Long-term results of carotid artery stenting

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Objective: **Data regarding the long-term efficacy of carotid artery stenting (CAS) are still scarce. As demonstrated by several major randomized controlled trials (RCT) comparing the efficacy of carotid endarterectomy (CEA) vs medical therapy, even after successful carotid revascularization late ipsilateral stroke occurs in 5-13% at 5 years. Therefore, major concerns also remain about the durability of the CAS procedure in terms of stroke prevention. The purpose of this study was to review long-term results after carotid stent implantation in a large cohort of patients.**

Methods: **This retrospective investigation involved 3179 CAS procedures performed at four European carotid high-volume centers. Echo-duplex scan using modified velocity criteria to recognize in-stent restenosis (ISR) and neurological examinations of all patients were carried out every 6 months after the procedure. Life-table analysis was used to determine freedom from mortality, stroke-related death, ipsilateral fatal/major stroke, and any ipsilateral stroke. Freedom from ISR and from reintervention were also reported. The secondary aim was to identify predictive risk factors for neurological complications and ISR.**

Results: **At 5 years freedom from mortality, stroke-related death, ipsilateral fatal/major stroke, and any stroke rate were 82%, 93.5%, 93.3%, and 91.9%, respectively. The only predictor for neurological complications was the presence of neurological symptoms before CAS (hazard ratio 1.38 [CI 1.05, 1.82] $P = .02$). Freedom from restenosis at 1, 3, and 5 years was, respectively, 98.4%, 96.1%, and 94%. Uni- and multi-variate analyses showed that stent characteristics (material/design/free-cell area) were not significantly associated with time to in-stent restenosis or time to reintervention.**

Conclusion: **Our long-term results in a large cohort of patients validated CAS as a durable procedure for stroke prevention. The annual rate of neurological complications after CAS was comparable to that of conventional surgery as demonstrated by large RCTs involving both symptomatic patients (North American Symptomatic Carotid Endarterectomy Trial [NASCET] and European Carotid Surgery Trial [ECST]) and asymptomatic patients (Asymptomatic Carotid Atherosclerosis Study [ACAS] and Asymptomatic Carotid Surgery Trial [ACST]). (J Vasc Surg 2008;48:1431-41.)**

In recent years, carotid artery stenting (CAS) has rapidly gained recognition worldwide as a possible alternative to carotid endarterectomy (CEA). Although excellent results from centers with a high-volume experience seem to demonstrate that CAS is technically feasible and safe,[1] the few randomized controlled trials (RCTs) conducted so far have not clarified the equivalence of this technique compared to CEA in terms of early results[2-4] in normal-risk patients. Moreover, these trials did neglect to publish long-term results after CAS, and only a few nonrandomized studies have focused their attention on long-term results with >5 years of follow-up.[5-9]

As demonstrated by several RCTs comparing the efficacy of CEA vs medical therapy, even after successful carotid revascularization late ipsilateral stroke occurs in 5.1-13% at 5 years.[10-14] The major concern for long-term results after CAS is, therefore, that the plaque, which is completely removed in CEA surgery, is only remodeled and contained behind the strut of the stent, so that the only protection against late embolization is the scaffolding of the emboligenic plaque by means of the stent. Moreover, long-term patency following CAS can be limited by restenosis due to neointimal hyperplasia or recurrent atherosclerosis, but no data has been reported regarding the influence of stent type on these endpoints.

The purpose of this analysis is to review long-term results after carotid stent implantation in a large cohort of patients. The primary aim was to analyze: a) freedom from death, stroke-related death, disabling stroke, or any type of neurological complication, and b) the behavior of different implanted stents in terms of patency and need for reintervention. The secondary aim was to identify predictive risk factors for neurological complications, restenosis, and need for reintervention during the follow-up after CAS.

METHODS

Cohort of patients. The subject of this investigation was a selected cohort of 3179 consecutive patients who underwent CAS procedures at four European carotid high-volume centers during the 8-year period from March 1998 to June 2006.[15-17] During the same period, 2672 patients underwent CEA (45.7%). A constant drop in the number of CEA procedures and a rapid growth of indication for CAS[18] has been observed during this 8-year period.

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Competition of interest: none.

