Coronary Atherosclerotic Plaque Activity and Future Coronary Events

David Newby, University of Edinburgh

Hot Line Session 7

28th August 2022

Prediction of Recurrent Events with 18F-Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction

EudraCT: 2014-004021-41

Trial Registration: NCT02278211

Declarations

Funder

- Wellcome Trust (WT103782AIA)

Sponsors

- University of Edinburgh and NHS Lothian

Clinical Trial Authorisation

- MHRA (EudraCT 2014-004021-41)

Conflicts of Interest

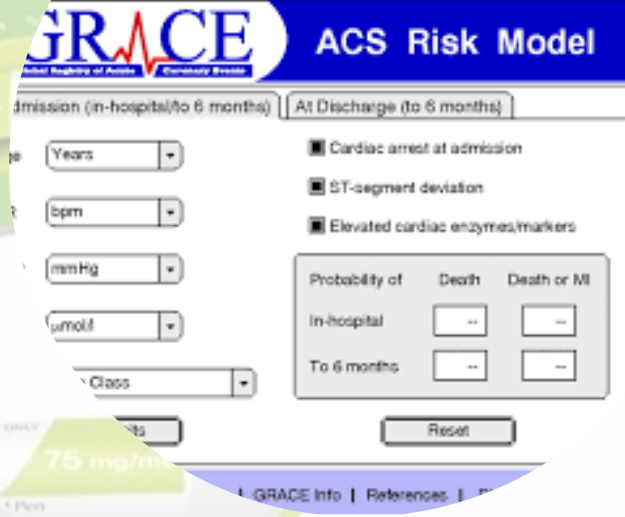
- DEN has held unrestricted research grant awards from Siemens Healthineers.
- PS developed FusionQuant (1R01HL135557)

