

Coronary Atherosclerotic Plaque Activity and Myocardial Infarction

A vessel-level analysis of the PRE¹⁸FFIR study

Running title: Coronary atherosclerotic plaque activity and MI

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Disclosure

AJM is a current employee of AstraZeneca. MCW has given talks for Canon Medical Systems, Novartis, and Siemens Healthineers. All other authors have no competing interests related to this manuscript to disclose.

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Abstract

Background

Total coronary atherosclerotic plaque activity across the entire coronary arterial tree is associated with patient-level clinical outcomes.

Objectives

We aimed to investigate whether vessel-level coronary atherosclerotic plaque activity is associated with vessel-level myocardial infarction.

Methods

In this secondary analysis of an international multicenter study of patients with recent myocardial infarction and multivessel coronary artery disease, we assessed vessel-level coronary atherosclerotic plaque activity using coronary ^{18}F -sodium fluoride positron emission tomography to identify vessel-level myocardial infarction.

Results

Increased ^{18}F -sodium fluoride uptake was found in 679 of 2094 coronary arteries and 414 of 691 patients respectively. Myocardial infarction occurred in 24 (4%) vessels with increased coronary atherosclerotic plaque activity and in 25 (2%) vessels without increased coronary atherosclerotic plaque activity (hazard ratio, 2.08; 95% confidence interval, 1.16 to 3.72; $P=0.013$). This association was not demonstrable in those treated with coronary revascularization (hazard ratio, 1.02; 95% confidence interval, 0.47 to 2.25) but was notable in untreated vessels (hazard ratio, 3.86; 95% confidence interval, 1.63 to 9.10) ($P_{\text{interaction}}=0.024$). Increased coronary atherosclerotic plaque activity in multiple coronary arteries was associated with heightened patient-level risk of cardiac death or myocardial

infarction (hazard ratio, 2.43; 95% confidence interval, 1.37 to 4.30; $P=0.002$) as well as first (hazard ratio, 2.19; 95% confidence interval, 1.18 to 4.06; $P=0.013$) and total (hazard ratio, 2.50; 95% confidence interval, 1.42 to 4.39; $P=0.002$) myocardial infarctions.

Conclusions

In patients with recent myocardial infarction and multivessel coronary artery disease, coronary atherosclerotic plaque activity prognosticates individual coronary arteries and patients at risk for myocardial infarction.

Keywords

Coronary atherosclerotic plaque activity, myocardial infarction, positron emission tomography.

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Condensed abstract

Total coronary atherosclerotic plaque activity across the entire coronary arterial tree is associated with patient-level coronary events. In this secondary analysis of the PRE¹⁸FFIR study, we examined the relationship between individual coronary atherosclerotic plaque activity in each coronary artery territory and myocardial infarction. Among 2094 vessels from 691 patients with recent myocardial infarction and multivessel coronary artery disease, coronary atherosclerotic plaque activity determined by ¹⁸F-sodium fluoride uptake is independently associated with myocardial infarction at the vessel level. Patients who have multivessel increase in coronary atherosclerotic plaque activity are at the greatest risk for fatal and non-fatal myocardial infarction.

Abbreviations

CTCA = computed tomography coronary angiography

PET = positron emission tomography

PRE¹⁸FFIR = Prediction of Recurrent Events with ¹⁸F-Fluoride to Identify Ruptured and high-risk coronary artery plaques in patients with myocardial infarction

Competency in Medical Knowledge

Assessment of coronary atherosclerotic plaque activity using coronary ^{18}F -sodium fluoride positron emission tomography provides incremental prognostic value and can identify coronary arteries and patients at risk for myocardial infarction.

Translational Outlook

Randomized clinical trials are necessary to determine whether the prophylactic intervention of high-risk vessels identified by coronary atherosclerotic plaque imaging with ^{18}F -sodium fluoride improves outcomes in patients with advanced coronary artery disease.

Introduction

Myocardial infarction continues to pose major challenges to healthcare systems in terms of high disease burden and poor patient outcomes.¹ At the population level, most first myocardial infarctions are potentially preventable through modifications of lifestyle and cardiovascular risk factors.² Following an event, the rate of recurrent myocardial infarction is 5–10% in the first year,³ and patients remain at substantial risk for fatal and non-fatal ischemic events throughout their lifespan.⁴ Hence, identifying those in whom these events are more likely to occur or to recur would help individualize patient risk and intensify preventative treatment, thereby providing better protection from myocardial infarction and its complications.