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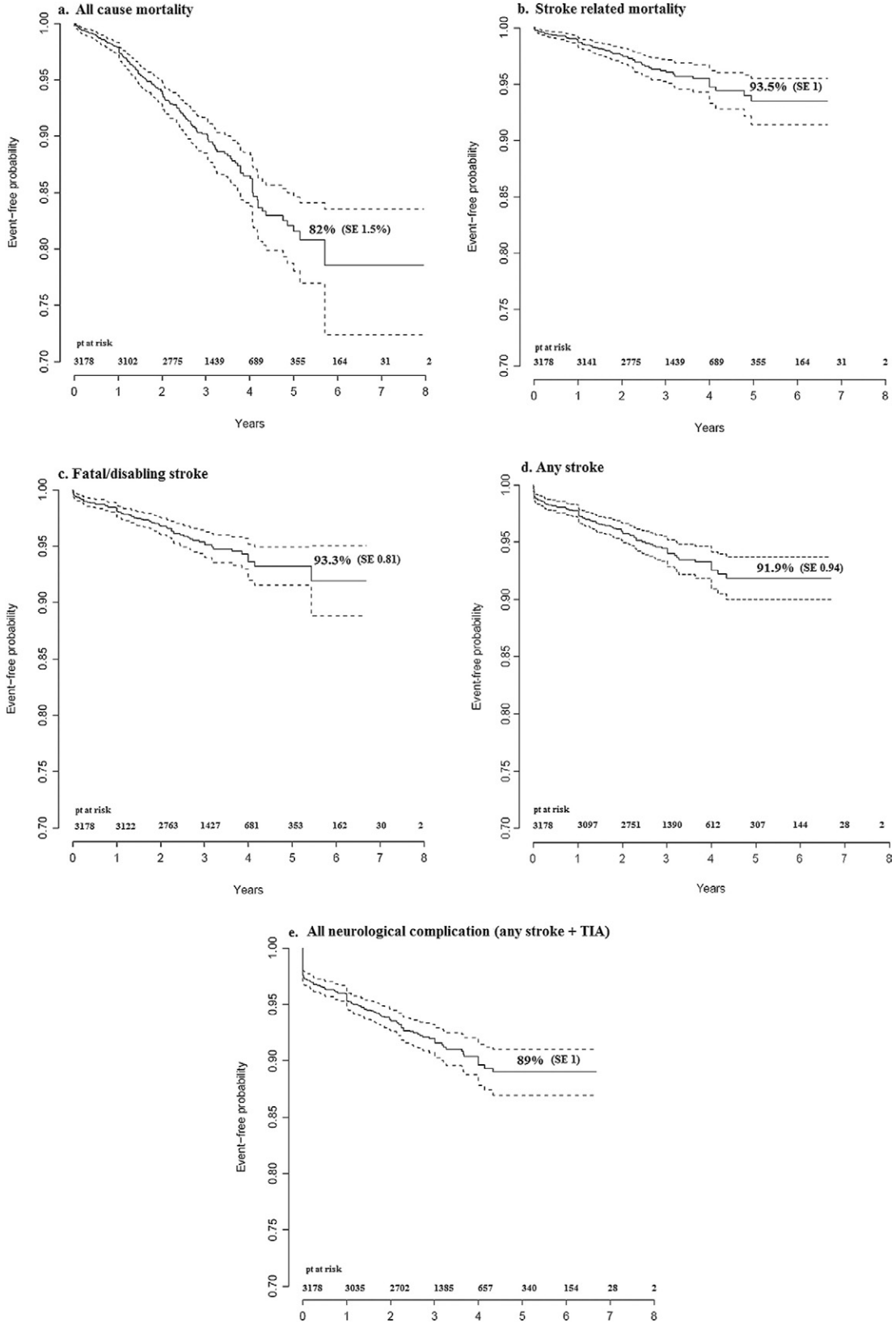

a. All cause mortality
Event−free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
82% (SE 1.5%)
pt at risk
3178 3102 2775 1439 689 355 164 31 2
0 1 2 3 4 5 6 7 8
Years
b. Stroke related mortality
93.5% (SE 1)
pt at risk
3178 3141 2775 1439 689 355 164 31 2
0 1 2 3 4 5 6 7 8
Years
c. Fatal/disabling stroke
93.3% (SE 0.81)
pt at risk
3178 3122 2763 1427 681 353 162 30 2
0 1 2 3 4 5 6 7 8
Years
d. Any stroke
91.9% (SE 0.94)
pt at risk
3178 3097 2751 1390 612 307 144 28 2
0 1 2 3 4 5 6 7 8
Years
e. All neurological complication (any stroke + TIA)
89% (SE 1)
pt at risk
3178 3035 2702 1385 657 340 154 28 2
0 1 2 3 4 5 6 7 8

All CAS patients were screened with pre-operative duplex ultrasound scan and magnetic resonance angiography, followed by digital subtraction angiography at the time of the procedure to confirm whether lesions were appropriate for treatment (symptomatic lesions ≥50%, asymptomatic lesions ≥80%, calculated according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria).[10]

Study population and risk factor distribution. The mean age was 72.4 ± 7.9 years, and the study population included 2130 (67.0%) men. In total, 1317 (41.4%) patients presented with symptomatic and 1862 (58.6%) with asymptomatic disease. Current or former nicotine abuse was confirmed in 1204 (37.9%) patients and arterial hypertension in 2291 (72.1%). Hypercholesterolemia was found in 2000 (62.9%) patients and history of coronary or peripheral artery disease in 1443 (45.1%). The study included 827 (26.0%) diabetic patients. In total, 2945 (92.6%) of the patients were treated for a de novo lesion and 234 (7.4%) for restenosis after CEA (n = 206) or after CAS (n = 28).

Medical treatment. All patients were treated with acetylsalicylic acid (ASA) at a mean dosage of 80-125 mg/day, associated with clopidogrel or ticlopidine at a mean dosage of 75 mg/day or 500 mg/day respectively for at least 3 days prior to admission. After the procedure, aspirin in combination with clopidogrel (75 mg/day) or ticlopidine (500 mg/day) was continued for at least 30 days. At the physician's discretion, and according to local reimbursement policies, mono anti-platelet therapy (either aspirin, clopidogrel, or ticlopidine) was to be continued indefinitely.

Procedures. CAS was performed according to each unit's existing standards of care, as described previously.[19] Each center had experience of over 50 CAS (before the start of data collection, the first 50 patients were not included).

Unprotected stenting was performed in 130 (4.1%) patients: the majority of these cases dated from the period in which EPDs were not yet widely available. In the remaining 3049 (95.9%) patients, commercially available EPDs were selected and applied: 2831 (92.9%) distal filters, 192 (6.4%) proximal occlusion, and 26 (0.8%) distal occlusion devices. Dedicated self-expanding carotid stents were used in all patients: nitinol stents were used in 1072 (33.7%) and stainless steel stents in 2107 (66.3%) patients.

Follow-up. Patients were requested to undergo echo-duplex scan and neurological examinations of all patients were carried out at 1, 3, 6, and 12 months after the procedure and then yearly. Patients were instructed to inform the physician when any new symptoms occurred after hospital discharge. Exact information about clinical events was obtained for all patients. Neurologic exam was performed primarily by the physician who did the echo-duplex scan. All new neurological events were confirmed by an independent neurologist and either a brain CT or MRI was performed if any change in neurological status was found.

