Diabetes is not a predictor of outcome for carotid revascularization with stenting as it may be for carotid endarterectomy

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Background: **Diabetes is prevalent in most patients undergoing carotid revascularization and is suggested as a marker of poor outcome after carotid endarterectomy (CEA). Data on outcome of diabetic patients undergoing carotid artery stenting (CAS) are limited. The aim of this study was to investigate early and 6-year outcomes of diabetic patients undergoing carotid revascularization with CAS and CEA.**

Methods: **The database of patients undergoing carotid revascularization for primary carotid stenosis was queried from 2001 to 2009. Diabetic patients were defined as those with established diagnosis and/or receiving oral hypoglycemic or insulin therapy. Multivariate and Kaplan- Meier analyses, stratified by type of treatment, were performed on perioperative (30 days) and late outcomes.**

Results: **A total of 2196 procedures, 1116 by CEA and 1080 by CAS (29% female, mean age 71.3 years), were reviewed. Diabetes was prevalent in 630 (28.7%). Diabetic patients were younger ($P < .0001$) and frequently had hypertension ($P = .018$) or coronary disease ($P = .019$). Perioperative stroke/death rate was 2.7% (17/630) in diabetic patients vs 2.3% (36/1566) in nondiabetic, ($P = .64$); the rate was 3.4% in diabetic CEA group and 2.1% in diabetic CAS group ($P = .46$). At multivariate analyses, diabetes was a predictor of perioperative stroke/death in the CEA group (odds ratio [OR], 2.83; 95% confidence interval [CI], 1.05-7.61; $P = .04$) but not in the CAS group ($P = .72$). Six-year survival was 76.0% in diabetics and 80.8% in nondiabetics ($P = .15$). Six-year late stroke estimates were 3.2% in diabetic and 4.6% in nondiabetic patients ($P = .90$). The 6-year risk of restenosis was similar (4.6% % vs 4.2%) in diabetic and nondiabetic patients ($P = .56$). Survival, late stroke, and restenosis rates between diabetics and nondiabetics were similar in CAS and CEA groups.**

Conclusions: **Diabetic patients are not at greater risk of perioperative morbidity and mortality or late stroke after CAS, however, the perioperative risk can be higher after CEA. This may help in selecting the appropriate technique for carotid revascularization in patients best suited for the type of procedure. (J Vasc Surg 2012;55:79-89.)**

Carotid artery stenting (CAS) has been recently endorsed by international guidelines as a valid alternative to carotid endarterectomy (CEA) for treatment of carotid stenosis in subgroups of patients less suitable or at higher risks for CEA.[1] One of these subgroups might be the diabetic population. Diabetes has been suggested as a marker of higher surgical/operative risk during open vascular procedures.[2-5] Specifically, a number of authors suggested that due to increased perioperative risks of stroke and death during CEA, the benefit of the procedure in stroke prevention might be decreased in this subgroup of patients with carotid stenosis. However, there is no uniform consensus, but there are conflicting results.[6] The limited evidence available today seems to suggest that diabetes is not risky for CAS procedure, nevertheless, data on outcome of diabetic patients after CAS are limited. Furthermore, since the overall cardiovascular morbidity is increased in diabetic patients, the long-term benefit of carotid revascularization (whichever the procedure) may be excluded by an excessive mortality and stroke rate.

The aim of this study was to investigate perioperative and 6-year outcomes of diabetic vs nondiabetic patients undergoing CAS and those undergoing CEA in a single center experience.

METHODS

Methodology was detailed in a previous study on the same cohort of patients.[7] With respect to the original cohort, follow-up was updated and six patients in whom no accurate information could be retrieved for the purpose of this study were excluded.[7] Briefly, a database of patients undergoing carotid revascularization at a single vascular surgical center from January 2001 to March 2009 was queried for all patients undergoing CEA and CAS for significant primary atherosclerotic occlusive disease. Vessels treated for intimal hyperplasia, recurrent atherosclerotic carotid stenosis, and bypass grafts were excluded. All patients had either >60% symptomatic or >70% asymptom-

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atic carotid stenosis and were treated by surgeons. The revascularization treatment choice (CAS/CEA) was left to the discretion of the treating surgeon and was based on general guidelines and team center experience according to morphologic and clinical data indicating best suitability and lower periprocedural risk for CAS and CEA. Criteria were detailed previously.[7,8] Usually, patients with unfavorable aortic arch anatomy, severe peripheral vascular disease precluding femoral access, or extremely tortuous carotid anatomy were excluded from CAS. Similarly, old age, unstable plaque, known allergies to aspirin, clopidogrel, or contrast media, and renal insufficiency were considered exclusion criteria for CAS. High-neck carotid bifurcation and long carotid lesions as well as obesity and ongoing double antiplatelet were relative contraindications for CEA.[7]

To avoid bias due to the learning curve effect of the operators, the first 195 CAS performed within the training phase (2001-2003) were excluded from the study.[8] In our center, with increasing experience, the number of CAS increased over time allowing CEA to be used for fewer and more complex cases (eg, acute stroke, unstable plaque, etc.) in recent years. Therefore, CEAs performed in the last 2 years (2008-2009), when higher-risk selection criteria were applied, were excluded from the present analysis to avoid possible overestimated risk in CEA.

Neurologic symptoms were evaluated by a team of neurologists who documented the presence, type, and severity (National Institutes of Health [NIH] Stroke Scale) of the event. Patients were defined as symptomatic when ipsilateral hemispheric or retinal symptoms occurred within 6 months from the procedure. Stroke was defined as any new hemispheric or retinal neurologic event persisting >24 hours and classified as fatal, disabling (modified Rankin Score ≥ 3), or nondisabling (modified Rankin Score < 3).

