

## Original Paper

# Demographic and Technical Risk Factors of 30-Day Stroke, Myocardial Infarction, and/or Death in Standard- and High-Risk Patients Who Underwent Carotid Angioplasty and Stenting

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## Key Words

Stroke · Carotid artery angioplasty and stenting · Outcome · Cerebrovascular disease

## Abstract

**Background:** Carotid angioplasty and stenting (CAS) is an accepted treatment to prevent stroke in patients with carotid artery stenosis. The purpose of this study is to identify risk factors for major complications after CAS. **Materials and Methods:** This is a prospective study that was conducted at Shiraz University of Medical Sciences in southern Iran from March 2011 to June 2014. Consecutive patients undergoing CAS were enrolled. Both standard- and high-risk patients for endarterectomy were enrolled. Demographic data, athero-

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sclerotic risk factors, site of stenosis, degree of stenosis, and data regarding technical factors were recorded. Thirty-day stroke, myocardial infarction, and/or death were considered as the composite primary outcomes of the study. **Results:** A total of 251 patients were recruited (mean age: 71.1 ± 9.6 years; male: 65.3%). Of these, 178 (70.9%) were symptomatic, 73 (29.1%) were diabetic, 129 (51.4%) were hyperlipidemic, 165 (65.7%) were hypertensive, and 62 (24.7%) patients were smokers. CAS was performed for left internal carotid artery (ICA) in 113 (45.4%) patients. Fourteen (5.6%) patients had sequential bilateral stenting. Mean stenosis of operated ICA was 80.2 ± 13.8%. An embolic protection device was used in 203 (96.2%) patients. Pre- and postdilation were performed in 39 (18.5%) and 182 (86.3%) patients, respectively. Composite outcomes were observed in 3.6% of patients (3.2% stroke, 0% myocardial infarction, and 1.2% death). Left-sided lesions and the presence of diabetes mellitus were significantly associated with poor short-term outcome ( $p = 0.025$  and  $p = 0.020$ , respectively). **Conclusion:** There was a higher risk of short-term major complications in diabetic patients and for left carotid artery intervention.

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## Introduction

Stroke is a major health problem in both developed and developing countries [1]. Carotid artery stenosis is the most common site of large artery disease in Iranian patients with ischemic stroke [2]. Carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) are two treatment options for carotid stenosis [3].

Charles W. Kerber performed the first carotid angioplasty in 1980 [4]. Since then, CAS has been increasingly used due to its minimally invasive nature and shorter hospitalization and recovery times. However, a higher morbidity and mortality in comparison to CEA has been reported in earlier studies [5].

Increased experience of endovascular surgeons, invention of new devices, particularly embolic protection devices (EPDs), and better case selection have improved CAS outcomes [6].

According to the American Stroke Association/American Heart Association guideline, CAS is reasonable for symptomatic patients with >70% stenosis and a high risk for CEA (class I; level of evidence B). For patients with symptomatic carotid disease and 50–69% stenosis, CAS is considered an alternative to CEA for patients at average or low risk for CAS or for those who are at high risk for CEA (class I; level of evidence B). High-risk patients show the following characteristics: congestive heart failure, heart surgery within 6 weeks, myocardial infarction within 4 weeks, unstable angina, severe pulmonary diseases, age >75 years, contralateral occlusion, contralateral laryngeal palsy, postradiation carotid stenosis, tandem lesion, high bifurcation, or post-CEA stenosis [7].

As there is scarce data about the short-term outcome of CAS in Middle Eastern countries, we investigated the frequency and predictors of 30-day morbidity and mortality in Iranian patients.

## Materials and Methods

This is an analysis of prospective data collected in a registry performed at Kowsar and Alzahra hospitals affiliated with Shiraz University of Medical Sciences in Iran from March 2011 to June 2014. These are high-volume referral centers for stroke patients in southern Iran. Patients were initially visited by general neurologists and noninterventionist stroke neurologists and then referred to the principal investigator (A.B.H.) for recruitment.