Modified velocity criteria were used to identify in-stent restenosis (ISR), according to the parameters of Lal, et al,[20] (peak systolic velocity [PSV] 210 to 300 cm/s with end-diastolic velocity less than 120 cm/s, to detect ISR 60% to 79%; PSV greater than 300 cm/s and end-diastolic velocity greater than 120 cm/s, or internal carotid to common carotid artery systolic velocity ratio greater than 3.2, for ISR >80% to 99%). ISR was defined as a narrowing of 50% or more (PSV >175 cm/s).[21] Indications for reinterven-

←

Fig 1. Survival curves in the total population (freedom from event at 5 year and standard error [SE]).

	Years									*Total (cumulative events)*
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	
a. All causes mortality										
Patient at risk	3178	3102	2775	1439	689	355	164	31	2	
Number of events *(per year)*	1	74	62	33	22	9	2	0	0	202
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
b. Stroke related mortality										
Patient at risk	3178	3141	2775	1439	689	355	164	31	2	
Number of events *(per year)*	1	32	15	11	6	3	0	0	0	68
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
c. Fatal/disabling stroke										
Patient at risk	3178	3122	2763	1427	681	353	162	30	2	
Number of events *(per year)*	1	56	23	14	7	1	1	0	0	103
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
d. Any stroke										
Patient at risk	3178	3097	2751	1390	612	307	144	28	2	
Number of events *(per year)*	1	75	20	11	6	2	1	0	0	116
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
e. All neurological complication (any stroke + TIA)										
Patient at risk	3178	3035	2702	1385	657	340	154	28	2	
Number of events *(per year)*	1	143	30	17	9	2	1	0	0	203
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133

Table I. Proportion (in %) in the total population with complications in the given period, with 95% confidence interval

Complication	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
All-cause mortality	2.1 (1.6-2.7)	6 (5.1-7.2)	9.8 (8.3-11)	14 (11-16)	18 (15-21)
Stroke-related mortality	1.2 (0.8-1.6)	2.4 (1.8-3.1)	3.8 (2.8-4.8)	5.2 (3.8-6.7)	6.5 (4.5-8.6)
Fatal/disabling stroke	1.9 (1.4-2.3)	3.2 (2.5-4)	4.6 (3.5-5.7)	6.4 (4.8-8)	6.7 (5-8.4)
Any stroke	2.3 (1.7-2.8)	4.2 (3.4-5)	5.6 (4.5-6.7)	7.5 (5.8-9.1)	8.1 (6.3-10)
All neurological complications	4.1 (3.4-4.8)	6.4 (5.5-7.4)	8 (6.8-9.3)	10 (8.5-12)	11 (9-13)

tion were ISR ≥80% in asymptomatic patients and ≥50% in symptomatic patients, as documented by echo-duplex scan and confirmed by intraprocedural angiography (NASCET criteria).

Stroke classification. Strokes were classified according to their probable location (ipsilateral, contralateral) and their consequences (fatal, disabling, or non-disabling). A stroke was considered fatal when it caused the death of the patient, either directly due to brain damage, or indirectly due to a non-neurological complication.

A disabling stroke was a stroke that was associated with disability 6 months afterward, with a modified Rankin scale score of at least 3 (ie, at least moderate disability from the index stroke, with the need for some help in daily affairs).

A non-disabling stroke was one that after 6 months was associated with a modified Rankin score of less than 3 (ie, at most only slight disability from the index stroke, without the need for assistance in daily affairs).

Aims and statistical analysis. The first aim of this study was to analyze long-term stroke prevention after CAS and to evaluate the long-term behavior of the implanted carotid stents concerning patency rate and need for reintervention.

Neurological complications were reported in terms of freedom from: overall mortality, stroke-related death, all ipsilateral neurological complications (transient ischemic attack [TIA], disabling or non-disabling stroke), and ipsilateral fatal/disabling stroke. The behavior of the implanted stent was reported in terms of freedom from ISR and reintervention.

Our secondary aim was to identify predictive risk factors for ipsilateral neurological complications and for ISR. The risk factors indicated by the various investigators as being potentially predictive of the late neurological event rate were: age, symptomatic status, male gender, nicotine abuse, hypertension, hypercholesterolemia, history of coronary or peripheral artery disease, diabetes, and restenosis after CEA/CAS.

The risk factors related to the stent properties and indicated as being potentially predictive of ISR and the necessity for reintervention were: stent material (stainless steel vs nitinol) and different free-cell area (stents were subdivided into four subgroups: <2.5 mm^2, 2.5-5 mm^2, 5-7.5 mm^2, and >7.5 mm^2).

Analysis of time to the different complications was based on Kaplan-Meier curves with 95% confidence bands. Because Kaplan-Meier curves ignore that death from other causes is a "competing risk", as they assume that patients who die from other causes still have a risk of stroke-related death, Kaplan-Meier analysis of all complication events, except overall mortality, were accommodated using a "competing risk analysis".[22-24]

Risk factors for complication events were detected in both a univariate and multivariate analysis, using Cox proportional hazards regression models. Effects were retained in the model when significant at the 5% significance level. In a secondary analysis, stepwise regression methods involving Akaike's Information Criterion were used, allowing for two-way interactions between any pair of variables. All analyses were conducted in R Version 2.3.0 using the Design package (by Frank Harrell, Vanderbilt University) for Kaplan-Meier curves, the Competing Risk package (Bob Gray, Harvard University) for competing risk analysis and the survival package for Cox proportional hazards modeling.

RESULTS

As previously published,[15] the 30-day rates for death, disabling stroke, non-disabling stroke and TIA were found to be 0.2, 0.4, 0.7, and 1.5%, respectively. This results in a cumulative 30-day event rate after CAS of 2.8%.

