Prognostic implications of non-culprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography

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Aims
Non-culprit plaques are responsible for a substantial number of future events in patients with acute coronary syndrome (ACS). In this study, we evaluated the prognostic implications of non-culprit plaques seen on coronary computed tomography angiography (CTA) in patients with ACS.

Methods and results
Coronary CTA was performed in 169 patients (mean 59 ± 11 years, 129 males) admitted with ACS. Data sets were assessed for the presence of obstructive non-culprit plaques (>50% luminal narrowing), segment involvement score, and quantitative measures of plaque burden, after censoring initial culprit plaques. Follow-up was performed for the occurrence of major adverse cardiovascular events (MACEs) unrelated to the initial culprit plaque; cardiac death, second ACS, or coronary revascularization after 90 days. After a median follow-up of 4.8 (IQR 2.6–6.6) years, MACE occurred in 36 (24%) patients: 6 cardiac deaths, 16 second ACS, and 14 coronary revascularizations. Dyslipidaemia (hazard ratio [HR] 3.1 [95% confidence interval 1.5–6.6]) and diabetes mellitus (HR 4.8 [2.3–10.3]) were univariable clinical predictors of MACE. Patients with remaining obstructive non-culprit plaques (HR 3.66 [1.52–8.80]) and higher plaque burden index (HR 1.22 [1.01–1.48]) had a more risk of MACE. In multivariate analysis, with diabetes, dyslipidaemia, and plaque burden index, obstructive non-culprit plaques (HR 3.76 [1.28–11.09]) remained an independent predictor of MACE.

Conclusion
Almost a quarter of the study population experienced a new event arising from a non-culprit plaque during a follow-up of almost 5 years. ACS patients with remaining obstructive non-culprit plaques or high plaque burden have an increased risk of future MACE.

Keywords
Acute coronary syndrome • Coronary CT angiography • Non-culprit plaques • Plaque burden • Prognosis

Introduction
Coronary computed tomography angiography (CTA) offers direct non-invasive assessment of atherosclerotic plaque throughout the entire coronary tree and has proved to be a reliable diagnostic tool in patients suspected of coronary artery disease with valuable prognostic information.1–3 While several publications have evaluated the prognostic value of coronary CTA in patients with stable chest pain complaints,6–9 little is known about the prognostic implications of non-culprit plaques on coronary CTA in patients with acute coronary syndrome (ACS). Follow-up studies using intravascular imaging techniques in patients with ACS have shown that a substantial number of second events arise from these non-culprit plaques.10 The aim of this study was to determine the prognostic implications of non-culprit plaques on coronary CTA in patients with ACS.

Methods
The study population consisted of patients admitted for ACS, including unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) according to the definitions of the European Society of
Cardiology in the period between August 2004 and March 2011. Patients from three separate diagnostic studies with consecutive enrolment were pooled for the current study population; patients requiring urgent invasive intervention underwent coronary CTA after coronary angiography (CAG).12–14 Treating physicians were not informed regarding the findings on CTA.

Information on the presence of cardiac risk factors was prospectively collected. Hypertension was defined as a blood pressure of ≥140/90 mmHg or undergoing treatment for hypertension. Dyslipidaemia was defined as total cholesterol of >5.0 mmol/L or current statin treatment. Diabetes mellitus was defined as treatment with oral anti-diabetic medication or use of insulin. Smoking was considered as a risk factor if patients were current smokers and family history of cardiovascular disease was considered as positive if a first-degree relative (males <55 years or females <65 years) was diagnosed with cardiovascular disease.15,16 The study complied with the Declaration of Helsinki and the institutional review board of Erasmus MC Rotterdam approved the study.

