

# Long-term survival of carotid stenting patients with regard to single- or double-vessel carotid artery disease: a propensity score matching analysis

Josef Veselka, Petr Hajek, Cyril Štěchovský, Martin Horváth, Radka Adlová, Robert Roland, Ingrid Homolová, Eva Hansvenclová, Petra Zimolová

Department of Cardiology, 2<sup>nd</sup> Medical School, Charles University, University Hospital Motol, Prague, Czech Republic

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## Corresponding author:

Josef Veselka  
Department  
of Cardiology  
2<sup>nd</sup> Medical School  
Charles University  
University Hospital Motol  
Prague, Czech Republic  
Phone: +42 224434900  
E-mail: [veselka.josef@seznam.cz](mailto:veselka.josef@seznam.cz)

## Abstract

**Introduction:** There is lack of long-term data outside of controlled clinical trials in carotid artery stenting (CAS). In this study, we compared the short-term outcome, long-term survival, and rate of re-interventions for restenosis in patients after CAS, related to the extent of carotid atherosclerosis classified as single-vessel (unilateral) or double-vessel (bilateral) carotid artery disease.

**Material and methods:** We retrospectively evaluated 599 patients with significant carotid artery stenosis, who underwent 763 CAS procedures, and used the propensity score to match 226 pairs (452 patients) in the single- or double-vessel carotid disease.

**Results:** There was no significant difference in the occurrence of in-hospital major adverse events (3.5% vs. 3.1% of patients in the double-vessel carotid group vs. the single-vessel carotid group;  $p = 1$ ). The mean follow-up was  $6.1 \pm 4.0$  years, and a total of 181 (40%) deaths occurred during 2759 patient-years, which translates into 7.8 and 5.3 deaths per 100 patient-years in the double-vessel carotid group and the single-vessel carotid group, respectively ( $p < 0.01$ ). The survival in the double-vessel carotid group vs. the single-vessel carotid group at 10 years was 46% (95% CI: 38–54%) vs. 55% (95% CI: 47–63%) ( $p < 0.01$ ). Twenty-four (11%) patients and 6 (3%) patients underwent re-interventions for restenosis in the double-vessel and the single-vessel carotid disease group, respectively ( $p < 0.01$ ).

**Conclusions:** Patients with CAS and significant double-vessel carotid artery disease had similar peri-procedural risk, but had a worse long-term survival, and a higher rate of re-interventions for restenosis compared to the single-vessel carotid artery disease patients.

**Key words:** carotid artery disease, stenting, survival.

## Introduction

Forty-five years ago, Doctors Burggraf and Parker described the clinical course of patients with coronary artery disease related to their angiographically-determined severity [1]. They showed that patients with single-, double-, or triple-vessel disease have entirely different long-term survival rates. Subsequently, this classification of coronary artery disease has become a part of basic knowledge in cardiology textbooks.

Based on one-year data published in the past [2], we hypothesised that patients with double-vessel carotid artery disease (carotid artery disease with symptomatic internal/common carotid artery stenosis  $\geq 50\%$  or asymptomatic stenosis  $\geq 70\%$ , and contralateral stenosis of the internal or common carotid artery  $\geq 50\%$ ) have worse long-term survival than patients with single-vessel carotid disease (unilateral carotid artery disease  $\geq 50\%$  for symptomatic or  $\geq 70\%$  for asymptomatic patients).

In this study, we report the short-term outcome, long-term survival, and rate of re-interventions for restenosis in patients after carotid artery stenting (CAS) related to the extent of carotid atherosclerosis classified as single-vessel (unilateral) or double-vessel (bilateral) carotid artery disease.

## Material and methods

We retrospectively evaluated data that had been collected prospectively from a single-centre institutional registry of 599 patients with significant carotid artery stenosis, who underwent 763 CAS procedures between 2005 and 2019 and were enrolled in this study. Some of the patients were included in previous reports [2–5].

### Patient assessment, procedure, and follow-up

The severity of the stenosis was assessed by Duplex ultrasound performed within two days prior to the procedure and, if necessary, confirmed by CT angiography. Patients were considered for endovascular revascularisation in the presence of  $\geq 70\%$  asymptomatic or  $\geq 50\%$  symptomatic stenosis of the internal and/or common carotid artery [6].

All patients provided their written informed consent before the CAS procedure.

