RESEARCH ARTICLE / *Araştırma Makalesi*

Impact of Smoking on Clinical Outcomes in ST-Elevated Myocardial Infarction Patients with Small Infarct Related Coronary Vessels

İnfarktla İlişkili Küçük Koroner Damarları Olan ST-Yükselmeli Miyokard İnfarktüslü Hastalarda Sigara İçiminin Klinik Sonuçlar Üzerine Etkisi

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Abstract

Objective	The impact of smoking status on clinical outcomes is unknown in ST-segment elevation myocardial infarction (STEMI) patients with small culprit vessel coronary artery disease (CAD). The aim of this study was to evaluate the in-hospital mortality and long-term outcomes of STEMI patients with small infarct related vessels according to smoking status.
Materials and Methods	Between January 2014 and May 2017, 310 consecutive STEMI patients with small infarct related coronary vessel who underwent primary percutaous intervention were included in this retrospective study. The patients were classified into two groups according to status of smoking, as smokers (n =163) and non-smokers (n =147). The primary outcome was major adverse cardiac events (MACE). The secondary end-point included in-hospital mortality.
Results	During the follow-up of 24 months, MACE occurred in 25 (15.70%) patients in smokers and 9 (6.30%) patients in non-smokers (p:0.008). The target-lesion revascularization (TLR), target-vessel revascularization (TVR) and myocardial infarction (MI) rates was found significantly higher in the smoker group as compared with the non-smoker group (p:0.024, p:0,014, p:0,011, respectively). The rate of in-hospital mortality was found similar between groups (p: 0.869). In multivariate Cox analysis for 2-year MACE, after accounting for all covariables, smoking was associated with increased risk in the small vessel CAD population (HR: 2.60, %95CI: 1.21-5.57). Moreover, smoking was associated with a increased TLR (HR: 3.25, %95 CI: 1.07-9.89), TVR (HR: 3.13, %95 CI: 1.15-8.50) and MI (HR: 2.81, %95 CI: 1,19-6,62) risk at 2-years follow up.
Conclusions	In our real-world registry of patients who underwent primary percutaneous coronary intervention (PPCI), groups had similar in-hospital mortality, but smoking is independently associated with poorer outcomes during 2-year follow-up.

Keywords percutaneous coronary intervention; myocardial infarction; smoking; coronary artery disease.

Öz

Amaç	*Sigara içme durumunun klinik sonuçlar üzerindeki etkisi, küçük sorumlu damar koroner arter hastalığı (KAH) olan ST segment elevasyonlu miyokard enfarktüsü (STEMI) hastalarında bilinmemektedir. Bu çalışmanın amacı, enfarktüs ile ilişkili küçük damarları olan STEMI hastalarının hastane içi mortalitesini ve uzun dönem sonuçlarını sigara içme durumuna göre değerlendirmektir.*
Gereç ve Yöntemler	*Bu retrospektif çalışmaya Ocak 2014 ve Mayıs 2017 tarihleri arasında primer perkütan girişim geçiren, enfarktüs ile ilişkili küçük koroner damarı bulunan 310 ardışık STEMI hastası alındı. Hastalar sigara içme durumuna göre sigara kullananlar (n = 163) ve sigara kullanmayanlar (n = 147) olmak üzere iki gruba ayrıldı. Birincil sonlanım majör advers kardiyak olaylardı (MACE). Sekonder sonlanım noktası hastane içi mortaliteyi içeriyordu.*
Bulgular	*24 aylık takipte sigara içenlerde 25 (%15,34) hastada, sigara içmeyenlerde 9 (%6,12) hastada MOKO gelişti (p:0,008). Sigara içen grupta hedef lezyon revaskülarizasyonu (HLR), hedef damar revaskülarizasyonu (HDR) ve miyokard infarktüsü (MI) oranları sigara içmeyenlere göre anlamlı derecede yüksek bulundu (sırasıyla, p:0.024, p:0,014, p:0,011). Hastane içi mortalite oranı iki grup arasında benzer bulundu (p: 0.869). 2 yıllık MOKO için çok değişkenli Cox analizinde, tüm değişkenler için hesap yapıldıktan sonra, sigara kullanımı, küçük damar KAH popülasyonunda artmış risk ile ilişkili bulunmuştur (HR: 2.60, %95 CI: 1.21-5.57). Ayrıca sigara içilmesi 2 yıllık takipte, HLR (HR: 3.25, %95 CI: 1.07-9.89), HDR (HR: 3.13, %95 CI: 1.15-8.50) ve MI (HR: 2.81, %95 CI: 1,19-6,62) için daha yüksek bir risk ile ilişkilendirildi.*
Sonuç	*Gerçek yaşam kayıt çalışmamızda primer perkutan koroner girişim (PPKG) yapılan küçük damar KAH olan hastalarda hastane içi ölüm oranları gruplar arasında benzer saptandı, ancak 2 yıllık takipte sigara kullanımı kötü sonlanımlar ile bağımsız ilişkili bulundu.*