Consecutive patients with ischemic stroke documented by a brain CT or an MRI were enrolled. Workup included noninvasive vascular and cardiac testing in addition to laboratory studies. Patients with intracranial hemorrhage, cerebral infarcts due to cardioaortic embolic causes, lacunar stroke, vasculitis, arterial dissection, and fibromuscular dysplasia were excluded. Patients with a Modified Rankin Scale score  $\geq 4$  after stroke were excluded from undergoing CAS. Patients who had relative contraindications of angiography were also excluded.

Patients with ischemic stroke/transient ischemic attack and  $>70\%$  stenosis of the ipsilateral internal carotid artery (ICA) by noninvasive imaging underwent digital subtraction angiography as part of a preoperative evaluation for CAS. The severity of stenosis was calculated according to the North American Symptomatic Carotid Endarterectomy (NASCET) criteria [8]. Symptomatic patients with  $>50\%$  stenosis as documented by catheter angiography and asymptomatic patients with  $>70\%$  stenosis were included. Patients at high and standard risk for CEA were included.

As confirmed low morbidity/mortality CEA was not available in our center, all included patients were referred for CAS. The study protocol was approved by the Institutional Review Board of Shiraz University of Medical Sciences (89-01-01-2614). Informed consent was obtained from each patient.

Data on major cerebrovascular risk factors were collected for all subjects: current or previous cigarette smoking, hyperlipidemia (positive history, fasting total cholesterol level  $>200$  mg/dl, low-density lipoprotein  $>130$  mg/dl, and/or fasting triglyceride level  $>180$  mg/dl), arterial hypertension (positive history, systolic blood pressure  $>140$  mm Hg, and/or diastolic pressure  $>90$  mm Hg, not in the acute phase, treated or not), and diabetes mellitus (positive history and /or fasting plasma glucose  $>126$  mg/dl, not in the acute phase).

Most of the patients received dual therapy (aspirin and clopidogrel) at least 2 weeks before the procedure. However, a minority of patients received 600 mg loading-dose clopidogrel. The time for loading was 3–4 h before the procedure. After the procedure, all patients were treated with 75 mg of clopidogrel daily for 12 months and 80 mg of aspirin for life. During the procedure, patients received heparin 80 U/kg after successful femoral artery puncture to maintain an activated clotting time of  $>250$  s.

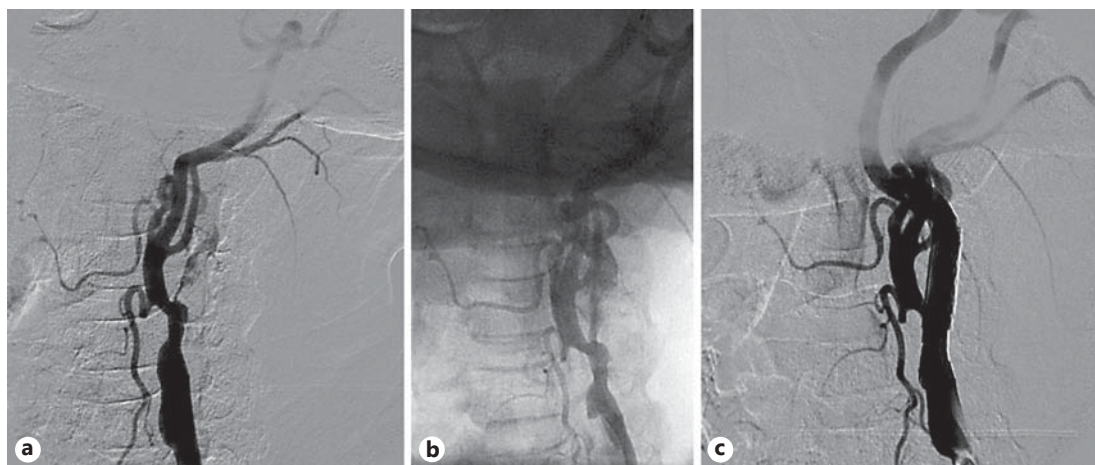
Distal EPDs were navigated across the lesion and opened before predilation if possible. If not, usually in the setting of a stenotic segment  $<1$  mm, predilation was performed before EPD insertion. Predilation balloon diameters were 2.5–3 mm. If the diameter of the stenotic segment was  $>3$  mm, we deployed the EPD without predilation.