The severity and the extent of coronary artery disease is associated with future myocardial infarction.^{5,6} However, most events are triggered by disruption of a coronary atherosclerotic plaque that has arisen from a non-obstructive lesion.⁷ Consequently, risk assessments based on stenosis severity from invasive coronary angiography have major limitations. Coronary ¹⁸F-sodium fluoride positron emission tomography (PET) is an emerging imaging technique that can identify active microcalcification. Uptake of ¹⁸F-sodium fluoride correlates with sites of coronary atherosclerotic plaque instability on histology,^{8,9} and it is also associated with coronary atherosclerotic plaque progression over time,^{10,11} therefore making it an appealing non-invasive modality to measure coronary atherosclerotic plaque activity due to inflammation-triggered microcalcification.

In the Prediction of Recurrent Events with ¹⁸F-Fluoride to Identify Ruptured and high-risk coronary artery plaques in patients with myocardial infarction (PRE¹⁸FFIR) study, increased total coronary atherosclerotic plaque activity determined by ¹⁸F-sodium fluoride uptake

across the entire coronary arterial tree was associated with higher risk of cardiac death or myocardial infarction, independent of obstructive coronary artery disease.¹² This patient-level analysis underscored the potential clinical utility of coronary ¹⁸F-sodium fluoride PET in risk stratification for patients with advanced coronary artery disease. However, the correlation between coronary atherosclerotic plaque activity and a subsequent clinical event at the vessel level has not yet been established. Moreover, it further raises the question of whether increased coronary atherosclerotic plaque activity in multiple coronary arteries is associated with a proportionally higher rate of cardiac death or myocardial infarction at the patient level. In this secondary analysis of the PRE¹⁸FFIR study, we aimed to elucidate the relationship between individual coronary atherosclerotic plaque activity in each coronary artery territory and myocardial infarction, considering both vessel-specific and patient-centered perspectives.

Methods

Study overview

The design and the results of the PRE¹⁸FFIR study (ClinicalTrials.gov identifier, NCT02278211) have been published previously.¹² In brief, the PRE¹⁸FFIR study was a prospective longitudinal cohort study conducted at nine sites across Australia, England, Scotland, and the United States, enrolling patients aged 50 years and older with recent type 1 myocardial infarction and multivessel coronary artery disease between September 2015 and February 2020. Patients were considered to have multivessel coronary artery disease if there was any combination of either: (1) 50% or more diameter stenosis on invasive coronary angiography; or (2) previous coronary revascularization in two or more epicardial coronary arteries. Exclusion criteria consisted of any contraindications (such as pregnancy, breastfeeding or child-bearing potential women, or renal dysfunction) or inability to undertake PET or computed tomography coronary angiography (CTCA), non-paroxysmal atrial fibrillation, or life expectancy less than 2 years.

After intravenous administration of a target dose of 250 MBq ¹⁸F-sodium fluoride, all patients underwent attenuation-correction computed tomography, dual cardiac and respiratory gated PET of the thorax, and electrocardiogram gated CTCA according to the study protocol. Image analysis was performed offline and was not used to inform clinical decision making. All site staff and patients were blinded to the findings of PET and CTCA. Afterwards, annual clinical follow-up continued for a minimum of 2 years.

The study protocol and all amendments were approved by the relevant ethics body at each participating site and was conducted in accordance with the Declaration of Helsinki, the

Good Clinical Practice guidelines, and local regulations. All patients gave written informed consent.

Image analysis

All images were analysed at the independent core laboratory (University of Edinburgh, Edinburgh, Scotland) without knowledge of clinical events. PET image analysis was performed with FusionQuant software, version 1.21.0421 (Cedars-Sinai Medical Center, Los Angeles, CA, USA) as described previously.^{13,14} Vessel-specific coronary atherosclerotic plaque activity of the left anterior descending artery, the left circumflex artery, the right coronary artery, and the ramus intermedius artery (if present) was measured separately using coronary artery microcalcification activity derived from both intensity and volume of ¹⁸F-sodium fluoride uptake regardless of the presence of coronary artery stents. The left main coronary artery was included in the left anterior descending artery volume of interest as described previously.¹⁵ Total coronary atherosclerotic plaque activity was the sum of individual coronary atherosclerotic plaque activity in each coronary artery territory. CTCA findings were reported according to the Society of Cardiovascular Computed Tomography guidelines,¹⁶ and residual coronary atherosclerotic plaque burden was calculated with the segment stenosis score.¹⁷

Study endpoints

For this study, the primary vessel-level outcome of interest was myocardial infarction in the vessel-specific territory. The secondary patient-level outcomes of interest were the composite of cardiac death or myocardial infarction as well as myocardial infarction considered in isolation as both the first event and the total events. These events were reported by site investigators using a standardized clinical pro forma, and the culprit vessel considered

responsible for myocardial infarction was defined by site investigators based on invasive coronary angiography or electrocardiography in the absence of invasive coronary angiography.

