Timing of stenting of symptomatic carotid stenosis is predictive of 30-day outcome

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Keywords:
angioplasty, carotid stenosis, complications, risk factors, stents, stroke

Received 3 January 2006
Accepted 28 March 2007

For patients with symptomatic carotid stenosis, benefit from carotid artery stenting (CAS) highly depends on the 30-day stroke and death rates. Identification of predictors of unfavourable outcome would help guide the patient selection. We analysed the influence of clinical and angiographic factors on the 30-day outcomes of 77 consecutive patients who underwent CAS for ≥60% symptomatic carotid stenosis within 180 days of transient ischaemic attack or moderate stroke (modified Rankin Scale score ≤3). The 30-day composite end-point for stroke (7.8%) and death of any cause (1.3%) was 9.1%. Patients with complicated CAS were older than patients with uncomplicated CAS (mean age 75.1 ± 8.2 vs. 65.9 ± 9.5 years, $P = 0.015$) and underwent stenting significantly earlier after the qualifying event: median delay 1.5 weeks (range: 0.2–3.0) vs. 3.2 weeks (range: 0.5–26), $P = 0.004$. In multivariate logistic regression analyses, age [odds ratio (OR) = 1.148; 95% confidence interval (CI): 1.011–1.304 and $P = 0.033$] and delay of treatment < 2 weeks (OR = 22.399; 95% CI: 2.245–223.445 and $P = 0.008$) remained the only variables significantly associated with 30-day outcome. CAS carries a considerable risk in old patients and when performed early (< 2 weeks) after the qualifying event. Future reports should address the timing of CAS.

Introduction

Large randomized trials have shown that in patients with symptomatic carotid artery stenosis carotid endarterectomy (CEA) plus 'best medical therapy' is superior to best medical treatment alone [1,2].

During the past decade, carotid artery stenting (CAS) has emerged as a potential alternative to surgery. In 2005, a Cochrane systematic review concluded that the evidence of randomized trials comparing endovascular treatment with surgery does not justify a shift away from recommending endarterectomy as the standard treatment for carotid stenosis [3]. In 2006, two major randomized controlled trials comparing CAS and CEA for severe symptomatic carotid stenosis confirmed these conclusions: the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial failed to prove non-inferiority of stenting compared with endarterectomy in terms of periprocedural complication rate, whilst the Endarterectomy Versus Angioplasty in patients with Severe Symptomatic carotid Stenosis (EVA-3S) trial showed significantly increased 30-day stroke and death rates in the CAS group [4,5].

Although recent trial results have been disappointing for the supporters of CAS, it is unlikely that the popularity of CAS will cease in the near future given the wide availability of stenting techniques in many centres. In fact, there is concern that CAS may be offered to patients who do not need CAS [6], but may run considerable risk of procedural complications. In this situation, knowledge on the predictors of unfavourable outcome and identification of patient subgroups which benefit most from CAS would help guide appropriate patient selection. However, data on predictors of 30-day outcome after CAS are sparse and controversial [7–9]. In contrast, a number of patient characteristics have been shown to be related to the risk-benefit ratio of surgery for symptomatic carotid stenosis. Benefit from surgery is greatest in high-degree stenosis, men, patients aged ≥75 years, and those undergoing surgery within 2 weeks after their last ipsilateral ischaemic event [10]. The absolute risk reduction from surgery is reduced by half if it is delayed beyond 2 weeks and further reduced by half if the surgery is delayed beyond 4 weeks [11].

Whilst the timing of endarterectomy after the index event is widely recognized to be of clinical importance,

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the related issue of the timing of stenting and its impact on the risk-benefit ratio have been neglected in literature. Even recently published recommendations on the reporting standards for CAS do not mention this issue at all [12]. However, the lack of systematically recorded information on the delay between qualifying event and treatment was considered to be a limitation of the SPACE trial [4]. Hence, when we aimed to identify predictors of 30-day outcome in patients who underwent CAS in our centre, the delay of the procedure in relation to the qualifying ischaemic event was considered in outcome analyses.

