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1 ORIGINAL ARTICLE

2
3 **Coronary Atherosclerotic Plaque Activity**
4 **and Future Coronary Events**

5
6 *The PRE¹⁸FFIR Study*

7
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47
48 **Keywords:** Coronary heart disease, positron emission tomography,
49 computed tomography, myocardial infarction.

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52 **Key Points**

53 **Question:** Can coronary atherosclerotic plaque activity (18F-sodium fluoride positron
54 emission tomography) predict coronary events in patients with myocardial infarction?

55 **Findings:** In 704 patients with myocardial infarction, coronary atherosclerotic plaque activity
56 was not associated with the primary composite endpoint of cardiac death, nonfatal
57 myocardial infarction, or revascularization. In a secondary analysis, elevated plaque activity
58 was associated with the composite endpoint of cardiac death or non-fatal myocardial
59 infarction.

60 **Meaning:** Coronary atherosclerotic plaque activity was not associated with the primary
61 composite endpoint of cardiac death, nonfatal myocardial infarction, or revascularization.

62 **Abstract**

63 **Importance:** Recurrent coronary events in patients with recent myocardial infarction remain
64 a major clinical problem. Non-invasive measures of coronary atherosclerotic disease activity
65 have the potential to identify those at greatest risk.

66 **Objective:** To determine whether non-invasive assessment of coronary atherosclerotic plaque
67 activity could be associated with recurrent coronary events.

68 **Design:** Prospective observational longitudinal cohort study recruiting participants between
69 September 2015 and February 2020 with a minimum 2 years follow up.

70 **Setting:** International multicenter study.

71 **Participants:** Patients with multivessel coronary artery disease and recent myocardial
72 infarction were eligible for inclusion. From 2,684 patients screened, 995 were eligible, 712
73 attended for imaging, and 704 had completed an interpretable scan and comprised the study
74 population.

75 **Intervention:** Coronary ¹⁸F-sodium fluoride positron emission tomography and coronary
76 computed tomography angiography.

77 **Main Outcomes and Measures:** Total coronary atherosclerotic plaque activity was assessed
78 by ¹⁸F-sodium fluoride uptake. The primary endpoint was cardiac death or non-fatal
79 myocardial infarction but was expanded during study conduct to include unscheduled
80 coronary revascularization due to lower than anticipated primary event rates.

81 **Results:** Participants were middle-aged (63.8±8.2 years) and predominantly male (85%).
82 Total coronary atherosclerotic plaque activity was identified in 421 (60%) participants. After
83 a median of 4 years follow-up, 141 participants experienced the primary endpoint: 9 had
84 cardiac death, 49 non-fatal myocardial infarction and 83 unscheduled coronary
85 revascularizations. Increased coronary plaque activity had no demonstrable association with
86 the primary endpoint (hazard ratio (HR) 1.25 [95% confidence interval (CI) 0.89 to 1.76],

87 P=0.20) or unscheduled revascularization (HR 0.98 [95% CI 0.64 to 1.49], P=0.91) but was
88 associated with the secondary endpoints of cardiac death or non-fatal myocardial infarction
89 (47 versus 19; HR 1.82 [95% CI 1.07 to 3.10], P=0.03) and all-cause mortality (30 versus 9;
90 HR 2.43 [95% CI 1.15 to 5.12], P=0.02). These associations were similar after adjustment for
91 differences in baseline clinical, coronary angiographic, and GRACE score characteristics
92 (HR 1.76 [95% CI 1.00 to 3.10] (P=0.05) and HR 2.01 [95% CI 0.90 to 4.49], (P=0.09)
93 respectively).

94 **Conclusions and Relevance:** In patients with recent myocardial infarction, coronary
95 atherosclerotic plaque activity was not associated with the primary composite endpoint. The
96 findings suggesting risk of cardiovascular death or myocardial infarction in patients with
97 elevated plaque activity warrants further research to explore its incremental prognostic
98 implications.