Anahtar Kelimeler *perkütan koroner girişim; miyokardiyal infarktüs; sigara içme; koroner arter hastalığı.*

Introduction

Smoking is a well-known risk factor for coronary artery disease (CAD) and is associated with increased rates of acute coronary syndrome (ACS) and cardiovascular death.[1,2] Due in part to the prothrombotic effects of smoking, 3 cigarette smokers are more likely to present with ST-segment elevation myocardial infarction (STEMI) than with non-ST segment elevated acute coronary syndrome (NSTE-ACS).[4] The risk of acute myocardial infarction (MI) is three times higher in patients who continue to smoke after an acute coronary event compared to patients who quit smoking.[5] The risk of re-infarction in patients who stop smoking is similar to the risk of non-smokers before the first infarction.[5] Previous studies have demonstrated a higher incidence of acute MI but improved survival after reperfusion among smokers.[6,7] This phenomenon, termed the smoker's paradox and typically described in studies where patients who were smoker and had acute STEMI.[8,9] It has been postulated to be due to the fact that smokers present at a younger age, typically with fewer comorbidities and and with a higher incidence of thrombo-occlusive disease that is optimally treatable.6,7 Moreover, smokers presenting with acute MI also have less extensive CAD than nonsmokers.[10]

Small-vessel (≤ 2.5 mm) CAD is common among patients undergoing percutaneous coronary intervention (PCI) and has been documented in 30% to 40% of cases.[11,12] Small vessels are more prone to restenosis than larger vessels because they are less able to accommodate neointimal tissue without compromising blood flow.[13] There are no previous study comparing smokers and non-smokers for small vessel CAD on clinical outcomes of patients with STEMI. In the current study, we evaluated in-hospital mortality and long term outcomes of smokers and non-smokers in STEMI patients undergoing a primary PCI for small vessel coronary culprit lesions.

Materials and Methods

Study Design and population

This was a single-centre retrospective cohort study of the clinical outcomes in STEMI patients treated with stenting of infarct related native small coronary arteries. Small vessel CAD was considered a need for implantation of stents ≤ 2.5 mm (diameter of the implanted stent: ≤ 2.5 mm). Between January 2014 and May 2017, 310 consecutive STEMI patients with small infarct related vessel who underwent primary percutaous intervention were included in this retrospective study. The patients were classified into two groups according to status of smoking, as smokers (n =163) and non-smokers (n =147). The primary outcome was major adverse cardiac events (MACE). The secondary end-point included in-hospital mortality. The exclusion criteria were a concomitant large diameter PCI in the same coronary artery, cardiogenic shock, a PCI consisting of in-stent restenosis (ISR) for the culprit lesion, contraindication to antithrombotic agents, known bleeding disorders, infarction related to the grafted vessel, life expectancy <12 months and pregnancy. An additional exclusion criterion was a lack of relevant patient- or procedural- related data. This study complied with the Declaration of Helsinki, and it was approved by the independent medical ethics committee of Sakarya University Education and Research Hospital (03/05/2019; 050.01.04/114).

Study protocol

Coronary stenting was considered angiographically successful if residual stenosis of <30% and coronary thrombolysis in myocardial infarction grade flow 3 were obtained at the end of the procedure. During the procedure, an intra-arterial bolus of unfractionated heparin was given at a dose of 80 U/kg. After the intervention, all patients received aspirin indefinitely, clopidogrel, prasugrel or ticagrelor for at least 12 months and other cardiac medications according to American College of Cardiology / American Heart Association (ACC/AHA) guidelines.[14] Angiographic findings such as vessel dimensions, pre- and post-procedural stenoses and lesion length were determined by

measure the reference vessel diameter by Quantitative Coronary Analysis (QCA). The angiographic characteristics were also further analysed by an independent interventional cardiologist not involved in the procedure and checked for inter-observer agreement. In this study, no-reflow phenomenon and edge dissection were defined as procedural complications.

