

## Risk factors and prognosis of acute ischemic stroke after coronary angiography and percutaneous coronary intervention

### Koroner anjiyografi ve perkütan koroner müdahale sonrası akut iskemik inmede risk faktörleri ve prognoz

Esra Erucar<sup>1</sup>, Hacı Ali Kurklu<sup>2</sup>, Ceyla Irkeç<sup>3</sup>

1 Phd, Department of Neurology, Lokman Hekim University Faculty of Medicine, Ankara, Turkey. eerucar@yaani.com, 0000-0002-1666-0084

2 M.D. Phd, Department of Cardiology, Lokman Hekim Akay Hospital, Ankara, Turkey. hacialikurklu@gmail.com, 0000-0002-6658-6652

3 M.D. Prof. Department of Neurology, Lokman Hekim University Faculty of Medicine, Ankara, Turkey. irkecc@lokmanhekim.edu.tr, 0000-0002-4713-8010

#### ABSTRACT

**Aim:** Aim of this study is to analyze the incidence, predictors and outcomes of stroke in patients who underwent coronary angiography and percutaneous coronary intervention at our center. **Materials-Methods:** This study was conducted in a tertiary health center in Ankara/Turkey. Sixteen patients who had a stroke after coronary angiography and percutaneous coronary intervention were included in the study as a case group. The control group consisted of 80 patients. It is a retrospective study. Hemorrhagic stroke cases were excluded. All participants are ischemic stroke cases. **Results:** The average age of the participants is 69.6+12.1 years. Of the participants, 59 (61.5%) were male and 37 (38.5%) were female. The incidence of symptomatic cerebral infarction after coronary angiography or percutaneous coronary intervention was 16 cases (0.16%). Coronary angiography and percutaneous coronary intervention was performed in eight patients. No significant difference was observed between the groups in terms of use of antiplatelet drugs, statins, beta-blockers, warfarin or oral anticoagulants. **Conclusion:** Multi-vessel disease, congestive heart failure, low ejection fraction and chronic renal failure were found to be risk factor for the development of coronary angiography or percutaneous coronary intervention related stroke.

#### ÖZ

**Amaç:** Bu çalışmanın amacı, merkezimizde koroner anjiyografi ve perkütan koroner girişim yapılan hastalarda inme insidansını, predispozan faktörleri ve sonuçlarını incelemektir. **Gereç-Yöntem:** Bu çalışma Ankara/Türkiye'de bir üçüncü basamak sağlık merkezinde yapılmıştır. Koroner anjiyografi ve perkütan koroner girişim sonrası inme geçiren 16 hasta vaka grubu olarak çalışmaya dâhil edilmiştir. Kontrol grubu 80 hastadan oluşturulmuştur. Retrospektif bir çalışmadır. Hemorajik inme vakaları çalışma dışı bırakılmıştır. Tüm katılımcılar iskemik inme vakalarıdır. **Bulgular:** Katılımcıların yaş ortalaması 69,6+12,1'dir. Katılımcıların 59'u (%61,5) erkek, 37'si (%38,5) kadındır. Koroner anjiyografi veya perkütan koroner girişim sonrası semptomatik serebral enfarktüs insidansı 16 vakadır (%0,16). Sekiz hastaya koroner anjiyografi ve perkütan koroner girişim uygulanmıştır. Gruplar arasında antitrombosit ilaç, statin, beta bloker, varfarin ve oral antikoagülan kullanımı açısından anlamlı fark gözlenmemiştir. **Sonuç:** Çoklu damar hastalığı, konjestif kalp yetmezliği, düşük ejeksiyon fraksiyonu ve kronik böbrek yetmezliği, koroner anjiyografi veya perkütan koroner girişime bağlı inme gelişimi için risk faktörleri olarak bulunmuştur.

#### ARTICLE INFO/MAKALE BİLGİSİ

**Key Words:** Acute Ischemic Stroke; Coronary Angiography; Percutaneous Coronary Intervention

**Anahtar Kelimeler:** Akut İskemik İnme; Koroner Anjiyografi; Perkütan Koroner Müdahale

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**Corresponding Author/Sorumlu Yazar:** Phd, Department of Neurology, Lokman Hekim University Faculty of Medicine, Ankara, Turkey. eerucar@yaani.com.

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#### INTRODUCTION

Coronary artery disease (CAD) is a condition in which adequate blood and oxygen cannot be supplied to the myocardium. It is caused by occlusion of the coronary arteries. Coronary arteries are blocked due to plaque formed in the lumen and blood flow is blocked. It is one of the leading causes of death worldwide. CAD-related deaths peaked in the mid-1960s (1). Coronary artery disease is very common in both developed and developing countries. It has been reported that CAD represents 2.2% of the overall global burden of disease and 32.7% of cardiovascular diseases (2). Today, the prevalence, morbidity and mortality of coronary artery

disease are increasing. Therefore, aggressive prevention and management practices are required (3).