99 **Trial Registration:** NCT02278211

100

101 **Word count:** 370 words

102

103 **Introduction**

104

105 Recurrent coronary events are common following acute myocardial infarction but are
106 challenging to predict. Clinical risk scores, such as the Global registry of Acute Cardiac
107 Events (GRACE) score,¹ estimate the risk of early events, but have limitations and lack
108 precision.^{2,3} The presence of obstructive coronary artery disease has also been seen as a major
109 determinant of future risk leading to strategies of coronary revascularization to reduce
110 subsequent events.^{4,5} However, most index myocardial infarctions arise from non-obstructive
111 coronary plaques and recurrent events commonly occur at sites remote from the culprit
112 plaque.⁵⁻⁷ This has led to attempts to detect high-risk coronary artery plaques that drive such
113 downstream events and thereby identify the ‘vulnerable’ patient.⁸ Previous studies have
114 assessed coronary plaque characteristics using invasive imaging approaches including
115 intravascular ultrasound either alone⁶ or in combination with near-infrared spectroscopy.⁷
116 Coronary plaques associated with high-risk features, such as thin-cap fibroatheroma or lipid-
117 rich plaque, are associated with future coronary events, especially those associated with
118 subsequent coronary revascularization. However, these techniques are impractical for
119 widespread application because of the requirement for direct instrumentation of the coronary
120 arteries with its attendant risks.

121

122 Advances in non-invasive imaging have enabled the assessment of coronary anatomy and
123 biology without the need to instrument the coronary arteries. Coronary computed tomography
124 angiography has comparable accuracy to invasive coronary angiography⁹ and is more
125 sensitive at detecting coronary atheroma.¹⁰ When complemented by positron emission
126 tomography, the anatomy and biology of coronary artery plaque can be assessed
127 simultaneously to identify coronary atherosclerotic plaque activity.^{11,12} We and others have

128 previously shown that combined 18F-sodium fluoride positron emission tomography and
129 coronary computed tomography angiography can identify high-risk and active coronary
130 atherosclerotic plaque in patients with recent myocardial infarction.^{11,13,14} Coronary artery
131 18F-sodium fluoride uptake is a marker of active calcification driven by the lipid-rich
132 necrotic core of the atheromatous plaque¹⁵⁻¹⁹ and is associated with progression of coronary
133 calcification.^{20,21} In retrospective post hoc pooled analyses of patients with cardiovascular
134 disease,^{22,23} increased coronary 18F-sodium fluoride uptake is associated with an increased
135 risk of fatal and non-fatal myocardial infarction. We therefore wished to establish whether
136 this technique was generalizable and sufficiently robust for clinical application. In a regulated
137 international multicenter prospective cohort study, we aimed to determine whether combined
138 18F-sodium fluoride positron emission tomography and coronary computed tomography
139 angiography would be associated with the future risk of coronary events in patients with
140 recent myocardial infarction.

141

142 **Methods**

143

144 **Study Design**

145 This was an international multicenter prospective longitudinal observational cohort study
146 conducted in 9 centers across 4 countries (eTable 1). The study was performed under a
147 Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency
148 (EudraCT 2014-004021-41), with the approval of the Research Ethics Committee (15-SS-
149 0059), in accordance with the Declaration of Helsinki, and with the written informed consent
150 of each participant. The study has been reported in line with STROBE guidelines.

151

152 **Study Population**

153 The study population consisted of patients aged 50 years or older with a recent (within 21
154 days) type 1 myocardial infarction and multi-vessel coronary artery disease on invasive
155 coronary angiography defined as at least two major epicardial vessels with either >50%
156 luminal stenosis or previous coronary revascularization (percutaneous coronary intervention
157 or coronary artery bypass graft surgery). Exclusion criteria were inability or unwillingness to
158 give informed consent, women who were pregnant, breastfeeding or of child-bearing
159 potential, major intercurrent illness with life expectancy <2 years, renal dysfunction
160 (estimated glomerular filtration rate ≤ 30 mL/min/1.73 m²), atrial fibrillation or
161 contraindication to iodinated contrast media, positron emission tomography or computed
162 tomography.

163

164 **Image Acquisition**

165 Study participants were administered a target dose of 250 MBq ¹⁸F-sodium fluoride
166 intravenously and rested in a quiet environment for 60 min. Participants underwent an

167 attenuation correction computed tomography scan followed by a dual cardiac and respiratory
168 gated positron emission tomography scan of the thorax in list-mode for 30 min.^{11,13,22,23}
169 Thereafter, electrocardiogram-gated coronary computed tomography angiography was
170 undertaken in held expiration either on the same hybrid scanner or an alternative computed
171 tomography scanner optimized for coronary angiography (eTable 2).²⁴ Where required,
172 patients received oral or intravenous beta-blockade, such as metoprolol 5-100 mg, to slow the
173 heart below 65 beats/min to maximize image quality and facilitate prospective gating to
174 reduce radiation exposure. Glyceryl trinitrate spray or tablet was administered sublingually
175 (200-400 µg) to induce coronary vasodilatation to enhance image quality of the coronary
176 angiogram. Injected activity and computed tomography dose-length product were recorded.
177 Effective radiation dose was calculated using a conversion factor of 0.024 mSv/MBq for 18F-
178 sodium fluoride and 0.014 mSv/Gy.cm for computed tomography.^{25,26}