Data collection

Baseline demographics, clinical characteristics and procedural data were collected retrospectively. Patients applied to our outpatient clinic for a control examination every 3 to 6 months.The in-hospital and 2-years follow-up information on clinical outcomes [e.g. in- hospital death, recurrent MIs, target-lesion revascularization (TLR), target-vessel revascularization (TVR) and definite stent thrombosis (ST)] were collected from electronic medical records, a registry database or phone calls, which asked about relevant end-point clinical events. Routine or control angiography during the follow-up without a clinical indication was not undertaken. However, event-driven coronary angiographies after the initial PCI were performed within the 2-years follow-up period.

Study endpoints and Definitions

The primary outcome was major adverse cardiac events (MACEs), which were defined as TLR, TVR, MI or definite ST during the follow-up period. The secondary end-point included in-hospital mortality. TVR was defined as any clinically driven PCI or bypass grafting of the target vessel. TLR was defined as any clinically driven repeat PCI or bypass grafting of the treated lesion, including the placement of an in-stent or in-segment 5 mm proximal or distal to the initial stent edges. An MI was defined according to current guidelines.[15] Definite ST was defined based on the criteria of the Academic Research Consortium.[16] In this study, no-reflow phenomenon and edge dissection were defined as procedural complications. Smokers were defined as those who were active smokers at the time of STEMI. Non smokers were patients who had never smoked in their life.

Statistical Analysis

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS), version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. Continuous data were expressed as mean ± standard deviation, and the categorical data were expressed as percentages. The normal distribution of the data was assessed by the Kolmogorov–Smirnov test. Comparisons between groups were performed using a chi-square or Fisher's exact tests for qualitative variables, as appropriate. An independent t-test was used for normally distributed continuous variables, and the Mann–Whitney U test was conducted for non-normally distributed continuous variables, as appropriate. The Kaplan–Meier analysis was used to calculate the time to the clinical end-point, and the log-rank test was applied to compare between-group differences. Univariate analyses were completed for 2-year MACE using time-to-event methodology, and the corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were determined. A multivariate Cox proportional hazards regression analysis, which was selected to take into account time to event data, was then performed on these variables. Covariates were selected using a forward stepwise procedure from clinical and demographic candidate variables: age, gender, LVEF, smoking status, CKD, DM, HT, previous MI, previous PCI, stent diameter and procedural complication. A significance level of 0.05 was required to allow a variable into the models, and a significance level of 0.10 was required to allow a variable to stay in the models. A p value < 0.05 was considered statistically significant in all tests.

Results

Characteristics of the patients

A total of 310 patients were included in the study. Patients were divided according to smoking status as current smokers (163 patients, 52.58 %) and non-smokers (147 patients, 47.42 %). The baseline demographics and clinical characteristics of groups are shown in Table 1. There was no significant difference between the two groups with respect to age, gender, LVEF, prevalence of diabetes mellitus

(DM), hypertension (HT), hyperlipidemia and chronic kidney disease (CKD), history of ischemic heart disease (IHD) and PCI.

Table 1. Comparation of baseline demographics and clinical presentations between smokers and non-smokers groups.

Variables	Non-Smoker (n=147)	Smoker (n=163)	p value
Gender(male), n (%)	113 (76.87)	135 (82.82)	0.123
Age, mean ± SD (years)	62.22 ± 9.51	60.66 ± 10.21	0.077
LVEF, mean ± SD (%)	46.46 ± 10.20	47.33 ± 10.20	0.400
Diabetes Mellitus, n (%)	64 (43.53)	54 (33.12)	0.060
Hypertension, n (%)	68 (46.25)	68 (41.71)	0.422
Hyperlipidemia, n (%)	39 (26.53)	31 (19.01)	0.115
Previous IHD, n (%)	8 (5.44)	18 (11.04)	0.076
Previous PCI, n (%)	10 (6.80)	17 (10.42)	0.259
CKD, n (%)	18 (12.24)	12 (7.36)	0.147

Data presented as mean ± standard deviation or number (%). LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; PCI, percutaneous coronary intervention; CKD, chronic kidney disease.