For long-term analysis, at least 1-year follow-up was completed for all patients. A total of 133 patients were lost at different times during the follow-up period. The mean follow-up period was 961 ± 488 days (range, 365-2863).

During the follow-up period, a total of 202 patients died, including 68 ipsilateral stroke-related deaths (fatal strokes) and 134 non-lesion related deaths, of which 7 were contralateral stroke-related and 127 due to other causes. The survival curve at 1, 3, and 5 years was, respectively, 97.9%, 90.2%, and 82% (Fig 1, *a*, Table I).

During the follow-up, 116 ipsilateral strokes (82 disabling and 34 non-disabling strokes), and 11 contralateral strokes were diagnosed. Only ipsilateral strokes were considered for the analysis. Freedom from ipsilateral stroke-related mortality at 1, 3, and 5 years was, respectively, 98.8%, 96.2%, and 93.5% (Fig 1, *b*, Table I).

Table I summarizes the results at years 1, 2, 3, 4, and 5 for the endpoints studied: all cause mortality, ipsilateral stroke-related mortality, ipsilateral fatal/disabling stroke, any stroke, and all ipsilateral neurological complications (TIA and any stroke). At 5 years, freedom from any ipsilateral stroke was 91.9% (Fig 1, *d*, Table I).

Annual rates (ie, expected number of events per year per 100 event-free patients) for each complication in the

Table II. Average Annual rates (ie, number of events per year per 100 event-free patients) for all complications in the total population, with 95% confidence interval

Complication	*Annual rate*	*95% CI*
All-cause mortality	3.43	(3-3.9)
Stroke-related mortality	1.31	(1-1.6)
All neurological complications	3.45	(3-3.9)
Any stroke	1.9	(1.7-2.4)
Fatal/disabling stroke	1.70	(1.4-2.1)
In-stent restenosis	1.49	(1.2-1.8)
Reintervention	1.08	(0.8-1.4)

total population are shown in Table II. Fig 2 and Table III show the event-free curves analyzed for symptomatic and asymptomatic populations.

ISR ≥50% was detected in 88 patients, of which only 8 were symptomatic. Life-table analysis showed freedom from event at 1, 3, and 5 years of 98.6%, 95.9%, and 93.5% (Fig 3, Table IV). No stent fracture was observed. Two asymptomatic cases of stent occlusion were detected at year 2 and 3.5. Reintervention was performed in 64 cases (56 asymptomatic ISR ≥80%, 8 symptomatic ISR ≥50%), including four stent removals (2 cases of acute CAS thrombosis[25] and 2 late surgical conversions), and 60 further endovascular approaches (23 angioplasties, 14 angioplasties followed by stenting, 15 cutting balloon angioplasties, and 8 cutting balloon angioplasties followed by stenting). Two patients had recurrence of ISR and were treated with further cutting balloon angioplasty. Table V reports the univariate comparison of all categorical risk factors in patients with and without complications during follow-up. It shows that the incidence of ipsilateral neurological complications (of any type) is 38% (95% confidence interval 5%-82%, $P = .02$) higher in the symptomatic population than in the asymptomatic population.

Tables VI and VII show that stent design material (stainless steel vs nitinol) and free-cell areas are not significantly associated with the incidence of in-stent restenosis and incidence of reintervention.

DISCUSSION

So far, only one RCT[26] comparing CEA vs CAS in high-risk patients has reported data in favor of CAS, while the recent EVA-3S (Endarterectomy vs Angioplasty and Stenting in Patients With Symptomatic Severe Carotid Stenosis)[27] and SPACE (Stent-Protected Angioplasty vs Carotid Endarterectomy)[28] RCTs failed to clarify whether stenting can be considered "equivalent" to CEA in normal-risk patients. Indications for and the outcome of CAS, therefore, remain a controversial topic, while no long-term (>5 years) data from any RCTs are currently available. The 3-year results from SAPPHIRE have been recently reported:[29] the composite rate of death, stroke, or myocardial infarction within 30 days or death or ipsilateral stroke between 31 days and 3 years was 26.2% in the stenting group and 30.3% in the endarterectomy group (P = ns).

Should the long-term data turn out to be unsatisfactory, the whole debate about indications, optimal techniques, equipment, and early outcomes would be no longer worthy of discussion.

We have already reported the 30-day outcome after CAS for this large cohort of patients,[15] and we have found that there is substantial evidence of differences in adverse event rates according to the stent used. In particular, the post-procedural complication rates in the symptomatic population were highest for the open-cell types and increased with a larger free-cell area, while no significant differences could be established in the asymptomatic population.

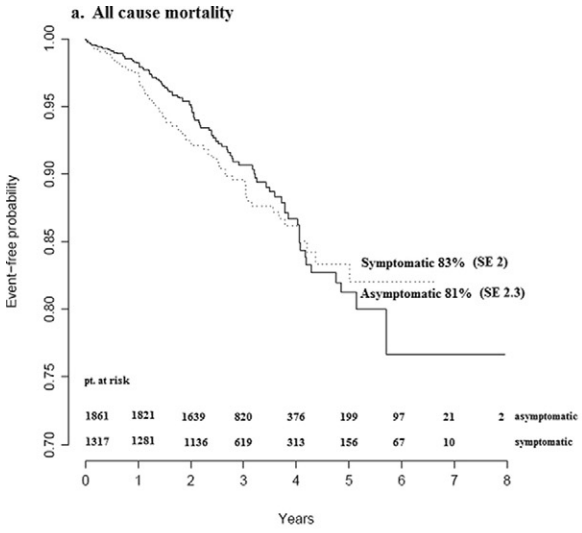
The aim of this analysis was to study the durability of the endovascular procedure in terms of stroke-prevention, restenosis, and need for reintervention. For the moment, only a few series of cases with long-term follow-up after CAS have been reported,[6-9,30] and no studies have analyzed the behavior of the implanted stent over time on the basis of the different stent materials.