Both coronary angiography (CAG) and percutaneous coronary intervention (PCI) are used in the diagnosis and treatment of coronary artery disease (4). Percutaneous coronary intervention (PCI) is a non-surgical, invasive procedure. It is performed to relieve congestion in the coronary artery and to improve blood flow to the ischemic tissue (4). Invasive coronary angiography remains the gold standard for diagnosing coronary artery disease (5).

Stroke or cerebrovascular disease (CVD) is the neuronal damage that occurs as a result of impaired blood flow

in the cerebral vessels. Approximately 85% is ischemic, the remainder is hemorrhagic. CVD is the leading cause of adult disability worldwide. Therefore, early diagnosis is very important to prevent or minimize morbidity and mortality (6). Cerebrovascular disease after coronary catheterization is rare. But sometimes it can be severe. In previous studies, the frequency of symptomatic CVD complications after CAG and PCI was reported as 0.1%-1%. However, the frequency of asymptomatic CVD is 10.2%-22% (7).

There are many risk factors for CVD after CAG and PCI. These include age, female gender, vascular disease, renal failure, hypertension, diabetes mellitus, previous stroke or transient ischemic attack (8). The prognosis is poor in patients who develop CVD after CAG or PCI. Strokes occurring after PCI are often ischemic. However, the mechanisms of cerebral ischemia are not fully understood (9).

This is a retrospective study. Its aim is to analyze the incidence, predictors and outcomes of stroke in patients who underwent CAG or PCI at our center.

## **MATERIAL-METHOD**

### **Study Design**

This retrospective study was conducted in a tertiary health center in Ankara/Turkey between July 2018 and December 2021. This is a retrospective study. Hemorrhagic stroke cases were excluded from the study. All participants included in the study are ischemic stroke cases.

### **Parameters Examined in the Study**

#### **Clinical presentation.**

Patient-related factors: age, gender, Hypertension (HT), Diabetes Mellitus (DM), hyperlipidemia (HL), Previous Coronary Artery Bypass Graft (CABG), Heart Failure (HF), Atrial fibrillation (AF) and Ejection Fraction (EF).

Comorbidities: chronic renal failure (CRI), anemia (hemoglobin (Hb) less than 7 mmol/L).

#### **Participants**

Sixteen patients who had a stroke after CAG/PCI who applied to our center between July 2018 and December 2021 were included in the study as a case group. The control group consisted of 80 patients admitted with different causes of stroke. The total number of participants is 96.

#### **Ethics**

Before participating in the study, all patients or their relatives were informed about the study. Written

informed consent was obtained. Participation in the study is on a voluntary basis. There was no compulsion. The study was conducted in accordance with the Declaration of Helsinki standards and current ethical guidelines. Required ethical permissions were obtained from the relevant institutional ethics committee.

### **Coronary angiography**

CAG was performed by experienced cardiologists using the standardized Judkins method. CAG procedures were chosen by the cardiologist's decision. The procedure was performed using a 6 Fr catheter via femoral access. Before starting the procedure, 5000 U of unfractionated heparin was administered intravenously to the patients. Non-ionic isoosmolar contrast material was used.

### **Measurements and definition of diseases**

- Blood samples were taken from all participants at the time of application.
- A systolic blood pressure of  $\geq 140$  mmHg and a diastolic blood pressure of  $\geq 90$  mmHg or the use of antihypertensive drugs were accepted as HT.
- HbA1c level of  $\geq 6.5\%$ , a blood glucose level of  $\geq 200$  mg/dL, a fasting blood glucose level of  $\geq 126$  mg/dl, or a history of diabetes treatment were accepted as DM.
- LDL-C level  $\geq 140$  mg/dL, triglyceride level  $\geq 150$  mg/dL, and HDL-C level  $\geq 40$  mg/dL or use of statin and fibrate group drugs were accepted as Dyslipidemia.
- CAD was defined as a diameter stenosis of the presence of  $\geq 1$  vessel with  $\geq 70\%$  luminal diameter narrowing, as detected by CAG during the present study or previous CAG by the American College of Cardiology/ American Heart Association for lesion classification in three coronary arteries.
- Prior heart failure was defined as having a principal discharge diagnosis of heart failure.
- Aortic stenosis was defined as mild or over, and aortic regurgitation was defined as trace or over, according to the guidelines.
- We diagnosed acute embolic infarction using the combination of magnetic resonance imaging and tomography.