Characteristics of the lesions, and PCI procedures

The lesional and procedural characteristics are summarized in Table 2. The target vessel and culprit lesion location were similar in both groups. Also, the two groups did not differ significantly with respect to the rate of predilation, postdilation and multivessel disease. The complication rate was not significantly different among smokers and non-smokers. The stent lenght was found similar among smokers and non-smokers. However, stent diameter was found significantly lower in non-smokers group than in smokers (p: 0.005).

Table 2. Comparation of lesions and procedural characteristics between smokers and non-smokers groups

Variables	Non-Smoker (n=147)	Smoker (n=163)	p value
Target artery			0.123
Left anterior descending	62 (42.17)	63 (38.65)	0.368
Left circumflex	23 (15.64)	19 (11.65)	
Right coronary	49 (33.33)	67 (41.10)	
Other	13 (8.84)	14 (8.58)	
Procedural characteristics			
Complication	15 (10.20)	19 (11.65)	0.684
Predilation	99 (67.34)	104 (63.80)	0.514
Post-dilation	17 (11.56)	21 (12.88)	0.725
Stent length , mean ± SD [mm]	21.57 ± 5.66	21.61 ± 5.83	0.950
Stent diameter , mean ± SD [mm]	2.43 ± 0.11	2.46 ± 0.08	0.005
Lesion Location			
Proksimal	50 (34.01)	60 (36.80)	0.286
Mid	74 (50.34)	86 (52.76)	
Distal	23 (15.64)	17 (10.42)	
Multivessel Disease	15 (10.20)	18 (11.04)	0.812

Data are presented as mean ± standard deviation or number (%).

Clinical outcomes

At the 2-years follow-up, 44 (27.01%) patients in the smoker group and 31 (21.09 %) patients in the non-smoker group were needed to underwent angiographic evaluations. The outcomes of the patients during the follow-up period are summarized in Table 3.

Table 3. Major Outcomes at 2-Year Follow-Up Stratified by Smoking Status.

Variables	2-YEAR RESULTS		
	Non-Smoker (n=147)	Smoker (n=163)	p-value
MI	7 (4.76)	21 (12.88)	0.011
TLR	4 (2.72)	14 (8.58)	0.024
TVR	5 (3.40)	17 (10.42)	0.014
ST	3 (2.04)	8 (4.90)	0.166
MACE	9 (6.12)	25 (15.33)	0.008

Data are n (%). MI, miyocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis; MACE, major adverse cardiovascular events.

At the 2-years follow-up, the primary composite end-point, MACEs, occurred higher in the smokers group (15.33 %) than in the non-smokers group (6.12 %) (p: 0.008). The TLR, TVR and MI rates was found significantly higher in the smoker group as compared with the non-smoker group (p: 0.024, p: 0,014, p: 0,011, respectively). Although stent thrombosis tended to be lower in the non-smoker group, there were no significant difference between groups (p : 0.166). The rate of in-hospital mortality, the secondary end-point, was found similar in smokers with small vessel CAD as compared with that in non-smokers (3.1 % vs 3.4 %, p: 0.869).

Kaplan-Meier survival analysis showed in Figure 1. The time-to-event curves reflected a higher incidence of MACE rates in the smokers group for small-vessel CAD (P log rank = .010). In multivariate Cox proportional hazards regression analysis for 2-year MACE, after accounting for all covariables, smoking was independently associated with increased risk in the small vessel CAD population (HR: 2.60, 95% CI: 1.21 to 5.57). Moreover, smoking was also independently associated with increased TLR (HR: 3.25, 95% CI: 1.07 to 9.89), TVR (HR: 3.13, 95% CI: 1.15 to 8.50) and MI (HR: 2.81, 95% CI: 1.19 to 6.62) risk at 2-years follow up (Table 4).

Table 4. The relationship between smoking and endpoints in univariate and multivariate cox analysis.

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
MI	3.09 (1.37 – 6.96)	0.006	2.81 (1.19 – 6.62)	0.018
TLR	4.80 (1.35 – 17.06)	0.015	3.25 (1.07 - 9.89)	0.037
TVR	4.49 (1.44 – 13.97)	0.009	3.13 (1.15 - 8.50)	0.015
MACE	3.39 (1.34 – 8.57)	0.010	2.60 (1.21 - 5.57)	0.014

MI, miyocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiovascular events.