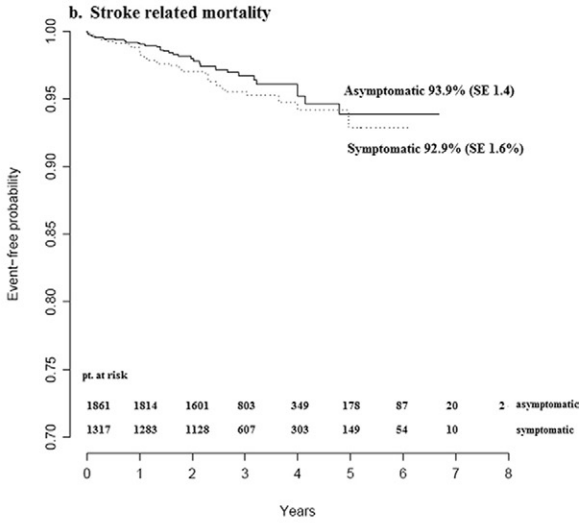
Bergeron, et al,[9] reported long-term results in a series of 221 CAS, with a 96% freedom from stroke rate at 3 years. In a series of 528 consecutive patients who underwent 604 carotid stenting procedures, Roubin, et al,[8] found a 3-year freedom from all fatal and nonfatal stroke rates of 88 ± 2%, and 95 ± 2%, respectively, with and without the inclusion of the 30-day periprocedural period.

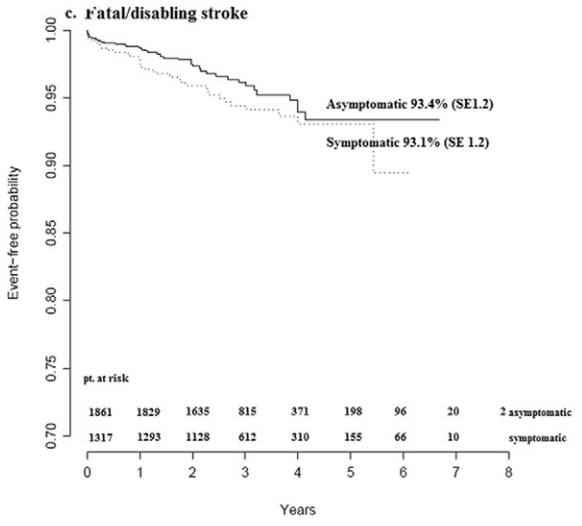
To our knowledge, our study is the largest patient cohort followed over the longest period of time in the literature that compares long-term stroke prevention and the influence of stent material. In this respect, in the absence of long-term results from RCTs comparing CEA vs CAS, this data could be compared to data from RCTs comparing CEA to medical therapy.

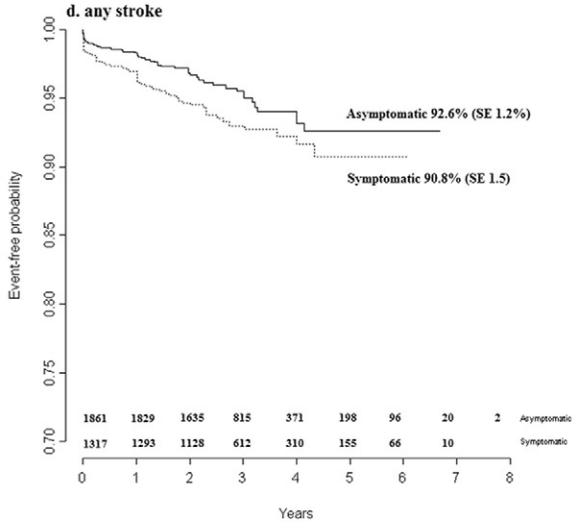
In our series, the annual rate of 1.7% (95% CI 1.4-2.1) for any type of ipsilateral fatal/disabling stroke, as reported in our total population, seems to be in the same range as that of post CEA complications reported by large RCTs.[10,12-14] In particular, the any type of stroke or perioperative death rate of 6.42% at 5 years reported for asymptomatic patients by the Asymptomatic Carotid Surgery Trial (ACST)[14] or of 5.1% reported by the Asymptomatic Carotid Atherosclerosis Study (ACAS)[13] are close to the 7.4% rate in our asymptomatic population (Table III). In our symptomatic population, the any ipsilateral stroke rate at 3 and 5 years were 7% and 9.2% (Table III), which are clearly comparable with the 8.5% rate of the European Carotid Surgery Trial (ECST)[12] at 3 years, and the 13% rate of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[10]

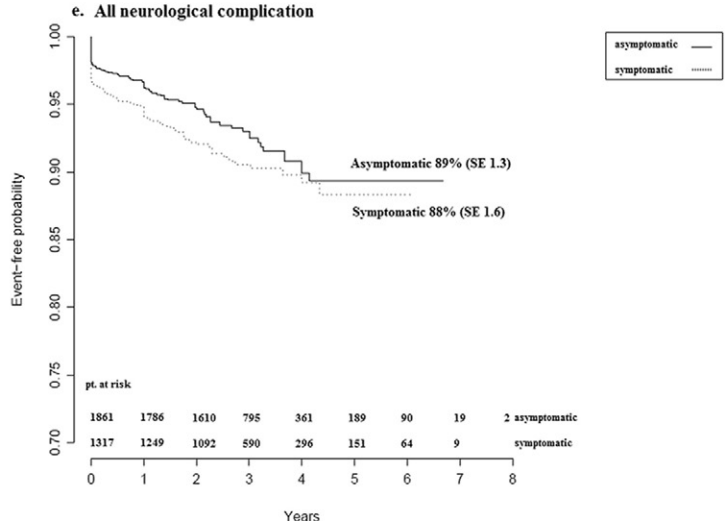
Moreover, if we take into account the natural history of the disease in untreated patients from RCTs (risk of stroke at 5 years of 11% in asymptomatic patients,[13] and of 25% in symptomatic patients),[10] our data seem to reveal an improved outcome in both asymptomatic (7.4%, aggregate risk reduction −32%) and symptomatic CAS patients (9.2%, aggregate risk reduction −63%).