Statistical analysis

Descriptive data were presented as median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables, and differences were compared with the Mann–Whitney U test, the Kruskal–Wallis H test, and the Fisher–Freeman–Halton test as appropriate.

All time-to-first event data, except for the composite of cardiac death or myocardial infarction, were subject to death as common competing risk to account for informative censoring and were presented using the Aalen–Johansen estimator. Between-group differences were compared with the homogeneity test of Gray.¹⁸ The data on the composite of cardiac death or myocardial infarction were presented using the Kaplan–Meier estimator, and the data on total myocardial infarctions, subject to death as common competing risk to account for informative censoring, were presented using the Ghosh–Lin estimator.¹⁹

The proportional hazards assumption was assessed using the Schoenfeld residuals and the Grambsch–Therneau test,²⁰ and, when met, Cox proportional hazards regression models were used to evaluate the effects of coronary atherosclerotic plaque activity on vessel-level and patient-level outcomes. To account for within-patient dependency in the vessel-level event, cause-specific hazards were analysed using the shared frailty model, under which the effect of vessel-specific coronary atherosclerotic plaque activity on myocardial infarction was evaluated, adjusted for study subject as a random-effects factor. For patient-level events,

cause-specific hazards were analysed using the shared frailty models, adjusted for study site as a random-effects factor to account for within-cluster homogeneity. We used the Andersen-Gill model—an extension of Cox proportional hazards regression model using the counting process approach—to estimate the effect of the number of coronary arteries with increased coronary atherosclerotic plaque activity on total myocardial infarctions.²¹

To control for confounders, additional multivariable Cox proportional hazards regression models were constructed. The potential covariates were first selected based on existing literature and biological plausibility, and, taking data availability into account, then the minimally sufficient adjustment set was determined using a Directed Acyclic Graph (Supplementary Figures 1 and 2).²² We also explored whether there was an effect modification of vessel-level coronary atherosclerotic plaque activity by coronary revascularization at index myocardial infarction by testing their interaction.

There was no adjustment for multiplicity as these analyses were exploratory. All analyses were performed using SAS software, version 9.4 (SAS institute, Cary, NC, USA).

Results

Study population

Of 706 patients who underwent coronary ^{18}F -sodium fluoride PET and CTCA, 15 were excluded from the current study due to incomplete data (Figure 1). The study population comprised of 691 patients of whom 414 (60%) had increased total coronary atherosclerotic plaque activity at the patient level. Among 1258 coronary arteries analysed in these 414 patients, 679 (54%) had increased coronary atherosclerotic plaque activity.

Baseline vessel characteristics

On CTCA, 2094 analysable coronary arteries were identified, of which 832 (40%) were and 1262 (60%) were not treated with percutaneous coronary intervention at index myocardial infarction. Whilst most vessels had less than 70% maximal residual diameter stenosis, residual coronary atherosclerotic plaque burden was greater in those with increased coronary atherosclerotic plaque activity than in those without increased coronary atherosclerotic plaque activity (Table 1).

Primary vessel-level outcome

During a median follow-up of 4 years (interquartile range, 3–5 years), myocardial infarction occurred in 24 (4%) of 679 vessels with increased coronary atherosclerotic plaque activity and in 25 (2%) of 1415 vessels without increased coronary atherosclerotic plaque activity (Figure 2). The cumulative incidence of myocardial infarction at 5 years was 3 percentage points (95% confidence interval, 1 to 6; Gray's $P=0.008$) higher for those with increased coronary atherosclerotic plaque activity than for those without increased coronary atherosclerotic plaque activity.

Increased coronary atherosclerotic plaque activity was associated with higher risk of myocardial infarction (hazard ratio, 2.08; 95% confidence interval, 1.16 to 3.72; $P=0.013$), and the association remained (adjusted hazard ratio, 1.89; 95% confidence interval, 1.04 to 3.43; $P=0.036$) after adjustments for confounders (Supplementary Table 1).

