Current but not past smoking increases the risk of cardiac events: insights from coronary computed tomographic angiography

Rine Nakanishi1, Daniel S. Berman2, Matthew J. Budoff1, Heidi Gransar2, Stephan Achenbach3, Mouaz Al-Mallah4, Daniele Andreini5, Filippo Cademartiri6,7, Tracy Q. Callister8, Hyuk-Jae Chang9, Victor Y. Cheng10, Kavitha Chinnaiyan11, Benjamin J.W. Chow12, Ricardo Cury13, Augustin Delago14, Martin Hadamitzky15, Jörg Hausleiter15, Gudrun Feuchtner16, Yong-Jin Kim17, Philipp A. Kaufmann18, Jonathon Leipsic19, Fay Y. Lin20, Erica Maffeì5,7, Gianluca Pontone5, Gilbert Raff11, Leslee J. Shaw21, Todd C. Villines22, Allison Dunning23, and James K. Min20*

1Department of Medicine, Harbor UCLA Medical Center, Torrance, CA, USA; 2Departments of Imaging and Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; 3Department of Medicine, University of Erlangen, Erlangen, Germany; 4Department of Medicine, Wayne State University, Henry Ford Hospital, Detroit, MI, USA; 5Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy; 6Cardio Vascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Italy; 7Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands; 8Department of Radiology, Weill Cornell Medical College and the New York Presbyterian Hospital, New York, NY, USA; 9Division of Cardiology, Severance Cardiovascular Hospital, Seoul, Republic of Korea; 10National University Hospital, Seoul, South Korea; 11William Beaumont Hospital, Royal Oak, MI, USA; 12Department of Medicine and Radiology, University of Ottawa, Ottawa, ON, Canada; 13Baptist Cardiac and Vascular Institute, Miami, FL, USA; 14Department of Radiology, University of Southern California, Los Angeles, CA, USA; 15Department of Nuclear Cardiology, Cardiovascular Center, University of Zurich, Zurich, Switzerland; 16Department of Medical Imaging and Division of Cardiology, St. Paul’s Hospital, University of British Columbia, Vancouver, BC, USA; 17Department of Radiology, Weill Cornell Medical College, and the New York Presbyterian Hospital, New York, NY, USA; 18Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA; 19Department of Medicine, Walter Reed National Medical Center, Bethesda, MD, USA; and 20Department of Public Health, Weill Cornell Medical College and the New York Presbyterian Hospital, New York, NY, USA

Keywords
Smoking risk ● Coronary atherosclerosis ● Coronary computed tomographic angiography ● Major adverse cardiovascular risk

Aims
We evaluated coronary artery disease (CAD) extent, severity, and major adverse cardiac events (MACEs) in never, past, and current smokers undergoing coronary CT angiography (CCTA).

Methods and results
We evaluated 9456 patients (57.1 ± 12.3 years, 55.5% male) without known CAD (1588 current smokers; 2183 past smokers who quit ≥3 months before CCTA; and 5685 never smokers). By risk-adjusted Cox proportional-hazards models, we related smoking status to MACE (all-cause death or non-fatal myocardial infarction). We further performed 1:1:1 propensity matching for 1000 in each group evaluate event risk among individuals with similar age, gender, CAD risk factors, and symptom presentation. During a mean follow-up of 2.8 ± 1.9 years, 297 MACE occurred. Compared with never smokers, current and past smokers had greater atherosclerotic burden including extent of plaque defined as segments with any plaque (2.1 ± 2.8 vs. 2.6 ± 3.2 vs. 3.1 ± 3.3, P < 0.0001) and prevalence of obstructive CAD [1-vessel disease (VD): 10.6% vs. 14.9% vs. 15.2%, P = 0.001; 2-VD: 6.1% vs. 4.3%, P = 0.001; 2-VD: 3.3% vs. 4.3%, P = 0.001]. Compared with never smokers, current smokers experienced higher MACE [hazard ratio (HR) 1.9, 95% confidence interval (CI) 1.4–2.6, P < 0.001], while past smokers did not (HR 1.2, 95% CI 0.8–1.6, P = 0.35). Among matched individuals, current smokers had higher MACE risk (HR 2.6, 95% CI 1.6–4.2, P < 0.001), while past smokers did not (HR 1.3, 95% CI 0.7–2.4, P = 0.39). Similar findings were observed for risk of all-cause death.