The degree and characteristics of carotid stenosis were assessed with Duplex ultrasound by experienced operators who defined plaque characteristics and vessel measurements as previously validated against angiography as a gold standard technique.[7] Contrast enhanced computed tomography (CTA) or, seldom, magnetic resonance (MR) of carotid vessels was performed selectively in case of uncertainty at ultrasound examination. Angiography was exclusively applied during CAS procedure. Cerebral CT scan was used in symptomatic patients to assess the extent of recent lesions if any.

For carotid stenting, the patient was given aspirin (125-325 mg once daily) in addition to clopidogrel (75 mg once daily) or ticlopidine (250 mg twice daily) beginning 3 days before the procedure. When clopidogrel therapy started <3 days before CAS a 300-mg loading dose was administered 6 to 12 hours before the procedure. After the stenting procedure, clopidogrel was continued for 1 month and aspirin was continued lifelong. All patients received an intravenous heparin bolus (100 U/kg) to achieve systemic anticoagulation during the carotid intervention. Carotid stenting was performed following a standardized protocol in an endovascular room equipped with a high quality fixed imaging system (Axiom Artus FA, Siemens, Berlin, Germany). Percutaneous transfemoral or transbrachial approaches under local anesthesia were used for selective engagement of the target carotid artery. Minimal or no sedation was used during the procedure and neurologic status was continuously monitored. Variable models of cerebral protection devices (CPD) and carotid stents (open cell, close cell, or hybrid configuration; tapered or straight) were employed in all procedures. The choice of specific material depended on vessel anatomy and lesion characteristics. Angioplasty was performed with a 5- to 6-mm diameter balloon. Closure devices for the access control have been used since 2006.

For CEA, patients were usually maintained on aspirin therapy. CEA was performed under local or general anesthesia with selective use of shunt. Both Dacron patch angioplasty and eversion endarterectomy (and exceptionally, primary closure) were performed.

Patients scheduled for CAS/CEA with antiplatelet intolerance or already under ticlopidine (250 mg twice daily) or under anticoagulation for coexisting medical comorbidities, continued to receive their baseline therapy at the usual dose. Written consent was obtained from all patients before revascularization.

Patients after both CEA and CAS were followed by duplex ultrasound scan at 6 months, 12 months, and yearly thereafter, and symptoms status was assessed. Carotid restenosis was set at >50% using ultrasound criteria.[9] Patients were instructed to report any new neurologic symptoms occurring after hospital discharge. In case of neurologic symptoms or uncertainty occurring anytime after the procedure, the patients were evaluated by a certified independent neurologist expert in vascular disease.

Outcome measures and definitions. Primary outcome was the combined risk of any stroke or death within 30 days (perioperative). Secondary end points were the rate of stroke, death, and restenosis at 6 years after the procedure.

The exposure variable for this study was the presence of diabetes mellitus at the time of carotid procedure. Diabetic patients were defined as those with established diagnosis and/or receiving oral hypoglycemic or insulin therapy.

Coronary artery disease was defined as a history of angina pectoris, myocardial infarction (MI), congestive heart disease, or prior coronary artery revascularizations. Restenosis was defined as the development of >50% stenosis. A major adverse clinical event (MACE) was defined as any stroke or MI or death. Any death, stroke, or MI <30 days from the procedure was considered procedure-related. Perioperative was defined as a stroke, death, or any event occurring during hospital admission and <30 days postprocedure.

Statistical analysis. Analysis of data was by treatment actually received. Measured values are reported as percentages or means ± standard deviations (SDs). Rates for comorbidities, complications, and 30-day outcomes were compared between patients with and without diabetes by χ^2 test.

Univariate analysis was used to quantify the association between each binary clinical variable and adverse event

outcome. Potential confounding and selection biases were addressed by analyzing the rate of the primary outcome (any stroke or death within 30 days) with multivariate analyses after using backwards elimination methods assuming diabetes as a covariate. The fit of the model was assessed with the Hosmer and Lemeshow goodness-of-fit test, where a *P* value less than .05 indicated an ill-fit model.[10]

The following variables were included in the model: diabetes, treatment (CAS, CEA), age, gender, preoperative symptoms, contralateral occlusion, coronary disease, peripheral artery disease, hypertension, on statin therapy, complex plaque, and use of aspirin. Since patients under insulin represented a subgroup within the diabetic population leading to potential overlapping data, insulin use was tested in separate repeated models.

Survival, restenosis, and stroke-free rates were calculated using Kaplan-Meier analysis to compensate for patient dropouts and are reported using the current Society for Vascular Surgery (SVS) criteria.[11] Standard errors (SE) are reported in Kaplan-Meier analyses and curves are displayed up to a value of SE <0.10. The log-rank test was used to determine survival differences between patients with and without diabetes.

Associations between diabetes and covariates with long-term outcome measures (death, stroke, and restenosis) were assessed by Cox regression analyses by including time-dependent interaction of each covariate with survival time.

To account for specific covariates in each CAS or CEA technique, subgroup analyses comparing diabetic vs nondiabetic patients for periprocedural and late outcomes were performed in models stratified by procedure.

A value of $P < .05$ was considered statistically significant for all measurements. SPSS/PC version 13.00 Win package (SPSS for Windows, SPSS, Inc., Chicago, Ill) was used for all data analyses.

RESULTS

Over the study period a total of 2196 interventions for primary carotid stenosis were performed in 2007 patients: 1080 by CAS (in 992 patients) and 1116 by CEA (in 1015 patients). There were 1558 males and 638 females; mean age was 71.3 years (range 46-92). Six hundred eighty-four (31.1%) were symptomatic and 1512 were asymptomatic carotid stenosis. General anesthesia was employed in 594 CEA procedures.

Six hundred thirty procedures were performed in diabetic patients (28.7%), 150 of these were on insulin.

