Effect of smoking on clinical outcomes in patients receiving rotational atherectomy in calcified coronary lesions: from the ROCK Registry, South Korea

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BACKGROUND: Tobacco smoking and its harmful health effects also increase economic burdens globally. Surprisingly, despite the detrimental health consequences of smoking, some studies have shown better survival among smokers compared with non-smokers, a phenomenon called “smoker’s paradox”. However, the impact of smoking status on clinical outcomes in severe calcified coronary artery disease (CAD) patients has yet to be reported.

OBJECTIVE: Investigate the impact of smoking on clinical outcomes in calcified CAD receiving rotational atherectomy (RA).

DESIGN: Retrospective review of medical records.

SETTING: Multicenter registry in South Korea.

PATIENTS AND METHODS: This multicenter registry included consecutive patients with calcified CAD who underwent RA at nine tertiary centers in Korea between January 2010 and October 2019.

MAIN OUTCOME MEASURES: Target-vessel failure (TVF) which included the composite of cardiac death, target-vessel myocardial infarction (TVMI), and target-vessel revascularization (TVR).

SAMPLE SIZE: 583 lesions in 540 patients followed for a median of 16.1 months.

RESULTS: Lesions were divided into two groups: non-smokers (n=472, 81.0%) and smokers (n=111, 19.0%). TVF in the smoker group was significantly more frequent than in non-smoker group (log rank \(P=0.016\)). The inverse probability of treatment weighting analysis also showed that smoking was significantly associated with a higher incidence of the primary outcome (HR: 1.617; 95% CI: 1.127-2.320; \(P=0.009\)), cardiac death (HR 1.912; 95% CI: 1.105-3.311; \(P=0.021\)), myocardial infarction (HR: 3.914; 95% CI: 1.884-8.132; \(P<.001\)), TVMI (HR: 3.234; 95% CI: 1.130-9.258; \(P=0.029\)), and TVR (HR: 1.661; 95% CI: 1.043-2.643; \(P=0.032\)). However, any bleeding was significantly observed less in the smokers.

CONCLUSION: Smoking is significantly associated with adverse clinical outcomes in CAD patients requiring RA.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.
Tobacco smoking is one of the leading preventable risk factors for development of coronary artery disease (CAD). Smoking increases the risk of major adverse cardiovascular events and mortality in CAD patients worldwide. Tobacco smoking and its harmful health effects also increase economic burdens globally. Surprisingly, despite the detrimental health consequences of smoking, some studies have shown better survival among smokers compared with non-smokers, a phenomenon called “smoker’s paradox.” The smoker’s paradox is mainly observed among patients with CAD in the thrombolysis era, acute myocardial infarction and heart failure.

In the percutaneous coronary intervention (PCI) era, severe calcified lesions are probably the most challenging and most likely to have an adverse impact on both the short- and the long-term outcomes of CAD. Calcified coronary lesions are associated with advanced age, diabetes, smoking and chronic kidney disease. Heavy calcium increases the complexity of the procedure by interfering with lesion preparation and balloon expansion, making device delivery difficult, and limiting final stent expansion. Coronary rotational atherectomy (RA) ablates and modifies calcified plaques leading to lumen enlargement, plaque softening, and consequently better stent expansion.

However, the impact of smoking status on clinical outcomes in severe calcified CAD patients has yet to be reported. Therefore, the objective of this study was to investigate the clinical outcomes in CAD patients requiring RA according to smoking status.

PATIENTS AND METHODS

The study population consisted of patients with calcified CAD who underwent PCI using RA between January 2010 and October 2019 at nine tertiary centers in Korea. Patients were included within the Rotational Atherectomy In Calcified Lesions in Korea (ROCK) registry. Data were collected at each site using a standardized case report form to record demographic and clinical characteristics, as well as procedural and follow-up data. Follow-up data were obtained from outpatient clinical records or via the telephone by independent researchers.

The treatment strategy was at the discretion of the attending cardiologists with careful consideration of clinical risk factors, anatomical complexity, and patient conditions (including decisions of burr size during the procedure). All RA procedures were performed using the Rotablator RA system (Boston Scientific, Marlborough, MA, USA). Medications including antiplatelet therapy and periprocedural anticoagulation were performed in accordance with the accepted guidelines. This study was approved by the local ethics committee of each hospital, and all patients provided written informed consent for use of their clinical data for the registry study.