Conclusion
Among patients without known CAD undergoing CCTA, current and past smokers had increased burden of atherosclerosis compared with never smokers; however, risk of MACE was heightened only in current smokers.

Keywords
Smoking risk ● Coronary atherosclerosis ● Coronary computed tomographic angiography ● Major adverse cardiovascular risk

* Corresponding author. Tel: +1 212 746 2620, Fax: +1 212 746 7969, Email: jkm2001@med.cornell.edu, runone123@gmail.com
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
Clinical Perspective

Although smoking is an established risk factor for major cardiac adverse events (MACE), the relative risk of current smoking vs. past smoking is less well studied. By using coronary CT angiography, our findings showed that when compared with never smokers, past smokers had increased plaque similar to current smokers; however, compared with never smokers, higher MACE risk was observed only in current smokers.

Introduction

Smoking is a major risk factor for coronary artery disease (CAD) and risk of future major adverse cardiac events (MACEs).\(^1\)–\(^4\) While the increased in risk of events applies to current smokers, several previous studies have shown that individuals who have quit smoking have risk of future MACE that is similar to individuals who have never smoked.\(^5\),\(^6\) The underlying pathophysiology explaining why event rates do not remain elevated in individuals who have quit smoking is not well understood.

Coronary CT angiography (CCTA) has emerged as a non-invasive method to identify the presence, extent, severity, and type of coronary artery plaque.\(^7\)–\(^9\) A large number of prognostic studies have shown that the degree of coronary atherosclerosis identified by CCTA is strongly predictive of subsequent cardiac events across a broad spectrum of clinical settings.\(^7\),\(^8\) To date, the relationship between smoking, CCTA findings, and subsequent MACE has not been evaluated. The purpose of this study is to examine whether there is a difference in the presence, extent, severity of CAD as well as plaque type by CCTA to explore the relationships of these CAD measurements to the risk of future MACE and all-cause death in patients who never smoked, past, and current smokers.

Methods

Study population

We studied 9456 patients (mean age 57.1 ± 12.3 years, 55.5% male) without known CAD from patients enrolled in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry\(^10\) whose smoking status was known. Of the 27 125 patients in the CONFIRM registry, the following patients were sequentially excluded from this study: those lacking smoking status information (n = 11 289), known CAD [prior myocardial infarction (MI) and prior revascularization, n = 1665], and lacking MACE follow-up (n = 4714). Patients were referred by physicians to CCTA for clinical reasons, including both asymptomatic and symptomatic patients. Patients were classified as never smokers (5685 [60%]), past smokers—individuals who quit smoking ≥ 3 months prior to CCTA (2183 [23%]), and current smokers—individuals who currently smoke or quit < 3 months prior CCTA (1588 [17%]) as previously described.\(^7\) Each participating institution obtained Institutional Review Board approval.

Pre-scan risk factor assessment

As previously described, clinical CAD risk factors including smoking history, hypertension, dyslipidemia, diabetes, and family history were collected prior to the CCTA examination by direct patient interview by a physician or nurse research coordinator and/or by standardized site questionnaires.\(^10\) Chest symptom status at the time of CCTA was categorized as asymptomatic, non-cardiac, atypical, typical chest pain, and dyspnea as previously described.\(^11\)–\(^13\)

Imaging analysis

Coronary CT angiography was performed in each institution using 64 slice or greater CT scanners.\(^2\)–\(^10\) A modified 16-segment American Heart Association coronary tree model was used to detect plaques. Plaque composition (presence, severity stenosis, number, and characteristics) on CCTA was evaluated by experienced level III equivalent readers in accordance with SCCT guideline.\(^14\) Coronary plaque was identified any hyper- or hypodense structure distinct from the lumen and > 1 mm in size. Coronary artery disease severity was classified for three groups: none (0% luminal stenosis), non-obstructive (1–49% luminal stenosis), and obstructive stenosis (≥ 50% luminal stenosis), which was sub-classified as 1-vessel disease (VD), 2-VD, and 3-VD (including left main disease). For measure of CAD extent, a segment involvement score (SIS) was defined as the total number of coronary artery segments with any plaque.\(^5\) The extent of CAD was classified for three groups: SIS with 0, 1–5 and > 5 in accordance as previously described.\(^5\) Non-calcified plaque (NCP) [containing no calcification], partially calcified plaque (PCP) [containing both of calcification and NCP], or calcified plaque (CP) [containing only calcification] was recoded as plaque characteristics.

