Inflammatory risk and cardiovascular events in patients without obstructive coronary artery disease: the ORFAN multicentre, longitudinal cohort study

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Summary

Background Coronary computed tomography angiography (CCTA) is the first line investigation for chest pain, and it is used to guide revascularisation. However, the widespread adoption of CCTA has revealed a large group of individuals without obstructive coronary artery disease (CAD), with unclear prognosis and management. Measurement of coronary inflammation from CCTA using the perivascular fat attenuation index (FAI) Score could enable cardiovascular risk prediction and guide the management of individuals without obstructive CAD. The Oxford Risk Factors And Non-invasive imaging (ORFAN) study aimed to evaluate the risk profile and event rates among patients undergoing CCTA as part of routine clinical care in the UK National Health Service (NHS); to test the hypothesis that coronary arterial inflammation drives cardiac mortality or major adverse cardiac events (MACE) in patients with or without CAD; and to externally validate the performance of the previously trained artificial intelligence (AI)-Risk prognostic algorithm and the related AI-Risk classification system in a UK population.

Methods This multicentre, longitudinal cohort study included 40 091 consecutive patients undergoing clinically indicated CCTA in eight UK hospitals, who were followed up for MACE (ie, myocardial infarction, new onset heart failure, or cardiac death) for a median of 2·7 years (IQR 1·4–5·3). The prognostic value of FAI Score in the presence and absence of obstructive CAD was evaluated in 3393 consecutive patients from the two hospitals with the longest follow-up (7·7 years [6·4–9·1]). An AI-enhanced cardiac risk prediction algorithm, which integrates FAI Score, coronary plaque metrics, and clinical risk factors, was then evaluated in this population.

Findings In the 2·7 year median follow-up period, patients without obstructive CAD (32 533 [81·1%] of 40 091) accounted for 2857 (66·3%) of the 4307 total MACE and 1118 (63·7%) of the 1754 total cardiac deaths in the whole of Cohort A. Increased FAI Score in all the three coronary arteries had an additive impact on the risk for cardiac mortality (hazard ratio [HR] 29·8 [95% CI 13·9–63·9], p<0·001) or MACE (12·6 [8·5–18·6], p<0·001) comparing three vessels with an FAI Score in the top versus bottom quartile for each artery. FAI Score in any coronary artery predicted cardiac mortality and MACE independently from cardiovascular risk factors and the presence or extent of CAD. The AI-Risk classification was positively associated with cardiac mortality (6·75 [5·17–8·82], p<0·001, for very high risk *vs* low or medium risk) and MACE (4·68 [3·93–5·57], p<0·001 for very high risk *vs* low or medium risk). Finally, the AI-Risk model was well calibrated against true events.

Interpretation The FAI Score captures inflammatory risk beyond the current clinical risk stratification and CCTA interpretation, particularly among patients without obstructive CAD. The AI-Risk integrates this information in a prognostic algorithm, which could be used as an alternative to traditional risk factor-based risk calculators.

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Introduction

Current clinical guidelines advise the use of coronary computed tomography angiography (CCTA) as a first line investigation for stable chest pain,[1–3] aiming to identify patients in need of coronary revascularisation due to the presence of obstructive coronary artery disease (CAD). However, this approach identifies numerous patients without obstructive CAD alongside those with no visible coronary atheroma,[4,5] who are often reassured and discharged without specific

Research in context

Evidence before this study

We searched PubMed using the terms: "inflammation" AND "coronary artery disease" AND "coronary computed tomography" for articles in any language published from database inception to Nov 16, 2023. There were 7366 publications before November 2023, of which 155 articles described coronary inflammation phenotyping on coronary computed tomography angiography (CCTA). Evidence from clinical and translational studies have established the role of inflammation at all stages of atherogenesis, including acute myocardial infarction as a thrombotic sequela of atherosclerotic plaque rupture. Recent meta-analyses of major clinical trials (PROMINENT, REDUCE-IT, and STRENGTH) showed vascular inflammation as a strong driver of cardiovascular events among patients already receiving lipid lowering treatments. Even in patients unable to tolerate intensive statin therapy, inflammation contributes substantially to cardiovascular risk. Adjunctive anti-inflammatory agents showed significant reduction in cardiovascular events (ie, colchicine in LoDoCo and COLCOT, and the anti-interleukin-1β canakinumab in CANTOS). High-sensitivity C-reactive protein can serve as a biomarker of systemic inflammation but does not report on arterial inflammation specifically. Clinical guidelines recommend CCTA as the first line investigation for patients with suspected coronary artery disease (CAD) for diagnosing obstructive CAD to guide coronary revascularisation. However, no validated and robust imaging tool can stratify risk in patients without obstructive CAD by CCTA, although such individuals remain at higher risk of cardiovascular events. Underlying inflammation can drive such events by rendering non-obstructive plaques vulnerable to rupture. Our previous work showed that CCTA can detect coronary inflammation non-invasively by interrogating perivascular adipose tissue (PVAT). The Fat Attenuation Index (FAI) Score quantifies inflammation-induced radiological changes in PVAT phenotype from routine CCTA scans. However, the value of FAI Score in assessing inflammatory risk in patients with no obstructive CAD is unclear. Further, an artificial intelligence (AI)-enhanced risk prediction algorithm (AI-Risk), that includes FAI Score, plaque burden, and the patients' risk factors, was previously trained on a cohort from the USA, but its performance in the UK population, and its ability to change clinical management effectively, are unknown.

Added value of this study

This study addresses the unmet need to stratify risk among individuals without obstructive CAD documented by routine CCTA. In a cohort of 40 091 consecutive patients undergoing CCTA in eight UK hospitals, there were nearly twice as many cardiac deaths and major adverse cardiac events (in absolute numbers) among the group without obstructive CAD (a group who makes up 81·1% of the cohort), compared with those with obstruction, over a median follow-up period of 2·7 years. This highlights the unmet need to develop tools to identify the patients at risk, particularly among those without obstructive CAD. A further nested investigation of 3393 patients with longer follow-up (median 7·7 years) showed that coronary inflammation assessed by FAI Score in any coronary artery predicted adverse cardiovascular events and cardiac mortality in an additive dose-response manner for the number of inflamed coronary arteries, and was independent from the presence or severity of CAD or traditional risk factors.

To better understand how standardised CCTA-based risk prognostication might affect routine practice, this study performed a national, UK-wide validation of the AI-Risk algorithm, which integrates FAI Score with traditional cardiovascular risk factors and coronary atherosclerotic plaque burden, previously trained to capture the absolute risk for a fatal cardiac event over an 8-year period in a US population. The AI-Risk algorithm classified individuals into very high risk (≥10% 8 year risk for fatal cardiac events), high risk (5% to <10%), and low or medium risk (<5%), with good alignment between predicted and observed events, leading to significant reclassification of risk, particularly among those without obstructive CAD on CCTA.

Implications of all the available evidence

Traditional tools for risk assessment were built and calibrated before the modern era of non-invasive imaging, and the previous dichotomy of primary and secondary prevention can be significantly improved by accurately quantifying the burden of atherosclerotic plaque and the extent of inflammation in the coronary circulation using non-invasive imaging. We need new tools that calibrate the risk across the spectrum of the natural history of CAD, from the early stages of inflammation to the development of high-risk plaque. The FAI Score and the new AI-Risk classification use routine CCTA to identify individuals with elevated risk partly due to inflammation, despite the absence of obstructive coronary disease. This approach offers more precise cardiovascular risk assessment and could inform patient management by optimising current lipid-lowering treatments or allocating additional anti-inflammatory therapies. These findings set the stage for prospective validation in rigorous randomised trials testing anti-inflammatory or other risk-reduction therapies.

treatment or follow-up as their management and outcome are unclear.