EPD was not used in poor vascular anatomy especially distal to the lesion. A self-expanding stent was then placed across the stenotic lesion. Stent diameters were 6 and 7 mm. In this study, we used an open cell stent, the Protégé<sup>®</sup> RX Carotid Stent (ev3 Endovascular, Inc., Plymouth, Mass., USA), a closed cell stent, the Wallstent (Boston Scientific, Natick, Mass., USA), and a hybrid open and closed design stent, the Cristallo Ideale (Invatec Technology, Frauenfeld, Switzerland).

After stenting, a residual stenosis was measured by angiography. The treatment was considered successful when the residual stenosis was  $<50\%$  with predilation and stenting. If the residual stenosis was  $>50\%$ , a balloon catheter was advanced for postdilation. Postdilation balloon diameters were 5–6 mm. We tried not to perform multiple balloon dilatations, neither for pre- nor for postdilations. Technical success after CAS was defined as residual stenosis  $<20\%$ . Before pre- or postdilation, atropine 1 mg was intravenously administered to all patients regardless of their baseline heart rate. Hemodynamic depression was defined as systolic blood pressure  $<90$  mm Hg and/or heart rate  $<50$  beats/min.

All patients were seen and examined by a single neurologist on a regular basis (immediately after the procedure and on days 1, 7, and 30) if the patients had no complications. If there was any major complication, patients were admitted to the intensive care unit and were visited more frequently. The primary outcome was the composite outcome of stroke, myocardial infarction and/or death. Secondary outcomes were individual components of the primary end point including ischemic stroke, hemorrhagic stroke, myocardial infarction, and death. The mid- and long-term follow-ups of the patients are continuing, and the results are beyond the scope of this paper.

Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, Ill., USA). Continuous data are presented as means  $\pm$  standard deviations, and categorical data are presented as counts (percentages). Fisher's exact test or Student's t test were used when appropriate. Logistic regression analysis models were used to assess the independent role of each variable on the occurrence of 30-day adverse events. A p value  $<0.05$  was considered statistically significant.



**Fig. 1.** A case of ICA angioplasty. **a** Angiography showing severe stenosis. **b** Angiography after predilation. **c** Angiography after stenting and postdilation.

## Results

A total of 251 patients were recruited in this study. Of these, 164 (65.3%) patients were male and 87 (34.7%) were female. For all patients, the mean age was  $71.1 \pm 9.6$  years (range: 43–93). The technical success rate was 99%. CAS was performed under conscious sedation in all patients. Overall, 73 (29.1%) patients were diabetic, 129 (51.4%) were hyperlipidemic, 165 (65.7%) were hypertensive, and 62 (24.7%) were smokers. In total, 193 (76.9%) patients were <80 years old, and 58 (23.1%) were  $\geq 80$  years old. One hundred and seventy-eight (70.9%) patients were symptomatic. CAS was performed for left ICA in 113 (45.4%) patients, and 14 (5.6%) patients had sequential bilateral stenting. Mean stenosis of the operated ICA was  $80.2 \pm 13.8\%$  and that of the contralateral side was  $41.2 \pm 33.6\%$ . Mean residual stenosis after CAS was 11.8% for the total population (fig. 1).

For 211 patients, procedural details were recorded: the length of stent used was 30 mm in 18 (8.5%) patients and 40 mm in 193 (91.5%). An EPD was used in 203 patients (96.2%). Pre- and postdilation were performed in 39 (18.5%) and 182 (86.3%) patients, respectively. Out of 211 patients, intraprocedural hemodynamic instability was observed in 3 (1.4%) patients and resolved immediately. Transient postprocedural hypotension was detected in 44 of 211 patients (20.9%).