Subjects and methods

Patient cohort and work-up

From August 1999 to June 2006, more than 200 CAS procedures were performed at the Academic Teaching Hospital Wagner-Jauregg, Linz. We aimed to analyse the data of a homogeneous cohort with symptomatic carotid stenosis because of atherosclerotic disease. This study focuses on all 77 consecutive patients who underwent CAS for ≥60% atherosclerotic internal carotid artery (ICA) stenosis at the extracranial bifurcation within 180 days of transient ischaemic attack (TIA) or moderate stroke [modified Rankin scale (mRS) score ≤3]. Patients excluded from this analysis had CAS for asymptomatic atherosclerotic stenosis, post-radiation stenosis, stenosis because of extracranial dissection, or restenosis after surgery or CAS.

All patients underwent systematic work-up including careful history taking with special attention to traditional cardiovascular risk factors and the type and time of the presenting cerebrovascular event. Complete neurological examinations were carried out by a stroke neurologist before the procedure, immediately after and 24 h after the procedure. Pre-procedural evaluation included routine laboratory studies, ECG, chest X ray, magnetic resonance imaging (MRI) of the brain, and magnetic resonance angiography of the intracranial and extracranial brain-supplying arteries. Computed tomography was carried out if MRI was contraindicated.

For pre-procedural assessment of carotid stenosis, colour-coded duplex sonography was performed by two experienced technicians. In our Neurosonology Laboratory, ultrasound criteria for carotid stenosis have been established and validated by comparison with conventional angiography. To quantify the local degree of stenosis, the peak systolic velocity (PSV), the end-diastolic velocity (EDV) and the ICA/common carotid artery (CCA) index were determined. PSV of 150, 200 and 300 cm/s identified 60%, 70% and 80% ICA stenosis respectively. PSV >300 cm/s, EDV ≥130 cm/s and ICA/CCA index ≥4 were equivalent with ICA stenosis of ≥90%.

Patients underwent cardiologic assessment and joint evaluation by neurologists, vascular surgeons and neuroradiologists. All patients received detailed information about treatment options and were explained that apart from best medical therapy, CEA is the standard treatment and CAS is currently being considered an investigational alternative. For both revascularization methods, patients were required to have a life expectancy >2 years. The decision to treat patients by CAS was taken on the basis of the patient's preference and comorbidity factors regarded as contraindications to surgery (history of myocardial infarction within previous 6 months or frequent episodes of angina pectoris, left ventricular ejection fraction <30%, chronic obstructive pulmonary disease with severely reduced vital capacity, moderate to severe chronic kidney disease, liver cirrhosis, severe obesity and contralateral carotid occlusion/high-degree stenosis). Factors regarded as contraindications to surgery were not recorded in our local stent registry. Our study was based on a prospective protocol approved by our institutional ethics review board. All patients signed informed consent for elective CAS.

Angioplasty and stenting technique

Two experienced neuroradiologists performed all procedures. Percutaneous access was gained through the common femoral artery under local anaesthesia. After selective angiography of at least the target vessel a 7F 90 cm long sheath was advanced in the distal CCA. In case of use of a protection device, the filter system was positioned in the distal ICA below the skull. In our centre, two types of distal emboli protection devices (EPI FilterWire EX, Boston Scientific, Natick, MA, USA; Guidant Accunet, Guidant, Santa Clara, CA, USA) have been in use since October 2001. In case of dilation before stent placement, a balloon (Bijou, Boston Scientific; Submarine, Invatec, Brescia, Italy) with 3–6 mm diameter was used after the application of i.v. atropine (0.5–1 mg). A self-expanding stent was inserted after the removal of the balloon. Three types of stents were used (Acculink, Guidant, Diegem, Belgium; Easy Wallstent, and Carotid Wallstent, Boston Scientific). In most patients post-stent dilation was performed for stent apposition or residual stenosis with a balloon (Bijou or Smash; Viatrac, Guidant) with 4–6 mm diameter. After control angiography and a brief neurological examination the common femoral arteriotomy site was treated with a compression bandage or closure device (Duett-Pro,