Vascular inflammation drives atherogenesis and can trigger acute coronary syndromes, even in the absence of obstructive CAD.[6] Identifying and treating patients with inflamed coronary arteries, with or without atherosclerotic plaques, particularly in the absence of obstructive CAD, presents a major unmet need in preventive medicine.[7] We recently developed a technology that allows standardised measurement of coronary inflammation from routine

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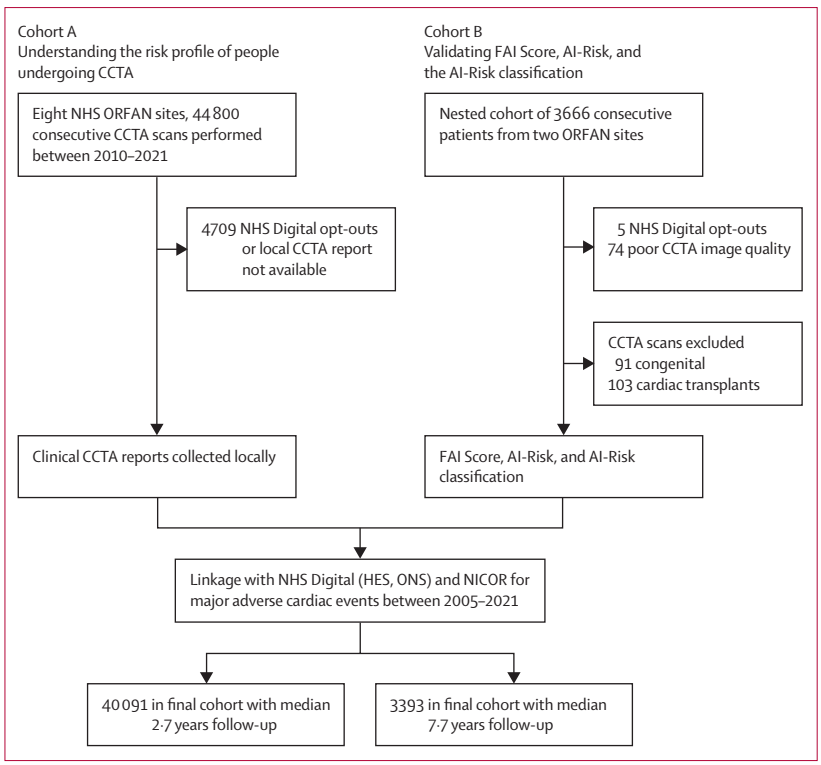

Figure 1: **Study design and data flow**
HES=hospital episodes statistics. NHS=UK National Health Service. NICOR=National Institute for Cardiovascular Outcomes Research. ONS=UK Office of National Statistics. ORFAN=Oxford Risk Factors and Non-invasive Imaging.

CCTA, by analysing spatial changes in perivascular adipose tissue driven by inflammatory signals secreted from the adjacent artery.[8] The fat attenuation index (FAI) and its standardised metric, the FAI Score, enable quantification of these changes, providing a useful estimate of coronary artery inflammation.[8–10] In addition, a recently developed artificial intelligence (AI)-assisted algorithm (AI-Risk)[9,10] incorporates the FAI Score of each coronary artery into a prognostic algorithm, together with the coronary atherosclerotic plaque burden and traditional risk factors, for enhanced cardiovascular risk estimation.[9,10]

The Oxford Risk Factors And Non-invasive imaging (ORFAN) study is the world's largest clinical cohort of consecutive individuals undergoing clinically indicated CCTA, followed up for more than a decade after their index scan for cardiovascular outcomes.

This study aimed to test the role of inflammation in the pathogenesis of cardiovascular events in individuals with and without visible atherosclerosis on CCTA, and to evaluate the ability of the AI-Risk prognostic algorithm to predict future cardiovascular events and guide clinical management in the ORFAN population.

For the **ORFAN study** to https://oxhvf.com/the-orfan-study/

For the **CIMAR gateway** see https://www.cimar.co.uk/cimar-gateway/

See Online for appendix

For the **ORFAN study arm 4** to https://oxhvf.com/orfan/gdpr-privacy-notice

Methods

Study design and participants

This study involved three aims: first, to evaluate the risk profile and event rates among patients undergoing CCTA as part of routine clinical care in the UK National Health Service (NHS); second, to test the hypothesis that coronary arterial inflammation (measured using the perivascular FAI Score in any coronary artery) drives cardiac mortality or major adverse cardiac events (MACE) in patients with or without CAD; and third, to externally validate the performance of the previously trained AI-Risk prognostic algorithm and the related AI-Risk classification system in a UK population. The first objective was assessed in a large longitudinal cohort (n=40 091, Cohort A), while the other two objectives were assessed in a nested longitudinal study with a longer follow-up (n=3393, Cohort B; figure 1).

To understand the risk profile of people undergoing CCTA, the analysis was performed on Cohort A within the ORFAN study (NCT05169333), and included 40 091 consecutive patients undergoing CCTA as part of routine clinical care in eight hospitals in the UK (Oxford University Hospitals, Royal United Hospital Bath, Royal Papworth Hospital, Royal Brompton Hospital, Harefield Hospital, Leicester University Hospital, Milton Keynes Hospital, and Leeds Teaching Hospitals) between 2010–2021. Adult patients aged 18–99 years were included. Patients who opted out from the use of their clinical data for research purposes were excluded. Patient information was collected under Section 251 of the UK National Health Service Act 2006, following approval by the UK Confidentiality Advisory Group (20/CAG/0157). Further information on the consent process followed in this study can be found online at ORFAN study arm 4. Obstructive CAD on CCTA was defined as stenosis of the left main stem of 50% or more or stenosis of any of the three major epicardial coronary arteries of 70% or more, in accordance with the Society of Cardiovascular Computed Tomography, American College of Cardiography, American College of Radiology, and North American Society for Cardiovascular Imaging consensus.[11,12] Coronary calcium scores (CCSs) were extracted from the clinical reports when a non-contrast scan was performed. Local databases were constructed based on electronic patient records within each hospital, and the clinical reporting was performed locally by trained clinicians. The CCTA scans were then transferred to the ORFAN study core laboratory at the Acute Multidisciplinary Imaging and Interventional Centre at the University of Oxford using a General Data Protection Regulation-compliant gateway (CIMAR gateway, provided by Caristo Diagnostics). Patient demographics and clinical outcomes data were collected via local resources and nationwide databases (NHS Digital and the National Institute of Cardiovascular Outcomes Research) using ICD-10 codes, and the study population was followed up prospectively for a median of 2·7 years (IQR 1·4–5·3; appendix pp 9–10). The study design, patient selection process, and data linkage approach are presented in figure 1. The ORFAN study was approved by the Oxfordshire Research Ethics Committee (REC 15/SC/0545).

	Cohort A (N=40 091)	Cohort B (N=3393)
Demographics		
Median age (IQR), years	59 (50–70)	62 (50–73)
Sex		
Male	21 366 (53·3%)	1914 (56·4%)
Female	18 725 (46·7%)	1479 (43·6%)
Ethnicity		
White	31 075 (77·5%)	2599 (76·6%)
Asian	3697 (9·2%)	279 (8·2%)
Black	1002 (2·5%)	100 (2·9%)
Other groups	2842 (7·1%)	334 (9·8%)
Unknown	1475 (3·7%)	81 (2·4%)
Median follow-up years (IQR)	2·7 (1·4–5·3)	7·7 (6·4–9·1)
Cardiovascular risk factors		
Hypertension	16 963 (42·3%)	2060 (60·7%)
Hyperlipidaemia	10 238 (25·5%)	1340 (39·5%)
Diabetes mellitus	7308 (18·2%)	552 (16·3%)
Smoking	4802 (12·0%)	608 (17·9%)
QRISK3 score		
Low or medium risk (<10%)	26 167 (65·3%)	2073 (61·1%)
High risk (10–19%)	10 281 (25·6%)	1003 (29·6%)
Very high risk (≥20%)	3643 (9·1%)	303 (8·9%)
Coronary calcium score 300 or greater	2012/9891 (20·3%)	397/1300 (30·5%)
History of myocardial infarction	1981 (4·9%)	203 (6·0%)
History of PCI	1656 (4·1%)	201 (5·9%)
History of CABG	733 (1·8%)	28 (0·8%)
Events or procedures after CCTA		
MACE	4307 (10·7%)	706 (20·8%)
Non-fatal myocardial infarction	1898 (4·7%)	297 (8·8%)
New heart failure	1727 (4·3%)	313 (9·2%)
Stroke	668 (1·7%)	110 (3·2%)
Cardiac death	1754 (4·4%)	339 (10·0%)
Non-cardiac death	3501 (8·7%)	662 (19·5%)
All-cause death	5255 (13·1%)	1001 (29·5%)
PCI	3116 (7·8%)	388 (11·4%)
CABG	1009 (2·5%)	139 (4·1%)

(Table 1 continues in next column)

(Continued from previous column)

	Cohort A (N=40 091)	Cohort B (N=3393)
Medications		
Antiplatelets	15 839 (39·5%)	1126 (33·2%)
Warfarin	2675 (6·7%)	272 (8·0%)
Beta blockers	17 329 (43·2%)	1191 (35·1%)
Calcium channel blockers	11 770 (29·4%)	824 (24·3%)
Nitrates	9153 (22·8%)	411 (12·1%)
Statins	22 844 (57·0%)	1716 (50·6%)
ACE inhibitors	12 379 (30·9%)	892 (26·3%)
Angiotensin receptor blockers	6993 (17·4%)	579 (17·1%)
Diuretics	12 939 (32·3%)	1024 (30·2%)
Digoxin	1261 (3·1%)	118 (3·5%)
Insulin	1610 (4·0%)	120 (3·5%)
Oral hypoglycaemics	5508 (13·7%)	455 (13·4%)
Direct oral anticoagulant	6308 (15·7%)	510 (15·0%)

Data are n (%) unless otherwise specified. ACE=angiotensin converting enzyme. CAD=coronary artery disease. CABG=coronary artery bypass graft. CCTA=coronary computed tomography angiography. MACE=major adverse cardiovascular events (myocardial infarction, new heart failure, and cardiac death). PCI=percutaneous coronary intervention.