The primary outcome was observed in 3.6% ( $n = 9$ ). Secondary outcomes were ischemic stroke in 3.2% ( $n = 8$ ), cerebral hemorrhage or hemorrhagic transformation in 0%, myocardial infarction in 0%, and death in 1.2% ( $n = 3$ ). Two out of 3 deaths were due to ischemic stroke and brain herniation, and 1 death was unexplainable since the patient did not refer to our center. Of 8 patients with ischemic stroke, 6 did not pass away.

Table 1 shows the effects of risk factors in patients who developed 30-day complications (myocardial infarction, stroke, and death) in comparison to the patients who did not.

In logistic regression analysis, only left-sided intervention was correlated with the incidence of 30-day end point events (odds ratio = 8.765, 95% confidence interval: 1.011–75.946;  $p = 0.049$ ).

**Table 1.** The correlation of variables with 30-day morbidity/mortality after CAS

Risk factors	Patients who developed 30-day morbidity/mortality after CAS (n = 9)	Patients who did not develop 30-day morbidity/mortality after CAS (n = 242)	p value
Age >80 years	2/9 (22.2)	56/242 (23.1)	0.99
Male	5/9 (55.6)	159/242 (65.7)	0.502
Diabetes mellitus	6/9 (66.7)	67/242 (27.7)	<b>0.020</b>
Hyperlipidemia	6/9 (66.7)	123/242 (50.8)	0.501
Hypertension	6/9 (66.7)	159/242 (65.7)	0.99
Smoking	2/9 (22.2)	60/242 (24.8)	0.99
Side of stenting			
Left ICA	7/8 (87.5)	106/242 (44)	<b>0.025</b>
Right ICA	1/8 (12.5)	135/242 (56)	
With predilation	1/8 (12.5)	38/203 (18.7)	0.99
With postdilation	8/8 (100)	174/203 (85.7)	0.603
Stent type			
Protégé	1/8 (12.5)	7/198 (4)	}*
Cristallo	2/8 (25)	77/198 (38)	
Wallstent	5/8 (62.5)	114/198 (58)	
Stent length			
30 mm	1/8 (12.5)	17/203 (8.4)	0.516
40 mm	7/8 (87.5)	186/203 (91.6)	
EPD applied	8/8 (100)	195/203 (96.1)	0.99
Previous stenting	2/9 (22.2)	12/240 (5)	0.067
Symptomatic	5/9 (55.6)	173/242 (71.8)	0.285
With intraprocedural hemodynamic instability	0/9 (0)	3/200 (1.5)	0.99
With postprocedural hypotension	0/9 (0)	44/203 (21.7)	0.209

Values in parentheses are percentages. Some data are missing; percentages refer to the available data. Significant p values are bolded. \* In the 2 by 3 table, 3 cells (50.0%) had an expected count of <5, and the  $\chi^2$  test was not valid. p values for the 2 by 2 table, calculated by Fisher's exact test, were: Cristallo versus Wallstent: p = 0.705; Cristallo versus Protégé: p = 0.254; Wallstent versus Protégé: p = 0.329.

## Discussion

Our study showed that in our center and in our population, CAS is safe and has a risk profile similar to that published in the literature. We found that left-sided lesions and the presence of diabetes mellitus increased the risk of complications. Technical aspects of the procedure did not have an impact on the risk of complications. In a pooled analysis of data from three major CAS trials, the rate of composite poor outcome (stroke and/or death within 30 days after CAS) was 7.7% [9].

Our results compare favorably with the published frequency of composite poor outcome among symptomatic patients and are similar to the results of trials that included both symptomatic and asymptomatic patients. In a pooled analysis of 2,104 patients, the rate of 30-day stroke and/or death in asymptomatic and symptomatic patients was 3.8 and 5.3%, respectively [10]. The absence of this difference in our study can be explained by the paucity of asymptomatic patients.