179

180 **Image Analysis**

181 All data were anonymized before transfer to the core laboratory for analysis. Coronary
182 computed tomography angiography findings were analysed according to the Society of
183 Cardiovascular Computed Tomography guidelines using the CAD-RADS 2.0 score.²⁷ The list
184 mode datasets of the positron emission tomography scans were reconstructed into 10
185 electrocardiogram-gated bins using a standard ordered expectation maximization algorithm
186 with time-of-flight, and point-spread-function correction.^{28,29} Coronary positron emission
187 tomography image analysis was performed using dedicated software (FusionQuant, Cedars
188 Sinai Medical Center, Los Angeles) as described previously.³⁰⁻³³ In brief, we extracted
189 whole-vessel tubular and three-dimensional volumes of interest (4-mm radius) from the
190 computed tomography angiogram and used these to measure the coronary microcalcification
191 activity (CMA) on positron emission tomography. This represents the overall coronary

192 atherosclerotic plaque activity based upon both the volume and intensity of 18F-sodium
193 fluoride uptake; analogous to the Agatston score used for coronary artery calcium scoring
194 (eFigure 1). All investigator site staff and study participants were blinded to the CMA
195 findings.

196

197 **Clinical Follow-up and Outcomes**

198 Participants were followed up by site investigators until the last recruited patient had
199 completed their 2-year follow-up visit. Because of concealment of the CMA findings, clinical
200 outcomes were reported by site investigators according to a standardized clinical
201 proforma.^{34,35} The primary clinical outcomes of interest were cardiac death or non-fatal
202 myocardial infarction, but this was expanded during study conduct to include unscheduled
203 coronary revascularization due to lower than anticipated event rates. The latter was defined as
204 any coronary revascularization that occurred beyond 6 weeks from the screening visit to
205 exclude planned staged revascularization procedures.

206

207 **Sample Size and Statistical Analysis**

208 At study inception, the primary endpoint was cardiac death or recurrent non-fatal myocardial
209 infarction. Given the inclusion criteria of patients with multivessel disease, we anticipated
210 that approximately one third of participants would have low coronary atherosclerotic plaque
211 activity (CMA=0)^{22,23} and an event rate of 20%, and two thirds would have increased
212 coronary atherosclerotic plaque activity (CMA>0) and an event rate of 30%. For 80% power
213 and two-sided P<0.05, we estimated a sample size of 692. As the time-to-first event analysis
214 would require approximately 10% fewer patients, this would allow for 10% missing data.
215 During study conduct, review of the total study population demonstrated a lower than
216 anticipated event rate. The Trial Steering Committee recommended extended follow up and

217 the inclusion of unscheduled coronary revascularization into the primary endpoint on the
218 basis that increased coronary atherosclerotic plaque activity may be associated with disease
219 progression and coronary revascularization.^{6,7}

220

221 Categorical data are presented as number (%), and continuous variables as mean \pm standard
222 deviation of the mean or median [interquartile interval]. The primary endpoint was defined
223 as the composite of cardiac death, non-fatal recurrent myocardial infarction, or unscheduled
224 coronary revascularization. Secondary analyses were performed for all-cause death, the
225 original primary endpoint of cardiac death or myocardial infarction, and each of the
226 components of the primary endpoint. The impact of active coronary atherosclerotic plaque
227 (CMA=0 versus CMA>0) on the time-to-first event was assessed using cumulative incidence
228 plots and log-rank test as well as hazard ratios with 95% confidence intervals using Cox
229 regression analysis. Requested post hoc analyses included comparisons of baseline
230 characteristics of participants' clinical profile and coronary computed tomography
231 angiography findings as well as further Cox regression models to explore adjustments for
232 clinical characteristics (where $p < 0.10$ between participants with (CMA > 0) or without (CMA
233 = 0) plaque activity), CAD-RADS 2.0 score, GRACE score and the severity of obstructive
234 coronary artery disease. Statistical significance was taken as a two-sided $P < 0.05$. For post
235 hoc analyses, P values should be considered indicative only.