Table 1: **Cohort demographics and clinical characteristics**

To validate the long-term prognostic value of FAI Score and the performance of the AI-Risk algorithm, a nested cohort (Cohort B) was designed within the ORFAN population, to include individuals who underwent CCTA in the two hospitals with the longest follow-up available (Royal Brompton and Harefield Hospitals). This cohort included 3393 consecutive unselected patients undergoing clinically indicated CCTA between the years 2010 and 2015 (table 1, figure 1). Patients referred for the evaluation of congenital heart disease or heart transplantation were excluded. These patients were followed up for a median of 7·7 years (IQR 6·4–9·1) via data-linkage with nationwide databases for incident MACE (ie, myocardial infarction, new heart failure, and cardiac mortality) and cardiac mortality as a separate endpoint (appendix pp 4, 9–12). The CCTA scans were transferred to the ORFAN core laboratory and were analysed using the CaRi-Heart version 2.5 device (Caristo Diagnostics, Oxford, UK) to generate the FAI Score for each coronary artery and the AI-Risk for the patient according to the quality standards regulating medical devices (appendix p 13).[13] The AI-Risk classification system, categorises patients depending on their AI-Risk and FAI Score.[9,10] The extent and severity of coronary stenosis was assessed by trained personnel in the ORFAN study core laboratory, by using the Coronary Artery Disease Reporting and Data System (CAD-RADS 2.0).[14] Clinical reports of the CCTA were obtained and cross-referenced with the core laboratory reports as an internal quality check of the study core laboratory's plaque assessment. The results of the FAI Scores and AI-Risk, as well as the AI-Risk classification, were compiled into a database, which was locked before it was merged with the outcomes database for statistical analysis. QRISK3 was calculated using age, sex, ethnicity, smoking, diabetes, family history, chronic kidney disease, atrial fibrillation, blood pressure treatment, migraines, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness, antipsychotic medication, steroid tablets, BMI, and lipid profile. The QRISK3 model was originally developed using NHS Digital data from the UK population from 1998 and 2015.[15] An extensive description of the data collection is presented in the appendix (pp 4–5).

For the **QRISK3 model** see https://qrisk.org

Procedures

Detailed analytical procedures are presented in the appendix (pp 5–6). Briefly, FAI Score and AI-Risk were computed using the CaRi-Heart version 2.5 medical device. Descriptions of the algorithms used in the device have been presented previously,[8–10] and a schematic overview of its functionality and outputs are presented in the appendix (p 13). The FAI Score assesses the degree of inflammation in each of the right coronary artery (RCA), the left anterior descending coronary artery (LAD), and the left circumflex artery (LCx), and is derived using a proprietary algorithm that incorporates the FAI with adjustments for age, sex, scan technical parameters, and biological and anatomical factors.[10,14]

The highest FAI Score (the most inflamed artery) was incorporated into a prognostic model together with traditional clinical risk factors (diabetes, smoking, hyperlipidaemia, and hypertension) and plaque burden (modified Duke CAD index, an angiographic score integrating proximal CAD, plaque extent, and left main disease)[16] to generate the 8-year percentage risk of the individual patient for a fatal cardiac event (AI-Risk algorithm).[10] Further details on the model are presented in the appendix (pp 5–6). The AI-Risk classification distributes patients into three risk categories (low or medium risk, high risk, and very high risk) based on a scoring system[15] that accounts for the FAI Score in each artery and AI-Risk (appendix pp 5–6, 13).

Finally, to evaluate the impact of AI-Risk classification on clinical decision-making, a prospective real-world evaluation survey was conducted in four NHS Hospitals, involving 744 consecutive patients undergoing CCTA for investigation of chest pain. Further details are described in the appendix (pp 5, 14–15).

Statistical analysis

Patient baseline characteristics were compared using Pearson's χ^2 or Fisher's exact test for categorical variables, and Student's *t* test and ANOVA (three groups) for continuous variables, as appropriate. Individual follow-up time was calculated from the date of the CCTA until the date of occurrence of first MACE or the last date of data extraction (March 31, 2021). Probabilities for any event for the first time since CCTA were plotted using Kaplan–Meier failure curves. A multivariable Cox regression model was fitted to estimate the hazard rates, hazard ratios (HRs), and the 95% CIs for obstructive CAD, FAI Scores, AI-Risk (as a continuous variable), and AI-Risk classification (as a categorical variable) on clinical outcomes including MACE and cardiac mortality. The HR for FAI Scores (already adjusted for age, sex, and technical parameters) were adjusted for the traditional clinical risk factors, the extent of CAD using the CAD-RADS 2.0 classification system,[11] medications, and previous coronary revascularisation.

Schoenfeld residuals plots visually assessed proportional hazards assumptions. There were none to minimal violations of the assumptions on FAI Score, AI-Risk, or AI-Risk classification for all the events. Patients who only contributed one timepoint were included in the analysis and assigned a follow-up time of one day. Missing values were imputed for smoking status using MICE package in R with the classification and regression trees (CART) method. Imputation for smoking status was performed based on patient demographic data (age, sex, and ethnicity) as well as smoking-related diseases recorded at the end of the follow-up period in 2022. Smoking-related diseases included cancer, respiratory diseases, circulatory diseases, mental health conditions, and other diseases outlined by Public Health England.[17] To get a single value out of the 20 imputed datasets, a ten-fold cross validation was used to find the best performing method out of k-nearest neighbour, naive Bayes, and CART. The CART method was preferred due to its high accuracy (0·82) compared to the other methods.

The output of the AI-Risk algorithm was compared to the baseline model of QRISK3 to understand its incremental prognostic value in this patient population. Improvement in discrimination was assessed by comparing the time-dependent c-statistic of the two models,[18] as well as by calculating the net reclassification improvement (continuous NRI) and integrated discrimination improvement (IDI; 95% CI calculated using bootstrapping with 200 replications) between the two models.[19] All analyses were done using a 10-year follow-up period. Calibration was assessed by fitting Kaplan–Meier estimates with the mean predicted survival probabilities across different follow-up times.

Statistical tests were performed using Stata 18.0 and the R environment using R studio version 4.0.2 and the packages rms, survival, riskRegression, survIDINRI, timeROC, and survivalROC. All tests were two-sided and values of $p<0·05$ were considered statistically significant. The trial was registered on ClinicalTrials.gov (NCT05169333).

Role of the funding source

The funders had no role in study design, data collection, data analysis and interpretation, or writing of the report.

Results

Between Jan 4, 2010, and March 31, 2021, 44 800 CCTA scans were performed in eight hospitals in the UK. 4709 individuals opted out of NHS Digital or did not have local CCTA reports, resulting in the ORFAN Cohort A, consisting of 40 091 individuals. This ethnically diverse cohort represents the UK population (table 1).

Within the whole population in Cohort A, 3643 (9·1%) were conventionally classified as very high risk (QRISK3 ≥20%) and 10 263 (25·6%) were classified as high risk (QRISK3 between 10 and 19%). Only 7558 (18·9%) of patients undergoing CCTA had obstructive CAD sufficient to require further investigations or interventions. The clinical characteristics of the

patients with obstructive CAD are summarised in the appendix (p 10). After adjusting for age, sex, cardiovascular risk factors, medications, and history of myocardial infarction or previous revascularisation, patients with obstructive CAD had significantly higher risk for both MACE and cardiac mortality (figure 2), as well as myocardial infarction, new heart failure, ischaemic stroke, and all-cause mortality (appendix p 16). The results were similar after excluding patients with congenital heart disease or history of heart transplant (appendix p 17). Importantly, in the 2·7 year median follow-up period, patients without obstructive CAD (32 533 [81·1%] of 40 091) accounted for 2857 (66·3%) of the 4307 total MACE and 1118 (63·7%) of the 1754 total cardiac deaths in the whole of Cohort A. This highlights the unmet need to improve risk stratification and management in the population without obstructive CAD.