All CAS procedures were performed by experienced interventional cardiologists after a detailed multidisciplinary evaluation as well as a discussion with the patient and/or his/her family and according to the current guidelines [7–9]. The procedural technique details were published previously [2, 3].

The selection of stents and embolic protection systems was performed at the operator's discretion. The majority of procedures were performed via the femoral approach using 7 or 8 Fr guiding catheter or 6 Fr guiding sheath. After CAS, all patients were repeatedly examined by nursing staff and physicians (including neurological examination), and all symptomatic patients were examined by board-certified neurologists. Post-procedural intracranial evaluation with magnetic resonance imaging or computed tomography was performed if the neurological status of the patient had changed. Asymptomatic patients after uncomplicated procedures were discharged the next day.

Angiology specialists performed the clinical and ultrasound follow-up at one month and 12 months after CAS, and annually thereafter. All patients were treated with two antiplatelet agents for 1 or more months, and aspirin indefinitely. Statins were prescribed to all patients. The indication for repeated interventions was at the discretion of each participating angiologist and interventionalist.

The survival of patients was checked in the National Database of Deaths.

### Definitions, study design, and endpoints

Early major adverse events consisted of minor stroke, major stroke, myocardial infarction, and death. Stroke was defined as a neurological deficit that persisted for more than 24 h; minor stroke was defined as a new neurological deficit that resolved completely or returned to baseline within 30 days; and major stroke was defined as a neurological deficit that did not resolve within 30 days. Myocardial infarction was defined as the appearance of new pathologic Q waves on a standard electrocardiogram in two or more leads and significant release of troponin above the upper limit of normal.

We divided the patients in two matched groups – with single-vessel carotid disease or double-vessel carotid disease – for whom we assessed the long-term survival as the primary endpoint and the in-hospital rate of adverse cardiovascular events and re-interventions for restenosis as the secondary endpoints.

This study was conducted in accordance with the Declaration of Helsinki principles and was approved by the Institutional Ethical Committee.

### Statistical analysis

Two experienced statisticians edited and evaluated the data, which are presented as means  $\pm$  SD or median and interquartile range (IQR) or counts and proportions. Student's *t*-test or Mann-Whitney test were used to evaluate the difference between continuous variables, and the Fisher's exact test was used between categorical variables. The data distribution was evaluated by the Kolmogorov-Smirnov test. Kaplan-Meier survival analysis was used to estimate survival with 95% confidence intervals.

Given the inherent differences between patients with single-vessel carotid disease and double-vessel carotid disease, we calculated a propensity score for the following variables:

– sex, age, smoking, renal failure, diabetes, hypertension, cerebral ischaemic symptoms in the last 6 months, previous coronary revascularisation (percutaneous or surgical), and previous myocardial infarction. The propensity score was estimat-

ed using a logit model. Matching was performed using the 1 : 1 nearest neighbour method without replacement, which yielded 226 subjects with single-vessel carotid disease matched with 226 subjects with double-vessel carotid disease.  $P < 0.05$  was considered statistically significant. All reported  $p$  values were two-sided. The software GraphPad (release 6.05, GraphPad Software Inc., La Jolla, California, USA) was used for statistical analysis.

## Results

A total of 599 consecutive patients who underwent 763 CAS were enrolled. We identified 244 (41%) patients with double-vessel carotid disease

and compared them with 355 (59%) patients with single-vessel carotid disease (Tables I–III).

The matched cohort comprised 452 (75%) patients (226 in the single-carotid disease group and 226 patients in the double-vessel carotid disease group) (Tables I–III).

Patients in the matched double-vessel carotid disease group needed more contrast medium during the procedure, were treated with shorter stents, and had longer procedural fluoroscopic times ( $p < 0.05$  for all) (Table III).

The comparison of in-hospital major adverse events is summarised in Table IV.

