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ORIGINAL ARTICLE

Coronary Atherosclerotic Plaque Activity and Future Coronary Events

The PRE[18]FFIR Study

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Key Points

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

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

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

Abstract

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

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

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

Setting: International multicenter study.

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

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

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

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

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

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

Trial Registration: NCT02278211

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Introduction

Recurrent coronary events are common following acute myocardial infarction but are challenging to predict. Clinical risk scores, such as the Global registry of Acute Cardiac Events (GRACE) score,[1] estimate the risk of early events, but have limitations and lack precision.[2,3] The presence of obstructive coronary artery disease has also been seen as a major determinant of future risk leading to strategies of coronary revascularization to reduce subsequent events.[4,5] However, most index myocardial infarctions arise from non-obstructive coronary plaques and recurrent events commonly occur at sites remote from the culprit plaque.[5-7] This has led to attempts to detect high-risk coronary artery plaques that drive such downstream events and thereby identify the 'vulnerable' patient.[8] Previous studies have assessed coronary plaque characteristics using invasive imaging approaches including intravascular ultrasound either alone[6] or in combination with near-infrared spectroscopy.[7] Coronary plaques associated with high-risk features, such as thin-cap fibroatheroma or lipid-rich plaque, are associated with future coronary events, especially those associated with subsequent coronary revascularization. However, these techniques are impractical for widespread application because of the requirement for direct instrumentation of the coronary arteries with its attendant risks.

Advances in non-invasive imaging have enabled the assessment of coronary anatomy and biology without the need to instrument the coronary arteries. Coronary computed tomography angiography has comparable accuracy to invasive coronary angiography[9] and is more sensitive at detecting coronary atheroma.[10] When complemented by positron emission tomography, the anatomy and biology of coronary artery plaque can be assessed simultaneously to identify coronary atherosclerotic plaque activity.[11,12] We and others have

previously shown that combined 18F-sodium fluoride positron emission tomography and coronary computed tomography angiography can identify high-risk and active coronary atherosclerotic plaque in patients with recent myocardial infarction.[11,13,14] Coronary artery 18F-sodium fluoride uptake is a marker of active calcification driven by the lipid-rich necrotic core of the atheromatous plaque[15-19] and is associated with progression of coronary calcification.[20,21] In retrospective post hoc pooled analyses of patients with cardiovascular disease,[22,23] increased coronary 18F-sodium fluoride uptake is associated with an increased risk of fatal and non-fatal myocardial infarction. We therefore wished to establish whether this technique was generalizable and sufficiently robust for clinical application. In a regulated international multicenter prospective cohort study, we aimed to determine whether combined 18F-sodium fluoride positron emission tomography and coronary computed tomography angiography would be associated with the future risk of coronary events in patients with recent myocardial infarction.

Methods

Study Design

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

Study Population

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

Image Acquisition

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

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

Image Analysis

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

the inclusion of unscheduled coronary revascularization into the primary endpoint on the basis that increased coronary atherosclerotic plaque activity may be associated with disease progression and coronary revascularization.[6,7]

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

Results

Study Population

Between September 2015 and February 2020, 712 participants were recruited and attended for baseline 18F-sodium fluoride positron emission tomography and computed tomography scans. Of these, 6 participants received the radiotracer but were unable to complete the scan, and 2 patients were scanned but image reconstruction could not be completed (eFigure 2). The study population comprised of 704 patients who were predominantly middle-aged men with a high prevalence of cardiovascular risk factors receiving guideline-directed medical therapy in whom 671 (95%) underwent index coronary revascularization (Table 1). Identifiable coronary atherosclerotic plaque activity (CMA > 0) was seen in 421 participants who had broadly similar clinical profile, CAD-RADS 2.0 score, mean GRACE score and severity of coronary artery disease to the 283 without demonstrable activity (CMA = 0; Table 1).

Clinical Outcomes

Clinical follow up was available for all study participants. At study completion, follow up was available in 693 (98.2%) participants (eFigure 2). Over a median of 4.0 [interquartile interval 3.0 to 5.0] years, there were 2582 patient-years of follow up and 141 (20%) participants experienced the composite primary endpoint: first event was cardiac death in 9, non-fatal myocardial infarction in 49 and unscheduled coronary revascularization in 83. There were no demonstrable differences in the primary endpoint or its components between those who did or did not have increased coronary atherosclerotic plaque activity (Figure 1, Table 2). In contrast, higher rates of the original primary endpoint of cardiac death or recurrent non-fatal myocardial infarction as well as all-cause death were observed in those