a. All cause mortality
Event-free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Symptomatic 83% (SE 2)
Asymptomatic 81% (SE 2.3)
pt. at risk
1861 1821 1639 820 376 199 97 21 2 asymptomatic
1317 1281 1136 619 313 156 67 10 symptomatic
0 1 2 3 4 5 6 7 8
Years


b. Stroke related mortality
Event-free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Asymptomatic 93.9% (SE 1.4)
Symptomatic 92.9% (SE 1.6%)
pt. at risk
1861 1814 1601 803 349 178 87 20 2 asymptomatic
1317 1283 1128 607 303 149 54 10 symptomatic
0 1 2 3 4 5 6 7 8
Years


c. Fatal/disabling stroke
Event-free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Asymptomatic 93.4% (SE1.2)
Symptomatic 93.1% (SE 1.2)
pt. at risk
1861 1829 1635 815 371 198 96 20 2 asymptomatic
1317 1293 1128 612 310 155 66 10 symptomatic
0 1 2 3 4 5 6 7 8
Years


d. any stroke
Event-free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Asymptomatic 92.6% (SE 1.2%)
Symptomatic 90.8% (SE 1.5)
1861 1829 1635 815 371 198 96 20 2 Asymptomatic
1317 1293 1128 612 310 155 66 10 Symptomatic
0 1 2 3 4 5 6 7 8
Years


e. All neurological complication
asymptomatic
symptomatic
Event-free probability
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Asymptomatic 89% (SE 1.3)
Symptomatic 88% (SE 1.6)
pt. at risk
1861 1786 1610 795 361 189 90 19 2 asymptomatic
1317 1249 1092 590 296 151 64 9 symptomatic
0 1 2 3 4 5 6 7 8
Years

Regarding the risk factors, Bergeron, et al,[9] also found that renal insufficiency, male sex, age >70 years, and a lesion located at the bifurcation were good predictors of early and late neurologic complications of CAS. In our study, the only factor to predict late neurological complications at univariate analysis was the presence of symptoms before CAS (hazard ratio 1.38 [95% CI 1.05-1.82], $P = .02$). To understand the pathophysiology of these late neurological events remains speculative. However, the high number of ipsilateral strokes compared to contralateral strokes, seems to suggest the excluded lesion behind the stent as the source of emboli, especially if this is symptomatic before the treatment.

The durability of CAS is also strictly related to the incidence of ISR, which continues to be the "Achilles' heel" of any catheter intervention. Despite several thousand CAS procedures being reported in the literature, the real incidence of ISR after CAS is unclear, with a range from <5%[31,32] to >21%.[33,34]

This variability is essentially related to the different US velocity criteria used to define ISR. It is now evident that CAS induces permanent alterations to the physiological flow behavior, in terms of compliance mismatch between the native carotid artery and the stented segment, positive arterial remodeling (stent expansion), and enhanced stiffness of the stent-arterial wall. These alterations lead to an increase in velocity also in the absence of ISR.

Using modified velocity criteria, as defined previously, we found an acceptable annual ISR ≥50% rate of 1.49%, (95% CI 1.19-1.83), and a cumulative rate at 5 years of 6%

←

Fig 2. Survival curves in the symptomatic and the asymptomatic population (freedom from event at 5 year and standard error [SE]).

	Years									*Total (cumulative events)*
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	
a. All cause mortality										
Patient at risk										
asymptomatic	1861	1821	1639	820	376	199	97	21	2	
symptomatic	1317	1281	1136	619	313	156	67	10	0	
Number of events *(per year)*										
asymptomatic	0	35	30	19	15	6	2	0	0	107
symptomatic	1	38	33	14	7	3	0	0	0	95
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
b. Stroke related mortality										
Patient at risk										
asymptomatic	1861	1814	1601	803	349	178	87	20	2	
symptomatic	1317	1283	1128	607	303	149	54	10	0	
Number of events *(per year)*										
asymptomatic	0	15	7	5	4	2	0	0	0	33
symptomatic	1	17	8	6	2	1	0	0	0	35
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
c. Fatal/disabling stroke										
Patient at risk										
asymptomatic	1861	1829	1635	815	371	198	96	20	2	
symptomatic	1317	1293	1128	612	310	155	66	10	0	
Number of events *(per year)*										
asymptomatic	0	24	12	7	5	1	0	0	0	33
symptomatic	1	22	21	7	2	0	1	0	0	35
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
d. Any stroke										
Patient at risk										
asymptomatic	1861	1829	1635	815	371	198	96	20	2	
symptomatic	1317	1293	1128	612	310	155	66	10	0	
Number of events *(per year)*										
asymptomatic	0	31	9	6	5	1	0	0	0	52
symptomatic	1	44	11	5	1	1	1	0	0	64
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
e. All neurological complication (any stroke + TIA)										
Patient at risk										
asymptomatic	1861	1786	1610	795	361	189	90	19	2	
symptomatic	1317	1249	1192	590	296	157	64	9	0	
Number of events *(per year)*										
asymptomatic	0	68	15	10	7	1	0	0	0	101
symptomatic	1	75	15	7	2	1	1	0	0	102
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133

Table III. Proportion (in %) in the symptomatic and asymptomatic population with complications in the given period, with 95% confidence interval