Influence of coronary revascularization at index myocardial infarction

Whether coronary arteries had been treated at index myocardial infarction appeared to modify the association between coronary atherosclerotic plaque activity and myocardial infarction ($P_{\text{interaction}}=0.024$). For those having undergone coronary revascularization, myocardial infarction occurred in 12 (3%) of 370 vessels with increased coronary atherosclerotic plaque activity and in 15 (3%) of 462 vessels without increased coronary atherosclerotic plaque activity (hazard ratio, 1.02; 95% confidence interval, 0.47 to 2.25) (Figure 3A). In contrast, for untreated vessels, myocardial infarction occurred in a substantially higher proportion of those with increased coronary atherosclerotic plaque activity than in those without increased coronary atherosclerotic plaque activity (4% versus 1%; hazard ratio, 3.86; 95% confidence interval, 1.63 to 9.10) (Figure 3B).

Secondary patient-level outcomes

Patients who had more coronary arteries with increased coronary atherosclerotic plaque activity were older and more likely to be men. They were also more likely to have a greater number of cardiovascular risk factors and prior coronary artery disease, a higher Global Registry of Acute Coronary Events score, and more extensive residual coronary atherosclerotic plaque burden (Table 2).

Overall, 66 patients experienced 12 cardiac deaths and 66 myocardial infarctions during follow-up (Supplementary Figure 3). Cardiac death or myocardial infarction occurred in 31 (15%) of 207 patients, 16 (8%) of 207 patients, and 19 (7%) of 277 patients who had two or more, one, and no coronary arteries with increased coronary atherosclerotic plaque activity respectively. The cumulative incidence of cardiac death or myocardial infarction at 5 years was 8% (95% confidence interval, 5 to 12) in patients with no increase in coronary atherosclerotic plaque activity as compared to 22% (95% confidence interval, 14 to 31) in those with multivessel increase (hazard ratio, 2.43; 95% confidence interval, 1.37 to 4.30; $P=0.002$) and 8% (95% confidence interval, 5 to 13) in those with single-vessel increase (hazard ratio, 1.23; 95% confidence interval, 0.63 to 2.38; $P=0.550$) (Figure 4A). The 5-year cumulative incidence of first myocardial infarction was 19% (95% confidence interval, 11 to 27) in patients with multivessel increase (hazard ratio, 2.19; 95% confidence interval, 1.18 to 4.06; $P=0.013$) and 6% (95% confidence interval, 3 to 10) in patients with single-vessel increase (hazard ratio, 1.03; 95% confidence interval, 0.49 to 2.17; $P=0.929$) as compared with 7% (95% confidence interval, 4 to 11) in those with no increase (Figure 4B). Moreover, the total number of first and subsequent myocardial infarctions was higher in those with multivessel increase (hazard ratio, 2.50; 95% confidence interval, 1.42 to 4.39; $P=0.002$) and similar in those with single-vessel increase (hazard ratio, 1.07; 95% confidence interval, 0.54 to 2.14; $P=0.839$) as compared with those with no increase (Figure 4C).

After accounting for cardiovascular risk factors and residual coronary atherosclerotic plaque burden, patients with multivessel increase in coronary atherosclerotic plaque activity continued to be at increased risk for cardiac death or myocardial infarction, first myocardial infarction, and total myocardial infarctions (Supplementary Tables 2, 3, and 4).

Discussion

In this secondary vessel-level analysis of the PRE¹⁸FFIR study, we have demonstrated that vessel-specific coronary atherosclerotic plaque activity was associated with myocardial infarction within the same coronary artery territory (Central Illustration), and increased coronary atherosclerotic plaque activity was predominantly seen in coronary arteries without residual obstructive lesions. Furthermore, patients with multivessel increase in coronary atherosclerotic plaque activity were at the highest risk for cardiac death or myocardial infarction (Central Illustration). These findings support the central role of coronary atherosclerotic plaque activity in the development of myocardial infarction and the importance of incorporating coronary atherosclerotic plaque activity in prediction of coronary atherothrombotic events at both the vessel and the patient level.