Demographic and baseline characteristics for diabetic and nondiabetic populations are displayed in Tables I and II.

Diabetes was more common in CAS than in CEA patients (30.7% vs 26.7%, $P = .038$). Diabetic patients were younger (70.16 ± 7.2 vs 71.75 ± 7.7 years; $P < .0001$) and more likely to have a history of coronary disease (35.2% vs 30.1%, $P = .019$) or hypertension (84.6% vs 80.3%, $P = .018$) with respect to nondiabetic populations. There were no substantial imbalances in the distribution of other factors.

Table I. Baseline characteristics in 2196 patients

	Diabetes (n = 630)		*No diabetes (n = 1566)*		
	N (%)		*N (%)*		P *value*
Age, years (SD)	70.16 (±7.2)		71.75 (±7.7)		<.0001
Females	184	29.2	454	28.9	.917
Hypertension	533	84.6	1257	80.3	.018
CAD	222	35.2	471	30.1	.019
Hyperlipidemia	358	56.8	893	57.0	.962
PAD	125	19.8	263	16.8	.095
Symptomatic disease	187	29.7	497	31.7	.359
Contralateral occlusion	44	6.9	119	7.6	.654
On statin	245	38.9	580	37.0	.378
Complex plaque	248	39.4	558	35.6	.117
CAS	332	52.7	748	47.8	.038

CAD, Coronary artery disease; *CAS,* carotid artery stenting; *PAD,* peripheral artery disease; *SD,* standard deviation.

Periprocedural outcomes. The 30-day (periprocedural) risk of stroke or death in overall populations was 2.4% (53/2.196) with no significant differences in rates between the two procedures: 2.8% (30/1080) in CAS and 2.1% (23/1116) in CEA ($P = .33$).

Periprocedural outcome measures in diabetics compared with nondiabetics by CAS and CEA procedure are reported in Fig 1. There were no significant differences in periprocedural risk of stroke or death between the two groups: 2.7% (17/630) in diabetics vs 2.3% (36/1566) in nondiabetics; $P = .64$.

Any perioperative MACE (including any stroke, death, and MI) occurred in 2.9% of diabetics and 2.6% of nondiabetics ($P = .662$). Rates of MI, transient ischemic attack (TIA), and cranial nerve injuries were also evenly distributed. Neck hematoma in the CEA population was more frequent in the diabetic group (3.0% vs 1.1%, $P = .03$) (Fig 1).

At univariate analysis, symptomatic stenosis was associated with increased risk of perioperative stroke and death: 3.5% in symptomatic vs 1.9% in asymptomatic; odds ratio (OR), 1.86; 95% confidence interval (CI), 1.07 to 3.21; $P = .034$ (Table III). Patients under insulin showed doubled risk (4.7% vs 2.2%) with respect to the others, but the difference did not achieve statistical relevance ($P = .09$). However, the difference was significant in the subgroup of CEA patients (6.5% vs 1.7%, $P = .017$; OR, 3.93; 95% CI, 1.42-10.92) but not in CAS patients (2.7% vs 2.8%, $P = 1$). There were no other factors associated with stroke and death in the CEA group, while the use of statin was associated with outcome in the CAS group ($P = .014$) (Table IV).

At multivariate analysis, using backward stepwise method to select among potentially relevant predictors of perioperative stroke and death, age ($P = .088$), contralateral occlusion ($P = .053$), and use of statin ($P = .032$) were retained in the last step of the model. However, only the use of statin was significantly associated with decreased risk

Table II. Baseline characteristics in diabetics vs nondiabetics by procedure

	Carotid stenting (n = 1080)					*Carotid endarterectomy (n = 1116)*				
	Diabetes (n = 332)		*Nondiabetes (n = 748)*			*Diabetes (n = 298)*		*Nondiabetes (n = 818)*		
Characteristic	*n*	*%*	*n*	*%*	P *value*	*n*	*%*	*n*	*%*	P *value*
Age, years +SD	70.31 ± 7.18		72.09 ± 75		<.0001	69.99 ± 7.08		71.45 ± 7.88		.003
Females	90	27.1	223	29.8	.38	94	31.5	231	28.2	.30
Hypertension	288	86.7	615	82.2	.75	245	82.2	642	78.5	.18
CAD	130	39.2	267	35.7	.30	92	31.0	204	24.9	.046
Hyperlipidemia	208	62.7	463	61.9	.84	150	50.3	430	52.6	.54
PAD	58	17.5	89	11.9	.02	67	22.6	174	21.3	.68
Symptomatic disease	77	23.2	191	25.5	.45	110	36.9	306	37.4	.89
Contralateral occlusion	23	6.9	59	7.9	.62	21	7.0	60	7.3	1.00
On insulin	73	22.0	—	—	—	77	25.8	—	—	—
On statin	145	43.7	319	42.6	.79	100	35.2	261	33.0	.51
On clopidogrel[b]	244	73.5	577	77.2	.19	—	—	—	—	—
Complex plaque	110	33.1	228	30.5	.39	138	46.9	330	41.1	.09
Open cell stent	99	29.9	215	28.9	.77	–	—	—	—	—
General anesthesia[a]	—	—	—	—	—	160	53.7	434	53.1	.89

CAD, Coronary artery disease; *PAD,* peripheral artery disease; *SD,* standard deviation.
[a]Only for patients with carotid endarterectomy: 594 general anesthesia, 522 locoregional anesthesia.
[b]Only for patients with carotid stenting.