Vascular Solutions, Minneapolis, MN, USA). After CAS, patients were monitored for at least 24 h in the stroke unit. Neurological evaluations were carried out by a stroke neurologist immediately and 24 h post-procedure. Continuous i.v. heparin was administered for 24 h after CAS with goal partial thromboplastin time of 2–2.5 times higher than baseline. Dual antiplatelet therapy with 100 mg aspirin and 75 mg clopidogrel daily was started at least 3 days before the procedure and maintained for 4–6 weeks after the procedure, followed by platelet inhibitor monotherapy after that period.

Outcome definitions

Outcomes were defined clinically and were confirmed radiologically by diffusion-weighted MRI in all patients with cerebrovascular complications after CAS.

Transient ischaemic attack
A focal neurological abnormality of sudden onset and brief duration (lasting < 24 h) that reflects dysfunction in the distribution of the affected artery. This definition includes transient hemispheric attacks and amaurosis fugax (transient monocular blindness lasting ≤10 min).

Stroke
Any sudden development of neurological deficits attributable to cerebral infarction.

Minor stroke
Increase of the National Institute of Health Stroke Scale (NIHSS) score of < 4 points without the presence of aphasia or hemianopsia.

Major stroke
Increase of the NIHSS score of ≥4 points or the presence of aphasia or hemianopsia.

Patient follow-up

Thirty-day outcomes were assessed through prospective neurological follow-up at the Vascular Outpatients Clinic. In the minority of patients who were followed up at other institutions outcomes were obtained by contacting the patient or treating physician. Patients were asked whether they had experienced any sudden episodes of weakness, blindness, numbness, or speech difficulty, or any other new abnormality. We recorded the occurrence of ipsilateral or contralateral TIA, minor stroke, major stroke, any kind of vascular intervention or surgery in relation to the index procedure, and the death of any cause.

Statistical analysis

All analyses were carried out on an intention-to-treat basis. Categorical variables are presented as counts and percentages. Continuous variables, normally distributed, are expressed as mean ± SD and skewed continuous data are presented as median (range). For univariate analyses, we used two-tailed Fisher's Exact test for categorical variables. For continuous variables, we used two-tailed independent samples' *t*-test for data with normal distribution, and Mann–Whitney *U*-test for data with skewed distribution.

To analyse the influence of pre-procedural ultrasonographic degree of carotid stenosis on outcomes, we used the European Carotid Surgery Trial definition of very severe stenosis [1] as cut-off (80–99% stenosis of local diameter). The influence of patient age on outcomes was analysed using the cut-off (≤75 years vs. > 75 years) used in the SPACE trial [4], and the influence of timing of CAS was analysed with the cut-off (< 2 weeks vs. ≥2 weeks) used by Rothwell *et al.* [10] in an analysis on the risk-benefit ratio of endarterectomy for symptomatic carotid stenosis in relation to the timing of surgery. Age and the timing of CAS were also analysed as continuous variables.

Multivariate logistic regression analysis, considering all clinical and angiographic variables tested in univariate analysis, was performed to determine independent predictors of unfavourable 30-day outcome. In a conditional stepwise forward selection procedure, variables with probability values > 0.1 were dropped from the final model. *P*-values < 0.05 were considered to be statistically significant. We used SPSS software (Version 14.0, SPSS Inc., Chicago, IL, USA) for all analyses.

Results

Baseline characteristics

Mean age was 66.7 years (range: 43–87); 16 (21%) patients were older than 75 years; 68% of all patients were men; 31% of the population were known to have coronary artery disease. The qualifying ischaemic event was retinal TIA in seven (9%) patients, hemispheric TIA in 22 (29%) patients and ischaemic stroke in 48 (62%) patients. Local degree of stenosis assessed by ultrasound was 60–69% in eight patients, 70–79% in 17 patients, 80–89% in 23 patients and ≥90% in 29 patients.

