Long-term Pedictors of Composite of Major Adverse Cardiovascular and Cerebrovascular Events in Carotid Artery Stenosis Patients After Stenting

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ABSTRACT

Introduction: We hypothesized that long-term morbidity and mortality can be identified by the presence of comorbidities in patients with carotid artery stenosis. In our study we aimed to investigate the relationship between clinical characteristics, laboratory findings and long-term prognosis in carotid artery stenosis patients after stenting.

Patients and Methods: We retrospectively enrolled 212 patients whom underwent carotid artery stenting (CAS) between January 2010 and December 2012 at Kartal Kosuyolu Training and Research Hospital. CAS was performed in symptomatic patients with > 60% stenosis and in asymptomatic patients with > 80% stenosis of extracranial carotid artery. Symptoms were defined by an ipsilateral cerebral or ocular minor or major ischemic event within the past 6 months.

Results: Mean age of study population was 67.4 ± 7.9 years and 158 patients (74.5%) were male. In the follow-up period 18 patients had MI, 18 patients had major stroke, 23 patients had transient ischemic attack. Twenty-one patients (9.9%) died from cerebral-cardiovascular causes. All MACCE was found in 64 patients (30.2%). Multivariate analysis revealed that age (OR: 1.09, 95% CI: 1.02-1.17, p= 0.05), heart failure (OR: 3.78, 95% CI: 1.48-9.62, p= 0.005), creatinine (OR: 3.54, 95% CI: 1.16-10.82, p= 0.026) and neutrophil-lymphocyte ratio (OR: 2.88, 95% CI: 1.90-4.36, p< 0.0001) were independent predictors of the MACCE.

Conclusion: Although, the short-term risk of patients undergoing CAS dominated by lesion-related factors, pre-existing comorbidities may be even more important for the long-term event. Age, heart failure, creatinine and neutrophil-lymphocyte ratio were found as the most important risk factors of MACCE.

Key Words: Predictors; long-term; carotid artery stenting.

Karotis Arter Darlığı Olan Hastalarda Karotis Artere Stent Yerleştirilmesi Sonrası Uzun Dönem Majör Serebrovasküler ve Kardiyovasküler Olay Gelişimin Belirleyicileri

ÖZ

Giriş: Karotis arter darlığı olan hastalarda bazı komorbid durumların uzun dönem morbidite ve mortalite üzerine etkisi olabileceği varsayımı ile yola çıkarak çalışma tasarlanmıştır. Çalışmada karotis arter darlığı olan hastalarda karotis artere stent (KAS) yerleştirilmesi sonrası uzun dönem serebrovasküler ve kardiyovasküler olay gelişiminin belirleyicilerinin tespit edilmesi amaçlanmıştır.

Hastalar ve Yöntem: Çalışmamıza Kartal Koşuyolu Eğitim ve Araştırma Hastanesinde Ocak 2010-Ekim 2012 tarihleri arasında KAS yerleştirilmesi işlemi yapılan 212 ardışık hasta retrospektif olarak tespit edilerek alındı. Semptomatik hastalarda %60'ın üzerindeki, asemptomatik hastalarda ise %80'in üzerindeki ekstrakraniyal karotis arter darlığına karotid arter stentleme işlemi uygulandı. Son altı ay içerisinde aynı taraf serebral ve oküler minör ya da majör iskemik olay semptom varlığı olarak kaydedildi.

Bulgular: Çalışma grubunun ortalama yaşı 67.4 ± 7.9 yıl olarak hesaplandı ve 150 (%74.5) hasta erkekti. Takip süresince 18 hastada miyokart enfarktüsü, 18 hastada majör inme, 23 (%9.9) hastada ise geçici iskemik atak gelişmiştir. Yirmi bir hastada ise serebral veya kardiyovasküler ölüm izlenmiştir. Tüm kardiyovasküler ve serebral istenmeyen olaylar (MACCE) ise 64 (%30.2) hastada izlenmiştir. Multivaryate analiz ile yaş (OR: 1.09 %95 GA: 1.02-1.17, p= 0.05), kalp yetersizliği (OR: 3.78, %95 GA: 1.48-9.62, p= 0.005), kreatinin (OR: 3.54, %95 GA: 1.16-10.82, p= 0.026) ve nötrofil-lenfosit oranının (OR: 2.88, %95 GA: 1.90-4.36, p< 0.0001) MACCE'nin bağımsız belirleyicileri olduğu saptanmıştır.