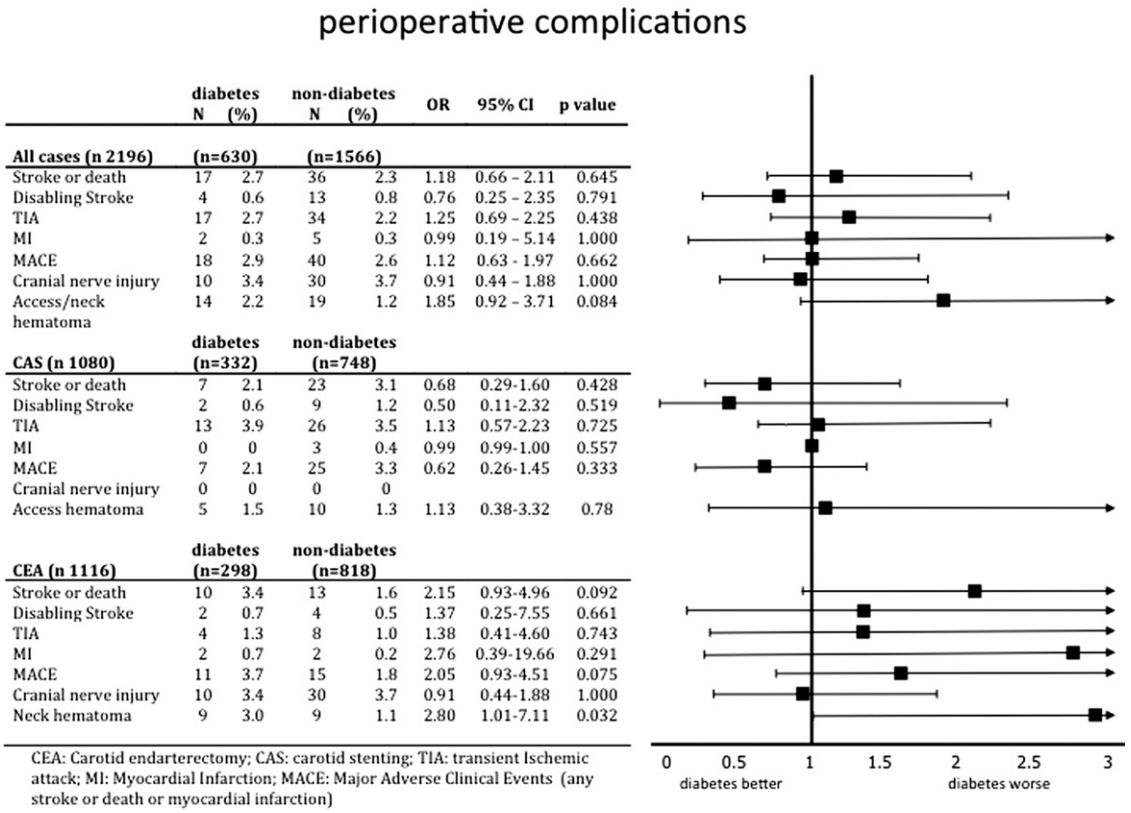


Fig 1. Perioperative outcome after carotid revascularization in 630 diabetic and 1566 nondiabetic patients.

(OR, 0.37; 95% CI, .15-.92). When the use of insulin was added to the model, insulin was borderline associated with stroke and death rates (OR, 2.27; 95% CI, 1.00-5.13; $P = .05$).

To address the potential differences in techniques and details affecting perioperative primary outcome, multivariate analysis was repeated separately for CEA and CAS procedures.

Table III. Univariate analysis on perioperative stroke and death in 2196 carotid procedures

	Events %	*OR*	*95% CI*	P *value*
Treatment				
CAS	2.8	1.358	0.78-2.35	.330
CEA	2.1			
Diabetes				
Yes	2.7	1.179	0.65-2.11	.645
No	2.3			
Insulin treatment				
Yes	4.7	2.128	0.94-4.79	.088
No	2.2			
Symptoms				
Yes	3.5	1.860	1.07-3.21	.034
No	1.9			
Female gender				
Yes	2.5	1.057	0.58-1.91	.879
No	2.4			
Hypertension				
Yes	2.6	1.503	0.67-3.35	.374
No	1.7			
CAD				
Yes	2.3	0.936	0.51-1.69	.882
No	2.5			
PAD				
Yes	1.8	0.703	0.31-1.57	.469
No	2.5			
Contralateral occlusion				
Yes	3.1	1.309	0.51-3.33	.591
No	2.4			
Complex plaque				
Yes	2.9	1.313	0.75-2.27	.388
No	2.2			
General anesthesia[a]				
Yes	2.9	2.534	0.99-6.47	.056
No	1.1			
Statins treatment				
Yes	1.7	0.7	0.37-1.31	.288
No	2.4			
ASA treatment				
Yes	2.6	0.853	0.34-2.12	.807
No	3.0			

ASA, Acetylsalicylic acid; *CAD,* coronary artery disease; *CAS,* carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *OR,* odds ratio; *PAD,* peripheral artery disease.
[a]Only in 1116 patients with carotid endarterectomy: 17/594 general anesthesia, 6/522 locoregional anesthesia.

For the 1116 CEA population, the only variable retained in the last step of multivariate model as significant independent predictor of perioperative higher stroke and death rate was the presence of diabetes: OR, 2.83; 95% CI, 1.05-7.60; $P = .04$. When insulin was added to the model, it was significantly associated with outcome but 95% CI widened (OR, 7.55; 95% CI, 2.50-22.87; $P < .0001$).

For the 1080 CAS procedures, the use of statin remains the only variable to be significantly associated with about threefold decreased risk of perioperative stroke and death: OR, 0.34; 95% CI, .14-.85; $P = .021$. Neither diabetes ($P = .47$) nor insulin ($P = .62$) was associated with perioperative primary outcome.

Late outcomes. Mean follow-up was 47.23 ± 28.5 months (from 1 to 123.4 months). During the observation period, 321 patients died and 59 ischemic strokes were recorded. In addition, 10 cerebral hemorrhages (1 nonfatal) occurred.