The current study showed that CAS for left ICA was associated with significantly more complications. This result is compatible with a systematic review of 56 studies and 34,398 patients [11]. It can be explained by the more difficult access of the left common carotid artery which prolongs the procedure and increases the risk of embolization.



In agreement with the studies by Schlüter et al. [12] and Wang et al. [13], we observed a higher short-term complication rate in diabetic patients. Potential explanations for this finding include platelet dysfunction and a higher coagulable state in diabetic patients; increased production of hyperreactive thrombocytes has been shown in diabetics [14]; increase in tissue factor procoagulant activity [15]; increased plasminogen activator inhibitor (PAI)-1 [16], or enhanced complement-fibrinogen binding activity leading to a prothrombotic clot with thinner fibers [17, 18]. All these vascular and inflammatory processes induce platelet aggregation and prothrombotic state in diabetics and increase periprocedural atherothrombotic events in CAS.

In spite of the facts that we did not consider any upper cutoff for age and that 23% of our patients were >80 years old, age was not predictive of complications in our study. In some studies, age per se was also not associated with increased complications [19]; however, in most studies, periprocedural events were higher in patients >80 years old [20–22].

Similar to our results, in the CAPTURE [21] and SPACE [23] studies, there were no significant differences in 30-day stroke and/or death rates between males and females who underwent CAS. In the CREST study [24], however, the rate was higher in women.

Because we used distal EPD in almost all of our patients, there was no significant difference in morbidity/mortality between patients who underwent CAS with EPD and those who underwent CAS without EPD. There are pros [25–28] and cons [29, 30] of using EPD in CAS. Proponents advocate EPD use because of its ability to eliminate emboli detected by transcranial Doppler sonography [31]. Detractors believe that advancing and retrieving the EPD adds extra time and risk to CAS [22]. In some studies, using EPDs was associated with a higher number of new diffusion-weighted MRI lesions after CAS [32, 33].

In the current study, performing predilation alone, postdilation alone or both pre- and postdilation was not associated with any significant difference in the rate of stroke and/or death. Other technical details such as stent type and length were also not associated with risk of complications. There are some debates about the role of pre- and postdilation in addition to the type of stent (open vs. close cell) in strokes induced by CAS [21]. In the CAPTURE study [21] and the Pro-CAS registry [34], predilation showed a consistent relationship with stroke/death. A Chinese single-center study reached opposite results [35].

In a systematic review by Khan and Qureshi [36], stent design was not associated with a higher stroke rate, but there have been some studies showing an advantage of closed cell stents in this regard [37–39].

The paucity of myocardial infarction in the current study can be explained by the detection by chest pain and electrocardiographic changes only. Troponin and creatinine phosphokinase (MB) were not regularly requested after CAS. The rate of myocardial infarction in the current study was lower than that in other studies [6, 40]; however, very low rates of myocardial infarction have been reported before [41, 42].

In the current study, hemodynamic depression after CAS was not associated with increased composite poor outcome. Postprocedural hypotension and/or bradycardia were associated with greater myocardial infarction and mortality in previous studies [43], but these results were not reproduced in other studies [44, 45].

The major shortcoming of the current study is the sample size. Although our population was comparable to that of previous single-center studies, the low rate of death and disability limits binary logistic regression and increases the chance of type II error. Also as drawbacks, the association between factors such as the aortic type arch, the angulation between common carotid artery/ICA, the length of the lesion, and the complication rate which has been investigated in previous trials were not studied in current series.

In conclusion, we studied the frequency of major complications of CAS in a high-volume single center in a developing country recruiting both high- and standard-risk patients. Left-

sided CAS and diabetes mellitus were the only predictors of death and stroke. Technical factors such as instrumentation dedicated to left-sided CAS and special therapeutic interventions for diabetic patients could be considered in future studies. Further multicenter studies for are highly recommended for determining the predictors of death and disability in standard-risk patients for CAS.

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### Disclosure Statement

The authors have no conflicts of interest to declare.

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