Sonuç: KAS işlemi yapılan hastalarda kısa dönem riskleri belirlemede lezyonla ilişkili faktörler ön plandayken, var olan komorbid durumlar ise uzun dönem olayları göstermede daha belirleyici olabilir. Yaş, kalp yetersizliği, kreatinin ve nötrofil/lenfosit oranı, MACCE ile ilişkili en önemli risk faktörleri olarak saptandı.

Anahtar Kelimeler: Belirleyiciler; uzun dönem; karotis arter stent.

Cite this article as: *Demir S, Kılıçgedik A, Güvendi Şengör B, Efe SÇ, Kocabay G, Yazıcıoğlu MV, et al. Long-term pedictors of composite of major adverse cardiovascular and cerebrovascular events in carotid artery stenosis patients aafter stenting. Koşuyolu Heart J 2021;24(3):229-237.*

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Submitted: 18.10.2021
Accepted: 22.11.2021
Available Online Date: 22.11.2021

INTRODUCTION

Carotid artery stenosis is known as one of the leading risk factors for the development of ischemic stroke[1]. Carotid endarterectomy (CEA) in combination with medical treatment of risk factors is currently the standard treatment for patients with symptomatic carotid artery stenosis and some selected patients with an asymptomatic carotid artery stenosis[2]. Nowadays, carotid angioplasty and stenting (CAS) has offered as an alternative treatment modality and may be used as a complementary treatment to CEA[3-5]. Although periprocedural outcome after CAS has been extensively investigated, risk factors regarding to long-term mortality have not been widely assessed. Unfortunately, prospective long-term data are sparse, and the current advantages and complications of CAS are still debated.

We hypothesized that long-term morbidity and mortality is determined by the presence of comorbidities in patients with CAS and we investigated which parameters were crucial determinants of cerebrovascular events and composite of major adverse cardiovascular and cerebrovascular events (MACCE). This study aimed to investigate the relationship between clinical characteristics, laboratory findings and long-term prognosis after CAS.

PATIENTS and METHODS

Study Population

We retrospectively enrolled 212 patients whom underwent CAS between January 2010 and December 2012 at Kartal Kosuyolu High Specialization Training and Research Hospital. CAS was carried out in symptomatic patients with > 60% stenosis and in asymptomatic patients with > 80% stenosis of extracranial carotid artery. Based on the European Carotid Surgery Trial (ECST) guidelines, the degree of stenosis was evaluated using carotid Duplex Doppler ultrasound imaging and confirmed by carotid angiography[6]. Symptoms were determined by an ipsilateral cerebral or ocular minor or major ischemic event within the past six months. All patients were informed about the nature of CAS procedure and gave their written and oral consent. The Institutional Ethics Review Board of Hospital approved the study protocol.

Baseline Characteristics

The venous blood samples were taken the day before CAS in order to evaluate the laboratory parameters. The following cerebrovascular risk factors were recorded: hypertension (blood pressure ≥ 140/90 mmHg or reported antihypertensive therapies), hyperlipidemia (LDL levels ≥ 130 mg/dL or cholesterol levels ≥ 200 mg/dL or current therapy with cholesterol-lowering drugs), medication of diabetes mellitus (history or fasting glucose ≥ 126 mg/dL) with inadequate glycemic control (hemoglobin A 1c > 7%) and smoking history. Based on the patient history of cardiovascular disease, we evaluated a prior CEA, known significant coronary artery disease [angiographically proven significant (> 50%)] stenosis, previously treated stenosis of coronary arteries, prior myocardial infarction (MI), bypass graft, and known peripheral arterial disease (PAD). MI and stroke were determined based on current clinical treatment guidelines[7,8]. Heart failure was determined regarding clinical decision supported with diagnostic findings such as decreased left ventricular ejection fraction and/or elevated brain natriuretic peptides.