During the median 7·7 year follow-up in Cohort B, FAI Score predicted cardiac mortality and MACE in patients both with or without obstructive CAD, an effect that was consistent across all coronary territories: ie, the LAD (figure 3), LCx, and RCA (table 2, appendix pp 18–19), reflecting the total inflammatory cardiovascular risk. Given that clinical cardiovascular risk factors contribute to atherogenesis at least partly by increasing vascular inflammation, the remaining residual inflammatory cardiovascular risk (beyond the clinical risk factors) was assessed by adjusting the respective HRs for cardiovascular risk factors (including hypertension, diabetes, hyperlipidaemia, and smoking status) and the extent of coronary atherosclerosis present (CAD-RADS 2.0 classification for coronary artery stenosis),[11] as shown in table 2 and the appendix (pp 21–24). The results showed that FAI Score captures the residual inflammatory risk of patients with or without obstructive CAD, even after adjusting for risk factors and the extent of any non-obstructive atheroma. In a post hoc subgroup analysis among patients without previous myocardial infarction or revascularisation (percutaneous coronary intervention or coronary artery bypass graft), FAI Score in any artery remained predictive of cardiac mortality and MACE (appendix p 25). In a further post hoc sensitivity analysis that included 1300 patients with non-contrast CT scans also available in addition to the CCTA, FAI Score in any coronary artery remained highly predictive of cardiac mortality or MACE in predicting cardiac mortality or MACE, even after adjusting for CCS, and FAI Score was also predictive among patients with chronic inflammatory diseases (appendix p 26). Furthermore, among patients with no or minimal atheroma on CCTA (CAD-RADS 2.0 score 0 or 1, n=1678; appendix p 12), FAI Score in any coronary artery remained predictive of both cardiac mortality and MACE (appendix p 20).

Although the presence of one inflamed artery was enough to provide substantial prognostic value independent from the vessel used for the measurement, an increase in the number of vessels with FAI Scores above the 75th percentile was related with a parallel increase in the risk for both cardiac mortality (HR 29·8 [95% CI 13·9–63·9] p<0·001) and MACE (12·6 [8·5–18·6] p<0·001) versus patients with all three arteries below the 25th percentile, in both the presence and absence of obstructive CAD (figure 4).

The performance of the AI-Risk algorithm was validated in Cohort B. Both the calibration curve for AI-Risk as a continuous output variable (8-year percentage risk of cardiac mortality; appendix p 28) and the AI-Risk classification system (as three risk categories; figure 5) showed excellent alignment between predicted and observed events in the overall population as well as in those without obstructive CAD. The AI-Risk classification appeared to overestimate risk in those with obstructive CAD, as the CCTA report triggered invasive coronary angiography and interventions (revascularisation, aggressive medical therapy, or both), which are expected to modify the link between coronary inflammation at the time of the scan and cardiovascular events happening during the initial years after the test. Given that pre-specified clinical endpoints included only cardiac death and MACE (ie, myocardial infarctions, new heart failure, and cardiac death), patients undergoing elective revascularisation procedures after the CCTA scan were not censored unless one of the study endpoints was met. This was more evident in the mid to low and high risk classes, where adjustment of the model for calcified and non-calcified plaque volume had minimal impact on the algorithm's performance (appendix p 29). In the Cox regression model, the AI-Risk algorithm remained a significant and independent predictor of both cardiac mortality (HR per SD 1·67 [95% CI 1·59–1·76], p<0·001) and MACE (1·57 [1·50–1·64], p<0·001) over a 10-year period (table 2). Using the AI-Risk classification system, patients in the very high risk category had a significantly higher risk for both cardiac mortality (6·75 [5·17–8·82], p<0·001) and MACE

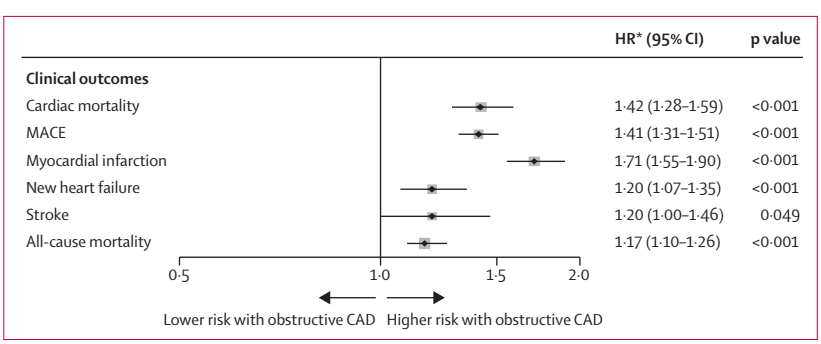

Figure 2: **Cardiovascular risk prediction in the presence or absence of obstructive CAD**
Forest plot showing HRs for individual clinical outcomes and MACE (ie, cardiac mortality, myocardial infarction, new heart failure) over a period of 10 years after CCTA in 40 091 Cohort A patients. CAD=coronary artery disease. CABG=coronary artery bypass graft. CCTA=coronary computed tomography angiography. HR=hazard ratio. MACE=major adverse cardiac events. PCI=percutaneous coronary intervention. *HR adjusted for age, sex, cardiovascular risk factors (ie, diabetes, hypertension, hyperlipidaemia, smoking status), medications (ie, β blockers, calcium channel blockers, nitrates, statins, angiotensin-converting enzyme inhibitors, antiplatelets, and direct oral anticoagulants), past myocardial infarction, and history of revascularisation (PCI or CABG)