236 **Results**

237

238 **Study Population**

239 Between September 2015 and February 2020, 712 participants were recruited and attended

240 for baseline ¹⁸F-sodium fluoride positron emission tomography and computed tomography

241 scans. Of these, 6 participants received the radiotracer but were unable to complete the scan,

242 and 2 patients were scanned but image reconstruction could not be completed (eFigure 2).

243 The study population comprised of 704 patients who were predominantly middle-aged men

244 with a high prevalence of cardiovascular risk factors receiving guideline-directed medical

245 therapy in whom 671 (95%) underwent index coronary revascularization (Table 1).

246 Identifiable coronary atherosclerotic plaque activity (CMA > 0) was seen in 421 participants

247 who had broadly similar clinical profile, CAD-RADS 2.0 score, mean GRACE score and

248 severity of coronary artery disease to the 283 without demonstrable activity (CMA = 0; Table

249 1).

250

251 **Clinical Outcomes**

252 Clinical follow up was available for all study participants. At study completion, follow up

253 was available in 693 (98.2%) participants (eFigure 2). Over a median of 4.0 [interquartile

254 interval 3.0 to 5.0] years, there were 2582 patient-years of follow up and 141 (20%)

255 participants experienced the composite primary endpoint: first event was cardiac death in 9,

256 non-fatal myocardial infarction in 49 and unscheduled coronary revascularization in 83.

257 There were no demonstrable differences in the primary endpoint or its components between

258 those who did or did not have increased coronary atherosclerotic plaque activity (Figure 1,

259 Table 2). In contrast, higher rates of the original primary endpoint of cardiac death or

260 recurrent non-fatal myocardial infarction as well as all-cause death were observed in those

261 with increased coronary atherosclerotic activity (Figure 2, Table 2). The magnitudes of these
262 associations were similar, but attenuated, after adjustment for clinical characteristics, the
263 CAD-RADS 2.0 score, the GRACE score, or the severity of obstructive coronary artery
264 disease either individually or combined (Table 3). Findings were also similar across quartiles
265 of increased coronary microcalcification of activity (eTable 3).

266

267 **Safety Endpoints**

268 The safety population comprised of all 712 participants who received the ¹⁸F-sodium
269 fluoride radiotracer. Radiation exposure attributable to the radiotracer was 6.0 ± 0.3 mSv
270 (injected activity 248 ± 13 MBq) and total radiation exposure for the computed tomography
271 scanning protocol was 4.9 ± 3.0 mSv (dose-length product of 348 ± 215 Gy.cm). Performance
272 of the positron emission tomography and coronary computed tomography angiogram was
273 associated with 15 adverse events which were predominantly iodinated contrast reactions.
274 Two events were graded as serious: palpitation and beta-blocker induced bradycardia (eTable
275 4).

276 **Discussion**

277

278 The prediction of recurrent coronary events in patients with myocardial infarction is
279 imprecise and currently relies on clinical risk scores and the presence of obstructive coronary
280 artery disease. We have tested the hypothesis that coronary atherosclerotic plaque activity
281 would identify ‘vulnerable’ patients and be associated with future coronary events. We did
282 not demonstrate that increased coronary atherosclerotic plaque activity was associated with
283 the primary composite endpoint of cardiac death, nonfatal myocardial infarction, or
284 unscheduled coronary revascularization. However, it was associated with the secondary
285 endpoints of cardiac death or non-fatal myocardial infarction as well as all-cause mortality.
286 This is consistent with the critical importance of coronary atherosclerotic plaque biology and
287 activity in the causation of spontaneous atherothrombotic events. The findings suggesting
288 risk of cardiovascular death or myocardial infarction in patients with elevated plaque activity
289 warrants further research to explore its incremental prognostic implications.