CAS Procedure

The procedures performed with using interventional distal protective devices (Emboshield NAV6, Abbott vascular). A 7F or 8F sheath was implanted for having a transfemoral access. closed-cell stent (Xact, Abbott vascular) or self-expandable open-cell stent (Protege, Abbott vascular) were used. The diameter of the stenosis was diagnosed based on the ECST criteria. All lesions were evaluated after the diagnostic procedure using a semiautomatic device (Hicor, Siemens, Erlangen-Deutchland). All angiograms were evaluated by at least 2 experienced physicians who were unaware of ultrasonic data and demographic and laboratory characteristics of the patients. Based on current treatment guidelines, acetylsalicylic acid (ASA) 100 mg/day and clopidogrel 75 mg/day were given to the patients at least 5 days before the procedure. Unfractionated intravenous heparin 100 IU/kg was given to provide ACT between 250 and 300 sec. Self-expanding stents were implanted into the stenosed carotid arteries. If needed, the lesion was post-dilated to achieve a residual stenosis ≤ 30% after stent deployment. To prevent bradycardia and hypotension, 0.5-1.0 mg of atropine was routinely administered prior to balloon inflation. The final biplane angiogram of the stented lesion and intracranial views were obtained before retrieval of the protection device. The procedure was determined successfully when the stenotic segment of the carotid artery was dilated up to optimal atmospheric pressure level (Adequate blood flow or residual stenosis below 30% in culprit segment of the artery). In the clinical follow-up, all patients were evaluated by a physician and all symptomatic patients were examined by a neurologist. According to treatment guidelines, anti-platelet therapy was continued after the procedure (clopidogrel for the first 4-6 weeks in asymptomatic patients, 3 months in symptomatic patients and ASA indefinitely).

Follow-up Protocol

All patients scheduled for a follow-up visit 1, 3, 6 and twelve months and yearly after the procedure. Information on any adverse event was confirmed with hospital discharge files and the records of death were updated with the National Health System.

Exclusion Criterion

The exclusion criteria were the total occlusion of the carotid artery or the contraindications for double anti-platelet therapy, the non-atherosclerotic carotid artery stenosis and the fibromuscular dysplasia. Severe tortuosity of the vessel, anomalies and atypical bifurcation of carotid arteries, type III aortic arch were contraindications for CAS procedure.

Study End Points

Outcomes were available for mean 3-year follow-up. Cerebrovascular events were defined as any stroke, while combined endpoint of major adverse cardiac and cerebral events (MACCE) was defined as death of any cause, MI and cerebrovascular events. Death due to MI, sudden cardiac arrest, acute or chronic failure or death of unknown cause was considered cardiac.

Statistical Methods

Continuous values are expressed as mean ± SD and nominal variables as counts and percentages. For comparisons of categorical data, 2-tailed λ2 statistics and univariate Fisher exact test were used. Student-t test was used for normally distributed independent numerical variables, and Mann-Whitney U used for not normally distributed independent numerical variables. A multiple logistic regression analyses was used to determine the independent preditor of variables on groups, using variables showing marginal association with it on univariate testing ($p< 0.10$). Results of the logistic regression model are presented as odds ratio (OR) and 95% confidence interval (CI). A P value of less than 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS (Mac version 19; SPSS, Chicago).

RESULTS

From January 2009 to February 2014, a total of 212 patients with carotid stenosis had been successfully treated with CAS at our institution were included in the final analysis. The median follow-up time was 2.5 years, accumulating to 530 years of follow-up.

Mean age of the population was 67.4 ± 7.9 years and 158 patients (74.5%) were male. 110 patients (51.9%) had diabetes mellitus and 49 patients (23.1%) had heart failure. Coronary artery disease was found in 147 patients (69.3%) and peripheral occlusive arterial disease was found in 42 patients (19.8%). Right sided carotid stenosis was found in 110 patients (51.9%) and contralateral carotid occlusion was found in 18 patients (8.5%). Eighty patients (33%) had any stroke, and 47 patients (22.2%) had a major stroke in the last 6 months. CEA had been performed in 7 patients (3.3%). The patient characteristics are shown in Table 1.

In the follow-up period 18 patients had MI, 18 patients had major stroke, 23 patients had minor stroke. Twenty-six patients (12.3%) died. Twenty-one patients (9.9%) died from cerebral and cardiovascular causes. All MACCE was found in 64 patients (30.2%). Detailed cerebral and cardiovascular events are given in Table 2.