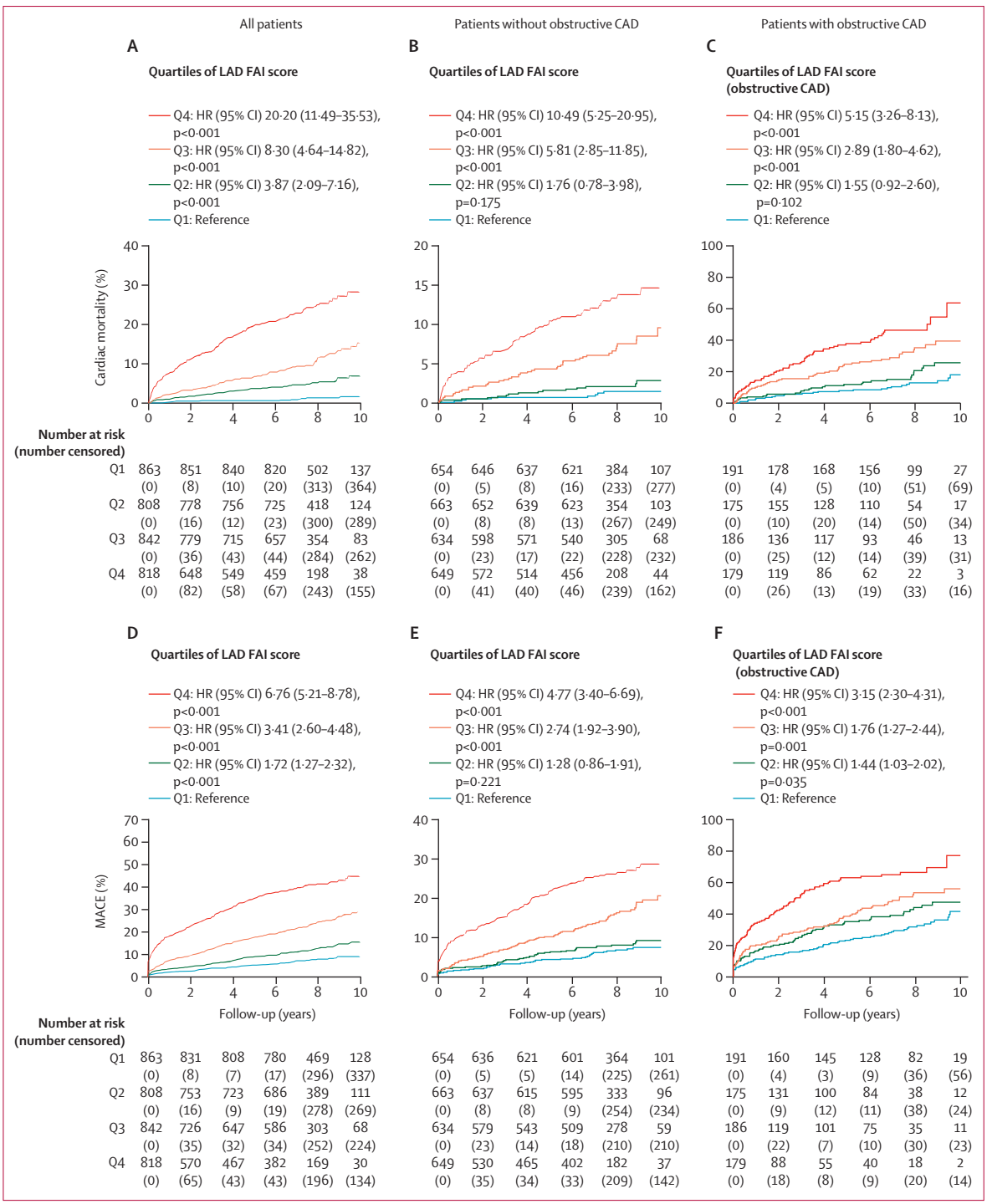

Figure 3: **FAI score and cardiovascular risk prediction: capturing the inflammatory risk**
Kaplan–Meier curves for the prognostic value of FAI score in the LAD for cardiac mortality in (A) the whole population, (B) patients with no obstructive CAD, and (C) patients with obstructive CAD. Prognostic value of FAI score in the LAD for MACE in (D) whole population, (E) patients with no obstructive CAD, and (F) patients with obstructive CAD. Unadjusted HR (95% CI) are represented in the images. See appendix (pp 18–19) for similar results in the LCx and RCA, and (p 21) for the HRs after adjustment for risk factors and CAD-RADS 2.0 coronary stenosis classification. CAD=coronary artery disease. FAI=fat attenuation index. HR=hazard ratio. LAD=left anterior descending artery. LCx=left circumflex artery. MACE=major adverse cardiac event. RCA=right coronary artery.

	Cardiac mortality				MACE			
	Total inflammatory risk		Residual inflammatory risk		Total inflammatory risk		Residual inflammatory risk	
	HR (95% CI)	p value	HR (95% CI)*	p value	HR (95% CI)	p value	HR (95% CI)*	p value
FAI score LAD								
Whole cohort	1·67 (1·58–1·76)	<0·001	1·30 (1·22–1·40)	<0·001	1·57 (1·50–1·63)	<0·001	1·30 (1·24–1·37)	<0·001
No or minimal atheroma†	1·51 (1·36–1·69)	<0·001	1·31 (1·16–1·49)	<0·001	1·45 (1·35–1·56)	<0·001	1·20 (1·11–1·30)	<0·001
No obstructive CAD	1·60 (1·49–1·71)	<0·001	1·29 (1·17–1·42)	<0·001	1·50 (1·42–1·57)	<0·001	1·27 (1·20–1·36)	<0·001
Obstructive CAD	1·55 (1·39–1·71)	<0·001	1·32 (1·17–1·48)	<0·001	1·43 (1·31–1·56)	<0·001	1·28 (1·16–1·340)	<0·001
FAI score LCx								
Whole cohort	1·95 (1·83–2·07)	<0·001	1·43 (1·32–1·55)	<0·001	1·75 (1·67–1·84)	<0·001	1·39 (1·31–1·47)	<0·001
No or minimal atheroma†	1·75 (1·55–1·99)	<0·001	1·45 (1·21–1·73)	<0·001	1·58 (1·45–1·72)	<0·001	1·48 (1·32–1·66)	<0·001
No obstructive CAD	1·86 (1·70–2·01)	<0·001	1·44 (1·28–1·61)	<0·001	1·65 (1·55–1·75)	<0·001	1·34 (1·24–1·45)	<0·001
Obstructive CAD	1·68 (1·49–1·87)	<0·001	1·41 (1·24–1·61)	<0·001	1·47 (1·34–1·62)	<0·001	1·34 (1·21–1·50)	<0·001
FAI score RCA								
Whole cohort	1·55 (1·47–1·63)	<0·001	1·25 (1·17–1·34)	<0·001	1·47 (1·41–1·53)	<0·001	1·23 (1·18–1·30)	<0·001
No or minimal atheroma†	1·51 (1·38–1·64)	<0·001	1·32 (1·16–1·51)	<0·001	1·41 (1·33–1·51)	<0·001	1·30 (1·19–1·42)	<0·001
No obstructive CAD	1·55 (1·44–1·66)	<0·001	1·25 (1·14–1·38)	<0·001	1·43 (1·36–1·51)	<0·001	1·24 (1·16–1·32)	<0·001
Obstructive CAD	1·40 (1·27–1·54)	<0·001	1·28 (1·14–1·42)	<0·001	1·32 (1·21–1·43)	<0·001	1·21 (1·10–1·32)	<0·001
AI-Risk								
Whole cohort	1·67 (1·59–1·76)	<0·001	1·58 (1·49–1·67)‡	<0·001	1·57 (1·50–1·64)	<0·001	1·53 (1·47–1·60)‡	<0·001
No or minimal atheroma†	1·44 (1·31–1·59)	<0·001	1·46 (1·33–1·62)‡	<0·001	1·37 (1·28–1·47)	<0·001	1·37 (1·27–1·47)‡	<0·001
No obstructive CAD	1·53 (1·42–1·64)	<0·001	1·51 (1·41–1·63)‡	<0·001	1·43 (1·36–1·51)	<0·001	1·45 (1·37–1·53)‡	<0·001
Obstructive CAD	1·56 (1·40–1·73)	<0·001	1·37 (1·23–1·53)‡	<0·001	1·45 (1·33–1·57)	<0·001	1·34 (1·23–1·47)‡	<0·001

HRs are expressed per 1 SD increment in the FAI Score or AI-Risk as continuous variable. All analyses are referred to 10-year risk. MACE=major adverse cardiac events. FAI score=fat attenuation index score. AI-Risk=the artificial intelligence-assisted algorithm predicted risk for cardiac mortality. LAD=left anterior descending coronary artery. CAD=Coronary artery disease. LCx=left circumflex artery. RCA=right coronary artery. HR=hazard ratios. *HR further adjusted for cardiovascular risk factors: diabetes, hypertension, hyperlipidaemia, smoking, medications (β blockers, calcium channel blockers, nitrates, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiplatelets, and direct oral anticoagulants), history of previous revascularisation, and CAD-RADS 2.0[11] stenosis classification status. †No or minimal atheroma corresponds to CAD-RADS 2.0 coronary stenosis score of 0 or 1. ‡HRs and p values adjusted for medications only.

Table 2: **Risk of cardiac mortality and MACE with FAI Score and AI-Risk**

(4·68 [3·93–5·57], p<0·001) compared to those in the low to medium risk category, a finding replicated both in patients with and without obstructive CAD (figure 5). Among patients with no or minimal atheroma (CAD-RADS 2.0 score of 0 or 1), the very high AI-Risk class was associated with 5·1 times higher risk for cardiac mortality and 4·0 times higher risk of MACE, compared with the low to medium AI-Risk category (appendix p 20).

Compared to QRISK3, the AI-Risk classification system significantly reclassified patients for both cardiac mortality (NRI 0·38 [95% CI 0·23–0·45] p<0·0001 and IDI 0·028 [95% CI 0·014–0·047] p<0·0001) and MACE (NRI 0·29 [95% CI 0·095–0·34] p<0·0001 and IDI 0·033 [95% CI 0·017–0·052] p<0·0001) over a 10-year period (appendix p 30). Importantly, the results were similar in the population without obstructive CAD, who are typically returned to primary care for further management.