290

291 Human coronary atherosclerosis is a slow and progressive condition that evolves over years
292 with a central role for the insudation of toxic and inflammatory oxidized lipids into the
293 arterial intima. This leads to a pro-calcific reaction that attempts to contain and constrain the
294 lipid-rich necrotic plaque and thereby prevent plaque rupture. The early stages of developing
295 microcalcification are markers of high-risk plaques that have the potential to rupture causing
296 acute coronary occlusion and myocardial infarction before macrocalcification can contain
297 and stabilize the atherosclerotic plaque.³⁶ This underlies the theoretical basis of ¹⁸F-sodium
298 fluoride uptake within coronary atherosclerotic plaques, identifying an active and potentially
299 unstable phase of the disease that appears associated with clinical atherothrombotic events.¹⁵⁻

300 ¹⁷ Its uptake is also associated with high-risk plaque features on intravascular ultrasound and

301 optical coherence tomography,^{11,14,37,38} and in a retrospective case series of 293 patients with
302 predominantly stable coronary artery disease,²² coronary microcalcification activity was
303 associated with the future risk of fatal or non-fatal myocardial infarction. In our prospective
304 study, we have again found that this non-invasive measure of coronary atherosclerotic plaque
305 activity is associated with the secondary outcome of cardiac death or non-fatal myocardial
306 infarction. In post hoc analyses, this was independent of clinical profile, GRACE score or the
307 severity of obstructive coronary artery disease and underscores the critical importance of
308 coronary plaque biology in the risk of fatal and non-fatal myocardial infarction.

309

310 We found no association between unscheduled coronary revascularization and coronary
311 atherosclerotic plaque activity, and our revised hypothesis that such activity would be
312 associated with unscheduled coronary revascularization was not established. The participant
313 profile and the frequency of revascularization events within our study are consistent with the
314 Providing Regional Observations to Study Predictors of Events in the Coronary Tree
315 (PROSPECT) study.⁶ In this intravascular ultrasound study, rates of recurrent coronary
316 revascularization were 17%, representing the largest component of the primary endpoint.
317 This dominance of coronary revascularization events was in keeping with the main study
318 findings that plaque burden over 70% and a small luminal area were the key predictors of
319 outcome. However, our findings suggest that such coronary revascularization events are
320 unrelated to coronary atherosclerotic plaque activity. Moreover, as with the PROSPECT
321 study, we observed that most of the coronary revascularization events occurred within the
322 first year of follow up. Such a time course would suggest that the predominant drivers of
323 these revascularization events were the characteristics of the index presentation, coronary
324 anatomy, and interventional procedures rather than the underlying atherosclerotic plaque
325 activity throughout the coronary circulation. Thus, coronary 18F-sodium fluoride uptake is

326 not associated with coronary revascularization, and as a marker of active calcification that is
327 attempting to constrain the atherosclerotic plaque, this is perhaps unsurprising.

328

329 We have observed an association between coronary atherosclerotic plaque activity and all-
330 cause mortality with a 2 to 3-fold increase in the risk of death although this was attenuated
331 and no longer met nominal statistical significance after multivariable adjustment. We also
332 demonstrated that coronary atherosclerotic plaque activity was associated with spontaneous
333 coronary events. Although we had lower numbers of events than anticipated, we observed
334 twice the number of cardiac death or non-fatal myocardial infarction events than prior
335 studies,^{6,7} likely reflecting our inclusion of patients with multivessel disease and the longer
336 follow up period. This enabled us to explore the question of whether coronary atherosclerotic
337 plaque activity is associated with spontaneous atherothrombotic coronary events rather than
338 relying on surrogates of plaque volumes and coronary revascularization events. We
339 demonstrate the central importance of coronary atherosclerotic plaque activity for these fatal
340 and non-fatal events, and that this is independent of the severity of obstructive coronary
341 artery disease. This suggests that identification of coronary atherosclerotic plaque activity is
342 associated with the likelihood of recurrent spontaneous coronary events and provides a
343 potential basis for intensification of preventive therapeutic interventions, such as more
344 intensive antiplatelet, lipid lowering or anti-inflammatory therapies.

345

346 Positron emission tomography is not a straightforward technique, and some would question
347 whether this approach is applicable to widespread clinical practice. However, positron
348 emission tomography is routinely employed in modern oncological practice and 18F-sodium
349 fluoride is a simple, inexpensive, and readily available radiotracer. Combined with the
350 widespread use of coronary computed tomography angiography in routine cardiological

351 practice, the delivery of such a technique is likely to become readily achievable particularly
352 as coronary 18F-sodium fluoride positron emission tomography assessments can be
353 combined with previously acquired coronary computed tomography angiograms.²⁴