We have shown that coronary atherosclerotic plaque activity tracks with myocardial infarction at the vessel level. This reaffirms and gives added plausibility to our prior patient-level results. It has also provided several additional notable findings. In particular, we demonstrated that the association was strongest in coronary arteries that had not undergone coronary revascularization at index myocardial infarction. There are two potential explanations for this observation. First, coronary revascularization had modified some of the coronary atherosclerotic plaques, thereby partially negating the influence of increased coronary atherosclerotic plaque activity. A prior study using intravascular ultrasound and near-infrared spectroscopy has suggested that prophylactic stenting may have a role in reducing risk in patients with non-obstructive coronary artery disease and adverse coronary atherosclerotic plaque morphology,²³ although this is unproven and remains contentious.²⁴ Second, and in our view more likely, this observation reflects the fact that increased coronary atherosclerotic plaque activity in the treated coronary arteries characterizes disruption of the

culprit coronary atherosclerotic plaque causing index myocardial infarction, thereby triggering coronary revascularization. Consequently, repeated disruption of the same coronary atherosclerotic plaque that has already been treated with percutaneous coronary intervention is unlikely to reoccur, and this will have diluted the overall association between vessel-level coronary atherosclerotic plaque activity and myocardial infarction.

Among untreated coronary arteries, those with increased coronary atherosclerotic plaque activity had a four-fold increment in risk of myocardial infarction as compared to those without increased coronary atherosclerotic plaque activity. These untreated vessels had predominantly non-obstructive lesions. This highlights the importance of coronary atherosclerotic plaque activity in determining clinical events and that a simplistic assessment of stenosis severity on invasive coronary angiography will not be the major determinant for myocardial infarction. This is consistent with the recent studies that used invasive assessments of coronary atherosclerotic plaque morphology and similarly found subsequent coronary events were driven by non-obstructive non-culprit lesions.^{25,26} Taken together, these findings underline the central importance of coronary atherosclerotic plaque activity in driving the cause of myocardial infarction irrespective of stenosis severity, and non-invasive assessment of coronary atherosclerotic plaque activity is going to be essential if we are to improve our approaches to risk stratification and the focused application of preventative treatment.

We explored whether there was a ‘dose-dependent’ association between vessel-level coronary atherosclerotic plaque activity and patient-level outcomes. Intuitively, patient-level risk would be anticipated to track with how many coronary arteries had increased coronary atherosclerotic plaque activity. Indeed, this is what we have observed. Patients with

multivessel increase in coronary atherosclerotic plaque activity had the highest rate of not only cardiac death or myocardial infarction but also first and total myocardial infarctions. The increment in patient-level events for those with single-vessel increase was modest in comparison to those without heightened coronary atherosclerotic plaque activity. This most likely reflects the fact that more than two-thirds of patients with single-vessel increase in coronary atherosclerotic plaque activity had undergone coronary revascularization on this coronary artery. Again, consistent with the vessel-level analysis, this likely reflects the dilutional effect of coronary revascularization at index myocardial infarction. Nevertheless, our overall findings underscore the importance of coronary atherosclerotic plaque activity in multiple coronary arteries, especially in those with untreated and non-obstructive coronary artery disease.

Limitations

Our study has some limitations which we would like to acknowledge. First, the diagnosis of myocardial infarction was made by treating physicians and documented by site investigators, rather than adjudicated by independent reviewers, and we cannot exclude diagnostic misclassification. However, there is no evidence that levels of agreement differ substantially between site investigators and adjudication committees,²⁷ and most of the culprit vessels were confirmed on invasive coronary angiography. Second, we have focused on the association between coronary atherosclerotic plaque activity and myocardial infarction, but further ongoing exploration of the influence of coronary atherosclerotic plaques on CTCA is warranted. Third, the PRE¹⁸FFIR study only enrolled patients with recent myocardial infarction who had multivessel coronary artery disease. As a result, our findings might not be generalisable to patients with stable coronary artery disease, in whom coronary atherosclerotic plaque activity and levels of systemic and local inflammation may be different. Finally, we used a dedicated software that measures integrated ¹⁸F-sodium fluoride uptake across the vessel of interest to define coronary atherosclerotic plaque activity. The generalisability of findings using other analytical techniques needs to be established.

Conclusions

Coronary atherosclerotic plaque activity was independently associated with myocardial infarction at the vessel level and further contributed to estimates of patient-level risk. These findings provide the foundations for strategies to individualize patient risk and enhance preventative treatment using coronary atherosclerotic plaque activity.