In the receiver operating characteristic analyses, the area under curve (AUC) for predicting cardiac mortality over a 10-year period using QRISK3 was 0·831 in the whole population, 0·786 in those with no obstructive CAD, and 0·747 in those with obstructive CAD. The addition of CAD stenoses severity (CAD-RADS 2.0) to QRISK3 did not significantly improve prediction of cardiac mortality, with AUC 0·838 (p=0·36 against QRISK3) in the whole population, 0·788 (p=0·83) in those with no obstructive CAD, and 0·732 (p=0·51) in those with obstructive CAD. Adding AI-Risk (as a continuous variable) to a baseline model that included CAD-RADS 2.0 and QRISK3 increased the AUC to 0·854 ($p=7\cdot7\times10^{-7}$ against QRISK3 plus CAD-RADS 2.0) in the whole population, 0·816 (p=0·0017) in those without obstructive CAD, and 0·773 ($p=8\cdot9\times10^{-4}$) in those with obstructive CAD. Similarly, for the prediction of MACE, QRISK3 had a good performance in this UK population (AUC 0·784 in the whole population, 0·731 in those with no obstructive CAD, and 0·750 in those with obstructive CAD). These estimates did not improve significantly after addition of CAD-RADS 2.0 (AUC 0·789, p=0·38 in the whole population, 0·734, p=0·73 in those without obstructive CAD, and 0·731, p=0·18 in those with obstructive CAD). The model that included QRISK3 and CAD-RADS 2.0 improved significantly by

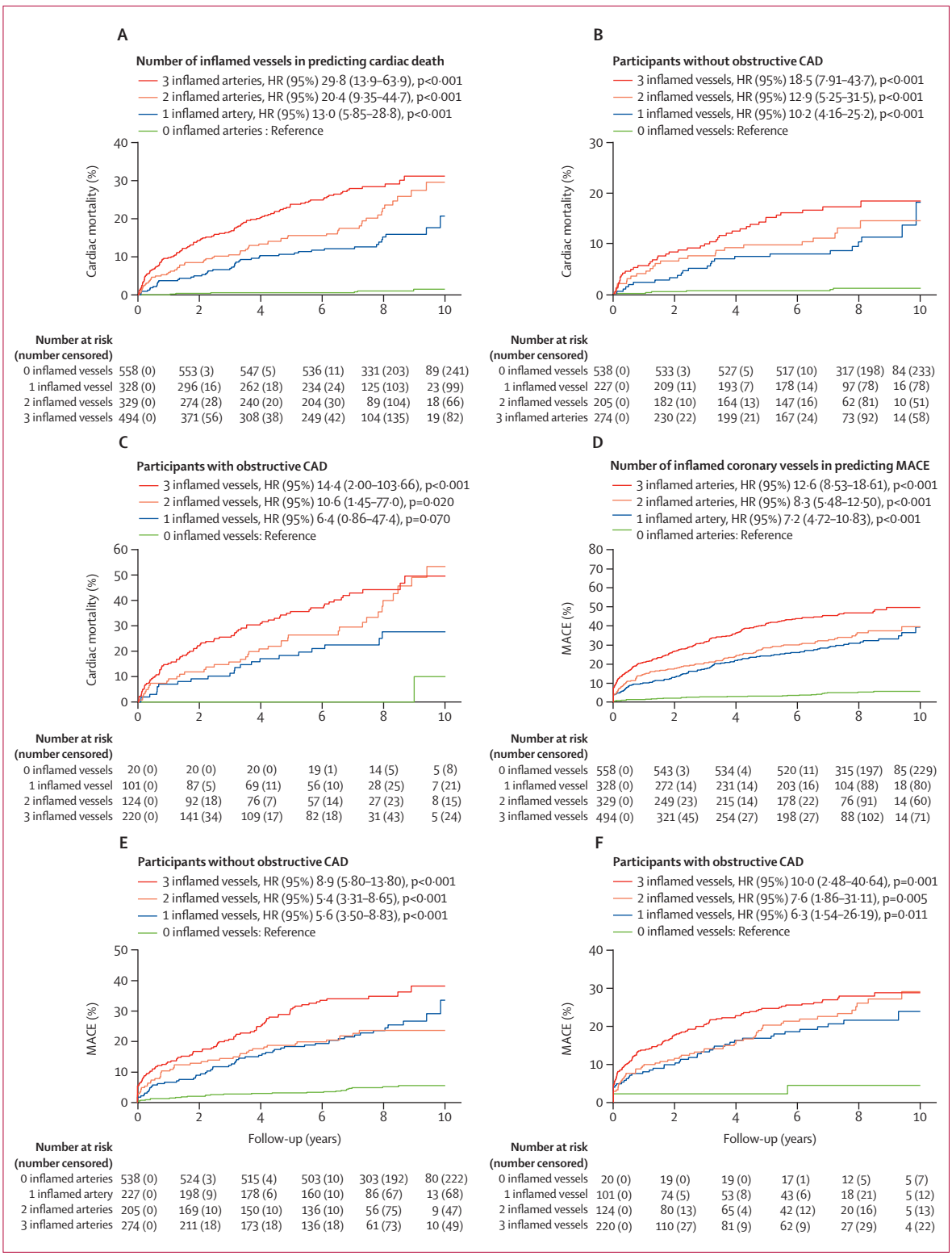

***Figure 4*: Additive prognostic value of high coronary inflammation recorded in one, two, or three epicardial arteries**

Prognostic value for cardiac mortality in the whole population (A), patients without obstructive CAD (B), or with obstructive CAD (C). Similarly, the prognostic value for MACE in the whole population (D), patients without obstructive CAD (E), or with obstructive CAD (F). Inflamed coronary artery defined as having an FAI score above the 75th percentile. Reference refers to all three coronary arteries (LAD, LCx, and RCA), with an FAI Score under the 25th percentile. CAD=coronary artery disease. FAI=fat attenuation index. HR=hazard ratio. LAD=left anterior descending artery. LCx=left circumflex artery. MACE=major adverse cardiac events. RCA=right coronary artery.

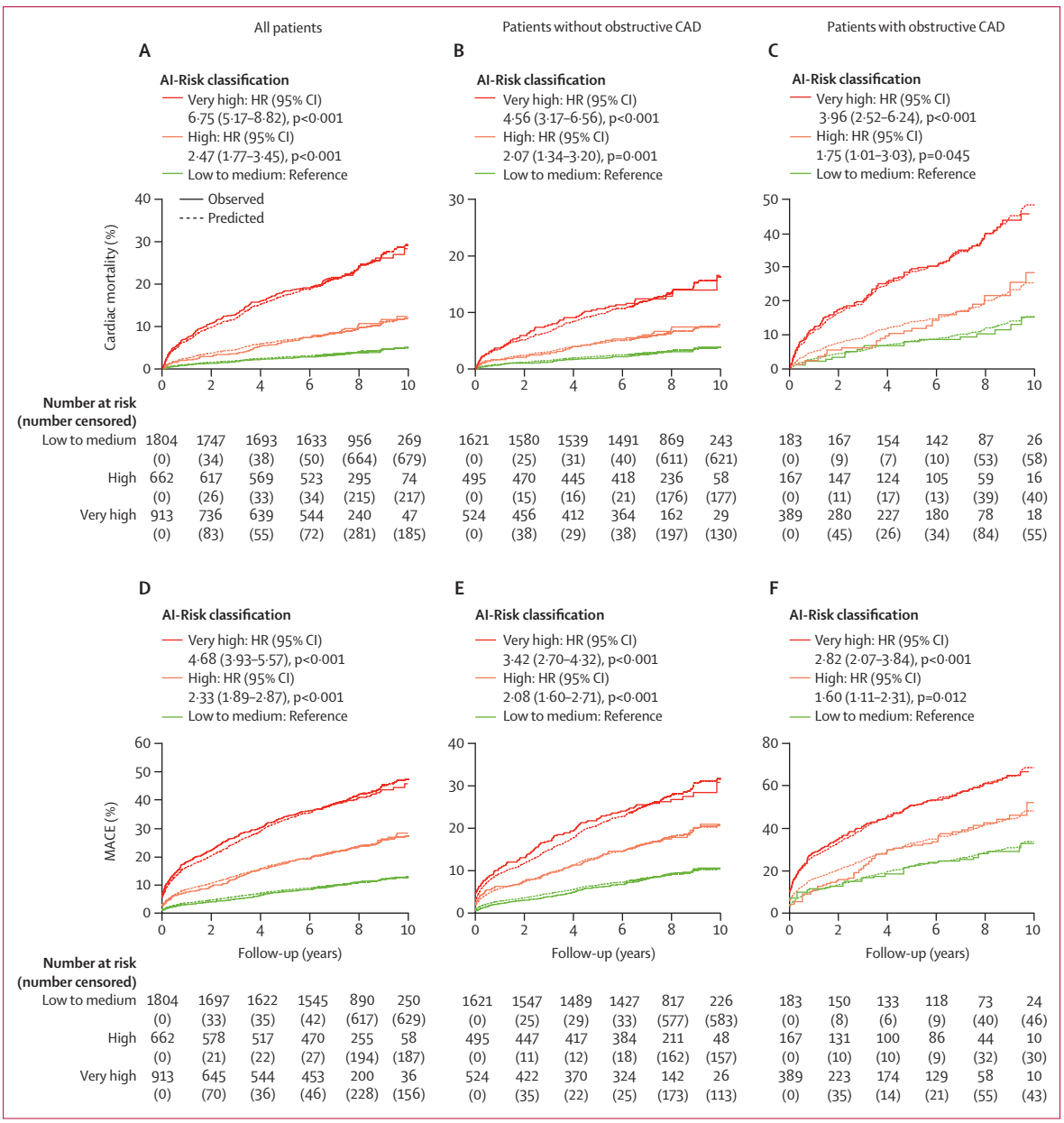

***Figure 5*: AI-Risk Classification and cardiovascular risk prediction**

Kaplan–Meier curves for the ability of AI-Risk classification to predict cardiac mortality in (A) the whole population, (B) patients with no obstructive CAD, and (C) patients with obstructive CAD. Kaplan–Meier curves for prediction of MACE using the same classification are presented for (D) the whole population, (E) patients with no obstructive CAD, and (F) patients with obstructive CAD. AI=artificial intelligence. AI-Risk=the AI-assisted algorithm predicted risk for cardiac mortality. CAD=coronary artery disease. HR=hazard ratio. MACE=major adverse cardiac events.