The primary clinical outcome was target-vessel failure (TVF), which included cardiac death, target-vessel spontaneous myocardial infarction (MI), or target-vessel revascularization (TVR). The secondary endpoint was all-cause death, cardiac death, any MI, target-vessel spontaneous MI, TVR, stent thrombosis (ST), and any bleeding.

Technical success was defined as achievement of residual stenosis <30% in the presence of grade III Thrombolysis in Myocardial Infarction (TIMI) 3 flow. Procedural success was defined as achievement of technical success without an in-hospital event or peri-procedural complication including in-hospital death, in-hospital CVA, urgent additional revascularization (CABG surgery or PCI), temporary pacemaker insertion due to procedure-related atrioventricular (AV) block, intervention or surgery due to cardiac tamponade, coronary perforation or dissection [type D-F, defined from The National Heart, Lung, and Blood Institute (NHLBI) classification system], and periprocedural MI.

Target-vessel spontaneous MI was spontaneous MI clearly attributable to the target vessel. Spontaneous MI was defined as any creatine kinase-myocardial band or troponin increase above the upper limit of the normal range with ischemic symptoms or signs during follow-up after discharge. Periprocedural MI was defined as peak elevations of the creatine kinase-myocardial band of >10-fold above the upper reference limit within 48 hours after the procedure. TVR was defined as any percutaneous or surgical revascularization of the treated vessel. All clinical events were confirmed by source documentation collected at each hospital and centrally adjudicated by an independent group of clinicians unaware of the revascularization type. Bleeding events were defined according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate < 60mL/min/1.73m², as calculated using the Modification of Renal Diet (MDRD) equation from baseline serum creatinine. Current smoking status at index admission was used to stratify the patient groups. Smokers were defined as patients who reported having smoked cigarettes within 3 months of index admission. Nonsmokers included patients who have never smoked and ex-smokers.

Continuous variables are presented as the median and interquartile range or mean and standard deviation using the t test. Categorical variables are expressed using the chi-square test.
as number and percentage and compared using the chi-square or the Fisher exact test. Primary clinical outcomes were determined using the Kaplan-Meier method and compared using the log-rank test. Cox regression analyses were performed to analyze the impact of smoking on clinical outcomes. Multivariate Cox regression analyses and inverse probability of treatment weighting (IPTW)-adjusted analysis were conducted with significant variables identified based on univariate Cox regression analyses (P<.01). The hazard ratio (HR) and 95% confidence interval (CI) were calculated. A P value <.05 was considered statistically significant. All statistical analyses were performed using Statistical Analysis Software (SAS, version 9.2, SAS Institute, Cary, NC, USA).

RESULTS
A total of 583 lesions in 540 patients were analyzed and followed for a median of 16.1 months (Table 1). The smoker group was younger, and had a higher concentration of hemoglobin, total lymphocyte count and triglyceride. The prevalence of male sex was significantly higher in the smoker group. However, the prevalence of hypertension was lower in the smoker group. There was no difference in baseline angiographic and procedural characteristics (Table 2).

The incidences of primary outcomes including cardiac death, TVMI, and TVR were significantly higher in the smoker group than the non-smoker group (22 [19.8%] versus 54 [11.4%], P=.018, Table 3). The incidences of MI and TVR were significantly higher in the smoker group than the non-smoker group (8 [7.2%] versus 10 [2.1%], P=.011 for MI, 13 [11.7%] versus 29 [6.1%], P=.041 for TVR, Table 3).

Multivariate Cox hazard regression analysis showed that smoking was significantly associated with higher incidence of primary outcome (HR: 2.030; 95% CI: 1.143-3.606; P=.016), all cause death (HR: 2.626; 95% CI: 1.156-5.968; P=.021), cardiac death (HR 2.861; 95% CI: 1.168-7.007; P=.022), and higher incidence of MI (HR: 4.367; 95% CI: 1.414-13.485; P=.010) (Table 4). IPTW analysis also revealed that smoking was significantly associated with higher incidence of primary outcome (HR: 1.617; 95% CI: 1.127-2.320; P=.009), cardiac death (HR 1.912; 95% CI: 1.105-3.311; P=.021), MI (HR: 3.914; 95% CI: 1.884-8.132; P<.001), TVMI (HR: 3.234; 95% CI: 1.130-9.258; P=.029), and TVR (HR: 1.661; 95% CI: 1.043-2.643; P=.032) (Table 4). However, any bleeding was significantly observed less in the smoker group. The primary outcomes in the smoker group were significantly more frequent than in the non-smoker group (log rank P=.016, Figure 1).