Procedural characteristics

Placement of a stent was successfully performed in 75 of 77 (97.4%) procedures. In two patients, stent placement

in the target vessel was impossible because of anatomical reasons. Stents were inserted but eventually had to be removed, and procedures were terminated without stent placement. Both patients were treated by best medical therapy. They remained in the intention-to-treat analysis, and there were no complications within 30 days. Balloon dilation before stenting was done in 15 (20%) procedures. Post-stent dilation was carried out in 72 (96%) of stented lesions. Protection devices were used in 51 (66%) procedures.

Thirty-day outcomes

During 30-day follow-up, stroke occurred in six (7.8%) patients (three minor strokes and three major strokes) and was ipsilateral to the stented vessel in four (5.2%) patients, and non-ipsilateral in two (2.6%) patients. All strokes occurred intraprocedural. One (1.3%) patient died within 30 days of treatment because of congestive heart failure. In univariate analyses, the 30-day composite end-point for stroke and death (9.1%) was significantly associated with 'advanced' patient age (Fig. 1) and 'early' treatment after the qualifying event (Fig. 2). The composite 30-day stroke and death rate was 25% (4/16) in patients aged >75 years compared with 4.9% (3/61) in patients ≤75 years, $P = 0.031$. In patients with a delay of CAS ≥2 weeks, the composite 30-day stroke and death rate was 1.9% (1/54), whilst 'early' CAS <2 weeks reached a composite 30-day stroke and death rate of 26.1% (6/23), $P = 0.002$. Thirty-day outcomes were not significantly influenced by other clinical or angiographic factors (Table 1) and were not dependent on the equipment or the operating individual.

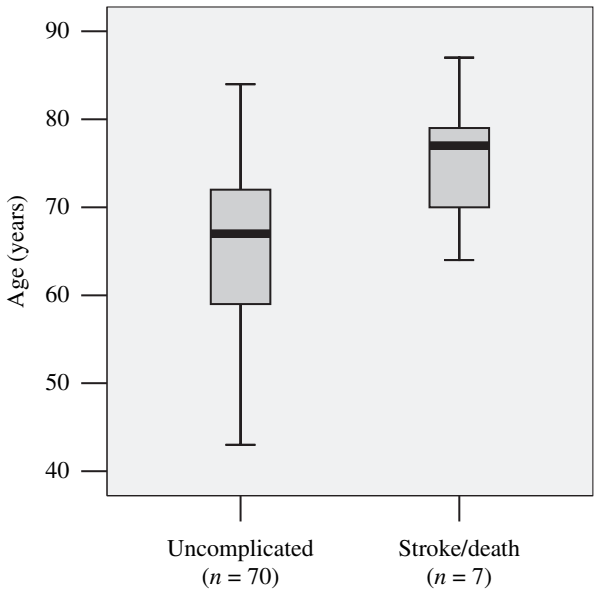

Figure 1 Association of age and 30-day outcome. Patients with peri/post-procedural complications were significantly older than patients with favourable 30-day outcome (mean age 75.1 ± 8.2 vs. 65.9 ± 9.5 years, $P = 0.015$).