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References

1. Timmis A, Kazakiewicz D, Townsend N, Huculeci R, Aboyans V, Vardas P. Global epidemiology of acute coronary syndromes. *Nat Rev Cardiol* 2023;20:778-788.
2. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
3. Hess CN, Clare RM, Neely ML et al. Differential occurrence, profile, and impact of first recurrent cardiovascular events after an acute coronary syndrome. *Am Heart J* 2017;187:194-203.
4. Kaasenbrood L, Boekholdt SM, van der Graaf Y et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. *Circulation* 2016;134:1419-1429.
5. Maddox TM, Stanislawski MA, Grunwald GK et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA* 2014;312:1754-63.
6. Fuchs A, Kuhl JT, Sigvardsen PE et al. Subclinical Coronary Atherosclerosis and Risk for Myocardial Infarction in a Danish Cohort : A Prospective Observational Cohort Study. *Ann Intern Med* 2023;176:433-442.
7. Stone GW, Maehara A, Lansky AJ et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-35.
8. Joshi NV, Vesey AT, Williams MC et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 2014;383:705-13.
9. 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.

10. 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.
11. Daghem M, Adamson PD, Wang KL et al. Temporal Changes in Coronary (18)F-Fluoride Plaque Uptake in Patients with Coronary Atherosclerosis. *J Nucl Med* 2023;64:1478-1486.
12. Moss A, Daghem M, Tzolos E et al. Coronary Atherosclerotic Plaque Activity and Future Coronary Events. *JAMA Cardiol* 2023;8:755-764.
13. Kwiecinski J, Cadet S, Daghem M et al. Whole-vessel coronary (18)F-sodium fluoride PET for assessment of the global coronary microcalcification burden. *Eur J Nucl Med Mol Imaging* 2020;47:1736-1745.
14. 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.
15. Kwiecinski J, Tzolos E, Adamson PD et al. Coronary (18)F-Sodium Fluoride Uptake Predicts Outcomes in Patients With Coronary Artery Disease. *J Am Coll Cardiol* 2020;75:3061-3074.
16. Cury RC, Leipsic J, Abbara S et al. CAD-RADS 2.0 - 2022 Coronary Artery Disease-Reporting and Data System: An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the North America Society of Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2022;16:536-557.
17. Min JK, Shaw LJ, Devereux RB et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.

18. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Annals of Statistics* 1988;16:1141-1154.
19. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. *Biometrics* 2000;56:554-62.
20. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika* 1994;81:515-526.
21. Andersen PK, Gill RD. Cox's Regression Model for Counting Processes: A Large Sample Study. *The Annals of Statistics* 1982;10:1100-1120.
22. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34:211-219.
23. Stone GW, Maehara A, Ali ZA et al. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J Am Coll Cardiol* 2020;76:2289-2301.
24. Ahn JM, Kang DY, Lee PH et al. Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: Rationale and design of the randomized, controlled PREVENT trial. *Am Heart J* 2023;264:83-96.
25. Waksman R, Di Mario C, Torguson R et al. 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.
26. Erlinge D, Maehara A, Ben-Yehuda O et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet* 2021;397:985-995.
27. Meah MN, Denvir MA, Mills NL, Norrie J, Newby DE. Clinical endpoint adjudication. *Lancet* 2020;395:1878-1882.

Figure legends

Figure 1. Study flowchart.

Sub-study population from the PRE¹⁸FFIR study and the distribution of coronary arteries with and without increased coronary atherosclerotic plaque activity.

CTCA = computed tomography coronary angiography; PET = positron emission tomography

Figure 2. Cumulative incidence of myocardial infarction.

Time-to-first event of vessel-level myocardial infarction according to the presence or absence of increased coronary atherosclerotic plaque activity.

Figure 3. Impact of coronary revascularization on myocardial infarction.

Cumulative incidence of myocardial infarction for coronary arteries that (A) had or (B) had not been treated with coronary revascularization prior to baseline imaging. Index coronary revascularization had a differential effect on the relationship between coronary atherosclerotic plaque activity and myocardial infarction.

CI = confidence interval; HR = hazard ratio

Figure 4. Patient-level events.

Cumulative incidence of (A) cardiac death or myocardial infarction, (B) first myocardial infarction, and (C) total myocardial infarctions (shown as the mean cumulative count per 100 patients) across the number of coronary arteries with increased coronary atherosclerotic plaque activity.

CI = confidence interval; HR = hazard ratio

Central Illustration

Vessel-level coronary atherosclerotic plaque activity identifies non-culprit coronary arteries and patients who are at heightened risk for future myocardial infarction.