Patient follow-up

As reported previously,\(^10\) the primary outcomes were assessed at each institution by direct interview, telephone contact, review of medical records, or using a mailed standardized questionnaire. In the USA, all-cause mortality was additionally searched by the Social Security Death Index. Major adverse cardiac event was defined as all-cause death or non-fatal MI. Myocardial infarction was defined by site physicians in accordance with ACC/AHA guideline and the World Health Organization Universal Definition of Myocardial Infarction.\(^15\)–\(^16\)

Statistical analysis

Continuous variables were expressed as the mean ± SD. The Wilcoxon rank-sum test was used to conduct intergroup comparisons among never, past, and current smoker groups. Categorical variables were compared using Pearson $\chi^2$ tests. An one-way ANOVA or the Kruskal–Wallis test was used to conduct intergroup comparisons among never, past, and current smoking groups.

The relationship of smoking status to the endpoints of time to MACE or all-cause death was examined using risk-adjusted Cox proportional-hazards models, the latter adjusted for age, sex, all other CAD risk factors (hypertension, dyslipidemia, diabetes, family history of early CAD), all chest symptoms (non-anginal, atypical, typical chest pain, and dyspnea), presence of obstructive CAD (≥ 50% stenosis), and SIS. Event rates were compared using the log-rank test. Also we generated MACE or all-cause-death-free survival curves among the never, past, and current smokers using Cox proportional-hazards models adjusting for the same variables within each stratum of smoking status. In addition, CAD stenosis severity (normal, non-obstructive, and obstructive CAD)
and extent (SIS 0, 1–5, and ≥5) were assessed among never, past, and current smoking groups in relation to MACE by Cox proportional-hazards models adjusted for age, gender, hypertension, diabetes, dyslipidemia, family history, and all chest symptoms.

Because of the potential differences of age, gender, other risk factors, and symptom presentations among the three smoking groups, MACE and death risk were also analysed in subgroups of the three smoking categories matched for age, gender, the other CAD risk factors, and the chest symptoms using propensity scores, where the propensity score was the resulting probabilities of a logistic regression model predicting being among never, past, and current smoking groups with age, gender, other CAD risk factors, and the chest symptoms as predictors. The resulting propensity score was then applied 1:1:1 to match every never smoker to a corresponding past or current smoker using a Mahalanobis nearest-neighbour matching algorithm. This matching resulted in 1000 never smokers being matched to 1000 past or 1000 current smokers, respectively. Multivariable Cox proportional-hazards models were used to assess the relationship of smoking status to an endpoint of time to MACE or all-cause death after adjusting for age, gender, other CAD risk factors, chest symptoms, presence of obstructive CAD, and SIS.

Scaled Schoenfeld residuals were used to verify the assumption of proportional hazards of the Cox models. A hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models. All statistical calculations were carried out using STATA (Version 12, StataCorp LP, College Station, TX, USA) for Windows.

### Results

#### Overall population

**Baseline characteristics**

The baseline characteristics among never, past, and current smokers are shown in Table 1. There were multiple differences between the groups. Notably, compared with never smokers, past and current smokers were predominantly male and more commonly symptomatic. Never and past smokers were older than current smokers (57.4 ± 12.6 years vs. 59.3 ± 11.0 years vs. 53.0 ± 11.9 years, P < 0.0001). Past smokers had a greater prevalence of hypertension, diabetes, and dyslipidemia compared with never or current smokers. More current smokers had a family history of premature CAD and were male than the never and past smokers (Table 1).