The following variables were significantly associated with outcome in MACCE (+) group; age, hs-CRP levels, neutrophil-lymphocyte ratio (NLR) (71.6 ± 6.2 vs. 65.6 ± 7.9, $p< 0.001$; 1.4 ± 1.4 vs. 0.9 ± 1.2, $p< 0.001$; 2.2 ± 2.5 vs. 2.3 ± 1.0, $p< 0.001$ respectively), male sex, tobacco use, inadequate glycemic control, CAD, PAD, prior MI, prior coronary stent, contralateral carotid stent, heart failure, serum creatinine, AST, neutrophil count, lymphocyte count. Other variables are shown in Table 3. There was no association between MACCE and other variables (Table 3). Also, the following factors were significantly associated with outcome in cerebrovascular events (+) group; age, inadequate glycemic control, prior coronary stent, heart failure, contralateral carotid stent, serum creatinine, hs-CRP levels, neutrophil count, lymphocyte counts and NLR. The association was not observed in terms of the other variables (Table 4).

Table 1. Baseline characteristics of patients

Variables	n (%)
Age (years, mean ± SD)	67.4 ± 7.9
Male sex	158 (74.5%)
Hyperlipidemia	116 (54.7%)
Arterial hypertension	164 (77.4%)
Tobacco use	99 (46.7%)
Diabetes mellitus	110 (51.9%)
Coronary artery disease	147 (69.3%)
Previus MI history	63 (29.7%)
Previus CABG history	51 (24.1%)
Previus coronary stent history	63 (29.7%)
Heart failure	49 (23.1%)
Peripheral occlusive arterial disease	42(19.8%)
Right sided carotid stenosis	110 (51.9%)
Symptomatic carotid stenosis	130 (61.3%)
Any stroke history (last 6 month)	70 (33.0 %)
Major stroke history (last 6 month)	47 (22.2%)
Contrlateral carotid occlusion	18 (8.5%)
Bilateral carotid stenosis	48 (22.6%)
Previus carotid endarterectomy history	7 (3.3%)

Variables are expressed as mean ± standard deviation or frequencies.
n: Number of patients, SD: Standard deviation, MI: Myocardial infarction, CABG: Coronary artery by-pass graft.

Table 2. Major adverse cardiac and cerebrovascular events within 36 month follow-up

Events	n (%)
MI	18 (8.5%)
Major stroke	18 (8.5%)
Minor stroke	23 (10.8%)
Any cerebrovascular event	37 (17.5%)
Cerebral-Cardiovascular death	21 (9.9%)
All deaths	26 (12.3%)
All MACCE	64 (30.2%)

Variables are expressed as mean ± standard deviation or frequencies.
n: Number of patients, MI: Myocardial infarction, MACCE: Major adverse cardiovascular and cerebrovascular events.

Table 3. Association of baseline characteristics with major adverse cardiac and cerebrovascular events