Six-year survival rates from any cause mortality were 76.0% in diabetic and 80.8% in nondiabetic ($P = .153$) populations (Fig 2).

Freedom from late stroke at 6 years rated 96.8% in diabetics vs 95.4% in nondiabetics ($P = .904$; Fig 3).

During follow-up, recurrent stenosis of 50% or more was detected in 80 patients (24 diabetics and 56 nondiabetics) without significant difference in Kaplan-Meier estimates at 6 years between diabetic and nondiabetic patients according to log-rank test: 4.6% vs 4.2%; $P = .558$ (Fig 4). Five recurrent stenoses occurred in patients who experienced late strokes.

There were no significant differences between diabetic and nondiabetic populations for each CAS or CEA subgroup in Kaplan-Meier estimates of survival (for CAS 81.7% vs

Table IV. Univariate analysis on perioperative stroke and death by procedure

	Carotid stenting (n = 1080)				*Carotid endarterectomy (n = 1116)*			
	Events %	*OR*	*95% CI*	P	*Events %*	*OR*	*95% CI*	P
Diabetes								
Yes	2.1	0.68	0.3-1.6	.42	3.4	2.1	0.9-4.3	.09
No	3.1				1.6			
On insulin								
Yes	2.7	0.98	0.2-4.2	1.00	6.5	3.93	1.4-10.9	.017
No	2.8				1.7			
Female								
Yes	2.2	0.74	0.3-1.7	.54	2.8	1.58	0.7-3.6	.35
No	3.0				1.8			
Symptoms								
Yes	4.5	2.07	0.9-4.3	.056	2.9	1.86	0.8-4.2	.19
No	2.2				1.6			
Hypertension								
Yes	2.7	0.77	0.3-1.9	.61	2.5	5.79	0.7-43.2	.06
No	3.4				0.4			
CAD								
Yes	2.5	0.86	0.4-1.8	.85	2.0	0.97	0.4-2.5	1.00
No	2.9				2.1			
PAD								
Yes	2.7	0.98	0.3-2.8	1.00	1.2	0.53	0.2-1.8	.44
No	2.8				2.3			
Occlusion contr.								
Yes	6.1	2.52	0.9-6.7	.07	0	—	—	.4
No	2.5				2.2			
Complex plaque								
Yes	3.6	1.48	0.7-3.1	.32	2.4	1.23	0.5-2.8	.67
No	2.4				1.9			
On statin								
Yes	1.3	0.32	0.1-0.8	.01	2.2	1.99	0.7-5.3	.18
No	3.9				1.1			
General anesthesia								
Yes					2.9	2.53	0.9-6.4	.056
No					1.1			

ASA, Acetylsalicylic acid; *CAD,* coronary artery disease; *CAS,* carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *OR,* odds ratio; *PAD,* peripheral artery disease.

87.5%, $P = .12$; for CEA 79.4% vs 82.8%, $P = .44$), freedom from late ischemic stroke (for CAS 96.0% vs 95.8%, $P = .13$; for CEA 97.2% vs 95.6%, $P = .48$), and from restenosis (for CAS 95.6% vs 96.0%, $P = .73$; for CEA 94.9% vs 96.8%, $P = .66$) rates at 5 years (due to small numbers in subgroup analyses, curves were trimmed at 5 years).

Cox regression analysis after adjusting for potential confounders with backwards elimination, demonstrated that diabetes was associated with 6-year mortality (hazard ratio [HR], 1.37; 95% CI, 1.07-1.74; $P = .011$). In addition, age (HR, 1.08; 95% CI, 1.06-1.10; $P < .0001$), symptomatic stenosis (HR, 1.34; 95% CI, 1.07-1.68; $P = .012$), coronary disease (HR, 1.40; 95% CI, 1.12-1.76; $P = .004$), and peripheral artery disease (HR, 1.52; 95% CI, 1.18-1.96; $P = .001$) were significant positive predictors while female gender (HR, 0.69; 95% CI, .52-.91; $P = .008$) and use of statins (HR, 0.51; 95% CI, .39-.66; $P < .0001$) were negative predictors of death.

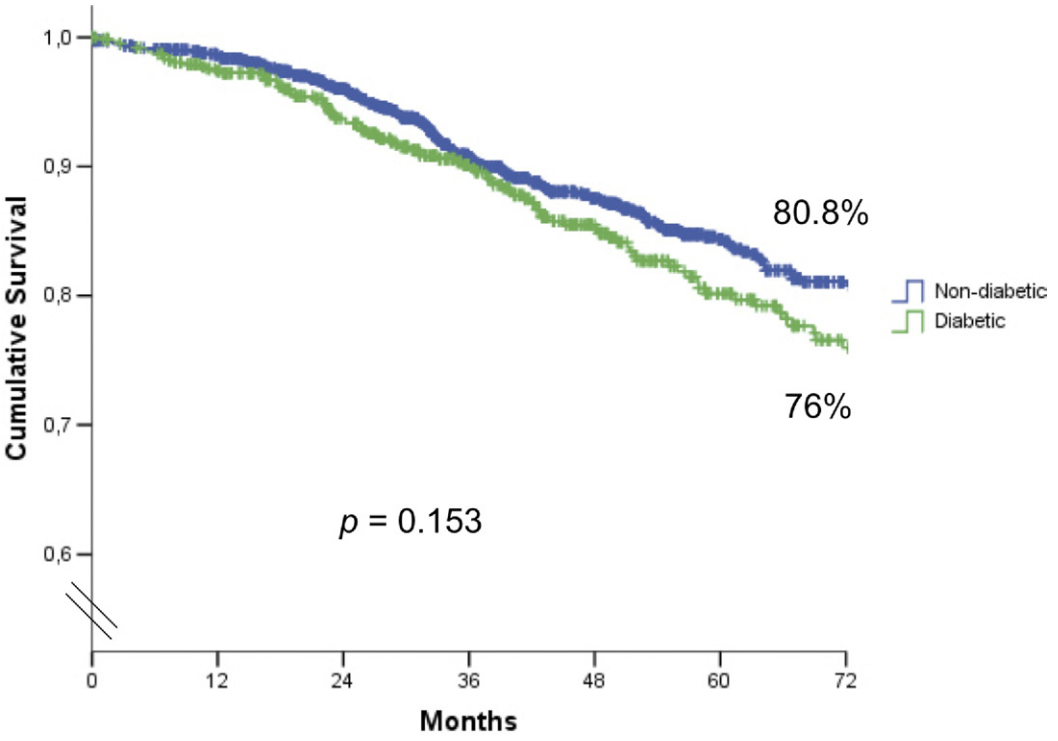
Age (HR, 1.08; 95% CI, 1.04-1.12; $P < .0001$) and symptomatic disease (HR, 1.99; 95% CI, 1.19-3.34; $P = .009$), but not diabetes (HR, 1.10; $P = .741$), were positive predictors while use of statins was a negative predictor (HR, 0.21; 95% CI, 0.09-0.46; $P < .0001$) of late ischemic stroke.