Complication	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Symptomatic population					
All-cause mortality	2.5 (1.8-3.6)	7.6 (6-9.6)	10.4 (8.3-13)	13.8 (11-17.3)	16.7 (13-21.3)
Stroke-related mortality	1.6 (0.9-2.4)	3 (1.9-4.1)	4.5 (2.9-6.1)	5.8 (3.6-8)	7.1 (3.8-10.4)
Fatal/disabling stroke	2.6 (1.7-3.5)	4.1 (2.8-5.3)	5.6 (3.9-7.3)	6.9 (4.6-9.2)	6.9 (4.6-9.2)
Any stroke	3 (2.1-4)	5.5 (4.1-6.9)	7 (5.2-8.8)	8.3 (6-11)	9.2 (6.3-12)
All neurological complications	5.1 (3.9-6.3)	7.9 (6.3-9.6)	9.4 (7.4-11.4)	10.8 (8.3-13.3)	11.7 (8.6-14.7)
Asymptomatic population					
All-cause mortality	1.8 (2.2-3.5)	4.9 (3.8-6.3)	9.3 (7.4-11.7)	13.3 (10.5-16.7)	18.7 (14.8-23.6)
Stroke-related mortality	0.9 (0.5-1.3)	2 (1.2-2.8)	3.3 (2-4.5)	4.8 (2.8-6.8)	6.1 (3.5-8.8)
Fatal/disabling stroke	1.3 (0.8-1.8)	2.6 (1.7-3.5)	3.9 (2.5-5.2)	6.1 (3.9-8.2)	6.6 (4.2-9)
Any stroke	1.7 (1.1-2.3)	3.3 (2.3-4.3)	4.5 (3.1-5.9)	6.8 (4.6-9.1)	7.4 (5-9.8)
All neurological complications	3.3 (2.5-4.2)	5.4 (4.2-6.6)	7 (5.4-8.6)	10.1 (7.5-12.7)	10.6 (7.9-13.4)

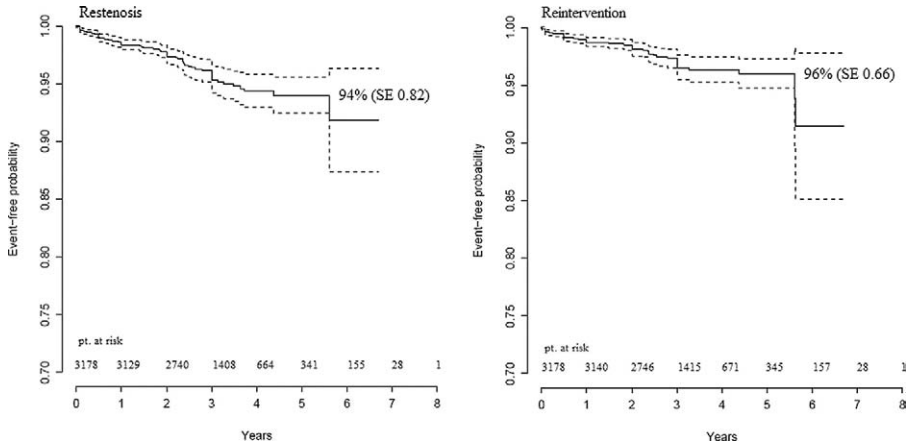


Fig 3. Restenosis and reintervention in the total population (freedom from event at 5 year and standard error [SE]).

	Years									*Total (cumulative events)*
	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	
a. Restenosis (≥50%)										
Patient at risk	3178	3129	2740	1408	664	341	155	28	1	
Number of events *(per year)*	0	49	14	18	5	1	1	0	0	88
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133
b. Reintervention										
Patient at risk	3178	3140	2746	1415	671	345	157	28	1	
Number of events *(per year)*	0	38	8	14	1	1	2	0	0	64
Patients lost at follow-up *(per year)*	0	0	22	14	21	12	17	32	15	133

(95% CI 4.4-7.6), which is very similar to the cumulative rate of ISR ≥80% of 6.4% at 60 months reported by Lal, et al,[20] using the same parameters.

ISR was correlated with neurologic events only in 8 out of 88 cases. The stroke rate in this group of patients (cumulative rate 9.1%) was only slightly superior to patients without ISR, so the benefit of reintervention in reducing stroke risk might be questionable. However, no studies in literature report stroke risk in patients with untreated ISR, so it seems acceptable to treat ISR ≥80% in symptomatic and ≥50% in asymptomatic patients.

We also studied the influence of different stent properties (stent material: stainless steel vs nitinol; free-cell area: <2.5 mm^2, 2.5-5 mm^2, 5-7.5 mm^2, and >7.5 mm^2) on the incidence of ISR and of reintervention. Although we have already demonstrated in this cohort of patients that there is substantial evidence for differences in early adverse event rates between different cell designs,[15] uni- and multi-

Table IV. Proportion (in %) of patients in the total population with in-stent restenosis >50% and reintervention in the given period, with 95% confidence interval

Complication	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
In-stent restenosis ≥50%	1.6 (1.2-2.1)	2.5 (1.9-3.2)	3.9 (2.9-4.9)	5.6 (4.2-7.1)	6 (4.4-7.6)
Reintervention	1.3 (0.9-1.7)	1.8 (1.2-2.3)	2.7 (1.9-3.5)	3.6 (2.6-4.7)	4 (2.7-5.3)

Table V. Univariate analysis: hazard ratios for all neurological complication in the total population

Risk factor	*Hazard ratios*	*95% confidence interval*	P
Gender (male)	0.92	(0.7-1.2)	.59
Octogenarian and older	1.02	(0.7-1.5)	.91
Symptoms	1.38	(1.1-1.8)	.02
Polivascular disease	1.03	(0.8-1.4)	.83
Hypertension	1.03	(0.7-1.4)	.87
Diabetes	1.17	(0.9-1.6)	.32
Hypercholesterolemia	0.99	(0.7-1.3)	.94
Restenotic lesion	0.87	(0.5-1.4)	.57
Nicotine	0.95	(0.7-1.3)	.73