Variables	MACCE (-) (n= 148)	MACCE (+) (n= 64)	p
General			
Mean age (years)	65.6 ± 7.9	71.6 ± 6.2	< 0.0001
Male	105 (70.9%)	53 (82.8%)	0.047
Baseline laboratory			
Hemoglobin (g/dL)	13.0 ± 1.4	12.7 ± 1.7	0.123
Fasting glucose (g/dL)	118.0 ± 39.6	118.7 ± 37.0	0.904
Creatinine (g/dL)	1.0 ± 0.3	1.4 ± 0.5	< 0.0001
Urea (mg/dL)	40.4 ± 12.9	42.5± 15.0	0.516
ALT (U/L)	19.3 ± 9.5	18.9 ± 11.2	0.204
AST (U/L)	20.8 ± 7.7	23.0 ± 8.1	0.044
Total cholesterol (mg/dL)	190.3 ± 44.5	188.7 ± 46.1	0.741
LDL (mg/dL)	115.2 ± 37.3	118.6 ± 38.1	0.704
HDL (mg/dL)	42.0 ± 10.6	39.7 ± 11.8	0.113
Triglyceride (mg/dL)	164.6 ± 84.7	155.7± 75.7	0.547
hs-CRP (mg/dL)	0.9 ± 1.2	1.4 ± 1.4	< 0.0001
Thrombocytes	259.0 ± 74.8	252.3 ± 77.7	0.559
Leukocytes	7.5 ± 1.7	7.6 ± 1.8	0.731
Neutrophils	4.4 ± 1.3	5.5 ± 1.4	< 0.0001
Lymphocytes	2.1 ± 0.7	1.5 ± 0.6	< 0.0001
Neutrophil-lymphocyte ratio	2.3 ± 1.0	2.2 ± 2.5	< 0.0001
Cardiovascular risk factors			
Hypertension	115 (77.7%)	49 (76.6%)	0.493
Diabetes mellitus	77 (52.0%)	33 (51.6%)	0.535
Inadequate glycemic control	19 (12.8%)	23 (35.9%)	< 0.0001
Hyperlipidemia	81 (54.7%)	35 (54.7%)	0.556
Tobacco use	63 (42.6%)	36 (56.3%)	0.046
Cardiovascular history			
Known CAD	99 (64.9%)	51 (79.1%)	0.022
Known PAD	24 (16.2%)	18 (28.1%)	0.037
Prior MI	43 (24.6%)	8 (21.6%)	0.038
Prior coronary stent	38 (25.7%)	25 (39.1%)	0.038
Prior CABG	34 (23.0%)	17 (26.6%)	0.346
Prior CEA	4 (2.7%)	3 (4.7%)	0.356
Heart failure	22 (14.9%)	27 (42.2%)	< 0.0001
Prior major stroke	31 (20.9%)	16 (25.0%)	0.315
Prior any cerebrovascular event	49 (33.1%)	21 (32.8%)	0.549
Interventional data			
Right side carotid artery stenosis	75 (50.7%)	27 (42.2%)	0.162
Contrlateral occlusion	11 (7.4%)	7 (10.9%)	0.277
Contrlateral carotidstent	10 (6.8%)	11 (17.2%)	0.021
Contrlateral carotid artery stenosis	29 (19.6%)	19 (29.7%)	0.077
Stent diameter, mm	6.6 ± 0.8	6.6 ± 0.8	0.933
Stent lenght, mm	36.4 ± 11.0	37.9 ± 6.7	0.127

Table 3. Association of baseline characteristics with major adverse cardiac and cerebrovascular events (continued)

Variables	MACCE (-) (n= 148)	MACCE (+) (n= 64)	p
Degree of stenosis (%)	84.0 ± 11.0	84.4 ± 11.9	0.282
Open stent design	98 (56.3%)	18 (48.6%)	0.418
Predilatation	11 (7.4%)	7 (10.9%)	0.277
Postdilatation	131 (88.5%)	58 (90.6%)	0.425
Current medication			
Statins	89 (60.1%)	36 (56.3%)	0.352
ACE inhibitors/ARBs	101 (48.2%)	45 (70.3%)	0.449
Beta blockers	64 (43.2%)	36 (56.3%)	0.056
Clopidogrel	146 (99.9%)	37 (100.0%)	0.825
ASA	139 (93.9%)	62 (96.9%)	0.302

Variables are expressed as mean ± standard deviation or frequencies.
n: number of patients, MACCE: Major adverse cardiovascular and cerebrovascular events, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low densiyt lipoprotein, HDL: High density lipoprotein, hs-CRP: High sensitivity C-rective protein, CAD: Coronary artery disease, PAD: Peripheral artery disease, MI: Myocardial infarction, CABG: Coronary artery by-pass graft, CEA: Carotid endarterectomy, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, ASA: Acetylsalycilic acyte.

Table 4. Association of baseline characteristics with adverse cerebrovascular events