adding AI-Risk, to 0·805 ($p=3·4\times10^{-8}$ against QRISK3 plus CAD-RADS 2.0) in the whole population, 0·748 ($p=1·2\times10^{-4}$) in those without obstructive CAD and 0·764 ($p=6·6\times10^{-2}$) in those with obstructive CAD. The prognostic performance of FAI Score of each coronary vessel is presented in the appendix (p 27).

In the prospective real-world evaluation survey of 744 participants, which made the AI-Risk classification available to the clinical care teams, there were changes in management recommendations in 45% of patients (initiation of statin treatment [24%], increase in statin dosage [13%], and adding additional treatments beyond statins [8%], which included aspirin [2·4%], colchicine [8·3%], or icosapent ethyl [0·4%]; appendix p 14).

Discussion

This study shows that in a large cohort of individuals undergoing clinically indicated CCTA, only a third of the

future MACE happen among patients with obstructive CAD, underlining the unmet need to develop tools that will identify the individuals at high risk in the absence of obstructive CAD. Measuring inflammation in any coronary artery by using the perivascular FAI Score revealed for the first time that a quarter of those individuals without obstructive disease had significantly elevated residual inflammatory risk, which translated into a ten times higher risk for cardiac mortality or MACE over a 10-year period. The number of inflamed coronary vessels, identified by elevated FAI Score, exhibited an additive increase in the risk of cardiac mortality or MACE. The AI-Risk algorithm, which incorporates FAI Score, the extent of coronary atheroma (if any), as well as the patient's traditional risk factors, was able to powerfully predict cardiac mortality and MACE over 10 years, both in the presence and absence of coronary atherosclerosis.

Since the introduction of CCTA as a first line investigation in the management of stable chest pain,[1–3,20] the global use of CCTA has increased sharply,[4] with the majority of patients being referred back to primary care after exclusion of obstructive CAD.[4,5] This practice highlights an opportunity for health-care systems to evaluate these individuals more closely, in order to forestall future cardiovascular events in those without occlusive lesions. This study demonstrates that, among approximately 40 000 consecutive CCTAs performed in the UK as part of routine clinical practice, approximately 19% revealed obstructive CAD that guided further investigations or interventions. Although the presence of obstructive CAD was associated with a higher relative risk of adverse cardiovascular outcomes, in absolute numbers there were nearly twice as many cardiovascular events during the follow-up period in the much larger population without obstructive CAD compared with those with obstructive CAD. This observation supports the notion that acute coronary syndromes frequently result from the disruption of non-obstructive (presumably inflamed) atherosclerotic plaques.[6] The use of current clinical risk prediction tools (eg, QRISK3) in these patients has restrictions, as such models were developed in apparently healthy individuals and do not capture information such as CAD plaque burden and residual inflammatory risk. A robust risk prediction tool could therefore identify the vulnerable patient with inflamed coronary arteries, particularly in those without obstructive CAD. This approach would transform CCTA from a test to triage a minority of patients for further intervention into a prevention tool that guides management for all patients undergoing CCTA.

Evidence from clinical trials suggests that anti-inflammatory treatments like statins,[21] colchicine,[22] or anti-inteleukin-1β[23] reduce cardiovascular events. Indeed, colchicine has been included in the European Society of Cardiology 2021 cardiovascular prevention guidelines,[24] and has received US Food and Drug Administration clearance with a broad cardiovascular risk reduction label.[7] Given the potential unwanted actions of anti-inflammatory treatments, targeting treatments specifically to patients with coronary artery inflammation could improve the allocation of the anti-inflammatory treatments more precisely than systemic markers such as high-sensitivity C-reactive protein assays. Translational studies have discovered that inflammatory signals originating from the vascular wall activate perivascular lipolysis, triggering spatial changes in the perivascular adipose tissue composition.[8] The FAI Score captures such findings on routine CCTA,[8–10] and it also appears to track the vascular effectiveness of anti-inflammatory treatments.[25–27]

Current clinical guidelines recommend primary prevention for patients with a 10 year risk of 10% or higher for MACE or 5% or higher for fatal cardiac events.[1,2] However, the current 10 year prediction models (eg, QRISK3) underestimate risk in young individuals and cannot capture the presence of non-obstructive CAD or the degree of coronary arterial inflammation. The FAI Score identifies a large group of patients with elevated coronary artery inflammation, who have high relative risk for cardiac events despite their low absolute 10-year risk as calculated by QRISK3 due to their young age. Integrating disease activity (via the FAI Score) with the CAD plaque burden and the patient's risk factors provides a powerful risk assessment tool in the form of the AI-Risk algorithm.[9,10] The AI-Risk model validated in this study uses the FAI Score of the artery with the highest value, and retraining was not performed due to regulatory restrictions on the locked model. However, the findings of an additive effect of the number of inflamed coronary vessels on risk prediction, together with emerging evidence on the prognostic value of plaque composition[28] and high-risk plaque characteristics,[29] might justify the retraining of the AI-Risk model in the future to include these additional metrics. The AI-Risk classification system (that incorporates FAI Score and AI-Risk) provides a decision-making tool that enables meaningful risk stratification, informing risk-driven changes in management within the existing prevention guidelines. In this study, the AI-Risk Classification system identified the very-high risk patients with significant risk for MACE and cardiac mortality, even among those with no or minimal coronary atheroma. By detecting coronary inflammation, the FAI Score identifies the disease activity, which precedes plaque formation and rupture, and could be involved in myocardial infarction without obstructed coronary arteries.[30] This enables risk stratification in patients who would otherwise be reassured by the absence of obstructive CAD, but warrant consideration for individualised preventative management to modify residual inflammatory risk. This could be particularly useful in patients with autoimmune or chronic inflammatory diseases. Conversely, understanding individualised inflammatory risk from CCTA could guide

the intensification of statin or adjunctive anti-inflammatory treatments, beyond the indications listed in current clinical guidelines (which go beyond treating high cholesterol).[1]

Our study has some limitations. The performance of QRISK3 was higher than expected in predicting cardiac mortality or MACE, probably because QRISK3 was originally trained using data from the same source (NHS Digital), a population of UK individuals, and same time period (before 2017) as the ORFAN population used in this study. By contrast, AI-Risk was trained in a US population. This might explain the lack of incremental value of CAD-RADS 2.0 when added in a baseline model that included QRISK3 in predicting either MACE or cardiac mortality. However, this did not prevent a significant improvement of the model when adding AI-Risk, confirming that the current study represents true external validation of the AI-Risk in a cohort of different demographics from a different continent. In the population with obstructive CAD, although both the FAI Score and the AI-Risk classification accurately predicted the true events in the very high risk population from the first year after the scan, the survival curves between mid to low risk and high risk classes only split after year 3. Patients diagnosed with obstructive CAD at the time of the CCTA undergo invasive angiograms and revascularisations, or at least intensification of their medical therapy after the CCTA, which affects risk prediction based on CCTA analysis. Finally, plasma levels of inflammatory biomarkers such as high sensitivity C reactive protein were not available in the current cohort, so the incremental value of FAI Score in predicting cardiovascular outcomes beyond these biomarkers needs to be documented in future prospective outcome studies.

This study showed that measuring coronary inflammation from routine CCTA captures cardiovascular inflammatory risk, particularly in patients without obstructive CAD, and even in those without any visible plaque or coronary calcification. An AI-assisted risk prediction tool incorporating FAI Score, atherosclerotic plaque burden, and the patient risk factor profile provides clinically meaningful risk reclassification in patients undergoing routine CCTA that could guide the more precise use of preventative treatments, including anti-inflammatory therapies.