### **Statistical Analysis**

Data were recorded used SPSS 21 package software. For categorical data Chi square test was used. For comparison of continuous numeric values; t test was for normal, Mann-Whitney U test for non-normal distributed data. Data were expressed as arithmetic mean  $\pm$

standard deviation (SS).  $p < 0.05$  were considered as statistically significant.

## RESULTS

The basic characteristics of the patients and laboratory analysis results are given in Table 1.

The average age of the participants is  $69.6 \pm 12.1$  years. Of the participants, 59 (61.5%) were male and 37 (38.5%) were female. Of all the participants, 59 (61.5%) had HT and 32 (33.3%) had DM. It was determined that

67 (69.8%) and 59 (61.5%) participants were admitted with HL and AF, respectively. In addition, 19 (19.8%) patients had CAD and congestive heart failure. The findings obtained in blood tests are presented in Table 2. No significant difference was observed between the groups in terms of use of antiplatelet drugs, statins, beta-blockers, warfarin or oral anticoagulants.

A total of 10,124 consecutive patients underwent CAG or PCI during the study period. The incidence of symptomatic cerebral infarction after CAG/PCI was 16 cases (0.16%). PCI and CAG was performed in eight

**Table 1.** Baseline Clinical Characteristics of Patients with CAG/PCI stroke and non-CAG/PCI stroke.

Variables	All patients	CAG/PCI stroke	non-CAG/PCI stroke	p value
	N=96	N=16	N=80	
Age (years)	69.6±12.1	69.9±9.9	69.5±12.5	0.941
Age ≥ 75 years	35 (36.5%)	5 (31.3%)	30 (37.5%)	0.850
Male	59 (61.5%)	12 (75%)	47 (58.8%)	0.348
Hypertension	59 (61.5%)	13 (81.3%)	46 (57.5%)	0.133
Diabetes mellitus	32 (33.3%)	7 (43.8%)	25 (31.3%)	0.498
Dyslipidemia	67 (69.8%)	12 (75%)	55 (68.8%)	0.770
Prior Heart failure	19 (19.8%)	10 (62.5%)	9 (11.3%)	<0.001
Coronary arter disease	19 (19.8%)	7 (43.8%)	12 (15%)	0.015
Multi-vessel disease	13 (13.5%)	12 (75%)	1 (1.3%)	<0.001
Ejection fraction	55.6±12.2	44.1±14.7	57.9±10.3	<0.001
Ejection fraction < %40	14 (14.6%)	5 (31.3%)	9 (11.3%)	0.054
Prior stroke	15 (15.6%)	0	15 (18.8%)	-
Prior CABG	12 (12.5%)	4 (25%)	8 (10%)	0.111
GFR < 60	35 (36.5%)	8 (50%)	27 (33.8%)	0.343
Atrial fibrillation	59 (61.5%)	12 (75%)	47 (58.8%)	0.348
Malignancy	4 (4.2%)	1 (6.3%)	3 (3.8%)	0.524
NIHSS	4.2±4.2	7.8±6.5	3.5±3.1	0.001

**Table 2.** Baseline Laboratory Characteristics of Patients with CAG/PCI stroke and non-CAG/PCI stroke.

Variables	All patients	CAG/PCI stroke	Non-CAG/PCI stroke	P value
	N=96	N=16	N=80	
Hemoglobin, g/dL	13.7±2.3	14.0±1.2	13.6±2.4	0.829
White blood cell, x10 <sup>9</sup> /L	10.0±8.2	12.4±6.0	9.5±8.6	0.007
Neutrophil %	6.3±3.2	9.5±5.2	5.7±2.1	0.004
Lymphocyte %	2.4±2.5	2.0±1.6	2.4±2.7	0.157
Monocyte %	0.8±0.9	0.8±0.3	0.8±1.0	0.038
Platelet x10 <sup>9</sup> /L	250.3±84.8	255.6±65.2	249.3±88.5	0.871
NLR	4.4±5.3	9.5±10.3	3.3±2.8	0.013
MLR	0.64±2.63	0.57±0.42	0.66±2.87	0.007
PLR	150.99±131.71	239.46±271.66	133.29±70.33	0.138
HDL-C mg/dL	44.9±13.7	44.6±11.8	45.0±14.1	0.871
LDL-C mg/dL	122.9±44.4	131.5±36.2	121.2±45.8	0.188
TG mg/dL	156.2±86.2	168.3±81.3	153.7±87.5	0.452
Creatinine mg/dL	1.3±2.6	2.7±6.2	1.0±0.4	0.014
CRP mg/dL	16.0±41.9	13.6±28.7	16.4±44.2	0.385

patients. Emergency CAG or PCI was performed in 13 patients with symptomatic cerebral infarction due to myocardial infarction. Eight patients had non-ST segment elevation myocardial infarction (NSTEMI), four patients had ST segment elevation myocardial infarction (STEMI), one patient had unstable angina, and one patient had stable ischemic heart disease.