Image acquisition

Image acquisition was performed using a multislice CT scanner (64-slice single source from August 2004 to September 2006, 64-slice dual source from September 2006 to April 2009, and 128-slice dual source from April 2009 to March 2011; Siemens, Forchheim, Germany) using the following scan parameters: 100–120 kV tube voltage, 850–960 mAs (64-slice single source), 370–412 mAs (64-slice dual source), and 320–412 mAs (128-slice dual source) tube current with X-ray tube modulation depending on patient size and variable pitch depending on the heart rate. A bolus of 80–100 mL of contrast material was injected intravenously followed by a 45-mL saline bolus chaser at a flow rate of 5.0–5.5 mL/s. A bolus-tracking technique was used to synchronize the arrival of contrast in the coronary arteries. Patients received sublingual nitroglycerine before the scan and beta-blockers were administered in patients with high heart rates.

Follow-up

The national mortality registry was consulted for all patients. Questionnaires, standardized telephonic interviews, and information from hospital visits were additionally used to determine the occurrence and nature of potential events.

To determine the nature of the second event, an independent cardiologist, blinded for CT information, interpreted all clinical information, including ECG, echocardiography, and CAG at the time of the new event. Based on the ECG and angiographic findings at the time of the second event, the same physician identified the coronary segment most likely associated with the new event. The outcome measure was major adverse cardiac event (MACE) unrelated to the index culprit plaque: cardiac death, second ACS, and coronary revascularization after 90 days. Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmias, refractory heart failure, or cardiogenic shock. ACS was defined as either myocardial reinfarction with a rise and fall of cardiac biomarkers (>99th percentile of the upper limit of normal) or unstable angina requiring revascularization.17,18

Morphological evaluation

Plaques causing a second presentation with ACS were evaluated for their morphological features and compared with those that remained clinically silent in age- and gender-matched patients. The following characteristics were assessed: minimal attenuation values, curved MPRs were created with perpendicular cross-sectional views using the dedicated software (Syngo.via; Siemens). Percent area stenosis was calculated by dividing the lumen area at the site of maximal narrowing by the vessel area at the same cross-sectional view.

Remodelling index was calculated by dividing the cross-sectional vessel area at the site of maximal luminal narrowing by the cross-sectional vessel area in a reference segment. For reference we used segments without detectable plaque preferably proximal and as close as possible to the lesion. In the absence of a disease-free segment, the least diseased segment or a segment distally, before major bifurcations, and close to the investigated lesion was used. Minimal attenuation values were determined by placing a region of interest with a minimum size of 0.25 mm² in a region with the lowest attenuation assessed visually. Regions with extensive calcification or motion artefacts were avoided and fully calcified lesions were excluded.

Spotty calcifications were defined as small calcified material <3 mm in size on MPRs, embedded in non-calcified material and one-sided on cross-sectional images.

Image evaluation

Coronary arteries were evaluated on axial images, multiplanar reconstructions (MPRs), and maximum intensity projections according to readers’ preferences. All plaques deemed responsible for ACS at baseline were censored. The presence of coronary atherosclerotic plaque was determined using the 16-segment AHA classification by two experienced readers.19 Stenosis grade was quantified as <20%, 20–50%, 50–70%, >70% stenosis or occluded. Segments of poor quality due to misalignment or movement artefacts and small segments (<1.5 mm) were excluded from analysis. After censoring for plaques causing ACS at baseline, we determined the segment involvement score: all lesions with a stenosis grade >20%.20 Coronary atherosclerotic plaque was classified as non-calcified, partially calcified (≤50% calcium), or predominantly calcified (>50% calcium). Interobserver disagreements were resolved by a joint reading. With the semi-automated software (QAngioCT Research Edition, Medis Medical Imaging Systems, Leiden, the Netherlands), we determined total plaque volume and plaque burden index, as described previously.11 In short, planimetry of the inner lumen and outer vessel areas was performed following a stepwise approach throughout the vessel. Plaque burden index was calculated by dividing the total plaque volume by the length of the evaluated vessel. Segments with chronic total occlusions or accountable for baseline ACS were not taken into account.