Peripheral artery disease was the only factor positively associated with the incidence of restenosis (HR, 1.85; 95% CI, 1.13-3.02; $P = .014$) according to Cox analysis that failed to show any significant interaction with diabetes (HR, 1.12; $P = .66$).

Similar diabetes-related associations with late outcomes were found in models stratified by CAS or CEA procedure: diabetes was confirmed a predictor of late death (HR, 1.63; 95% CI, 1.04-2.54; $P = .032$) in CAS and, with borderline significance, in CEA (HR, 1.333; 95% CI, .99-1.79; $P = .055$). There were no significant associations between diabetes and late stroke or restenosis after each of the two procedures.

DISCUSSION

Patients with diabetes and severe carotid stenosis share similar periprocedural stroke and death risks of nondiabetic patients when carotid stenting is applied for treatment (perioperative stroke and death rate: 2.7% vs 2.3%; $P = .64$). However, with a surgical approach to treat carotid



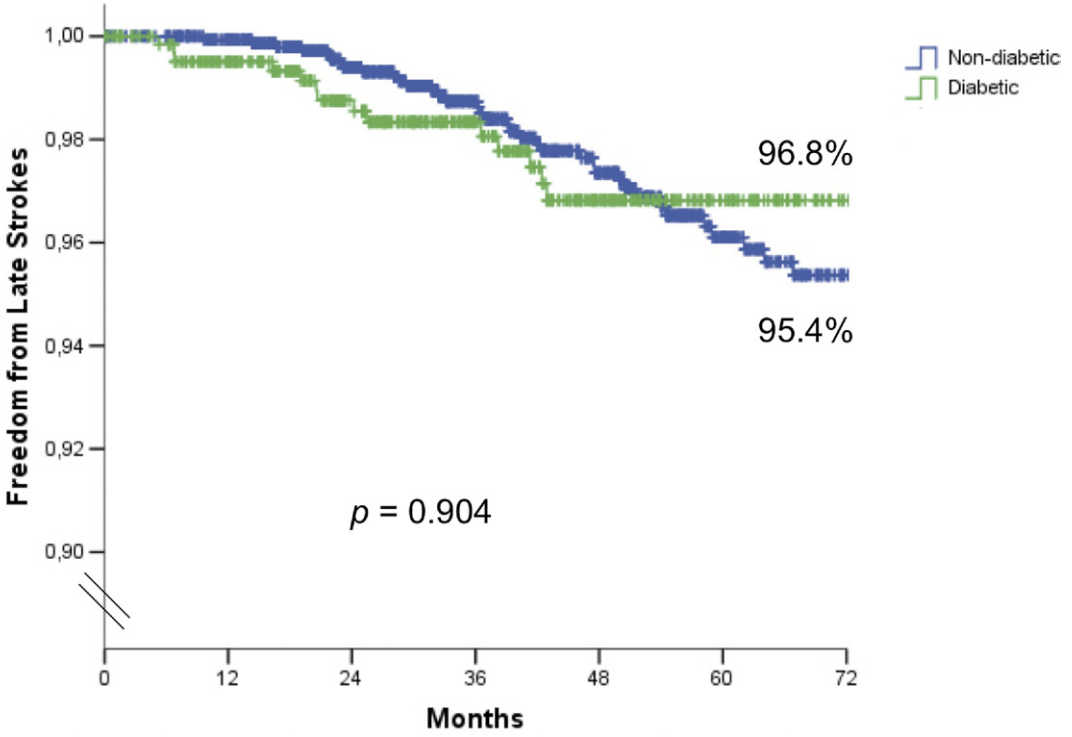
Months	0	12	24	36	48	60	72
Non diabetic							
N at risk	1566	1459	1202	890	685	440	326
Standard Error	0	.003	.005	.008	.01	.012	.014
Diabetic							
N at risk	630	577	482	357	261	171	129
Standard Error	0	.006	.01	.013	.017	.021	.024

Fig 2. Six-year Kaplan-Meier estimates of survival in diabetic and nondiabetic populations after carotid revascularization.

stenosis, the perioperative risk of stroke and death might be threefold higher (OR, 2.83; 95% CI, 1.05-7.61; $P = .04$) in diabetic patients. After perioperative period, the rate of stroke is <5% at 6 years with both procedures confirming that the efficacy of carotid revascularization in stroke prevention may persist in the long term also in diabetic settings. These data might suggest the presence of diabetes as an indicator to identify subgroups of patients better suited for CAS than for CEA due to the proportionally higher surgical risks of the CEA procedure.