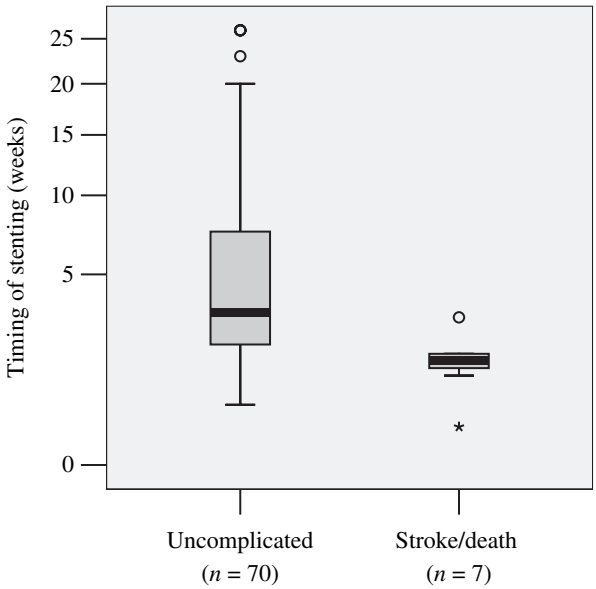

Figure 2 Timing of stenting and 30-day outcome. Patients with peri/post-procedural complications underwent treatment significantly earlier in relation to the qualifying event than patients without complications: median delay 1.5 weeks (range: 0.2–3.0) vs. 3.2 weeks (range: 0.5–26.0), $P = 0.004$.

In multivariate logistic regression analyses, age [odds ratio (OR) = 1.148; 95% confidence interval (CI): 1.011–1.304 and $P = 0.033$] and delay of treatment <2 weeks (OR = 22.399; 95% CI: 2.245–223.445 and $P = 0.008$) remained the only variables significantly associated with 30-day outcome.

Discussion

In a consecutive series of patients with CAS for symptomatic carotid stenosis, we identified patient age and the timing of the procedure in relation to the qualifying event as predictors of 30-day outcome. Several authors have already reported advanced age to be associated with unfavourable 30-day outcome of CAS [7,13–15].

To the best of our knowledge, this is the first study to demonstrate the impact of timing of CAS on 30-day outcome by comparing 'early' (<2 weeks of the qualifying event) and 'delayed' stenting for symptomatic carotid stenosis. In patients with 'delayed' CAS the 30-day stroke and death rate was 1.9%, whilst this composite end-point exploded to unacceptable 26.1%, when the procedure was carried out <2 weeks of the qualifying event.

Table 1 Univariate analysis of clinical and angiographic characteristics

	Uncomplicated CAS ($n = 70$), n (%)	Complicated CAS ($n = 7$), n (%)	P-value
Age >75 years			
Yes	12 (17)	4 (57)	0.031
No	58 (83)	3 (43)	
Male sex			
Yes	46 (66)	6 (86)	0.417
No	24 (34)	1 (14)	
Hypertension			
Yes	61 (87)	7 (100)	0.590
No	9 (13)	0	
Diabetes			
Yes	24 (34)	2 (29)	1.0
No	46 (66)	5 (71)	
Coronary artery disease			
Yes	23 (33)	1 (14)	0.424
No	47 (67)	6 (86)	
Severe contralateral lesion			
Yes	7 (10)	0	1.0
No	63 (90)	7 (100)	
Smoking (current)			
Yes	24 (34)	2 (29)	1.0
No	46 (66)	5 (71)	
Preprocedural mRS score			
mRS 0	28 (40)	1 (14)	
mRS 1	23 (33)	3 (43)	
mRS 2	13 (18)	1 (14)	
mRS 3	6 (9)	2 (29)	
mRS 0–1	19 (27)	3 (43)	0.401
mRS 2–3	51 (73)	4 (57)	
Stenosis on US ≥80%			
Yes	46 (66)	6 (86)	0.417
No	24 (34)	1 (14)	
Left artery treated			
Yes	41 (59)	6 (86)	0.237
No	29 (41)	1 (14)	
Stent material			
Stainless steel	9 (13)	0	0.590
Nitinol	61 (87)	7 (100)	
Use of protection device			
Yes	46 (66)	5 (71)	1.0
No	24 (34)	2 (29)	
Dilation before stenting			
Yes	14 (20)	1 (14)	1.0
No	56 (80)	6 (86)	
Delay of CAS <2 weeks			
Yes	17 (24)	6 (86)	0.002
No	53 (76)	1 (14)	

CAS, carotid artery stenting; mRS, modified Rankin Scale; US, ultrasound; TIA, transitory ischaemic attack.