354

355 There are several study limitations that we should acknowledge. We had a lower than
356 anticipated event rate in our study population despite recruiting patients with myocardial
357 infarction and multivessel disease. This may in part reflect our inclusion criteria for
358 multivessel disease: at least two major epicardial vessels with either >50% luminal stenosis
359 or previous coronary revascularization. The low event rate also led us to change our primary
360 endpoint during the conduct of the trial. Unfortunately, the inclusion of unscheduled coronary
361 revascularization was misplaced, and the occurrence of this event does not appear to correlate
362 with plaque activity as determined by 18F-sodium fluoride uptake. Our study was a
363 longitudinal cohort study, and we can only assess associations rather than causality. We had a
364 disappointingly low inclusion of women in our study, which predominantly reflects the lower
365 proportion of women who present with ST-segment elevation myocardial infarction and
366 multivessel disease and is comparable to rates reported in prior studies and prospective
367 registries.^{5,6,39} We intentionally did not undertake endpoint adjudication because there was
368 strict blinding of the study imaging findings, and there was no opportunity for the site
369 investigators to be influenced by the results of the positron emission tomography scan. In
370 such circumstances, systematic reviews have found no differences in outcomes whether
371 events have been assessed by site investigators or independent clinical endpoint adjudication
372 committees.^{34,35}

373

374 Although the severity of coronary artery disease was very similar, there were some
375 differences in the patient characteristics between those with and without increased coronary

376 atherosclerotic plaque activity. Those with increased activity were on average 3 years older
377 and more likely to be male as well as having a higher frequency of hypertension, and prior
378 diagnosis of coronary artery disease. These overall differences should not be surprising given
379 their known association with coronary artery disease and their potential role in promoting
380 atherosclerotic plaque activity. Moreover, these differences are consistent with contemporary
381 prospective registry data of over 3,000 patients with recent myocardial infarction.³⁹ Here,
382 patients with recurrent coronary events were also older, more likely to be male and had a
383 higher frequency of hypertension, and prior coronary artery disease. It would therefore be
384 very unexpected and incongruous if coronary atherosclerotic plaque activity did not track
385 with these characteristics. Current standard of care uses the GRACE score for risk prediction
386 which, in large meta-analyses, has the best predictive performance and incorporates factors,
387 such as age.¹ It is also predictive of not only short-term outcomes but also 5-year outcomes.⁴⁰
388 We found that coronary atherosclerotic plaque activity was associated with the secondary
389 endpoint of cardiac death or non-fatal myocardial infarction despite adjustment for a range of
390 co-variables including baseline clinical characteristics, coronary computed tomography
391 angiography findings, GRACE score and extent of obstructive disease on invasive coronary
392 angiography. It would therefore appear to provide added prognostic value for spontaneous
393 atherothrombotic coronary events.

394

395 In conclusion, we have demonstrated that coronary atherosclerotic plaque activity is not
396 associated with the primary composite endpoint of cardiac death, nonfatal myocardial
397 infarction, or unplanned revascularization. In a secondary analysis, plaque activity appears to
398 be associated with combine cardiac death and myocardial infarction, warranting further
399 prospective study to explore the incremental prognostic implications of these findings.

400

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428

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430 Neither the funder nor the sponsor had a role in the design and conduct of the study;
431 collection, management, analysis, and interpretation of the data; preparation, review, or
432 approval of the manuscript; and decision to submit the manuscript for publication.

433

434 **Data Sharing**

435 Deidentified individual participant data will be made available one year after publication of
436 the primary manuscript. Data requests should be submitted to the corresponding author.