#### Coronary artery disease extent, severity, and plaque type

Coronary artery disease extent, severity, and plaque type are presented in Table 2. Regarding CAD extent as defined by SIS, compared with never smokers, past and current smokers had greater extent of coronary plaque, and past smokers had more plaque than current smokers. Regarding plaque severity, compared with never smokers, past and current smokers had a greater prevalence of obstructive CAD and the obstructive CAD categories including 1-, 2-, and 3VD. Past smokers possessed more non-obstructive CAD compared with never and current smokers. The absence of plaque was most frequent in the never smokers. Non-calcified plaque and PCP were more prevalent among past and current smokers compared with never smokers.

#### Rates and adjusted risk of major adverse cardiac event and death by smoking categories

At a mean follow-up of 2.8 ± 1.9 years, 297 subjects experienced MACE (3.1%). Major adverse cardiac event occurred more often in current smokers compared with the past or never smokers (4.8% vs. 2.9% vs. 2.8%, P < 0.001 for all); however, the MACE rates were similar in the never and past smokers. With respect to all-cause death (192 patients), a higher proportion of current smokers died compared with past or never smokers (3.0% vs. 1.8% vs. 1.9%, P = 0.02 for all); however, the death rates were similar in never and past smokers (Table 3). In a multivariable Cox proportional-hazards model, adjusting for age, sex, hypertension, diabetes, dyslipidemia, family history, all symptoms, coronary stenosis severity ≥50%, and SIS, current smokers experienced higher MACE risk compared with never smokers (HR 1.9, 95% CI 1.4–2.6, P < 0.001), while past smokers did not (HR 1.2, 95% CI 0.8–1.6, P = 0.35). Similarly,

### Table 1 Study population among never, past, and current smokers (n = 9456)

<table>
<thead>
<tr>
<th></th>
<th>Never (n = 5685)</th>
<th>Past (n = 2183)</th>
<th>Current (n = 1588)</th>
<th>P-value for all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.4 ± 12.6</td>
<td>59.3 ± 11.0†</td>
<td>53.0 ± 11.91+</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>2951 (51.9)</td>
<td>1287 (59.0)†</td>
<td>1006 (63.4)††</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2629 (46.7)</td>
<td>1116 (51.7)†</td>
<td>721 (45.8)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>667 (11.8)</td>
<td>297 (13.6)†</td>
<td>160 (10.1)†</td>
<td>0.004</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2853 (50.8)</td>
<td>1262 (58.5)†</td>
<td>823 (52.2)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>2119 (38.3)</td>
<td>808 (38.5)</td>
<td>687 (44.8)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1812 (32.1)</td>
<td>621 (28.8)†</td>
<td>416 (26.7)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>626 (11.1)</td>
<td>242 (11.2)</td>
<td>230 (14.8)††</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atypical</td>
<td>2270 (40.3)</td>
<td>768 (35.7)†</td>
<td>657 (42.1)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Typical</td>
<td>518 (9.2)</td>
<td>224 (10.4)</td>
<td>154 (9.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>412 (7.3)</td>
<td>299 (13.9)†</td>
<td>102 (6.5)†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Non-cardiac, atypical, and typical refer to chest pain types.
†P < 0.001 and ††P < 0.05 for the comparison with never smoking group.
*P < 0.001 and †*P < 0.05 for the comparison with past smoking group.
after adjustment for the same factors, the risk of death was higher in the current smokers (HR 2.0, 95% CI 1.4–2.9, P < 0.001) than in the never smokers, but not in the past smokers (HR 1.2, 95% CI 0.8–1.8, P = 0.31) (Table 3). Major adverse cardiac event or all-cause-death-free survival curves similarly showed increased risk of MACE or death only in current smokers (Figure 1A and B).

**Major adverse cardiac event risk assessed by smoking categories and coronary plaque extent and severity**

Figure 2A demonstrates results of risk-adjusted Cox proportional-hazards models for MACE by SIS category among never, past, and current smokers. Compared with the never smokers with SIS 0, past (HR 1.0, 95% CI 0.4–2.4, P = 0.996) or current smokers with SIS 0 (HR 1.7, 95% CI 0.8–2.4, P = 0.20) did not have increased MACE risk. In the SIS 1–5 category, the MACE risk was higher than that of the patients with SIS 0 in all smoking categories. While the risk among past smokers (HR 2.0, 95% CI 1.2–3.3, P = 0.01) was slightly higher than that of the never smokers (HR 1.7, 95% CI 1.1–2.5, P = 0.02), it was much higher in the current smokers (HR 3.1, 95% CI 1.9–5.2, P < 0.001). In the SIS >5 category, the MACE risk was further increased in all smoking categories. Of note, as with the SIS 1–5 category, the risk was slightly higher in the past smokers (HR 2.7, 95% CI 1.6–4.8, P < 0.001) than in the never smokers (HR 2.3, 95% CI 1.4–3.7, P = 0.001), but was much higher in the current smokers (HR 5.1, 95% CI 3.0–8.6, P < 0.001).