Statistical analysis

Statistical analyses were performed using the SPSS software (version 15.0, SPSS, Inc., Chicago, IL, USA) and STATA software (version 12.0, StataCorp, College Station, TX, USA). All probability values refer to two-tailed tests of significance; a P-value of <0.05 was considered significant. Categorical variables are presented as proportions. Continuous variables are expressed as mean (± SD) or median (± IQR). Differences between independent groups were compared using the two-sided unpaired t-test, χ² test, Wilcoxon rank-sum test or Fisher’s exact test, as appropriate. Cox regression analysis was used to assess any associations between outcome and clinical characteristics or coronary CTA results. A second regression analysis was performed for the combined outcome cardiac death and ACS. Hazard ratios (HRs) were calculated with their corresponding 95% confidence intervals. Risk-adjusted models were corrected for significant (P < 0.05) univariable clinical variables and used to create adjusted survival curves. The global χ² value was.
calculated to determine the incremental value of coronary CTA. Receiver operating characteristic (ROC) curves with estimates of the area under the curve (AUC) were obtained to compare discriminative model performances.

**Results**

The study population consisted of 169 ACS patients (mean age 59 ± 11 years, 129 males) who underwent coronary CTA during their admission.

Follow-up was obtained for 152 (90%) patients with a median follow-up time of 4.8 (2.7–6.6 years; Table 1). Diagnosis at the discharge of index hospitalization was unstable angina pectoris in 65 (43%) patients, NSTEMI in 59 (39%), and STEMI in 28 (18%) (Table 1). The composite endpoint MACE occurred in 36 (24%) patients, consisting of 6 cardiac deaths, 16 second ACS, and 14 late revascularizations unrelated to the plaque causing ACS at baseline. Coronary revascularization was driven by recurrent symptoms in 11 patients and by ischaemia on non-invasive testing in 3 patients. The overall annual event rate was 4.9%. In addition, seven patients had died of a non-cardiac cause (all-cause mortality = 13 [9%]).

**Coronary CTA results**

A total of 2432 segments were evaluated; of which 87 (3.6%) were considered non-diagnostic, 317 (13.0%) too small for evaluation (<1.5 mm in diameter), and 172 (7.0%) were censored because of index ACS treatment.

On a per-patient level, obstructive non-culprit plaques (>50% luminal narrowing) were more often seen in patients with MACE than in those without (83 vs. 52%, P = 0.001, Table 2). A total of 263 non-calcified, 185 partially calcified, and 274 predominantly calcified plaques were seen in the whole group. Predominantly calcified plaques were more frequently seen in patients with MACE than in those without, although the difference did not reach statistical significance (P = 0.08). Plaque burden index was significantly higher in patients with MACE, respectively, 8.4 vs. 7.2 mm² (P = 0.009).

**Prediction of clinical outcome**

Patients with dyslipidaemia and diabetes mellitus experienced MACE more often during follow-up (Table 3). Obstructive non-culprit plaques and plaque burden index were significant predictors of MACE. For the combined outcome cardiac death and second ACS, both variables remained significant predictors. In multivariable analysis, correcting for dyslipidaemia and diabetes mellitus, the presence of obstructive non-culprit plaques on CT remained an independent predictor (Figure 1 and Table 4). Model discrimination performance increased with the addition of CTA to a clinical model consisting of dyslipidaemia and diabetes (Figure 2).

**Comparison with CAG**

In this study, 143 patients underwent CAG with an obstructive non-culprit lesion visible in 24 cases. During the follow-up, 10 of these patients experienced MACE, while 26 patients who experienced MACE had no obstructive lesions on CAG after initial treatment. In a model with CAG, CT remained a significant predictor (HR 3.60 [1.36–9.59], P = 0.01 for MACE and HR 4.27 [1.24–14.71], P = 0.02 for cardiac death and ACS).