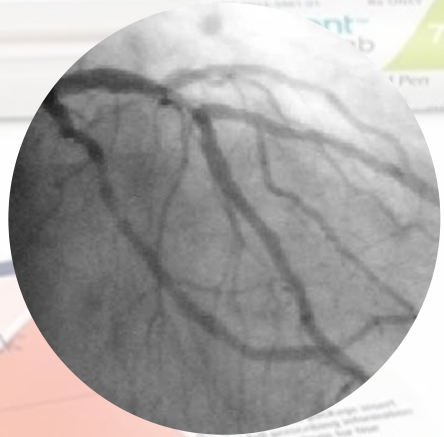
The PRE FFIR Study

Prediction of Coronary Events after Myocardial Infarction

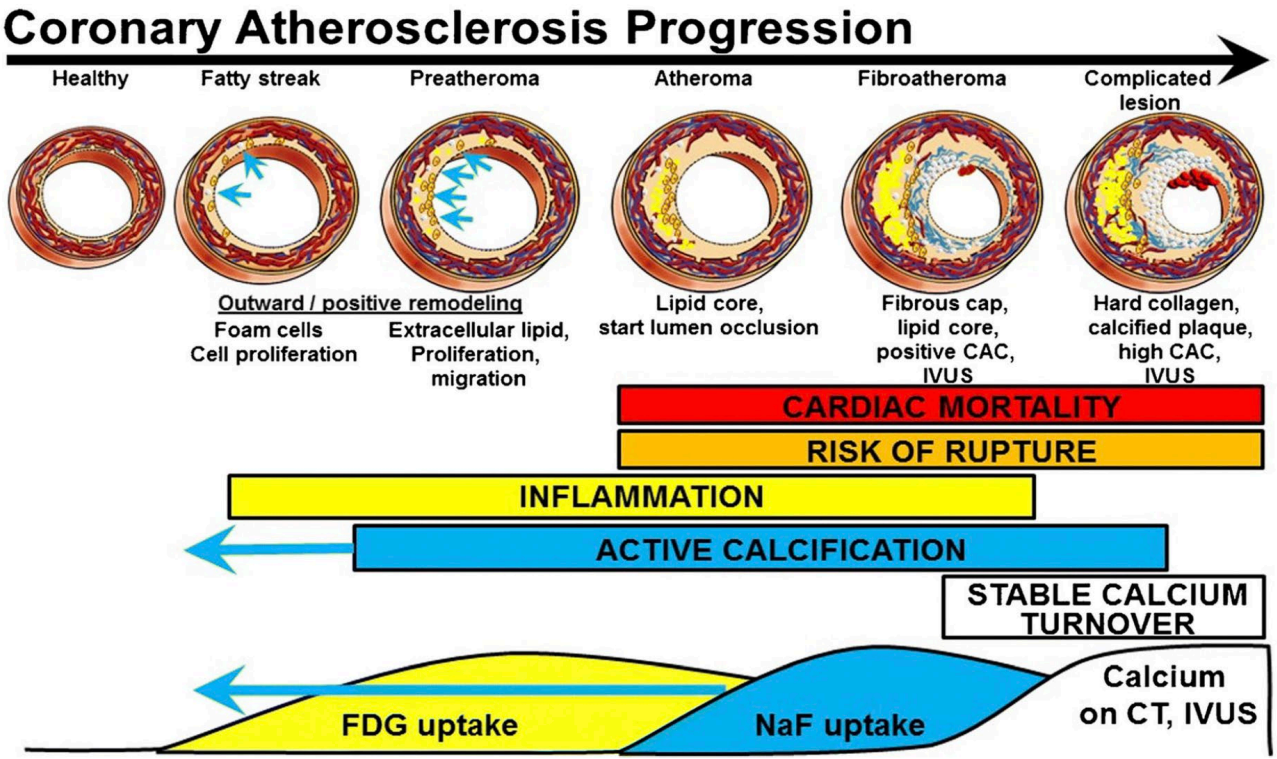
"'It's tough to make predictions, especially about the future'"