Table 1. Baseline characteristics of coronary arteries by coronary atherosclerotic plaque activity.

	With increased coronary atherosclerotic plaque activity (N = 679)	Without increased coronary atherosclerotic plaque activity (N = 1415)	<i>P</i> value
Coronary revascularization at index myocardial infarction	370 (54)	462 (33)	<0.001
Type of treatment			0.047
Balloon angioplasty	2 (1)	12 (3)	
Bare metal stent	3 (1)	6 (1)	
Drug-eluting stent	365 (99)	442 (96)	
Maximal diameter stenosis on ICA			<0.001
<10%	51 (8)	324 (23)	
10–49%	44 (6)	119 (8)	
50–69%	89 (13)	277 (20)	
≥70%	495 (73)	695 (49)	

Maximal residual diameter stenosis on <0.001

CTCA

Stented or <10%	81 (12)	270 (19)	
10–49%	274 (40)	589 (42)	
50–69%	159 (23)	278 (20)	
≥70%	165 (24)	278 (20)	
Residual segment stenosis score on	3 (1 – 5)	2 (1 – 4)	<0.001

CTCA

* Values are median (interquartile range) or n (%).

† Coronary revascularization at index myocardial infarction includes coronary revascularization at index hospitalization or before the baseline study visit for index myocardial infarction.

‡ Maximal diameter stenosis is determined by ICA at index hospitalization.

§ Maximal residual diameter stenosis and residual segment stenosis score are determined by CTCA at the baseline study visit.

CTCA = computed tomography coronary angiography; ICA = invasive coronary angiography

Table 2. Baseline characteristics of patients by number of coronary arteries with increased coronary atherosclerotic plaque activity.

	Multiple (N = 207)	Single (N = 207)	None (N = 277)	<i>P</i> value
Age, years	66 (58 – 72)	64 (58 – 71)	61 (56 – 67)	<0.001
Male sex	189 (91)	184 (89)	216 (78)	<0.001
Cardiovascular risk factor				
Hypertension	124 (60)	104 (50)	116 (42)	<0.001
Diabetes mellitus	47 (23)	30 (14)	39 (14)	0.030
Dyslipidemia	113 (55)	118 (57)	158 (58)	0.754
Former or current smoker	103 (50)	131 (63)	177 (64)	0.003
Prior coronary artery disease				
Myocardial infarction	40 (19)	25 (12)	34 (12)	0.057

Coronary revascularization	45 (22)	35 (17)	34 (12)	0.022
Extent of obstructive coronary artery disease on ICA				0.190
One vessel	6 (3)	9 (4)	12 (4)	
Two vessels	103 (50)	116 (56)	160 (58)	
Three vessels	86 (42)	63 (30)	87 (31)	
Left main stem	12 (46)	19 (9)	18 (6)	
Number of coronary arteries treated at index myocardial infarction	1 (1 – 1)	1 (1 – 1)	1 (1 – 1)	0.670
Killip class				0.061
I	200 (97)	192 (93)	269 (97)	
II and higher	7 (3)	15 (7)	8 (3)	
GRACE score	119 (104 – 132)	115 (102 – 131)	107 (98 – 120)	<0.001

Residual segment stenosis score on CTCA	10 (7 – 13)	8 (5 – 11)	6 (4 – 10)	<0.001
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Preventative treatment

Aspirin	195 (94)	203 (98)	262 (95)	0.082
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P2Y ₁₂ receptor antagonist	200 (97)	202 (98)	273 (99)	0.365
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Statin	192 (93)	194 (94)	255 (92)	0.793
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Renin–angiotensin system blocker	184 (89)	182 (88)	244 (88)	0.966
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Beta-blocker	168 (81)	168 (81)	227 (82)	0.976
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Mineralocorticoid receptor antagonist	8 (4)	13 (6)	21 (8)	0.227
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* Values are median (interquartile range) or n (%).

† Extent of obstructive coronary artery disease is determined by ICA at index hospitalization.

‡ Coronary arteries treated at index myocardial infarction are vessels that had undergone coronary revascularization at index hospitalization or before the baseline study visit for index myocardial infarction.

§ Residual segment stenosis score is determined by CTCA at the baseline study visit.

CTCA = computed tomography coronary angiography; GRACE = Global Registry of Acute Coronary Events; ICA = invasive coronary angiography