| Table 1. Baseline demographic, clinical, and laboratory characteristics (n=540 patients). |
|----------------------------------|------------------|------------------|------------------|
|                                 | Non-smoker (n=472 lesions) | Smoker (n=111 lesions) | P value |
| Age (years)                     | 72.9 (9.2)         | 64.8 (10.6)       | <.001 |
| Male                            | 252 (53.4)         | 102 (91.9)        | <.001 |
| Body mass index                 | 24.3 (4.0)         | 23.7 (3.4)        | .154  |
| Risk factor                     |                   |                   |       |
| Hypertension                    | 375 (79.5)         | 78 (70.3)         | .037  |
| Diabetes mellitus               | 274 (58.1)         | 58 (52.3)         | .267  |
| Dyslipidemia                    | 214 (45.3)         | 42 (37.8)         | .152  |
| Family history of coronary artery disease | 11 (2.3)         | 1 (0.9)           | .479  |
| Chronic kidney disease, n (%)   | 87 (18.4)          | 20 (18.0)         | .919  |
| Previous percutaneous coronary intervention | 125 (26.5)       | 28 (25.2)         | .786  |
| Previous myocardial infarction  | 54 (11.4)          | 17 (15.3)         | .261  |
| Cerebro-vascular accident       | 69 (14.6)          | 11 (9.9)          | .195  |
| Heart failure                   | 73 (15.5)          | 13 (11.7)         | .316  |
| Atrial fibrillation             | 47 (10.0)          | 7 (6.3)           | .233  |
| Treatment                       |                   |                   |       |
| Non-vitamin K anticoagulant     | 16 (3.4)           | 1 (0.9)           | .218  |
| Dual antiplatelet therapy       | 457 (96.8)         | 104 (93.7)        | .160  |
| Aspirin                         | 461 (97.7)         | 110 (99.1)        | .479  |
| P2Y12 inhibitor                 | 463 (98.1)         | 109 (98.2)        | >.999 |
| Cilostazol                      | 66 (14.0)          | 17 (15.3)         | .718  |
| Beta blocker                    | 332 (70.3)         | 79 (71.2)         | .863  |
| Angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker | 299 (63.4) | 68 (61.3) | .682 |
| Statin                          | 439 (93.0)         | 105 (94.6)        | .547  |
| Laboratory finding              |                   |                   |       |
| Hemoglobin (g/dL)               | 12.2 (2.4)         | 12.9 (1.9)        | .003  |
| Platelet (>10^9/L)              | 219.3 (69.8)       | 222.6 (76.5)      | .658  |
| Total lymphocyte count (>10^7/L) | 2.0 (1.4-3.6)     | 2.6 (1.6-6.3)     | .004  |
| Glycated hemoglobin (%)         | 6.65 (1.43)        | 6.73 (1.44)       | .656  |
| High-sensitivity C-reactive protein (mg/dL) | 3.3 (12.6) | 3.2 (7.3) | .950 |
| Total cholesterol (mg/dL)       | 144.5 (39.6)       | 141.2 (34.6)      | .431  |
| Low density lipoprotein cholesterol (mg/dL) | 85.8 (41.1) | 80.0 (29.8) | .195 |
| HDL cholesterol (mg/dL)         | 46.7 (14.8)        | 43.8 (12.4)       | .074  |
| High density lipoprotein (mg/dL) | 116.0 (67.8)      | 137.5 (98.8)      | .011  |

Data are expressed as mean (standard deviation) or number (%);
DISCUSSION

In this study, we explored the impact of smoking on clinical outcomes in patients with calcified CAD receiving RA. Approximately 19% of the study population were smokers at admission, which was associated with an increased risk for death from cardiac causes. TVF in the smoker group was significantly higher than in the non-smoker group. Smoking is one of the strongest modifiable risk factors for cardiovascular disease and sudden cardiac death. Smoking cessation reduces the risk of subsequent cardiovascular events. Based on available evidence, it is reasonable to recommend smoking cessation in patients after coronary revascularization. In the real world, the number of smokers was reduced by half after coronary revascularization, suggesting that most patients followed the advice of smoking cessation. Nevertheless, cigarette smoking remains a major problem in patients with ischemic heart disease.