437 **References**

438
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551 **Tables**

552

553 **Table 1.**

554 Baseline Characteristics of the Study Population.

555

	Total Population	Low coronary atherosclerotic plaque activity	High coronary atherosclerotic plaque activity	P value[§]
		CMA = 0	CMA > 0	
Number	704	283	421	
Age (years)	63.8±8.2	61.8±7.4	65.1±8.4	<0.001
Sex (female)	103 (15%)	61 (22%)	42 (10%)	<0.001
Body-mass index (kg/m²)	28.3±4.4	28.6±4.7	28.1±4.2	0.11
Cardiovascular risk factors				
Smoking habit				
Current Smoker	193 (27%)	90 (32%)	103 (24%)	0.06
Ex-smoker	225 (32%)	91 (32%)	134 (32%)	
Non-smoker	286 (41%)	102 (36%)	184 (44%)	
Hypertension	351 (50%)	119 (42%)	232 (55%)	<0.001
Hypercholesterolaemia	398 (57%)	162 (58%)	236 (56%)	0.62
Diabetes mellitus	118 (17%)	40 (14%)	78 (19%)	0.15
Prior cardiovascular disease				
Coronary artery disease	139 (20%)	41 (14%)	98 (23%)	0.006
Myocardial infarction	102 (14%)	36 (13%)	66 (16%)	0.33
Percutaneous coronary intervention	100 (14%)	28 (10%)	72 (17%)	0.01
Coronary artery bypass graft surgery	31 (4%)	12 (4%)	19 (5%)	>0.99
Peripheral vascular disease	21 (3%)	12 (4%)	9 (2%)	0.17
Cerebrovascular disease	33 (5%)	10 (4%)	23 (5%)	0.31
Presentation electrocardiogram*				0.76
ST-segment elevation myocardial infarction	463 (66%)	189 (67%)	274 (65%)	
Non-ST-segment elevation myocardial infarction	239 (34%)	94 (33%)	145 (35%)	
GRACE score	118±25	113±22	121±26	<0.001
Severity of obstructive coronary artery disease†				0.64
One-vessel coronary artery disease	28 (4%)	12 (4%)	16 (4%)	
Two-vessel coronary artery disease	387 (55%)	163 (58%)	224 (53%)	
Three-vessel coronary artery disease	239 (34%)	90 (32%)	149 (35%)	
Left main stem disease	50 (7%)	18 (6%)	32 (8%)	
Percutaneous coronary intervention	671 (95%)	267 (94%)	404 (96%)	0.42
CT coronary angiogram:				<0.001
CAD-RADS 2.0 score‡				
0	31 (4%)	21 (7%)	10 (2%)	
1 or 2				
P1/2	108 (15%)	52 (18%)	56 (13%)	
P3/4	59 (8%)	18 (6%)	41 (10%)	
3				
P1/2	64 (9%)	31 (11%)	33 (8%)	
P3/4	119 (17%)	46 (16%)	73 (17%)	

4 or 5				
P1/2	51 (7%)	27 (10%)	24 (6%)	
P3/4	272 (39%)	88 (31%)	184 (44%)	
Medication				
Aspirin	673 (96%)	268 (95%)	405 (96%)	0.45
P2Y12 receptor antagonist	688 (98%)	279 (99%)	409 (97%)	0.32
Anticoagulant therapy	42 (6%)	17 (6%)	25 (6%)	>0.99
Statin	653 (93%)	260 (92%)	393 (93%)	0.55
ACE inhibition or ARB	623 (88%)	250 (88%)	373 (89%)	>0.99
Beta-adrenergic receptor antagonist	573 (82%)	233 (82%)	340 (81%)	0.67
Calcium-channel antagonist	64 (9%)	19 (7%)	45 (11%)	0.10
Nitrate	384 (55%)	158 (56%)	226 (54%)	0.63
Other anti-anginal therapy	22 (3%)	8 (3%)	14 (3%)	0.88
Mineralocorticoid receptor antagonist	42 (6%)	21 (7%)	21 (5%)	0.24
Other diuretic therapy	54 (8%)	22 (8%)	32 (8%)	>0.99

556

557 CMA - coronary microcalcification activity

558 CMA = 0 indicative of low coronary atherosclerotic plaque activity

559 CMA > 0 indicative of high coronary atherosclerotic plaque activity

560 CAD-RADS 2.0 - 2022 Coronary Artery Disease – Reporting and Data System²⁷

561 GRACE – Global Registry of Acute Coronary Events; ACE - angiotensin-converting enzyme;

562 ARB – angiotensin receptor blocker

563 *n=2 missing data points

564 †From index invasive coronary angiogram

565 §P value – comparison between CMA = 0 and CMA > 0 (two-sample *t*-test for continuous variables and the χ^2 test for categorical variables). This was a post-hoc analysis and should be taken as indicative values.

568 ‡For those with residual CAD-RADS 2.0 score of 0, 6 had two or more stented vessels and 20

569 had limited CT coronary angiogram image quality.