Variables	CVE (-) (n= 175)	CVE (+) (n= 37)	p
General			
Mean age (years)	66.5 ± 8.0	71.6 ± 5.9	< 0.0001
Male	128 (73.1%)	30 (81.1%)	0.215
Baseline laboratory			
Hemoglobin (g/dL)	13.0 ± 1.5	12.6 ± 1.7	0.181
Fasting glucose (g/dL)	116.7 ± 39.5	124.0 ± 34.9	0.110
Creatinine (mg/dL)	1.0 ± 0.4	1.3 ± 0.5	0.003
Urea (mg/dL)	41.1 ± 13.3	40.8 ± 14.7	0.627
ALT (U/L)	19.0 ± 9.7	20.0 ± 11.5	0.763
AST (U/L)	21.1 ± 7.9	23.2 ± 7.8	0.060
Total cholesterol (mg/dL)	190.1 ± 44.2	188.7 ± 49.0	0.900
LDL (mg/dL)	116.6 ± 37.0	114.8 ± 40.8	0.792
HDL (mg/dL)	41.2 ± 10.3	41.1 ± 14.0	0.536
Triglyceride (mg/dL)	161.6 ± 82.8	163.2 ± 79.6	0.777
hs-CRP (mg/dL)	1.0 ± 1.3	1.2 ± 0.8	0.001
Thrombocytes (g/L)	258.0 ± 740	252.7 ± 84.0	0.701
Leukocytes (g/L)	7.7 ± 1.8	7.4 ± 1.7	0.369
Neutrophils (g/L)	4.6 ± 1.4	5.5 ± 1.5	0.001
Lymphocytes (g/L)	2.0 ± 0.7	1.4 ± 0.5	< 0.0001
Neutrophil-lmphocyte ratio	2.6 ± 1.4	4.3 ± 2.6	< 0.0001
Cardiovascular risk factors			
Hypertension	134 (76.6%)	30 (81.1%)	0.361
Diabetes mellitus	89 (59.9%)	21 (56.8%)	0.319
Inadequate glycemic control	27 (15.4%)	15 (40.5%)	0.001
Hyperlipidemia	94 (53.7%)	22 (59.5%)	0.325
Tobacco use	79 (45.1%)	20 (54.1%)	0.210

Table 4. Association of baseline characteristics with adverse cerebrovascular events (continued)

Variables	MACCE (-) (n= 148)	MACCE (+) (n= 64)	p
Cardiovascular history			
Known CAD	118 (67.4%)	29 (78.4%)	0.131
Known PAD	33 (18.9%)	9 (24.3%)	0.291
Prior MI	50 (28.6%)	13 (35.1%)	0.272
Prior coronary stent	44 (25.1%)	19 (51.9%)	0.002
Prior CABG	43 (24.6%)	8 (21.6%)	0.442
Prior CEA	6 (3.4%)	1 (2.7%)	0.647
Heart failiure	36 (20.6%)	13 (35.1%)	0.049
Prior major stroke	35 (20.0%)	12 (32.4%)	0.549
Prior any cerebrovascular event	55 (31.4%)	15 (40.5%)	0.189
Interventional data			
Right side carotid artery stenosis	89 (50.9%)	13 (35.1%)	0.059
Contrlateral occlusion	16 (9.1%)	2 (5.4%)	0.359
Contrlateral carotid stent	12 (6.9%)	9 (24,3%)	0.004
Contrlateral carotid artery stenosis	37 (21.1%)	11 (29,7%)	0.178
Stent diameter, mm	36.8 ± 5.5	37.3 ± 7.7	0.771
Stent lenght, mm	6.7 ± 0.8	6.7 ± 0.9	0.945
Degree of stenosis (%)	84.4 ± 11.1	84.4 ± 12.0	0.887
Open stent design	98 (56.3%)	18 (48.6%)	0.251
Predilatation	14 (8.0%)	4 (10.8%)	0.386
Postdilatation	156 (89.1%)	33 (89.2%)	0.629
Current medication			
Statins	106 (60.6%)	19 (51.4%)	0.197
ACE inhibitors/ARB	117(66.9%)	29 (78.4%)	0.118
Beta blockers	83 (47.4%)	17 (45.9%)	0.508
Clopidogrel	173 (99.4%)	37 (100.0%)	0.825
ASA	166 (94.9%)	35 (94.6%)	0.623

Variables are expressed as mean ± standard deviation or frequencies.
n: Number of patients, CVE: Cerebrovascular events, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low densiyt lipoprotein, HDL: High density lipoprotein, hs-CRP: High sensitivity C-reactive protein, CAD: Coronary artery disease, PAD: Peripheral artery disease, MI: Myocardial infarction, CABG: Coronary artery by-pass graft, CEA: Carotid endarterectomy, ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blockers, ASA: Acetylsalycilic acyte.

To determine risk factors of MACCE, univariate analysis was performed. The factors that reached statistical significance were as follows: Age, inadequate glycemic control, CAD, PAD, heart failure, contralateral carotid stent, creatinine, hs-CRP and NLR. After applying binominal multivariate analysis which were imbalanced on univariate analysis, following variables were identified as risk factor of predicting of the MACCE: Multivariate analysis revealed that age (OR: 1.09, 95% CI: 1.02-1.17, p= 0.05), heart failure (OR: 3.78, 95% CI: 1.48-9.62, p= 0.005), creatinine (OR: 3.54, 95% CI: 1.16-10.82, p= 0.026) and NLR (OR: 2.88, 95% CI: 1.90-4.36, p< 0.0001) were independent predictors of the MACCE (Table 5).