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

Safety Endpoints

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

Discussion

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

Human coronary atherosclerosis is a slow and progressive condition that evolves over years with a central role for the insudation of toxic and inflammatory oxidized lipids into the arterial intima. This leads to a pro-calcific reaction that attempts to contain and constrain the lipid-rich necrotic plaque and thereby prevent plaque rupture. The early stages of developing microcalcification are markers of high-risk plaques that have the potential to rupture causing acute coronary occlusion and myocardial infarction before macrocalcification can contain and stabilize the atherosclerotic plaque.[36] This underlies the theoretical basis of 18F-sodium fluoride uptake within coronary atherosclerotic plaques, identifying an active and potentially unstable phase of the disease that appears associated with clinical atherothrombotic events.[15-17] Its uptake is also associated with high-risk plaque features on intravascular ultrasound and

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

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

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

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

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

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

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

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

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

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

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Role of the Funder and Sponsor

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

Data Sharing

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

References

1. D'Ascenzo F, Biondi-Zoccai G, Moretti C, et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials. 2012;33:507-14.

2. Granger CB, Goldberg RJ, Dabbous O, et al. Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.

3. van der Sangen NMR, Azzahhafi J, Chan Pin Yin DRPP, et al. External validation of the GRACE risk score and the risk-treatment paradox in patients with acute coronary syndrome. Open Heart. 2022;9:e001984.

4. Collet JP, Thiele H, Barbato E, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation**.** Eur Heart J. 2021;42:1289-1367.

5. Mehta SR, Wood DA, Storey RF, et al; COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med. 2019;381:1411-1421.

6. Stone GW, Maehara A, Lansky AJ, et al; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226-235.

7. Waksman R, Di Mario C, Torguson R, et al; LRP Investigators. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. Lancet. 2019;394:1629-1637.

8. Arbab-Zadeh A, Fuster V. From detecting the vulnerable plaque to managing the vulnerable patient. J Am Coll Cardiol. 2019;74:1582-1593.

9. Haase R, Schlattmann P, Andreini D, et al; COME-CCT Consortium. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. Br Med J 2019;365:l1945.

10. Maurovich-Horvat P, Bosserdt M, Kofoed KF, et al; DISCHARGE Trial Group. CT or invasive coronary angiography in stable chest pain. N Engl J Med. 2022;386:1591-1602.

11. Joshi NV, Vesey AT, Williams MC, et al. 18F-Fluoride positron emission tomography identifies ruptured and high-risk coronary atherosclerotic plaques. Lancet 2014;383:705-713.

12. Tarkin JM, Joshi FR, Evans NR, et al. Detection of atherosclerotic inflammation by ^{68}Ga-DOTATATE PET compared to [^{18}F]FDG PET imaging. J Am Coll Cardiol. 2017;69:1774-1791.

13. Dweck MR, Chow MWL, Joshi N, et al. Coronary arterial 18F-NaF uptake: a novel marker of cardiovascular risk. J Am Coll Cardiol 2012;59:1539-1548.

14. Majeed K, Bellinge JW, Butcher SC, et al. Coronary ^{18}F-sodium fluoride PET detects high-risk plaque features on optical coherence tomography and CT-angiography in patients with acute coronary syndrome. Atherosclerosis. 2021;319:142-148.

15. Irkle A, Vesey AT, Lewis DY, et al. Identifying active vascular microcalcification by ^{18}F-sodium fluoride positron emission tomography. Nat Commun. 2015;6:7495.

16. Creager MD, Hohl T, Hutcheson JD, et al. ^{18}F-Fluoride signal amplification identifies microcalcifications associated with atherosclerotic plaque instability in PET-CT images. Circ Cardiovasc Imaging. 2019;12:e007835.

17. Moss AJ, Sim AM, Adamson PD, et al. Ex vivo 18F-fluoride uptake and hydroxyapatite deposition in human coronary atherosclerosis. Sci Rep. 2020;10:20172.

18. Youn T, Al'Aref SJ, Narula N, et al. ^{18}F-Sodium fluoride positron emission tomography/computed tomography in ex vivo human coronary arteries with histological correlation. Arterioscler Thromb Vasc Biol. 2020;40:404-411.

19. Wen W, Gao M, Yun M, et al. In vivo coronary 18F-sodium fluoride activity. correlations with coronary plaque histological vulnerability and physiological environment. JACC Cardiovasc Imaging 2022; in press.

20. Bellinge JW, Francis RJ, Lee SC, et al. ^{18}F-Sodium fluoride positron emission tomography activity predicts the development of new coronary artery calcifications. Arterioscler Thromb Vasc Biol. 2021;41:534-541.

21. Doris MK, Meah MN, Moss AJ, et al. Coronary ^{18}F-fluoride uptake and progression of coronary artery calcification. Circ Cardiovasc Imaging. 2020;13:e011438.

22. Kwiecinski J, Tzolos E, Adamson PD, et al. ^{18}F-Sodium fluoride coronary uptake predicts outcome in patients with coronary artery disease. J Am Coll Cardiol 2020;75:3061-3074.