Figure 2B demonstrates results of risk-adjusted Cox proportional-hazards models for MACE by normal, non-obstructive, and obstructive CAD among never, past, and current smokers. The MACE risk

---

### Table 2  Coronary artery plaque extent, severity, and characteristics among never, past, and current smokers (n = 9456)

<table>
<thead>
<tr>
<th>Vessel disease (%)</th>
<th>Never (n = 5685)</th>
<th>Past (n = 2183)</th>
<th>Current (n = 1588)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2586 (45.49)</td>
<td>671 (30.74)†</td>
<td>625 (39.36)‡*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-obstructive</td>
<td>2072 (36.45)</td>
<td>952 (43.61)†</td>
<td>548 (34.51)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructive</td>
<td>1027 (18.07)</td>
<td>560 (25.65)‡</td>
<td>415 (26.13)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-vessel</td>
<td>601 (10.57)</td>
<td>331 (15.16)‡</td>
<td>236 (14.86)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-vessel</td>
<td>250 (4.40)</td>
<td>136 (6.23)‡</td>
<td>97 (6.11)‡</td>
<td>0.001</td>
</tr>
<tr>
<td>3-vessel</td>
<td>176 (3.10)</td>
<td>93 (4.26)‡</td>
<td>82 (5.16)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIS (mean ± SD)</td>
<td>2.1 ± 2.8</td>
<td>3.1 ± 3.3†</td>
<td>2.6 ± 3.2***</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SIS 1–5</td>
<td>2309 (40.62)</td>
<td>1008 (46.17)†</td>
<td>659 (41.50)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SIS &gt;5</td>
<td>790 (13.90)†</td>
<td>504 (23.09)†</td>
<td>304 (19.14)***</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Prevalence of any plaque type (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Never (n = 5685)</th>
<th>Past (n = 2183)</th>
<th>Current (n = 1588)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCP</td>
<td>975 (17.2)</td>
<td>525 (24.1)†</td>
<td>357 (22.5)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCP</td>
<td>1185 (20.8)</td>
<td>668 (30.6)†</td>
<td>508 (32.0)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CP</td>
<td>1280 (22.5)</td>
<td>663 (30.4)†</td>
<td>388 (24.4)*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SIS, segment involvement score; NCP, non-calcified plaque; PCP, partially calcified plaque; CP, calcified plaque.

*P < 0.001 and †P < 0.05 for the comparison with never smoking group.

**P < 0.001 and ***P < 0.05 for the comparison with past smoking group.

---

### Table 3  Rates and adjusted Cox proportional-hazard risk of major adverse cardiac event and all-cause death among whole population (n = 9456)

<table>
<thead>
<tr>
<th>Rates of MACE and all-cause death (n, %)</th>
<th>Never (n = 5685)</th>
<th>Past (n = 2183)</th>
<th>Current (n = 1588)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>158 (2.8)</td>
<td>63 (2.9)</td>
<td>76 (4.8)‡**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>106 (1.9)</td>
<td>39 (1.8)</td>
<td>47 (3.0)†**</td>
<td>0.02</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted risk of MACE and all-cause death</td>
<td>1.0 (reference)</td>
<td>1.2 (0.8–1.6)</td>
<td>1.9 (1.4–2.6)†</td>
<td>–</td>
</tr>
<tr>
<td>MACE</td>
<td>1.0 (reference)</td>
<td>1.2 (0.8–1.8)</td>
<td>2.0 (1.4–2.9)‡</td>
<td>–</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiac event.

*P < 0.001 and †P < 0.05 for the comparison with never smoking group.