The characteristics of the participants in the CVD and control groups associated with CAG/PCI were compared. The groups were similar in terms of age, gender, DM, HL, HT, previous CABG, malignancy and AF. In the CAG/PCI associated CVD group, CAD, vascular disease and congestive heart failure were higher than the control group, which was statistically significant.  $p=0.015$ ,  $p<0.01$  and  $p<0.01$ , respectively.

Mean EF ( $44.1\pm 14.7$ ) was found in the CAG/PCI related CVD group. This value is lower in the control group. The difference between the groups was statistically significant ( $p<0.001$ ). National Institutes of Health Stroke Scale (NIHSS) values were statistically significantly higher in the CAG/PCI-related CVD group than in the control group ( $p<0.01$ ). In the CAG/PCI-associated CVD group, 3 of 16 patients died (18.8%). There was no death in the control group.

Laboratory analysis results are presented in Table 2. Hemoglobin, Platelet (PLT), LDL-C, HDL-C, TG, Platelet lymphocyte ratio (PLR), C-reactive protein (CRP), Glomerular Filtration Rate (GFR) levels were found to be similar among the groups.

White blood cell levels were significantly higher in the CAG/PCI-associated CVD group compared to the control group ( $p<0.01$ ). Neutrophil, monocytes, and creatinine levels were also found to be significantly higher in the CAG/PCI-related CVD group compared to the control group.  $p<0.01$ ,  $p=0.03$ ,  $p=0.014$ , respectively.

## DISCUSSION

Serebrovascular diseases related to CAG and PCI is a rare complication, which can be potentially life-threatening and can lead to serious disability. The incidence of post-PCI stroke has been assessed in several single-center studies, national registries, and meta-analyses of PCI trials. The previously available registries indicate that periprocedural stroke occurs in 0.05%–0.1% of CAG and 0.18%–0.44% of PCI (10,11). However, formerly provided data may be limited because the majority of these studies included selected groups of patients and were performed more than a decade ago. The last years have shown a significant upward trend in the number of elder patients with a higher number of risk factors treated with cardiovascular procedures (12).

Despite all the improvements in reperfusion strategies, such as using radial access, smaller catheters, and pharmacotherapy, achieved in the last few years, the incidence of periprocedural stroke remains the same or has even slightly increased (11,13).

The last reported incidence of post-PCI stroke 0.22% to 1.6% by Alkhouli et al. Stroke was consistently higher for STEMI and NSTEMI after PCI than UA or SIHD after PCI (10). A total of 10.124 consecutive patients underwent CAG or PCI in this study. The incidence of symptomatic CVD complication after CAG/PCI was 0.16% (16 cases). 8 (8.3%) patients underwent PCI and 8 (8.2%) CAG. 13 of these 16 patients had emergency CAG or PCI for MI. The indication for CAG/PCI was NSTEMI in 8, STEMI in 4 and UA in 1 patient and SIHD in the remaining 3 patients. All of the clinically evident CAG/PCI-related stroke cases occurred within 24 hours of the procedure. This complication rate was found to be compatible with previous studies but lower than that of new recent studies. This may be due to the low number of patients who underwent CAG/PCI in the study.

CAG and PCI related CVD complications have been reported to be caused by thrombus formation in the catheter itself and lumen, attachment of the thrombus to the exchange wire, air embolisms, and debris from arteriosclerosis dislodged by guide catheter (14). Probability of thrombus formation and the risk of CVD after CAG/PCI are strictly related to more advanced and disseminated atherosclerosis, more severe state, lower left ventricular EF or use of left ventricular support mechanical devices (10). Khatibzadeh et al. demonstrated that localization of atherosclerotic plaques prone to dislodgement in the thoracic aorta (descending and arch) predispose to ischemic stroke in patients treated from femoral access (15).