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 152)</th>
<th>MACE + (n = 36)</th>
<th>MACE – (n = 116)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>58 ± 10</td>
<td>58 ± 10</td>
<td>59 ± 10</td>
<td>0.56</td>
</tr>
<tr>
<td>Gender, male</td>
<td>116 (76)</td>
<td>30 (83)</td>
<td>86 (74)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>76 (50)</td>
<td>19 (53)</td>
<td>57 (49)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77 (51)</td>
<td>23 (64)</td>
<td>54 (47)</td>
<td>0.07</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>81 (53)</td>
<td>27 (75)</td>
<td>54 (47)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (13)</td>
<td>10 (28)</td>
<td>10 (9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive family history</td>
<td>74 (49)</td>
<td>18 (50)</td>
<td>56 (48)</td>
<td>0.86</td>
</tr>
<tr>
<td>Creatinine (µmol/L)*</td>
<td>84 ± 14</td>
<td>86 ± 16</td>
<td>84 ± 14</td>
<td>0.33</td>
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<tr>
<td>Heart rate (bpm)*</td>
<td>62 ± 9</td>
<td>62 ± 11</td>
<td>62 ± 8</td>
<td>0.90</td>
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<tr>
<td>Index diagnosis</td>
<td></td>
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<tr>
<td>Unstable angina</td>
<td>65 (43)</td>
<td>17 (39)</td>
<td>48 (39)</td>
<td>0.69</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>59 (39)</td>
<td>14 (47)</td>
<td>45 (41)</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>28 (18)</td>
<td>5 (14)</td>
<td>23 (20)</td>
<td></td>
</tr>
<tr>
<td>Index management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive angiography</td>
<td>143 (94)</td>
<td>35 (97)</td>
<td>108 (93)</td>
<td>0.36</td>
</tr>
<tr>
<td>PCI</td>
<td>126 (83)</td>
<td>34 (94)</td>
<td>92 (79)</td>
<td>0.04</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (5)</td>
<td>0</td>
<td>8 (7)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

MACE, major adverse cardiac event (cardiac death, second ACS, and late coronary revascularization); NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

*Data are means ± standard deviations.
Morphological comparison

Second ACS occurred in 16 patients; among whom, a culprit lesion could be identified in 13 cases. Percent area stenosis (0.81% [0.76–0.88] vs. 0.71% [0.63–0.78], \( P = 0.02 \)) was significantly higher in plaques causing second ACS. Total volume of plaques causing second ACS was 175 mm\(^3\) (IQR 95–254) and 120 mm\(^3\) (IQR 101–151) of control plaques (\( P = 0.22 \)). No difference was found for remodelling index (1.11 + 0.42 in culprit plaques vs. 1.08 + 0.16 in control plaques, \( P = 0.83 \)), minimal plaque attenuation (98 HU [65–147] vs. 104 HU [72–168], \( P = 0.79 \)), and presence of spotty calcification (5 vs. 3, \( P = 0.67 \)) types.

Discussion

During a follow-up of almost 5 years, almost a quarter of patients with ACS at baseline experienced a second event and patients with higher plaque burden or obstructive non-culprit plaques on CT had a significantly higher risk of MACE.

As a reliable gatekeeper for invasive angiography, coronary CTA has become a part of the diagnostic armamentarium for patients...
suspected of ACS. Once patients have been diagnosed with ACS and treated accordingly, their risk of new cardiac events will determine future therapy. With intravascular imaging techniques, the natural history of coronary atherosclerosis in patients admitted with ACS has been evaluated thoroughly. The investigators of the PROSPECT study detected high residual plaque burden even after the treatment of all angiographically significant lesions. Non-culprit plaques were responsible for a substantial number of second events and patients with higher plaque burden had an increased risk of MACE. More recently, investigators of the PRAMI trial showed that preventive percutaneous coronary intervention (PCI) of non-culprit lesions with major stenoses significantly reduced the risk of adverse cardiovascular events in patients with STEMI and multivessel disease. Although currently not recommended and without immediate suggestion in differentiation of post-ACS treatment, our intention was to perform an exploratory study to understand the role of non-culprit lesions better. Looking beyond luminology, coronary CTA provides detailed information regarding total plaque burden, accounting for non-obstructive lesions as well, and specific plaque characteristics that might be important for understanding of the occurrence of second cardiac events in these patients. We found that remaining obstructive plaques and quantitatively measured higher plaque burden are associated with an increased risk of cardiac events. Also, CT remained an independent predictor of MACE next to CAG, suggesting that CT picks up lesions which do not look important on CAG, but over time do cause cardiac events, which might be due to the additional information provided by CT over sheer luminology.