Early removal of the unstable plaque by CEA is the currently recommended treatment of patients with symptomatic high-grade carotid stenosis who are fit enough for surgery [16]. The benefit from surgery is highly dependent on time since the ischaemic event, as the absolute risk reduction is decreased by half, if surgery is delayed beyond 2 weeks [11].

Our finding that 'early' stenting may carry considerable hazards, whilst 'delayed' CAS seems to be relatively safe, has important clinical implications. First, when comparing stenting with surgery in randomized controlled trials, the delay between the qualifying event and the revascularization method should be considered in the 30-day outcomes analyses, because imbalances in delay time may heavily affect the risk-benefit ratio of the procedures and bias the comparability of results. Secondly, in selected patients with symptomatic carotid stenosis but contraindications to surgery, such as high cervical lesions inaccessible to surgery, CAS may represent a safe revascularization method when carried out ≥2 weeks after the qualifying event.

The dependency of procedural risk on the timing of CAS may be related to the supposed 'metamorphosis' of symptomatic plaques. Patients with recently symptomatic carotid stenosis carry a high risk of repeat embolism and recurrent stroke during the first weeks if treated by medical therapy alone [17], but this risk seems to fall rapidly over the subsequent period. The decline in stroke risk over time may correspond with 'healing' mechanisms at vulnerable plaques [10] transforming unstable plaques into more stable ones. With regard to our findings we speculate that 'early' mechanical interventions on recently symptomatic, still vulnerable plaques are more probably to cause plaque dislodgement and embolism than 'delayed' interventions on rather stabilized plaques.

The risk of distal embolization during CAS has increased interest in the use of emboli protection devices [18–20]. Whether emboli protection devices can or will improve the safety of CAS remains a continuing debate, because there are potential disadvantages. For example, distal protection devices may lead to prolonged procedure time and increased embolism risk when traversing ulcerated lesions. When in 2004 the EVA-3S investigators changed their protocol to use embolic protection devices during all CAS procedures, their decision raised criticism because it was based on a non-significant difference in outcomes after inclusion of only 73 patients [21]. The SPACE trial did not show significant differences in CAS-related complications in patients treated with and without a protection device [4]. In our series, neither use of distal protection devices nor performing stenting without pre-dilation did affect the 30-day complication rates.

Our combined 30-day stroke and death rate (9.1%) seems rather high but lies in the range of results of the endovascular treatment arms of the SPACE trial (7.7%), the EVA-3S trial (9.6%), and the Carotid And Vertebral Artery Transluminal Angioplasty Study (10%), [4,5,22]. SPACE was the only trial with the inclusion of patients with a pre-procedural mRS score

up to three. Hence, one has to be careful when comparing data from randomized trials and case series because of potential differences in patient selection, definitions of outcomes and methods of follow-up.

Our study has important strengths and limitations. The recruitment, systematic work-up and follow-up of patients were carried out by neurologists. This in contrast to most large case series and registries which do not include independent verification of outcome and may therefore be prone to observer bias [3]. Our cohort was homogeneous in that aetiology of carotid stenosis was atherosclerosis. Patients with arterial dissection, post-radiation stenosis, or restenosis after CEA or CAS may have other risks of procedural complications and therefore should be analysed separately.

A major limitation of the paper is the low number of patients potentially leading to a type II error. We identified the timing of carotid stenting in relation to the qualifying event as a predictor of 30-day outcome, but the contribution of this factor to outcome remains to be further elucidated in larger cohorts, before the results of our single-centre study can be generalized. Factors not included in our analysis may also contribute to outcome. One example of such 'candidate' variables is ultrasonic plaque morphology. However, there is conflicting evidence whether plaque echolucency is associated with the risk of embolic stroke in CAS [23,24].

In conclusion, our findings suggest that carotid stenting carries a considerable risk in patients with advanced age and when performed early (<2 weeks) after the qualifying event. We recommend the timing of the stenting procedure should be addressed in future reports on 30-day outcomes of stenting for symptomatic carotid stenosis.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Substantive contribution of individuals other than the authors

None.

Funding for this work

None.

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