Contributors

CA, SN, KMC, and JD conceptualised and designed the study. KC contributed to image and data analysis, statistical analysis, interpretation, and writing of the report. EW and ASA contributed to data and statistical analysis, and writing of the report. AT, PP, ML, HW, LV, TH, RAK, MCM, PT, and MS contributed to image and data analysis. YS, LK, EN, TKM, DA, BM, JR, NSc, AKe, JPG, NSa, GLDM, EKO, SM, EM, AKa, FP, SEP, RB, MD, and SA coordinated the collection of clinical data and critically reviewed the report. CA and CS raised the funding for image and data analysis, provided scientific direction, and contributed to writing the report. CA coordinated and directed the project, and wrote the report. KC, EW, and CA verified the data in the study and take full responsibility for the integrity of the data. PL, BJG, JD, KMC, and SN provided crucial input into the interpretation, analysis, and presentation of the data. All authors had full access to all the data in this study and provided final approval to submit the manuscript for publication.

Declaration of interests

AT has received research funding from National Institute of Health and Care Research (NIHR) Oxford Health Biomedical Research Center and NIHR Applied Research Collaboration Oxford. AKa has received grants from Lantheus Medical USA and honoraria from Bracco UK/Philips Medical. BM has received honoraria from Chiesi, Sanofi, Novartis, and Boston Scientific. CA has a leadership role in British Atherosclerosis Society, and participates in several European Commission Marie Curie panels, has received honoraria from Amarin and Covance, and has received consulting fees from Slience Therapeutics. DA has a leadership role in the Spontaneous Coronary Artery Dissection Study group, is inventor of patents related to a cardiac assist device (EP3277337A1, PCT/GB2017/050877), and has received grant support from AstraZeneca and Abbott Vascular, and consulting fees from General Electric. EM has received research support from the NHS AI award. EN has a leadership role in the Society of Cardiovascular Computed Tomography and has received consulting fees from Caristo Diagnostics. EKO is a stock option holder of Caristo Diagnostics, is co-founder of Evidence2Health, and is inventor of patents (WO2018078395A1, WO2020058713A1, US17/720,068, 63/619,241, 63/177,117, 63/580,137, 63/606,203, and 63/562,335). JD has a leadership role and has received consulting fees from Novo Nordisk, has received honoraria from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer. JR has a leadership role in Heart & Lung Imaging, has received consulting fees from NHSX and HeartFlow, and honoraria from Sanofi, Aidence, and 4-C. KMC has received consulting fees from Caristo Diagnostics. MD has received consulting fees from Bristol Myers Squibb, Tenaya Therapeutics, and VizAL, and has participated on an advisory board for Caristo Diagnostics. NSa receives royalties from a patent (PCT/GB2015/052359). PL has received research support from National Heart, Lung and Blood Institute, Simard Fund, and RRM Charitable Fund, grants from Novartis, Novo Nordisk, and Genentech, honoraria from Pri-Med and Medtelligence, has a leadership role in XBiotech, is the inventor of patents (US20240043525A1, US20220041710A1 and US20220389090A1), and has advisory roles for Novartis, DalCor, XBiotech, TenSixteen Bio, and Soley Therapeutics. RB has a leadership role in the Society of Cardiovascular Computed Tomography, has received grants from Amgen, Novartis, and Nanox AI, and consulting fees from Caristo Diagnostics and Heartflow. SEP has a leadership role for the European Association of Cardiovascular Imaging, has received consulting fees from Circle Cardiovascular Imaging, and holds an advisory role for PROTEUS Trial. PT, YS, and MS are employees of Caristo Diagnostics. SN, KMC, and CA are founders, shareholders, and directors of Caristo Diagnostics, a CT-image analysis company. CA is the inventor of patents US10695023B2, US11393137B2, GB2018/1818049.7, GR20180100490, and GR20180100510. ASA, SN, and KMC are co-inventors of patent US10695023B2. These are licensed to Caristo Diagnostics. All other authors declare no competing interests.

Data sharing

Aggregated data will be shared upon reasonable request, addressed to the Principle Investigator at charalambos.antoniades@cardiov.ox.ac.uk. The requests will be reviewed by the ORFAN study Publication and Data Sharing committee in line with the governance structures of the consortium and individual site restrictions.

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References

1 National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification [NG238]. https://www.nice.org.uk/guidance/ng238 (accessed May 2, 2024).

2 Visseren FLK, Mach F, Smulders YM et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2021; **42:** 3227–337.

3 National Institute for Health and Care Excellence. NICE guidance for stable chest pain patients (CG95 & MTG32) to appropriately diagnose patients with suspected coronary artery disease. 2019. https://www.nice.org.uk/sharedlearning/nice-guidance-for-stable-chest-pain-patients-cg95-mtg32-to-appropriately-diagnose-patients-with-suspected-coronary-artery (accessed Nov 20, 2023).

4 Dreisbach JG, Nicol ED, Roobottom CA, Padley S, Roditi G. Challenges in delivering computed tomography coronary angiography as the first line test for stable chest pain. *Heart* 2018; **104:** 921–27.

5 SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015; **385:** 2383–91.

6 Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol* 2014; **64:** 684–92.

7 US Food and Drug Administration (FDA). LODOCO (colchicine) highlights of prescribing information. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215727s000lbl.pdf (accessed May 2, 2024).

8 Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat. *Sci Transl Med* 2017; **9:** eaal2658.

9 Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 2018; **392:** 929–39.

10 Oikonomou EK, Antonopoulos AS, Schottlander D, et al. Standardized measurement of coronary inflammation using cardiovascular computed tomography: integration in clinical care as a prognostic medical device. *Cardiovasc Res* 2021; **117:** 2677–90.

11 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:** 536–57.

12 Newby DE, Adamson PD, Berry C, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018; **379:** 924–33.

13 Medicines and Healthcare products Regulatory Agency. Regulating medical devices in the UK. Feb 8, 2024. https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk (accessed May 2, 2024).

14 Antoniades C, Tousoulis D, Vavlukis M, et al. Perivascular adipose tissue as a source of therapeutic targets and clinical biomarkers. *Eur Heart J* 2023; **44:** 3827–44.

15 Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017; **357:** j2099.

16 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.

17 Public Health England. Consultation on proposed changes to the calculation of smoking-attributable mortality and hospital admissions. 2020. https://assets.publishing.service.gov.uk/media/60365fd0e90e0740b06b68a8/Consultation_response_on_proposed_changes_to_smoking_relative_risks.pdf (accessed May 2, 2024).

18 Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013; **32:** 5381–97.

19 Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011; **30:** 11–21.

20 Saraste A, Knuuti J. ESC 2019 guidelines for the diagnosis and management of chronic coronary syndromes: recommendations for cardiovascular imaging. *Herz* 2020; **45:** 409–20.

21 Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–207.

22 Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; **383:** 1838–47.

23 Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377:** 1119–31.

24 Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; **42:** 3227–337.

25 Elnabawi YA, Oikonomou EK, Dey AK, et al. Association of biologic therapy with coronary inflammation in patients with psoriasis as assessed by perivascular fat attenuation index. *JAMA Cardiol* 2019; **4:** 885–91.

26 Oikonomou EK, Williams MC, Kotanidis CP, et al. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J* 2019; **40:** 3529–43.

27 Farina CJ, Davidson MH, Shah PK, et al. Inhibition of oxidized low-density lipoprotein with orticumab inhibits coronary inflammation and reduces residual inflammatory risk in psoriasis: a pilot randomized, double-blind placebo-controlled trial. *Cardiovasc Res* 2024; published online March 25. https://doi:10.1093/cvr/cvae057.

28 Tzolos E, Williams MC, McElhinney P, et al. Pericoronary adipose tissue attenuation, low-attenuation plaque burden, and 5-year risk of myocardial infarction. *JACC Cardiovasc Imaging* 2022; **15:** 1078–88.

29 Goeller M, Achenbach S, Cadet S, et al. Pericoronary adipose tissue computed tomography attenuation and high-risk plaque characteristics in acute coronary syndrome compared with stable coronary artery disease. *JAMA Cardiol* 2018; **3:** 858–63.

30 Gaibazzi N, Martini C, Botti A, Pinazzi A, Bottazzi B, Palumbo AA. Coronary inflammation by computed tomography pericoronary fat attenuation in MINOCA and Tako-Tsubo syndrome. *J Am Heart Assoc* 2019; **8:** e013235.