Extensively studied in populations with stable complaints, CT has shown to be a strong predictor of mortality and cardiac-specific adverse outcomes. However, there is a paucity of data in the group patients with ACS. In a study by Kristensen et al., there was a significant correlation found between the total amount of non-obstructive plaque and adverse cardiac events in NSTEMI patients after 16 months. In the present study, we included all non-culprit plaques for quantitative measurement of plaque burden, confirming this correlation for a more heterogeneous ACS population.

Morphological plaque features are next to stenosis severity also determinates of plaque progression and rupture. Intravascular imaging techniques allow a more detailed assessment of plaques and can visualize specific characteristics like thin fibrous caps or large necrotic cores. It has been postulated that a thin fibrous cap is a major determinant in discrimination between a vulnerable plaque and a stable plaque. Limited by its spatial resolution, CT cannot detect thin-cap fibroatheromas, but there are specific CT plaque features, such as low-attenuation, positive remodelling, and spotty calcifications (Figure 3), that are associated with a higher risk of future cardiac events. In a sub-analysis, we examined morphological features of lesions causing ACS. Percent area stenosis was significantly higher in lesions causing second ACS compared with those that remained silent. There was no significant difference

### Table 4 Multivariable analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk-adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model I</td>
<td>SIS 1.03 (0.94–1.13) 0.49</td>
<td>Obstructive non-culprit plaque (&gt;50%) 3.22 (1.10–9.43) 0.03</td>
</tr>
<tr>
<td>Model II</td>
<td>Plaque burden index 1.16 (0.94–1.44) 0.19</td>
<td>Obstructive non-culprit plaque (&gt;50%) 3.76 (1.28–11.09) 0.02</td>
</tr>
</tbody>
</table>

Risk-adjusted for dyslipidaemia and diabetes mellitus. SIS, segment involvement score.

**Figure 2** ROC curves for clinical characteristics alone, i.e. dyslipidaemia and diabetes mellitus (red line AUC 0.68 [0.58–0.78]) and with obstructive non-culprit plaque on CTA (blue line AUC 0.76 [0.66–0.85]).
found for other morphological features, possibly because of the small sample size, limited observation time, or methods of measuring, and also due to the high-risk nature of the study population. All patients had already experienced ACS at baseline and high-risk features of interest might have been frequent in the control group as well.

Limitations
There are several limitations to the present study. First, this is a single-centre study of a retrospective nature. Therefore, our results may not necessarily reflect populations or practices elsewhere and may be subject to a selection bias. In this study, we reached considerable follow-up (90%); however, incomplete follow-up may result in underreporting of events. Allocation of deaths to cardiac or non-cardiac was made by an independent cardiologist, blinded for CT information, who reviewed clinical records and information provided by the general practitioners. Autopsy was either not performed or results were not available in many patients who had died during follow-up and we cannot exclude that baseline ACS or its complications influenced or were the direct cause of subsequent cardiac deaths during follow-up. By censoring initial culprit lesions, we tried to minimize misclassification of cardiac deaths.

Most importantly, our goal was to exclude clear non-cardiac cases or those with clinical information suggesting a clear link between cause of death and index event. Considering the observational methodology and modest sized population, our results should be considered exploratory and we do not advocate regular use of CT in ACS patients. Finally, the sample size in the present study might lack power to detect existing associations between clinical characteristics, CT, and outcome.

Conclusions
Almost a quarter of the study population experienced a second event caused by a non-culprit plaque during 5-year follow-up. ACS patients with obstructive non-culprit plaques or high plaque burden have an increased risk of future MACE.

Conflict of interest: none declared.

References