**P < 0.001 and ***P < 0.05 for the comparison with past smoking group.
Current but not past smoking increases the risk of cardiac events

Rates and adjusted risk of major adverse cardiac event and death

A higher proportion of current smokers experienced MACE (6.9%, \( P < 0.001 \) vs. both other groups); however, MACE occurred in a similar proportion of the past smokers and the never smokers (2.4% vs. 2.2%, \( P = 0.77 \)). Current smokers had a higher rate of death than the other two groups (4.2%, \( P < 0.001 \) vs. both other groups); however, the death rate was not different between the past and never smokers (1.1% vs. 1.4%, \( P = 0.55 \) (Table 6). In multi-variable Cox proportional analysis, adjusting for age, sex, hypertension, diabetes, dyslipidemia, family history, all symptoms, coronary stenosis severity \( \geq 50\% \), and SIS, current smokers experienced a higher risk of MACE compared with never smokers (HR 2.6, 95% CI 1.6–4.2, \( P < 0.001 \)), but past smokers did not (HR 1.3, 95% CI 0.7–2.4, \( P = 0.39 \)). Similarly, after adjustment for the same factors, the risk of death was higher in current smokers (HR 2.5, 95% CI 1.3–4.6, \( P = 0.005 \)), compared with the never smokers, while it was not higher in the past smokers (HR 1.1, 95% CI 0.5–2.6, \( P = 0.75 \) (Table 6). Major adverse cardiac event or all-cause-death-free survival curves showed increased risk of MACE or death only in current smokers (Figure 3A and B).

Discussion

This report from the CONFIRM registry is the first study to examine the relationship between the extent and severity of CAD by coronary CT angiography, smoking status, and the risk of subsequent MACE events. We demonstrated that past and current smokers had similar extent and severity of coronary atherosclerosis, which was greater than that of never smokers; however, only current smokers had greater risk-adjusted cardiac events. We observed similar findings with respect to the extent and severity of CAD and cardiac events in a subgroup that was propensity matched to achieve similarities of age, gender, other CAD risk factors, and chest symptoms. In the matched population, compared with never smokers, both past and current smokers had a higher prevalence of non-obstructive or obstructive CAD and greater extent of CAD; however, only current smokers experienced a significantly higher MACE risk. This risk among past smokers was slightly but not significantly higher than that of never smokers.

Numerous prior investigators have observed that smoking was associated with the atherosclerosis formation, progression, and future MACE risk.\(^1\)\(^–\)\(^6\)\(^,\)\(^19\)\(^–\)\(^21\) Active smoking is strongly associated with endothelial dysfunction and coronary thrombosis.\(^19\)\(^,\)\(^22\)\(^–\)\(^28\) In current smokers, the impaired release of tissue plasminogen activator antigen and reduced coronary blood flow has been reported compared with non-smokers.\(^19\)\(^,\)\(^22\) Further, platelet aggregation is increased among active smokers.\(^24\)\(^–\)\(^27\) These factors, along with the increased amounts of coronary atherosclerosis, may be responsible for the reported increase in risk of acute coronary thrombosis\(^22\)\(^,\)\(^24\)\(^–\)\(^27\) and potentially contribute to the association of current smokers with higher MACE risk noted in the present study.

Our finding that future MACE risk was similar among never and past smokers is concordant with numerous prior studies.\(^3\)\(^,\)\(^4\) Regarding the angiographic correlates of these observations, previous studies using invasive coronary angiography have assessed the relationship of the extent CAD and MACE risk according to smoking...
As was found in the present study, these prior reports showed that smoking cessation was associated with reduced risk of death, MI, or revascularization regardless of the angiographic extent of CAD.

The potential mechanism of the similar risks of events in past and never smokers despite the increased burden of atherosclerosis is unclear. It may be due to improvement of endothelial function, decreased fibrinogen and inflammatory markers that have been associated with smoking cessation, or some other biologic protective effect reducing the risk of coronary artery plaque rupture. As another potential contributing factor, smokers who successfully quit may also have adopted other heart-healthy lifestyle behaviours such as diet,
exercise, and the use of medications that reduce risk of coronary artery event to a greater degree than the never smokers.