To determine risk factors of cerebrovascular event, univariate analysis was performed. The factors that reached statistical significance were as follows: Age, inadequate glycemic control, heart failure, contralateral carotid stent, prior coronary stent, creatinine, hs-CRP and NLR. Multivariate analysis revealed that age (OR: 1.06, 95% CI: 1.00-1.13, p= 0.036), inadequate glycemic control (OR: 2.93, 95% CI: 1.14-7.52, p= 0.025), prior coronary stent (OR: 2.5, 95% CI: 1.08-5.75, p= 0.031) and NLR (OR: 1.34, 95% CI: 1.02-1.75, p= 0.032) were independent predictors of the cerebrovascular event (Table 6).

Table 5. Predictors of major adverse cardiac-cerebrovascular events (MACCE) using logistic regression analysis

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	1.12	1.07-1.18	< 0.001	1.09	1.02-1.17	0.05
Male sex	1.97	0.94-4.13	0.072	-	-	-
Tobaccouse	1.73	0.96-3.13	0.068	-	-	-
Inadequate glycemic control	3.80	1.88-7.68	< 0.0001	2.37	0.86-6.61	0.094
Known CAD	2.12	1.05-4.26	0.034	0.81	0.32-2.06	0.665
Known PAD	2.02	1.00-4.06	0.048	1.34	0.48-3.70	0.569
Prior MI	1.85	0.99-3.46	0.052	-	-	-
Heart failure	4.17	2.13-8.18	< 0.0001	3.78	1.48-9.62	0.005
Prior coronary stent	1.85	0.99-3.46	0.052	-	-	-
Contrlateral carotid stent	2.86	1.14-7.13	0.024	2.75	0.67-11.17	0.157
Creatinine (mg/dL)	1.74	4.70-29.30	< 0.0001	3.54	1.16-10.82	0.026
hs-CRP (mg/dL)	1.32	1.05-1.66	0.014	0.96	0.70-1.30	0.792
AST	1.03	0.99-1.07	0.072	-	-	-
NLR	2.93	2.07-4.16	< 0.0001	2.88	1.90-4.36	< 0.0001

MACCE: Major adverse cardiovascular and cerebrovascular events, CAD: Coronary artery disease, PAD: Peripheral artery disease, MI: Myocardial infarction, hs-CRP: High sensitivity C-reactive protein, AST: Aspartate aminotransferase, NLR: Neutrophil-lmphocyte ratio, OR: Odds ratio, CI: Confidence interval.

Table 6. Predictors of adverse cerebrovascular events using logistic regression analysis

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	1.10	1.04-1.16	< 0.001	1.06	1.00-1.13	0.036
Creatinine (mg/dL)	3.85	1.76-8.38	0.001	1.28	0.48-3.35	0.616
hs-CRP (mg/dL)	1.10	0.8 –1.2	0.415	-	-	-
NLR	1.62	1.27-2.06	< 0.0001	1.34	1.02-1.75	0.032
Heart failure	2.09	0.97-4.50	0.60	-	-	-
Inadequate glycemic control	3.73	1.72-8.10	0.001	2,93	1.14-7.52	0.025
Prior coronary stent	3.14	1.51-6.51	0.002	2,50	1.08-5.75	0.031
Contrlateral carotid stent	4.36	1.68-11.32	0.002	2.85	0.87-9.65	0.090

hs-CRP: High sensitivity C-reactive protein, AST: Aspartate aminotransferase, NLR: Neutrophil-lmphocyte ratio, OR: Odds ratio, CI: Confidence interval.

DISCUSSION

According to our study, age, inadequate glycemic control, presence of coronary stent and NLR were found to be the most important risk factors of cerebrovascular events, while age, heart failure, creatinine and NLR were found as the most important risk factors of MACCE.

