (3.8)	
E Examinations			
BMI, mean (SD), kg/m²	26.2 (4.3)	26.5 (4.1)	0.47
Systolic BP, mean (SD), mmHg	147 (24)	149 (22)	0.33
Diastolic BP, mean (SD), mmHg	82 (14)	79 (13)	0.40
Glucose, median (IQR), mg/dl	105 (91-134)	105 (92-136)	0.82
Total cholesterol, mean (SD), mg/dl	189 (45)	192 (50)	0.13
LDL-cholesterol, mean (SD), mg/dl	117 (38)	116 (44)	0.03
HDL-cholesterol, mean (SD), mg/dl	47 (14)	48 (15)	0.19
Triglyceride, median (IQR), mg/dl	124 (93-168)	133 (98-184)	0.13

Data are number (percentage) unless otherwise indicated
Abbreviation: BMI=body mass index; BP=blood pressure; HDL-C=high-density lipoprotein; IQR=interquartile range; LDL-C=low-density lipoprotein; SD=standard deviation; TIA=transient ischemic attack

Supplementary table II. Post-procedural risk of major vascular events according to CEA/CAS (cases) or not (controls), restricted to controls selected among patients with large artery atherosclerosis at baseline among patients with large artery atherosclerosis

	Case *N=187*	**Control** *N=374*	Crude HR (95% CI)	*P*	Adjusted†HR (95% CI)	*P*
	*No. event (%)**					
MVE	14 (7.6)	16 (4.4)	1.78 (0.87-3.65)	0.11	1.69 (0.82-3.50)	0.15
Nonfatal Stroke	12 (6.5)	15 (4.1)	1.63 (0.76-3.48)	0.20	1.54 (0.71-3.33)	0.27
Cardiovascular death	2 (1.1)	1 (0.3)	NC	NC	NC	NC
Nonfatal Acute coronary syndrome	1 (0.6)	1 (0.3)	NC	NC	NC	NC

*Values are number (%) Kaplan-Meier estimates

CAS denotes carotid artery stenting; CEA denotes carotid endarterectomy; CI denotes confidence interval; MVE denotes major vascular events; NC denotes non calculable; HR denotes Hazard-ratio;

†Adjusted on hypertension, current smoking and number of TIA episode

Cases were defined as patients with a CEA/CAS during the 1-year follow-up and controls are defined as patient with a follow-up time greater than the time from qualifying event CEA/CAS, they were randomly selected among large artery atherosclerosis phenotype and matched by age and sex

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