Large observational studies have demonstrated that the age of patients who stopped smoking was an important factor in explaining known decrease in mortality risk associated with smoking cessation.31,32 In a study of 34 439 men followed up to 50 years,31 patients who quit smoking before 30 years of age avoided most all of mortality risk, whereas reduction in mortality risk associated with smoking cessation decreased progressively as the age at time of quitting increased. Similarly, a study of 1.2 million women resurveyed 3–8 years after initial recording of smoking status,32 demonstrated that cessation of smoking before age 30 avoided almost all of the excess mortality caused by smoking, and that the mortality benefit of quitting smoking compared with not quitting decreased progressively as the age at the time of smoking cessation increased. Other studies have also demonstrated that there is decreased incidence of coronary artery calcification as a marker of atherosclerosis in past smokers compared with current smokers and that the degree of this

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Matched (1:1:1) population among never, past, and current smokers (n = 3000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never (n = 1000)</td>
</tr>
<tr>
<td>Age</td>
<td>53.4 ± 11.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>636 (63.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>446 (44.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>86 (8.6)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>516 (51.6)</td>
</tr>
<tr>
<td>Family history</td>
<td>481 (48.1)</td>
</tr>
</tbody>
</table>

Chest symptom
Asymptomatic 261 (26.1) 274 (27.4) 267 (26.7) 0.81
Non-cardiac 141 (14.1) 142 (14.2) 143 (14.3) 0.99
Atypical 455 (45.5) 420 (42.0) 422 (42.2) 0.21
Typical 95 (9.5) 112 (11.2) 108 (10.8) 0.43
Dyspnoea 48 (4.8) 52 (5.2) 60 (6.0) 0.48

Non-cardiac, atypical, and typical refer to chest pain types.
†P < 0.001 and ‡P < 0.05 for the comparison with never smoking group.
*P < 0.001 and **P < 0.05 for the comparison with past smoking group.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Coronary artery plaque extent, severity, and characteristics among matched never, past, and current smokers (n = 3000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel disease (%)</td>
<td>Never (n = 1000)</td>
</tr>
<tr>
<td>Normal</td>
<td>472 (47.2)</td>
</tr>
<tr>
<td>Non-obstructive disease</td>
<td>338 (33.8)</td>
</tr>
<tr>
<td>Obstructive disease</td>
<td>190 (19.0)</td>
</tr>
<tr>
<td>1-vessel</td>
<td>101 (10.1)</td>
</tr>
<tr>
<td>2-vessel</td>
<td>50 (5.0)</td>
</tr>
<tr>
<td>3-vessel</td>
<td>39 (3.9)</td>
</tr>
<tr>
<td>SIS (mean ± SD)</td>
<td>2.0 ± 2.8</td>
</tr>
<tr>
<td>SIS 1–5</td>
<td>398 (39.8)</td>
</tr>
<tr>
<td>SIS &gt;5</td>
<td>130 (13.0)</td>
</tr>
</tbody>
</table>

Prevalence of any plaque type (%)
NCP 176 (17.6) 233 (23.3)‡ 231 (23.1)‡ 0.002
PCP 195 (19.5) 274 (27.4)‡ 335 (33.5)‡ |** 0.001
CP 193 (19.3) 250 (25.0)‡ 258 (25.8)‡ 0.001

SIS, segment involvement score; NCP, non-calcified plaque; PCP, partially calcified plaque; CP, calcified plaque.
†P < 0.001 and ‡P < 0.05 for the comparison with never smoking group.
*P < 0.001 and **P < 0.05 for the comparison with past smoking group.
decreased incidence is age related.\textsuperscript{33,34} In our study, the risk of MACE events in the past smokers appeared to improve over time in our unmatched population. The results in our matched population, however, suggest that the risk of MACE events is similar between past and never smokers early after testing. Whether the difference in our matched and unmatched populations in this regard is related to increased risk factor burden in the past smokers of the unmatched population compared with the never smokers or to other factors cannot be determined from our data. We did not have information regarding the age at which smoking was stopped in the past smokers of this study.