In the thrombolytic therapy era, numerous studies have reported that smokers are associated with favorable clinical outcomes compared with non-smokers. However, recent previous studies have shown that this hypothesized survival benefit in smokers with CAD no longer exists in the PCI era, even though some studies still report on the “smoker’s paradox” A recent report investigated the effect of baseline smoking sta-
Coronary artery calcification is associated with worse prognosis not only in stable patients, but also in acute myocardial infarction patients. Therefore, there have been many studies on factors associated with coronary artery calcification. With the aging society, the number of patients with CAD accompanied by heavy calcium is increasing, leading to difficulties when performing PCI. Severe coronary calcific lesions increase the complexity of the procedure by interfering with lesion preparation and balloon expansion, making device delivery difficult and limiting final stent expansion. Coronary RA ablates and modifies the calcified plaque, leading to lumen dilatation, plaque softening, and consequently better stent expansion.

The mechanisms by which smoking might have been associated with worse clinical outcomes in patients with severely calcified lesions have not been completely elucidated. Smoking contributes to atherosclerosis and plaque progression, causing low density lipoprotein and high density lipoprotein cholesterol changes. Smokers usually have high levels of fibrinogen and increased platelet aggregation, which can lead to hypercoagulability. In addition, smoking also alters prostacyclin production, causing vasoconstriction, and causes endothelial dysfunction.

In the present study, smokers were significantly younger, and had a higher level of hemoglobin, triglyceride and total lymphocyte count. A previous study demonstrated that smoking was associated with up-regulation of the CD40/CD40 ligand dyad and platelet-monocyte aggregation. They concluded that these results might provide a major contribution to the mechanisms whereby smoking promotes atherosclerosis and is associated with development of adverse cardiovascular events. In the present study, smokers had a worse prognosis in the unadjusted analysis and the adverse effects of smoking persisted even after adjustments for multivariable factors.

Our study has several limitations. First, we obtained the information on smoking status only at the time of the index event and not during follow-up. Based on the beneficial effect of smoking cessation, information on smoking status at serial time points would have provided additional useful information. Second, smoking status presented here is self-reported. In addition, detailed data on smoking intensity and duration of smoking were not recorded. Third, the period
Table 4. Independent risk for clinical events by multivariate Cox hazard regression model.

| Event                              | Univariate hazard ratio | P value | Multivariate hazard ratio | P value | Adjusted hazard ratio by IPTW* | P value |
|------------------------------------|-------------------------|---------|---------------------------|---------|-------------------------------|---------|
| Target vessel failure              | 1.825 (1.111-2.996)     | .018    | 2.030 (1.143-3.606)       | .016    | 1.617 (1.127-2.320)           | .009    |
| All cause death                    | 1.256 (0.620-2.542)     | .527    | 2.626 (1.156-5.968)       | .021    | 1.561 (0.969-2.515)           | .067    |
| Cardiac death                      | 1.597 (0.742-3.435)     | .231    | 2.861 (1.168-7.007)       | .022    | 1.912 (1.105-3.311)           | .021    |
| Myocardial infarction              | 3.540 (1.397-8.970)     | .008    | 4.367 (1.414-13.485)      | .010    | 3.914 (1.884-8.132)           | <.001   |
| Target vessel myocardial infarction| 3.472 (0.932-12.933)    | .064    | 4.041 (0.824-19.813)      | .085    | 3.234 (1.130-9.258)           | .029    |
| Target vessel revascularization    | 2.032 (1.056-3.909)     | .034    | 1.842 (0.866-3.920)       | .113    | 1.661 (1.043-2.643)           | .032    |
| Stent thrombosis                   | 1.686 (0.327-8.691)     | .532    | 2.608 (0.393-17.314)      | .321    | 1.725 (0.615-4.838)           | .300    |
| Any bleeding                       | 0.279 (0.067-1.168)     | .081    | 0.506 (0.114-2.254)       | .372    | 0.374 (0.179-0.781)           | .009    |

*Adjusted by age, sex, hypertension, hemoglobin, total lymphocyte count, triglyceride, high density lipoprotein cholesterol. IPTA: inverse probability of treatment weighting

The recruitment of the research population was relatively long. Therefore, there might have been a lot of technological advances in the meantime. Finally, we could not quantify the degree of coronary artery calcification. Nonetheless, despite these limitations, our results emphasize the impact of smoking on clinical outcomes in CAD patients with severe calcific lesions.

In conclusion, to our knowledge, we are the first to demonstrate that smoking is independently predictive of worse clinical outcomes after multivariate analysis among patients with calcified CAD receiving RA. Therefore, physicians should encourage smoking cessation to reduce the burden of cardiovascular disease in the general population.
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