Diabetes mellitus is one of the most common and disabling diseases in western countries affecting about one of every five adults aged >60 years with a strong cardiovascular burden.[12-14] Epidemiologic studies have confirmed that diabetes independently increases risks of ischemic stroke (with relative risk ranging from 1.8-fold to sixfold) and that stroke functional outcome is worse and stroke-related mortality is higher in diabetic patients.[15-18] Therefore, it is expected that the benefit of stroke prevention measures, as carotid revascularization in those with severe carotid stenosis, might be higher in these patients. Nevertheless, surgical carotid intervention conveys a perioperative burden that could offset the long-term benefit. This likely does not apply to carotid stenting procedure.

Very few studies have analyzed the role of diabetes in CAS population.[19] Siewiorek et al, who specifically analyzed the association of clinical variables and 30-day outcomes in 203 CAS procedures, found that diabetes (OR, 2.8; 95% CI, 1.0-7.6; $P = .04$) and prior CEA (OR, 1.8; 95% CI, 1.1-3.1; $P = .03$) were significantly associated with adverse outcome in terms of increased combined rate of stroke, TIA, and death within 30 days.[19] Nevertheless, the inclusion of minor neurologic complications (TIA) influenced significance for the combined outcome. Indeed, rates of stroke alone ($P = .28$) or mortality alone ($P = .41$) were not significantly higher in diabetic patients.[19] According to the pooled analysis of outcomes from randomized clinical trials (RCTs) (International Carotid Stenting Study [ICSS], Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis [EVA-3S], Stent-Protected Angioplasty versus Carotid Endarterectomy [SPACE]) comparing CAS vs CEA in 3454 symptomatic patients, CAS was shown to increase perioperative



Months	0	12	24	36	48	60	72
Non diabetic							
N at risk	1566	1459	1203	887	671	438	322
Standard Error	0	.001	.002	.003	.005	.007	.008
Diabetic							
N at risk	630	574	479	355	260	177	127
Standard Error	0	.003	.005	.006	.009	.009	.009

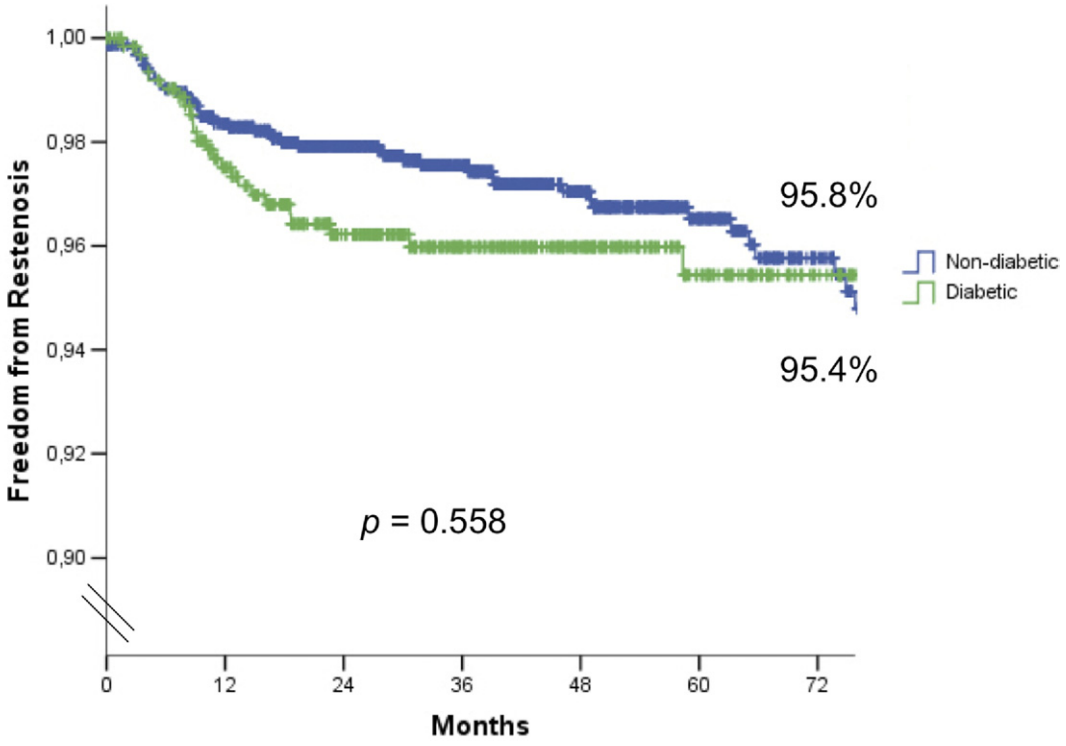
Fig 3. Six-year Kaplan-Meier estimates of freedom from ischemic stroke in diabetic and nondiabetic populations after carotid revascularization.

risk in the nondiabetic (OR, 1.67; 95% CI, 1.24-2.24) population, but not in the diabetic subgroup (OR, 1.21; 95% CI, .78-1.88).[20] Specifically, cumulative stroke and death risks within 120 days were 9.8% in diabetics vs 8.5% in nondiabetics in the CAS population and 8.0% in diabetics vs 5.1% in nondiabetics in the CEA population.[20] These RCT data agree with our findings not supporting higher perioperative risk in diabetic CAS populations.

A number of differences in techniques and approaches between procedures could explain the different perioperative exposure risk of diabetic patients during stenting vs during CEA.[21] The more diffuse intracranial small vessel disease associated with lower clamping tolerance in the diabetic population may be a factor, another could be the use of general anesthesia or the overall higher surgical stress during open surgery that can influence the adverse outcome of surgery in diabetics. Nevertheless, the true reasons and mechanisms for different perioperative risks between CAS and CEA diabetic patients remain largely unsettled and future studies should be specifically conducted to provide further insight in this direction.