Table 2
Clinical Outcomes

	Total Population	Low coronary atherosclerotic plaque activity	High coronary atherosclerotic plaque activity	Hazard Ratio (95% Confidence Interval)	P value
		CMA = 0	CMA > 0		
Number	704	283	421		
Primary endpoint	141 (20.0%)	51 (18.0%)	90 (21.4%)	1.25 (0.89 to 1.76)	0.20
All-cause Death	39 (5.5%)	9 (3.2%)	30 (7.1%)	2.43 (1.15 to 5.12)	0.02
Components of the primary endpoint					
Cardiac death	12 (1.7%)	2 (0.7%)	10 (2.4%)	3.51 (0.77 to 16.04)	0.10
Non-fatal myocardial infarction	54 (7.7%)	17 (6.0%)	37 (8.8%)	1.61 (0.91 to 2.86)	0.10
Unscheduled coronary revascularization	87 (12.4%)	36 (12.7%)	51 (12.1%)	0.98 (0.64 to 1.49)	0.91
Cardiac death or non-fatal myocardial infarction	66 (9.4%)	19 (6.7%)	47 (11.2%)	1.82 (1.07 to 3.10)	0.03

CMA - coronary microcalcification activity

CMA = 0 indicative of low coronary atherosclerotic plaque activity

CMA > 0 indicative of high coronary atherosclerotic plaque activity

Table 3.**Adjusted Analyses for Clinical Outcomes**

Post hoc analysis of association between coronary microcalcification activity and cardiac death or non-fatal recurrent myocardial infarction, and all-cause death from Cox proportional hazards regression models adjusting for clinical characteristics, CAD-RADS 2.0 score, GRACE score, and invasive angiographic severity of obstructive coronary artery disease.

	Adjusted Hazard Ratio (95% Confidence Interval)	P value[§]
Cardiac death or non-fatal myocardial infarction		
CMA > 0 versus CMA = 0 adjusting for:		
Age, sex, smoking habit, hypertension, history of coronary artery disease, and prior percutaneous coronary intervention	1.76 (1.02 to 3.04)	0.04
CAD-RADS 2.0 score	1.78 (1.03 to 3.06)	0.04
GRACE score*	1.73 (1.01 to 2.97)	0.05
Severity of obstructive coronary artery disease	1.76 (1.03 to 3.00)	0.04
Age, sex, smoking habit, hypertension, history of coronary artery disease, prior percutaneous coronary intervention, CAD-RADS 2.0 score, GRACE score, and severity of obstructive coronary artery disease	1.76 (1.00 to 3.10)	0.05
All-cause death		
CMA > 0 versus CMA = 0 adjusting for:		
Age, sex, smoking habit, hypertension, history of coronary artery disease, and prior percutaneous coronary intervention	2.12 (0.98 to 4.55)	0.06
CAD-RADS 2.0 score	2.32 (1.09 to 4.95)	0.03
GRACE score [†]	1.80 (0.84 to 3.86)	0.13
Severity of obstructive coronary artery disease	2.25 (1.06 to 4.74)	0.03
Age, sex, smoking habit, hypertension, history of coronary artery disease, prior percutaneous coronary intervention, CAD-RADS 2.0 score, GRACE score, and severity of obstructive coronary artery disease	2.01 (0.90 to 4.49)	0.09

CMA - coronary microcalcification activity

CMA = 0 indicative of low coronary atherosclerotic plaque activity

CMA > 0 indicative of high coronary atherosclerotic plaque activity

GRACE - Global Registry of Acute Coronary Events

*GRACE risk score for prediction of death or myocardial infarction at 6 months after discharge

†GRACE risk score for prediction of death at 6 months after discharge

Severity of obstructive coronary artery disease by invasive coronary angiography was categorised into four groups: (i) one-vessel, (ii) two-vessel, (iii) three-vessel and (iv) left main stem disease.

CAD-RADS 2.0 - 2022 Coronary Artery Disease – Reporting And Data System,²⁷ Segment Involvement Score was used to represent overall coronary plaque burden.

§P value – this was a post-hoc analysis and should be taken as indicative values.

Figure Legends

Figure 1

Cumulative incidence plots of (A) the primary endpoint of cardiac death, non-fatal myocardial infarction, or unscheduled coronary revascularization, (B) cardiac death, (C) non-fatal myocardial infarction, and (C) unscheduled coronary revascularization.

Low coronary atherosclerotic plaque activity (coronary microcalcification activity (CMA) = 0) shown in yellow and high coronary atherosclerotic plaque activity (CMA > 0) shown in blue.

Figure 2

Cumulative incidence plots of (A) all-cause death, and (B) cardiac death or non-fatal myocardial infarction.

Low coronary atherosclerotic plaque activity (coronary microcalcification activity (CMA) = 0) shown in yellow and high coronary atherosclerotic plaque activity (CMA > 0) shown in blue.