In several previously published studies, a relationship between PCI in patients with triple vessel disease and procedure related stroke has been verified (11). In various publications, prior stroke (as well as female sex, AF, HF, DM, CRI, atherosclerotic cardiovascular disease, left ventricular thrombus, hypercoagulable state and CABG during admission) was confirmed as a predictor of periprocedural stroke in patients treated with PCI due to acute MI (13,16). In previously published studies, it has been reported that prior CABG was found to be independently related to periprocedural stroke in patients undergoing CAG (3). Kawamura et al, it was demonstrated by multivariable logistic regression analysis that left ventricular EF was the only independent predictor for stroke in patients treated with PCI due to acute MI (17). Similar to other research in our study, CAD ( $p=0,015$ ), multi-vessel disease ( $p<0,001$ ) and congestive heart failure ( $p<0,001$ ) were predictor for

CAG/PCI related CVD. But age, sex, AF, HT, DM were similar between in two group. In most publications, older age was present among the predictors of PCI-related stroke; however, in our study, this was confirmed only for isolated CAG (18).

Most CAG/PCI related strokes are ischemic and embolic in nature secondary to dislodgment of atherosclerotic plaque or embolization of coronary or catheter derived thrombus, with a lower incidence of hemorrhagic strokes. Clinically silent embolic events after cardiac catheterization are relatively common; a meta-analysis of 10 studies demonstrated 8% incidence of radiographic brain infarct, of which <10% were symptomatic (17). In this study all of the stroke cases were ischemic, we were not able to assess silent embolic events.

NIHSS values were significantly higher in CAG/PCI group than in non-CAG/PCI group ( $p=0,001$ ) The mortality rate was %18.8 (3 patients out of 16 patients) in the CAG/PCI group, there was no death in the control group. In previous studies, in hospital mortality rate after symptomatic CVD complications during catheter examination and treatment has been reported to be 22%–37%, which is a very poor prognosis (3,19,20). These findings show that patients who develop stroke after CAG/PCI progress with more severe clinical findings and are more mortal than non-CAG/PCI strokes.

The role of inflammation is well described in the initiation and progression of coronary atherosclerosis and stroke, high levels of inflammatory markers have been found in association with the severity and the prognosis of CAD and CVD patients (18,21). After stroke, the inflammatory response is activated and plays a significant role in secondary brain injury. At the same time, stroke could trigger a special immunosuppressive state such as the activation of neutrophils, which leads to a decrease in lymphocytes and certain types of lymphocytes are considered to be important brain protective immune regulators; the decrease of these lymphocytes may lead to deterioration of nerve function (22-24). Recently, NLR has become a powerful predictor of death in patients with cardiovascular disease or peripheral arterial occlusive disease. Previous studies reported a correlation between stroke severity and NLR determined at admission. Several studies suggested that the initial NLR was associated with mortality and infarct size in ischemic stroke patients (24). High NLR is independently and strongly associated with increased risk of complications and mortality in post MI patients (25). NLR is a noninvasive, inexpensive and widely available hematologic marker of inflammation. NLR is independently associated with mortality and HF readmissions (26). The high NLR and MLR rates in our CAG/PCI patients can be explained by MI, CAD and low

EF. The fact that these rates are higher, especially in patients with post-stroke mortality is valuable in terms of prognosis.

Both acute kidney injury and chronic kidney disease are associated with an increased risk of stroke and cerebrovascular events. Prior studies have found renal insufficiency to be independent predictors of post-PCI stroke (19,27). In the study of Alkhouli et al, post-PCI stroke was found to be more common in patients with CRI (16). Compared to the general population, patients with CRI are at heightened risk for all subtypes of stroke. This is due to a multitude of mechanisms linking nephropathy with altered cerebral perfusion, cerebral neurovascular coupling and blood vessel integrity. In this study CAG/PCI stroke patients had high Cr levels.

Mechanical thrombectomy and IV thrombolytic treatment is becoming more and more common after stroke. It should not be forgotten that mortality will decrease with early diagnosis and early treatment of these patients. In this study two patients had mechanical thrombectomy and two patients had iv thrombolytic treatment. Patients who underwent mechanical thrombectomy had a poor prognosis and died.

### Study Limitations

There are several limitations in this study. The small number of patients is statistically insufficient to analyze risk factors. Further studies with large sample sizes are needed. The other limitation is that the characteristics of all CAG/PCI patients cannot be compared.

### CONCLUSIONS

Multi-vessel disease, congestive heart failure, low EF and CRI were found to be risk factor for the development of CAG/PCI related stroke. NIHSS values were significantly higher after CAG/PCI procedure. These findings showed that CAG/PCI stroke are more serious and mortal than non-CAG/PCI strokes.

High levels of inflammatory markers to be independently and strongly associated with increased risk of stroke and poor prognosis after post-procedure. The high NLR and MLR rates can be explained by MI, CAD and low EF in CAG/PCI strokes. The fact that these rates are higher, especially in patients with post-stroke mortality is valuable in terms of prognosis. This study is valuable in terms of estimating the risk of stroke and early treatment in patients who will undergo CAG or PCI.

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