Yogi Berra





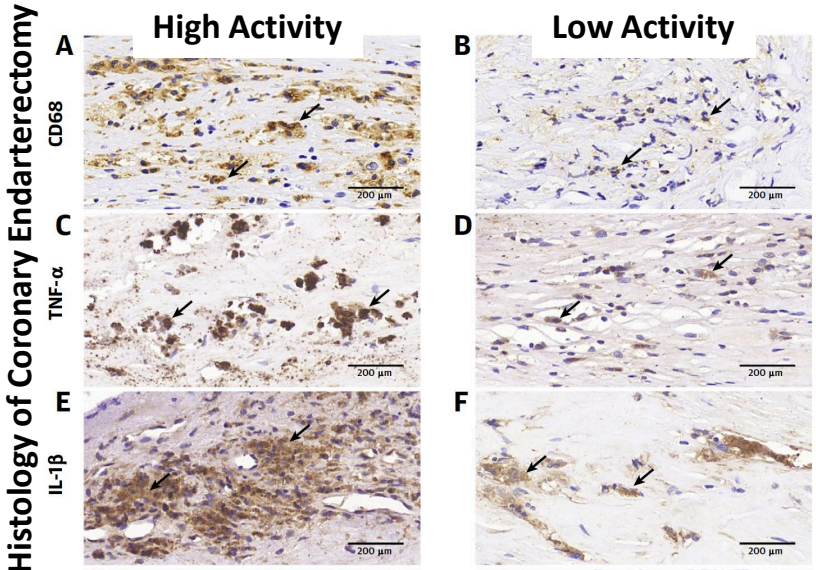
Coronary ^{18}F-Sodium Fluoride Uptake

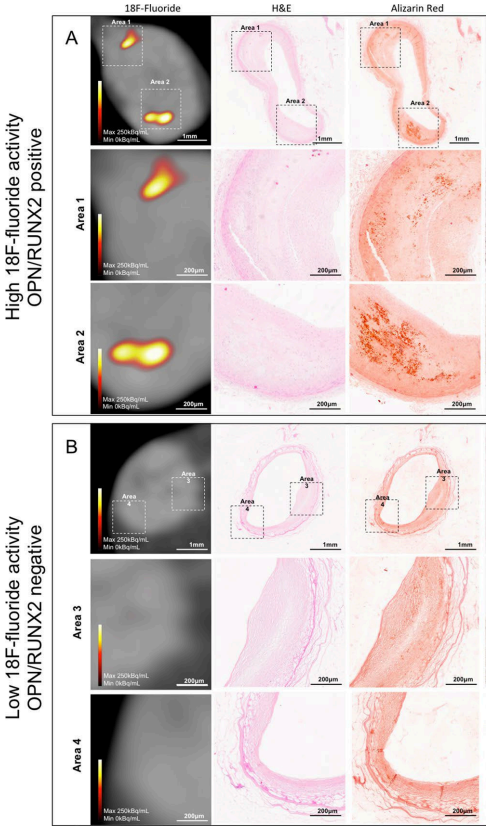


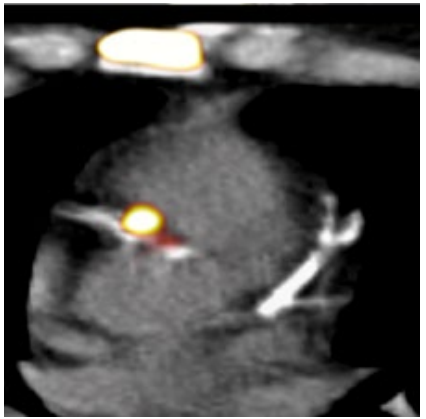
Raynor et al. J Nucl Cardiol 2021;28:2706-2711

Coronary ^{18}F-Sodium Fluoride Uptake

The PRE 18 FFIR Study







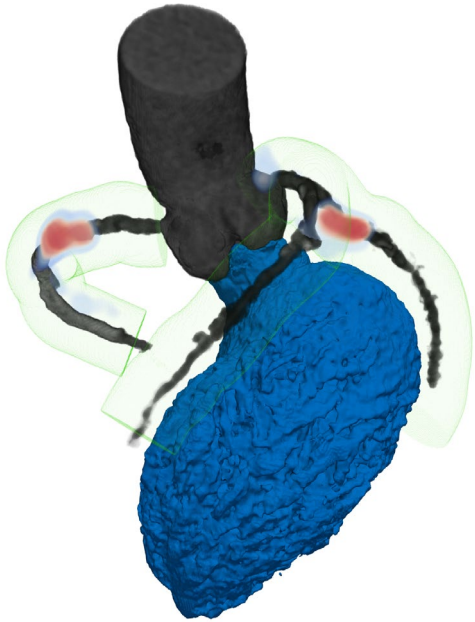
Wen et al. JACC Cardiovasc Imaging 2022; in press

Moss et al. Sci Rep 2020;10:21072

Joshi et al. Lancet 2014;383:705-713

The PREFFIR Study

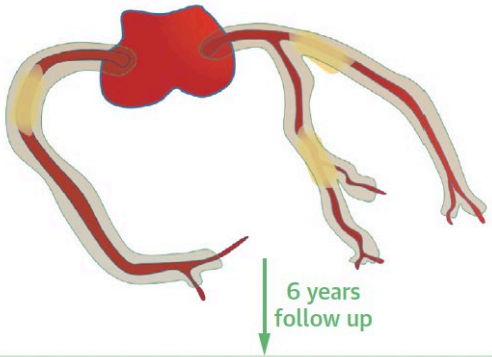
Coronary ^{18}F-Sodium Fluoride Uptake
Coronary Microcalcification Activity



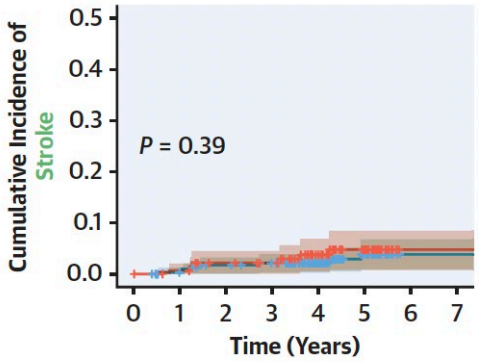
Coronary Microcalcification Activity (CMA)