Table VI. Hazard ratios for in-stent restenosis in the total population

Risk factor	*Hazard ratios*	*95% confidence interval*	P
Stent design	1.28	(0.8-2.1)	.35
Free cell area (mm^2)			.64*
<2.5	1		
2.5-5	0.33	(0.1-2.3)	.27
5-7.5	0.80	(0.4-1.7)	.58
>7.5	0.87	(0.5-1.7)	.69

**P* value of global test for association between free cell area and time to in-stent restenosis.

Table VII. Hazard ratios for reintervention in the total population

Risk factor	*Hazard ratios*	*95% confidence interval*	P
Stent design	0.98	(0.6-1.7)	.95
Free cell area (mm^2)			.86*
<2.5	1		
2.5-5	0.48	(0.1-3.5)	.47
5-7.5	1.00	(0.4-2.3)	.99
>7.5	1.16	(0.6-2.3)	.68

**P* value of global test for association between free cell area and time to reintervention.

variate analyses on long-term results showed that stent characteristics (material/design/free-cell area) were not significantly associated with ISR or reintervention. Considering the wide confidex intervals, these results lead only to a hypothesis: the scaffolding properties of the stent play an important role in the early postoperative period, but this ends when the intravascular stent endothelialization process is completed (generally after 30 days), and has no influence on the long-term patency rate.

CONCLUSION

Long-term results in a large cohort of patients validate CAS as a durable procedure for stroke prevention. The ISR rate appears to be acceptable, and the need for reintervention is low and unrelated to the characteristics of the device. The annual rate of neurological complications after CAS is comparable to that of conventional surgery, as demonstrated by large RCTs both for symptomatic patients (NASCET and ECST) and asymptomatic patients (ACAS and ACST).

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AUTHOR CONTRIBUTIONS

Conception and design: GdD, CS, KD, PP, AC, MB
Analysis and interpretation: GdD, MB
Data collection: GdD, KD, PP, AC, MB
Writing the article: GdD
Critical revision of the article: CS, AC, MB
Final approval of the article: CS, KD, PP, AC, MB
Statistical analysis: GdD, MB
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Overall responsibility: GdD

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DISCUSSION

Dr Richard Cambria (Boston, Mass). I would like to open with one question about the follow-up on the issue of restenosis. You expressed your data in actuarial methods. Can you tell us how many patients actually completed the 5-years of follow-up in terms of assessing the risk of restenosis?

Dr de Donato. We have a mean follow-up of 3 years, but patients who have completed the 5-year follow-up are about 550. The number of patients at risk were shown under each curve on my slides.

Dr Wesley Moore (Los Angeles, Calif). I was following your presentation until you got to the point where you compared the results of carotid artery stenting with the surgical results from NASCET and ACAS. Remember that those surgical results are now 15 to 20-years-old. It is very clear from a number of presentations here and from current publications that the results of carotid endarterectomy have improved over time. Therefore, it is unreasonable to compare the results of a contemporary angioplasty series with 20-year-old carotid endarterectomy data. It would be far better if you looked at the current national discharge data study that has shown contemporary results of carotid endarterectomy. Mortality and stroke morbidity have dropped with carotid endarterectomy over time. If you were to use current carotid endarterectomy data, you would find that the current results of stent/angioplasty come in second best.

Dr de Donato. Yes, I totally agree with you. But I think that up to now the old randomized control trials have been of value as a benchmark to be compared to, while we are still waiting for long-term results from randomized controlled trials comparing carotid artery stenting and carotid endarterectomy. The aim of this presentation was to show that long-term results of CAS are comparable to CEA.

Dr John Ricotta (Stony Brook, NY). The previous paper showed excellent results in a very broad study that involved multiple centers and multiple surgeons. You have tremendous results from three centers, each of which performed at least an average of 1000 carotid stents. How are we going to deal with the issue of volume-

related results? Should we all fly to Europe when we need our carotid stent? And what's going to happen when this methodology is disseminated widely? Do you think it should be disseminated widely, or do you think it should be done only in very selected centers?

Dr de Donato. Yes, this is true. We think that the learning curve is very important. We think that the volume experience is another key factor for successful results. Actually, there were four centers. But anyway, all four centers are classified in our opinion as high-volume centers, that means at least they treat more than 100 or 150 CAS procedures every year. So we think that the volume and patient selection are important to reach the right result.

Dr Jacob Schneiderman (Ramat Gan, Israel). Beyond your impressive long-term results, aren't you concerned about the potential of premature dementia in patients undergoing CAS, taking into consideration the numerous published data regarding subclinical cerebral ischemic events, as demonstrated by diffusion weighted MRI after CAS?

Dr de Donato. I think that we don't have this data about dementia. And we have only data about disabling or non-disabling stroke. We don't have this data, I'm sorry.

Dr Christos Liapis (Athens, Greece). Was neurological examination part of the protocol for all patients or was a neurologist called after a neurological event?

Dr de Donato. No, absolutely. To be honest, our patients had an independent neurologist follow-up only in case of symptoms. During the normal follow-up, it was the physician that performed the ultrasound scan who also performed the neurological examination.

Dr Amy Reed (Cincinnati, Ohio). I just had a question on the follow-up. Do you have any information on how long clopidogrel, or Plavix, was used postprocedure in these patients?

Dr de Donato. Actually, this is a difficult point to explain, because we have different local reimbursement policies. So for example, in Italy, the patients have to pay for this drug. Our medical protocol involves double antiplatelet therapy for at least 1 month after the procedure, and then only one anti-aggregation drug with either aspirin, ticlopidine, or clopidogrel. But I think that only about 25% of our patients received Plavix for a long period of time.