Other literature data analyzing medical management of diabetes in CEA supported an increased operative risk for insulin takers, to some extent confirmed by our data.[15,22,23] The need for insulin might be associated with more than sevenfold increased risks of perioperative stroke and deaths after CEA: 6.5% vs 1.7% in patients with and without insulin, respectively; (OR, 7.55; 95% CI, 2.50-22.87; $P < .0001$, multivariate analysis). This may suggest that a more advanced diabetic disease, or a different metabolic status requiring more aggressive glycemic control in diabetic patients requiring insulin could lead to higher ischemic events and mortality. However, our data may be unbalanced and underpowered to prove differences between treatments and should be interpreted with caution. Nevertheless, other studies also reported conflicting data on the role of insulin-dependent treatment and CEA risk.[3,23] Irrespective of the overall effect, the mechanisms of the suggested insulin-increased risks of CEA are unknown.

Despite the lower life expectancy due to increased all-cause mortality (6-year survival 76.0% vs 80.8%), in the



Months	0	12	24	36	48	60	72
Non diabetic							
N at risk	1566	1425	1177	866	658	432	315
Standard Error	0	.003	.004	.004	.005	.006	.007
Diabetic							
N at risk	630	561	465	341	249	169	120
Standard Error	0	.006	.008	.008	.008	.01	.01

Fig 4. Six-year Kaplan-Meier estimates of freedom from restenosis in diabetic and nondiabetic populations after carotid revascularization.

long-term diabetic patients after carotid revascularization did not perform worse in terms of increased stroke or restenosis risks at 6 years. These data confirm the durability of the carotid repair (whichever the treatment applied) and the efficacy of stroke prevention of carotid revascularization. Our long-term results are of relevance especially for the CAS group since the durability of the procedure is still questioned. According to our findings, low stroke rates (4%) and restenosis rates (4.4%) can be achieved with CAS after 5 years also in subgroups of patients with higher cardiovascular mortality and morbidity such as diabetic patients.

The presence of diabetes might both increase neointimal hyperplasia and accelerate the growth of new carotid plaques at the site of arterial injury, thereby implying an increased restenosis risk after revascularization.[3,24] However, this hypothesis has not been supported by large evidence. Our study, as well as others in the literature,[2,25,26] confirmed that diabetic patients have similar restenosis rates compared with nondiabetic patients, whichever treatment was applied to treat carotid stenosis.

Study limitations. This study is retrospective in nature and clinical decision-making was based on physician-guided indications and not on a randomization list.

We did not perform biochemical assessments to evaluate glycemic or metabolic control in diabetic and nondiabetic groups, and patients' adherence to prescribed therapy was not supervised. Subgroup analyses (on-insulin, general anesthesia, CAS) might be underpowered to provide reliable data.

CONCLUSIONS

Diabetes is prevalent among patients with carotid stenosis affecting about almost one third of those undergoing carotid revascularization (28.7%). Diabetic patients undergoing CAS are not at greater risk of perioperative morbidity as well as stroke and restenosis at 6 years after the procedure compared with patients without diabetes. Therefore, long-term stroke prevention with carotid revascularization may be fulfilled also in the presence of diabetes. Nevertheless, diabetes may be considered a significant risk factor during the perioperative period for patients undergoing carotid endarterectomy. This may help in selecting the appropriate

technique for carotid revascularization in patients best suited for type of procedure.

AUTHOR CONTRIBUTIONS

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

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DISCUSSION

Dr Christos Liapis (*Athens, Greece*). Excellent paper. I have one question and one comment. Did you analyze separately patients with type A and type B diabetes? And my comment is that only 35% of your patients in both groups were on statins, yet, the main statistical outcome difference was in favor of the statin users. I think that this should be the take home message of your study.

Dr Enrico Cieri. We did not analyze specifically type A and type B diabetes, but our aged population was mainly affected by type B diabetes independently of their current use of insulin or oral hypoglycemic agents. But I am sorry. I have no data about type A and type B diabetes. And for sure, statins is a very protective factor for both the procedures (endarterectomy and stenting). I agree absolutely with you.

Dr John Ricotta (*Washington, DC*). Do you have data on hemoglobin A1C levels in the two patient groups that might give us an idea of whether they were comparable at the time of surgery? Do you have any data on that?

Dr Cieri. No, I am sorry, because the study was a retrospective analysis of a prospective database and we did not record this data.

Dr Ricotta. Do you think that the fact that there seemed to be a greater burden of atherosclerosis in the endarterectomy patients, for example, they had more peripheral vascular disease and more tortuous arch anatomy, do you think that might influence your results in any way?

Dr Cieri. I really think that diabetes is in itself a marker of a poor systemic condition, and several studies are analyzing the effect of diabetes or its medications (eg, insulin) on the inflammatory process of atherosclerosis. So, I think that the surgical stress in carotid endarterectomy might be a key point in diabetic patients' risk and this, more than arch or vessel anatomy, might have influenced our results.

Dr Jean-Baptiste Ricco (*Poitiers, France*). Did you do any propensity analysis between carotid stenting vs carotid endarterectomy to make sure that the observed effect is not due to differences in participants in the two groups rather than or in addition to the intervention?

Dr Cieri. No, we did not perform propensity analysis. Really, the aim of our study was not to compare carotid endarterectomy with carotid stenting, but to see whether diabetes could affect in carotid revascularization, whichever the technique used. So we did not perform a propensity adjustment of patients for carotid endarterectomy vs carotid stenting.

Dr Robert Zwolak (*Lebanon, NH*). Did you have equal percentages of symptomatic and asymptomatic patients in the endarterectomy and carotid stenting groups?

Dr Cieri. Yes. No statistical difference was found in distribution of symptomatic and asymptomatic patients between carotid endarterectomy and carotid stenting group or between diabetic and nondiabetic patients.