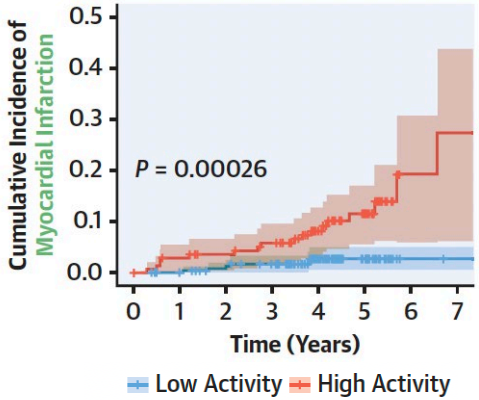
Stable Patients with Cardiovascular Disease

Coronary ^{18}F-sodium fluoride activity



Associated With Myocardial Infarction, But not Stroke





Fletcher et al. JACC Cardiovasc Imaging 2022;15:1274-1288

The PREFFIR Study

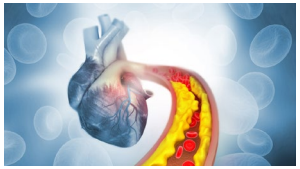
Prediction of Recurrent Events with ^{18}F-Sodium Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction

MHRA

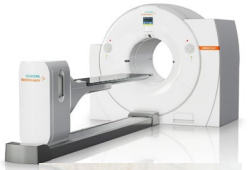
Study Design: International multicentre prospective longitudinal cohort trial

Regulation: Clinical Trial Authorisation by MHRA

Study Population: Patients with recent myocardial infarction and multivessel coronary artery disease

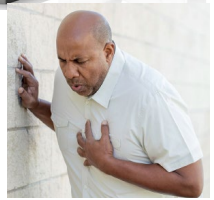


Intervention: ^{18}F-sodium fluoride positron emission tomography and coronary computed tomography angiography



Follow up: Minimum of 2 years follow up

Clinical Endpoints: Cardiac death, non-fatal myocardial infarction, coronary revascularisation, all-cause death.



Primary Endpoint and Study Power

Primary Endpoint: Cardiac death or non-fatal myocardial infarction

Assuming event rate of 20-30% and effect size of 50%, 692 patients were required for 80% power and $P<0.05$.

Despite inclusion of multivessel disease, review of event rate at mid-point of the trial suggested an event rate of ~10%.

Trial Steering Committee recommended inclusion of unscheduled coronary revascularisation into the combined primary endpoint as increased coronary activity could lead to plaque expansion.

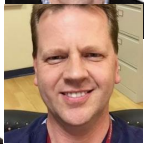
Revised Primary Endpoint: Cardiac death, non-fatal myocardial infarction or unscheduled coronary revascularisation.

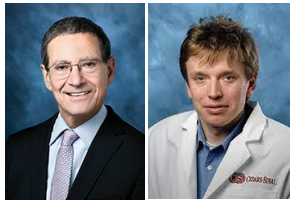
PRE[18]FIR Investigator Sites

9 Sites, 4 Countries

Dana Dawson, Aberdeen Royal Infirmary
Dave Newby, Royal Infirmary of Edinburgh

Parthiban Arumugam, Manchester Royal Infirmary
Nikant Sabharwal, John Radcliffe Hospital
John Greenwood, Leeds General Infirmary
Patrick Calvert, Addenbrookes & Papworth Hospitals
Jon Townend, Queen Elizabeth Hospital





Dan Berman, Cedars-Sinai
Piotr Slomka, Cedars-Sinai

Johan Verjans, Royal Adelaide Hospital

Trial Recruitment and Population

Patients approached to participate in study (n = 2,684)