Until now, risk evaluation in patients with CAS has focused on the periprocedural outcome[9-11]. Nevertheless, data on long term outcome after CAS are quite rare[12]. Available data about risk evaluation of long-term outcome mainly focused on isolated variables[13]. Blood NLR is a simple, well-known marker of inflammation that can be easily obtained from the WBC count. Although previous studies have shown that NLR may be an independent predictor of restenosis after CAS, no data have been reported on NLR regarding long term MACCE after CAS[14,15]. In our study, NLR was one of the strongest independent isolated predictors of the cerebrovascular event and MACCE. Hs-CRP, a well-known inflammation marker, has been shown to predict short term stroke and death in patients undergoing carotid stenting[16]. However, there is no data demonstrating the effect of hs-CRP on long term prognosis in CAS patients. Although we found a relation between hs-CRP and MACCE in the univariate analysis, hs-CRP did not have a significant effect as a predictor in the multivariate analysis. In this context, patients with CAS might benefit from routine WBC count more than hs-CRP levels as an inflammatory marker.

Hoke and collegues searched for a validated risk score to predict outcomes after CAS and found that age, presence of heart failure and diabetes were the strongest risk factors for long term mortality[17]. We also found the age as a predictor of the cerebrovascular event and MACCE such as previous other studies[18-20]. In addition, we showed that heart failure was a robust predictor of long term MACCE, but it was not found to be a predictor of the cerebrovascular event. This difference may be attributed to the effect of heart failure on the mortality and cardiac events. Arif et al. reported that the presence of coronary artery disease increased the risk of MACCE in patients undergoing CAS during long-term follow-up[21]. We also found that prior coronary stent was a predictor of cerebrovascular event in CAS patients. It may be attributed to the burden of the coronary and peripheral artery disease. Therefore, patients with carotid artery disease may benefit from routine screening for heart failure and prior coronary artery disease.

A study reported by Hoffman demonstrated that diabetes with an irregular glycemic control was the strongest independent risk predictor for interventional complications after carotid artery stenting, because of hyperglycemia induced vascular endothelial cell damage with subsequent vasomotor dysfunction and increased extra- and intracellular proliferation, therefore, they strongly advised the correction of an inadequate glycemic control in patients with DM before elective CAS[22]. Hoke et al. also found inadequate glycemic control as a predictor of mortality; but we found inadequate glycemic control as only a predictor of cerebrovascular event[17]. Although previous studies have shown that patients with chronic kidney disease are at high risk for cardiovascular disease, its effect on long-term MACCE after CAS has not been well investigated. Chronic renal insufficiency has shown as a risk factor for patients undergoing CAS[23]. The study of outcomes after CAS in hemodialysis patients, demonstrated relatively poor long-term survival and prohibitive operative stroke and death risk. Therefore, the authors recommended avoidance of CAS in asymptomatic dialysis patients and cautious consideration when planning CAS in symptomatic patients[24]. Our findings also suggested creatinine levels as one of the most predictor of long-term MACCE, however, it was not found as a predictor for cerebrovascular events in the multivariate analysis.

In this study, we identified prognosticators of long-term cerebrovascular event and MACCE in carotid artery stenosis patients after CAS. It is so far the longest observation of such a large group of patients in Turkey. The significant clinical value of this study is related to the broad spectrum of patients selected for CAS procedure, the procedures being conducted by the same group of operators, extensive investigations and complex treatment of peripheral and coronary arteries atherosclerosis.

LIMITATIONS

There are several limitations of our study. Some medications may influence the occurrence of clinical adverse events. In particular, statins and platelet inhibitors may play a relevant role in this context. Although we adjusted statistically for the use of these drugs at baseline, we are unable to exclude residual confounding by changes of the medication during the study. Also, the follow-up time is relatively short.

CONCLUSION

Even though the short-term risk of patients underwent CAS dominated by lesion-related factors, pre-existing comorbidities might be more important for the long-term events. While prior coronary stent, irregular glycemic control, age and NLR were found to be the most important risk factors of cerebrovascular events; age, heart failure, creatinine and NLR also were found as the most important risk factors of MACCE.

Ethics Committee Approval: This study was approved by the Kartal Kosuyolu High Specialization Training and Research Hospital Ethics Committee (Decision number: 2021/10/522, Date: 24.08.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - SD; Analysis/Interpretation - SD, CK; Data Collection - SD, AK, MY; Writing - SD, AK, BŞ; Critical Revision - SE, GK; Statistical Analysis - SD; Overall Responsibility - SD; Final Approval - All of Authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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