None of the patients were lost to follow-up. In the matched population, the mean follow-up was

**Table I.** Baseline patient characteristics

Parameter	Unmatched cohort			Matched cohort		
	Double-vessel disease ( <i>n</i> = 244 patients)	Single-vessel disease ( <i>n</i> = 375 patients)	<i>P</i> -value	Double-vessel disease ( <i>n</i> = 226 patients)	Single-vessel disease ( <i>n</i> = 226 patients)	<i>P</i> -value
Age, mean ± SD [years]	69.6 ± 7.6	68.2 ± 8.9	0.076	69.1 ± 7.6	69.1 ± 8.4	0.779
Range	46–89	24–91		46–89	47–91	
Men	68%	62%	0.122	67%	67%	1.000
Angina pectoris	16%	17%	0.913	17%	14%	0.516
Dyspnoea, NYHA class > 1	33%	35%	0.665	33%	34%	1.000
Previous myocardial infarction	31%	25%	0.140	28%	27%	0.833
Current smokers	40%	39%	0.737	40%	38%	0.630
Hypertension	94%	89%	0.034	93%	90%	0.235
LDL-cholesterol [mmol/l; mg/dl]	2.5 ± 0.9; 96.8 ± 34.8	2.4 ± 0.8; 92.9 ± 30.9	0.165	2.5 ± 0.9; 96.8 ± 34.8	2.4 ± 0.8; 92.9 ± 30.9	0.110
HDL-cholesterol [mmol/l; mg/dl]	1.1 ± 0.3; 42.6 ± 11.6	1.1 ± 0.3; 42.6 ± 11.6	0.957	1.1 ± 0.3; 42.6 ± 11.6	1.1 ± 0.3; 42.6 ± 11.6	0.792
Plasma triglyceride [mmol/l; mg/dl]	1.8 ± 1.0; 157.5 ± 87.5	1.8 ± 1.1; 157.5 ± 96.3	0.720	1.8 ± 1.1; 157.5 ± 96.3	1.8 ± 1.0; 157.5 ± 87.5	0.680
Diabetes mellitus	41%	42%	0.802	40%	40%	1.000
Renal failure	24%	22%	0.559	23%	24%	0.824
Severe bronchopulmonary disease	14%	12%	0.538	14%	12%	0.678
Peripheral arterial disease	40%	35%	0.173	39%	32%	0.141
Ejection fraction < 40%	12%	9%	0.345	12%	12%	1.000
History of coronary artery bypass grafting	16%	19%	0.332	15%	17%	0.521
Need of open-heart surgery within 30 days	11%	9%	0.405	11%	9%	0.641
Previous coronary artery intervention	30%	32%	0.535	31%	28%	0.605
Known multivessel coronary artery disease	38%	42%	0.315	37%	40%	0.562
Previous stroke	37%	32%	0.222	36%	33%	0.552

**Table II.** Medication prior to stenting

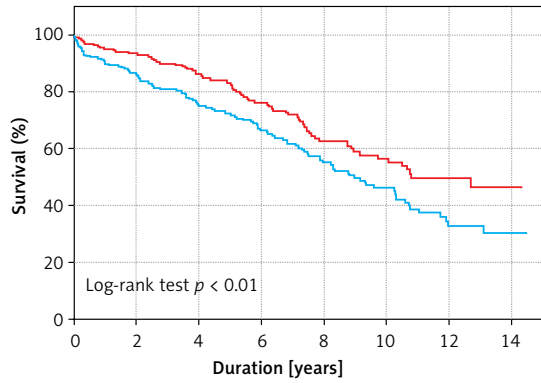
Medication	Unmatched cohort			Matched cohort		
	Double-vessel disease (n = 244 patients)	Single-vessel disease (n = 355 patients)	P-value	Double-vessel disease (n = 226 patients)	Single-vessel disease (n = 226 patients)	P-value
Aspirin	85%	83%	0.579	85%	82%	0.525
Clopidogrel	39%	42%	0.454	40%	42%	0.848
Statin	76%	80%	0.370	76%	81%	0.252
ACE inhibitor	73%	74%	0.926	74%	78%	0.379
Beta-blocker	60%	62%	0.673	60%	57%	0.633