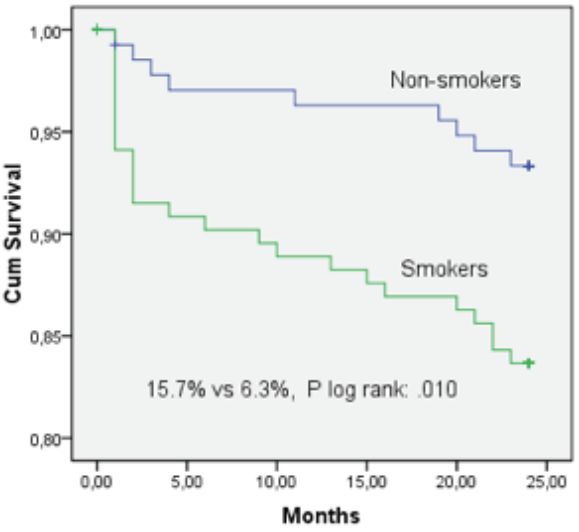

Figure 1. Kaplan–Meier curves estimate of freedom from MACE at 24 months follow-up.

Discussion

In this study, we showed that smoking was an independent predictor of 2-year MACE in the cohort of STEMI patients that undergoing a primary PCI for small vessel CAD. Additionally, we demonstrated that smokers presenting with STEMI that have small vessel CAD have significantly higher TLR, TVR and MI rate at 2-year follow up to those seen in nonsmokers. The results of this study in small vessel disease are different from the previously observed relationship between smoking and CAD in STEMI patients.

Despite a major technical evolution in revascularization interventions, the optimal treatment for small vessel CAD remains under discussion because the risk of adverse outcomes is inversely correlated with the vessel diameter.[17] Small vessels are more prone to restenosis than larger vessels because they are less able to accommodate neointimal tissue without compromising blood flow.[13] One-year stent thrombosis (ST), major adverse cardiac event (MACE), myocardial infarction (MI) and clinically indicated target-lesion revascularization (TLR) rates are higher in patients with small vessel CAD as compared with those with non-small vessel CAD, whereas mortality rates in small

vessel CAD and non-small-vessel CAD are similar.[18]

Smoking is a well-established cardiovascular risk factor and remains an important preventable cause of death. Smoking increases endothelial dysfunction, thrombogenicity and coronary vasoconstriction, making patients susceptible to ACS events.[19] The previous studies showed that smokers are younger and have typically fewer comorbidities and these factors cause smoker's paradox.[6,7] In, the present study, consistent with these results, smokers were younger, had higher LVEFs, and had lower DM, HT, CKD rates than non-smokers. The 'smoker's paradox' in patients with acute coronary syndromes suggests there could be potential survival benefit seen in smokers.[20] In our study, smokers and non-smokers had similar mortality rates in in-hospital term after undergoing primary PCI. In a recent study, Ciccarelli et al. showed that being non-smoker and ongoing DAPT at admission, in patients with STEMI undergoing PPCI, represent independent negative prognostic value.[21] In an another study, Symons et al. showed that smoking was an independent protective predictor against adverse LV remodelling in patients with reperfused STEMI.[22] Reinstadler et al. reported that smokers had lower MACE rates at 12 months, and explained by differences in baseline risk characteristics.[23] The most of the studies showed that reperfusion by thrombolysis might be more effective in smokers due to a greater thrombus burden than in non-smokers.[7] However, this benefit might no longer exist when using mechanical reperfusion strategies. Because the smoker's paradox has been demonstrated almost entirely in the pre-PCI era.[20] All patients in our study treated with primary stenting. Morever, in the present study, we showed that smoking represents negative prognostic value on composite end-points.

Limitations

Several limitations of the present study should be acknowledged. These include its small sample size and non-randomized nature. Moreover, as this was a single-centre observational retrospective analysis, there is an inherent selection bias. The information on smoking status was only available on admission. The potential impact of changes in smoking habits after the index event might affect clinical event rate and could not be assessed in this study. In addition, low rate of our patients received follow-up coronary angiography according to clinical indications, and the potential bias related to the incomplete angiographic follow-up might have had a substantial impact on the analytic results.

Conclusions

This study has demonstrated important impact of smoking on in-hospital and long term outcomes in STEMI patients with small culprit vessel CAD who underwent primary PCI. Non-smokers had more favourable 2-year clinical outcomes than smokers. It is necessary to confirm these results with prospective and randomized studies with larger patient groups. Our results showed that there are no effect of smoker's paradox on long term outcomes in STEMI patients with small vessel CAD.

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