The study has several limitations. The study includes patients undergoing clinical indicated CCTA studies and whether the present results can be extrapolated to population-based cohorts remains unknown. The follow-up period was for an average of 2.8 years. The hazard ratio for MACE was slightly but not significantly higher in past smokers than in never smokers (1.2 and 1.3 in the whole and the matched populations, respectively). A longer follow-up with more clinical events is needed to determine whether there is a difference in the event rates in these two groups. From the CONFIRM registry, only patients in whom smoking status was reported and follow-up for MACE was available were included. Smoking information was limited to identification of patients who were current, past, or never smokers. There was no information regarding duration and amount of smoking, time interval from smoking cessation to testing, or exposure to passive smoking, all of which are associated with CAD and the future risk.\textsuperscript{21,31,32,35,36} There was no information regarding lifestyle behaviour in the various groups.

**Conclusion**

Among patients without known CAD undergoing CCTA, current and past smokers had increased burden of atherosclerosis compared with never smokers; however, the risk of death and MACE was heightened only in the current smokers.

**Funding**

Research reported in this publication was supported by the Heart Lung and Blood Institute of the National Institutes of Health (1R01HL115150). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research was supported by Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (MSIP).
Current but not past smoking increases the risk of cardiac events

(2012027176). This study was also funded, in part, by a generous gift from the Dalio Institute of Cardiovascular Imaging and the Michael Wolk Foundation.

Conflict of interest: S.A. received support from Siemens and Bayer Schering Pharma and has consulted for Servier. D.A. has served on the Speakers’ Bureau of GE Healthcare. M.J.B has consulted for GE Healthcare. F.C. received grant support from GE Healthcare and has served on the Speakers’ Bureau of Bracco, and has consulted for Servier. K.C. received grant support from Bayer Pharma. B.J.W.C. received research and fellowship support from GE Healthcare, research support from Servier, and educational support from TeraRecon. R.C. has served as a consultant for Astellas Pharma, GE Healthcare, and Novartis. J.H. received a research grant from Siemens Medical Systems. P.A.K. received research support from GE Healthcare. J.L. received research support from GE Healthcare and speakers’ bureau. Siemens and Bayer Pharma. A.D. was partially supported by Clinical care. G.P. received grant support from GE Healthcare. J.L. received research support and fellowship support from GE Healthcare, research support from GE Healthcare and Heartflow. G.R. received grant support from Siemens and Bayer Pharma. A.D. was partially supported by Clinical Translational Science Center (grant UL1-RR024996). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

References

CARDIOVASCULAR FLASHLIGHT

Serial imaging observations of vascular healing in a denervation-induced renal artery dissection

Antonios Karanasos, Nicolas M. Van Mieghem, Evelyn Regar, and Joost Daemen*

Department of Cardiology, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

A 75-year-old woman underwent bilateral renal denervation with an ultrasound-based balloon denervation system (Paradise™; Recor Medical, Palo Alto, CA, USA) due to resistant hypertension. The procedure was successfully completed without clinical adverse events; however, the post-procedural right renal artery angiogram showed non-flow limiting lumen irregularities, associated with micro-thrombi and dissections with intramural hematoma formation by optical coherence tomography (OCT). No further treatment was performed and the patient was discharged on aspirin for 1 month. Six-month follow-up magnetic resonance angiography (MRA) showed no signs of stenosis. At 1 year, severe refractory hypertension persisted (mean office 193/93 mmHg) and the patient suffered a cerebrovascular accident. In view of the persistent elevated blood pressure, a repeat procedure was performed 19 months after the baseline procedure. Prior to the repeat procedure, OCT was performed in the right renal artery demonstrating no evidence of vascular trauma with complete healing of the dissections and resolution of the hematoma.

Although small dissections and micro-thrombi have been reported as direct vascular consequences of renal denervation with several different devices, their clinical significance remains unclear. We present for the first time the follow-up of a denervation-induced dissection showing a completed healing process with no evidence of persistent vascular trauma or development of stenosis.

Angiographic and optical coherence tomography (OCT) images from the right renal artery from pre-denervation, post-denervation, and at the repeat procedure. Follow-up angiography demonstrates the resolution of lumen irregularities, while OCT images disclose the complete healing of dissections and intramural hematoma. White arrow, dissection; yellow arrow, thrombus; cross, hematoma.

A.K. has received support for OCT-related research from St Jude.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: Journals.permissions@oup.com.