**Table III.** Interventional and angiographic characteristics

Parameter	Unmatched cohort			Matched cohort		
	Double-vessel disease (n = 244 patients 367 procedures)	Single-vessel disease (n = 355 patients 396 procedures)	P-value	Double-vessel disease (n = 226 patients; 343 procedures)	Single-vessel disease (n = 226 patients; 236 procedures)	P-value
Lesion located in LICA/ RICA	53%/47%	53%/47%	1.000	53%/47%	51%/49%	0.555
Stenosis 90–99%	40%	43%	0.339	39%	43%	0.390
Ostial ICA lesion	71%	67%	0.310	71%	64%	0.084
Stenosis at baseline	82.4 ±9.5	83.2 ±10.3	0.188	82.4 ±9.4	83.0 ±10.5	0.308
Residual stenosis	11.3 ±12.1	9.8 ±11.7	0.034	11.4 ±12.0	10.2 ±10.6	0.272
Contrast medium [ml]	122 ±42	115 ±43	0.012	121 ±43	114 ±44	0.021
Mean stent length [mm]	35 ±14	37 ±12	0.033	35 ±14	37 ±11	0.045
Atropine during procedure	49%	51%	0.612	48%	48%	0.866
Number of post-dilations	1.1 ±0.7	1.1 ±0.6	0.768	1.1 ±0.7	1.0 ±0.5	0.862
Fluoroscopic time, median (IQR) [min]	7.0 (5.3; 9.9)	6.1 (5.0; 9.0)	0.015	7.0 (5.3; 9.9)	6.2 (4.5; 9.2)	0.046

**Table IV.** In-hospital major adverse events

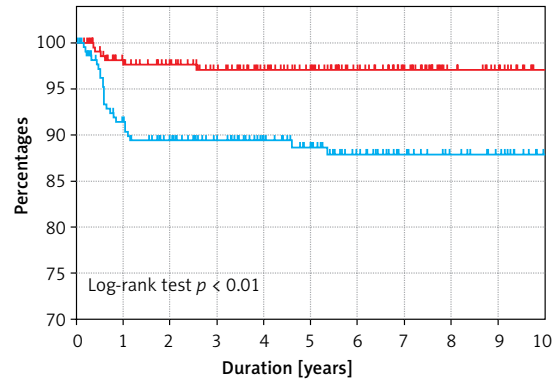
Parameter	Unmatched cohort			Matched cohort		
	Double-vessel disease (n = 244 patients)	Single-vessel disease (n = 355 patients)	P-value	Double-vessel disease (n = 226 patients)	Single-vessel disease (n = 226 patients)	P-value
Minor stroke, n (%)	6 (2.5)	6 (1.6)	0.554	6 (2.7)	4 (1.8)	0.751
Major stroke, n (%)	1 (0.4)	6 (1.6)	0.254	1 (0.4)	3 (1.3)	0.623
Myocardial infarction, n (%)	1 (0.4)	0	0.394	1 (0.4)	1 (0.4)	1.000
Death, n (%)	2 (0.8)	2 (0.5)	1.000	1 (0.4)	0	1.000
Patients with one or more major adverse events, n (%)	9 (3.7)	12 (3.2)	0.821	8 (3.5)	7 (3.1)	1.000



No. at risk:

226	194	153	112	70	47	21	6
226	186	148	107	74	48	22	6
— Single-carotid disease				— Double-carotid disease			

**Figure 1.** Kaplan-Meier survival curves describing freedom of all-cause mortality in single- versus double-vessel carotid disease in patients after an index carotid artery stenting



No. at risk:

226	201	186	172	148	128	110	91	68	58	47
226	185	169	152	132	115	94	76	63	57	43
— Single-carotid disease					— Double-carotid disease					

**Figure 2.** Kaplan-Meier survival curves describing freedom of re-intervention for restenosis in single- versus double-vessel carotid disease in patients after an index carotid artery stenting

6.1 ±4.0 years, and a total of 181 (40%) deaths occurred during 2759 patient-years, which translates into 7.8 and 5.3 deaths per 100 patient-years in the double-vessel carotid group and the single-vessel carotid group, respectively ( $p < 0.01$ ). Survival in the double-vessel carotid group vs. the single-vessel-carotid group at 5 and 10 years was 72% (95% confidence interval (CI): 66–78%) vs. 83% (95% CI: 77–87%), and 46% (95% CI: 38–54%) vs. 55% (95% CI: 47–63%), respectively (log rank  $p < 0.01$ ). The Kaplan-Meier curves of all-cause death are shown in Figure 1.

Twenty-four (11%) patients and 6 (3%) patients underwent re-interventions for restenosis in the double-vessel and the single-vessel carotid disease groups, respectively ( $p < 0.01$ ) (Figure 2).