23. Fletcher AJ, Tew YY, Tzolos E, et al. Thoracic aortic 18F-sodium fluoride activity and ischemic stroke in patients with established cardiovascular disease. JACC Cardiovasc Imaging. 2022; in press.

24. Kwiecinski J, Adamson PD, Lassen ML, et al. Feasibility of coronary ^{18}F-sodium fluoride PET assessment with the utilization of previously acquired CT angiography. Circ Cardiovasc Imaging. 2018;11;e008325.

25. Halliburton SS, Abbara S, Chen MY, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr. 2011;5:198–224.

26. Segall G, Delbeke D, Stabin MG, et al. SNM practice guideline for sodium 18F-fluoride PET/CT bone scans 1.0. J Nucl Med. 2010;51:1813-20.

27. Cury RC, Leipsic J, Abbara S, et al. CAD-RADS 2.0 - 2022 Coronary Artery Disease – Reporting and Data System. J Cardiovasc Comput Tomogr. 2022;16:536-557.

28. Doris MK, Otaki Y, Krishnan SK, et al. Optimization of reconstruction and quantification of motion-corrected coronary PET-CT. J Nucl Cardiol. 2020;27:494-504.

29. Rubeaux M, Joshi N, Dweck MR, et al. Motion correction of 18F-sodium fluoride PET for imaging coronary atherosclerotic plaques. J Nucl Med. 2016;57:54-59.

30. Kwiecinski J, Cadet S, Daghem M, et al. Whole-vessel coronary 18F-sodium fluoride PET for assessment of the global coronary microcalcification burden. Eur J Nucl Med Mol Imaging. 2020;47:1736-1745.

31. Kwiecinski J, Dey D, Cadet S, et al. 18F-Sodium fluoride uptake in patients with stable coronary artery disease and adverse plaque features on computed tomography angiography. Eur Heart J Cardiovasc Imaging. 2020;21:58-66.

32. Tzolos E, Kwiecinski J, Lassen ML, et al. Observer repeatability and interscan reproducibility of 18F-sodium fluoride coronary microcalcification activity. J Nucl Cardiol 2022;29:126-135.

33. Tzolos E, Lassen ML, Pan T, et al. Respiration-averaged CT versus standard CT attenuation map for correction of ^{18}F-Sodium Fluoride uptake in coronary atherosclerotic lesions on hybrid PET/CT. J Nucl Cardiol 2022;29:430-439.

34. Meah MN, Denvir MA, Mills NL, Norrie J, Newby DE. Clinical endpoint adjudication. Lancet. 2020;395:1878-1882.

35. Ndounga Diakou LA, Trinquart L, Hróbjartsson A, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev. 2016 Mar 10;3(3):MR000043

536 36. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography
537 characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome.
538 J Am Coll Cardiol. 2009;54:49-57.
539 37. Lee JM, Bang J-I, Koo B-K, et al. Clinical relevance of 18F-sodium fluoride positron-
540 emission tomography in non-invasive identification of high-risk plaque in patients with
541 coronary artery disease. Circ Cardiovasc Imaging. 2017;10:e006704.
542 38. Wurster TH, Landmesser U, Abdelwahed YS, et al. Simultaneous [18F]fluoride and
543 gadobutrol enhanced coronary positron emission tomography/magnetic resonance imaging
544 for in vivo plaque characterization. Eur Heart J Cardiovasc Imaging. 2022; in press.
545 39. Song J, Murugiah K, Hu S, et al, for the China PEACE Collaborative Group.
546 Incidence, predictors, and prognostic impact of recurrent acute myocardial infarction in
547 China. Heart. 2020;107:313-318.
548 40. Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the
549 late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J.
550 2010;31:2755-64.

Tables

Table 1.
Baseline Characteristics of the Study Population.

	Total Population	**Low coronary atherosclerotic plaque activity CMA = 0**	**High coronary atherosclerotic plaque activity CMA > 0**	**P value§**
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/m^2)	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: CAD-RADS 2.0 score‡				<0.001
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

CMA - coronary microcalcification activity
CMA = 0 indicative of low coronary atherosclerotic plaque activity
CMA > 0 indicative of high coronary atherosclerotic plaque activity
CAD-RADS 2.0 - 2022 Coronary Artery Disease – Reporting and Data System[27]
GRACE – Global Registry of Acute Coronary Events; ACE - angiotensin-converting enzyme; ARB – angiotensin receptor blocker
*n=2 missing data points
†From index invasive coronary angiogram
§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.
‡For those with residual CAD-RADS 2.0 score of 0, 6 had two or more stented vessels and 20 had limited CT coronary angiogram image quality.

Table 2
Clinical Outcomes

	Total Population	**Low coronary atherosclerotic plaque activity** **CMA = 0**	**High coronary atherosclerotic plaque activity** **CMA > 0**	**Hazard Ratio (95% Confidence Interval)**	**P value**
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.