## Discussion

To our knowledge, this study is the first evaluating the long-term survival of carotid artery stenting patients with regard to significant unilateral or bilateral carotid stenosis assessed by angiography. This study, using propensity score matching analysis, was designed to test our hypothesis that patients with significant atherosclerosis that affects both carotid arteries have worse long-term survival. Here, we report the following essential findings: (1) the long-term survival of patients with double-vessel carotid disease treated with carotid artery stenting was significantly worse than that of patients with single-vessel carotid disease; (2) patients in both matched groups had a high annual mortality rate; (3) the occurrence of in-hospital major adverse events was similar in both groups of the matched patients; and (4) patients in the double-vessel

carotid group underwent more frequent re-interventions for restenosis.

The concept that more severe atherosclerosis is associated with a worse prognosis, has been known for decades. It found its first application in coronary arteries, with the subsequent emergence of a classification showing different prognoses in the natural course of coronary artery disease in patients with single versus multi-vessel disease [1, 10]. The same concept was applied later, only in a more sophisticated way, helping in the creation of a SYNTAX Score. The SYNTAX Score is a tool that evaluates the complexity of coronary artery disease, in which patients with a higher score have a worse course of coronary artery disease and worse long-term prognosis [11]. With continuous development of non-invasive cardiovascular examinations, the same concept was introduced into clinical algorithms using CT angiography and/or duplex ultrasound. Several studies have confirmed the basic paradigm that more severe atherosclerosis in more arterial territories is associated with a worse cardiovascular prognosis [12, 13].

In line with the same concept, we demonstrate that patients suffering from extensive carotid disease are at high risk of death and should be further clinically stratified. In such patients, the main focus should be placed on aggressive conservative treatment including the use of statins and antithrombotic medication, as well as use of antihypertensive and antidiabetic medication if necessary. Additionally, life-style modifications with smoking cessation and maintaining regular physical activity are of crucial importance. Notably, the majority of patients in the presented cohort had a high cardiovascular risk, which resulted in an estimated 10-year all-cause mortality rate of approximately 50%.

Interestingly, the all-cause mortality rate in this study was much higher than was demonstrated in the long-term follow-up of two recent and important randomised studies comparing CAS and endarterectomy (CREST study: CAS patients,  $n = 1262$ ; 10-year risk of death or stroke  $\approx 11\%$ ; ACT 1 study: CAS patients,  $n = 1809$ , 5-year mortality rate  $\approx 13\%$ ) [14, 15]. On the other hand, the patients' characteristics in "real-world" registries show greater risk, which translates into higher long-term mortality rates (Columbo *et al.*: CAS patients,  $n = 4415$ , 5-year mortality rate  $\approx 18\%$ ; Mudra *et al.*, CAS patients,  $n = 878$ , median follow-up 5.5 years, mortality rate = 33%) [16, 17]. These differences suggest that controlled clinical trials may under-represent groups of high-risk patients in whom the investigated technique is used in daily clinical practice, and therefore we should carefully stratify our patients to more objectively assess their long-term prognosis.

A series of patients with carotid artery restenosis, examined by intravascular ultrasound and near-infrared spectroscopy, showed that early restenosis is mainly caused by neointimal hyperplasia and/or an insufficient stent expansion [18]. On the other hand, late restenosis occurring years after the index procedure is often caused by neoatherosclerosis, which histologically resembles the primary atherosclerotic plaque [18, 19]. In this study, reinterventions for restenosis were mostly performed in the first year. Thus, we can speculate that neointimal hyperplasia or insufficient final results of the primary CAS might be a probable factor leading to the higher occurrence of early restenosis. Similarly, Tekieli *et al.* identified bilateral carotid disease as an independent risk factor of restenosis [20], and Wasser *et al.* showed contralateral carotid artery occlusion as a strong independent predictor of in-stent restenosis (hazard ratio  $\approx 10$ ) [21].

This study has several limitations. First, because the data were collected in a single centre, the results cannot be generalised in a simple manner. Second, propensity matching estimates an average effect from observational data, which is associated with many inherent limitations. However, in the context of studies performed in other vascular territories it seems to be highly probable that significant double-vessel carotid disease is an important marker of unfavourable prognosis. Third, we did not analyse causes of death in the studied cohort of patients.

In conclusion, patients with CAS and significant double-vessel carotid disease had similar periprocedural risk but had a worse long-term survival and a higher rate of re-interventions for restenosis compared to the single-vessel carotid artery disease patients.

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## Conflict of interest

The authors declare no conflict of interest.

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