Excluded (n = 1,689)
- Ineligible (n = 388)
- Declined to participate (n = 812)
- Clinician/investigator decision (n = 197)
- Other (n = 292)

Initially assessed as eligible, written informed consent obtained, and screening visit done (n = 995)

Excluded (n = 283)
- Changed their mind about participating (n = 142)
- Unable to scan within protocol window (n = 82)
- Health subsequently deteriorated precluding inclusion (n = 22)
- Unable to contact patient (n = 19)
- Ineligible (n = 10)
- Deceased (n = 6)
- Clinician/investigator decision (n = 2)

Attended baseline visit and received radioactive tracer [^{18}F-NaF] (n = 712)

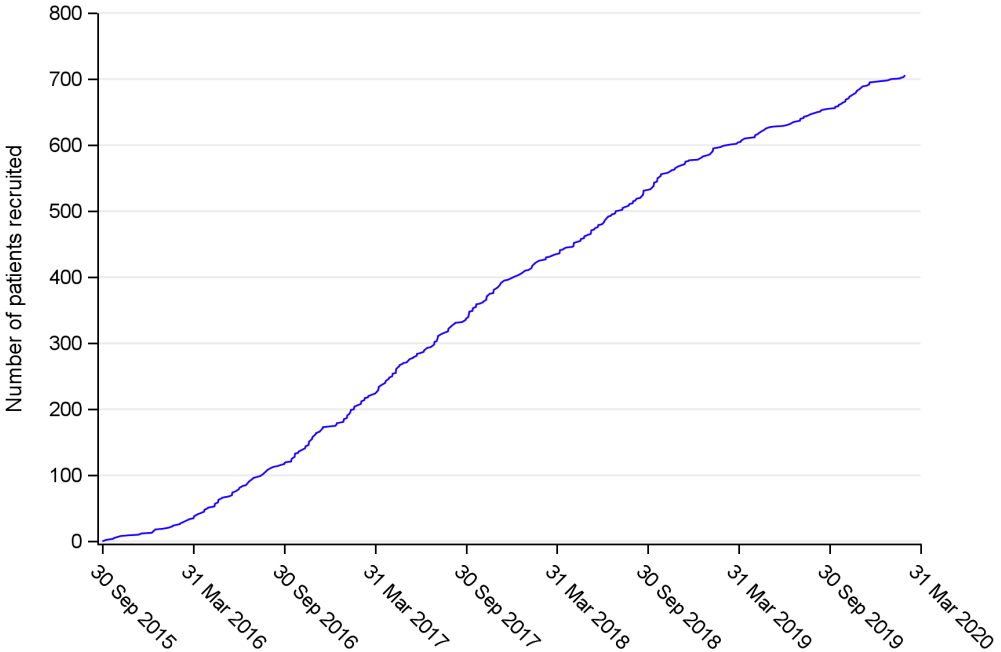
PET-CT scan incomplete (n = 6)
- Claustrophobia (n = 3)
- Panic attack (n = 1)
- Patient very anxious (n = 1)
- Scanner malfunction (n = 1)

PET-CT scan completed (n = 706)

Follow-up discontinued prematurely (n = 13)
- Withdrew consent to any further follow-up (n = 3)
- Withdrawn from study by clinician (n = 4)
- Lost to follow-up (n = 2)
- Final annual follow-up not completed (n = 4)

At study completion, follow up was available in 693 (98·2%) participants

Analysis population for the primary outcome (n = 704)



The PREFFIR Study

Trial Population Characteristics

	Total Population	Low coronary atherosclerotic plaque activity CMA = 0	High coronary atherosclerotic plaque activity CMA > 0
Number	704	283	421
Age (years)	63·8±8·2	61·8±7·4	65·1±8·4
Sex (female)	103 (15%)	61 (22%)	42 (10%)
Body-mass index (kg/m^2)	28·3±4·4	28·6±4·7	28·1±4·2
Cardiovascular risk factors			
Smoking habit Current Smoker	193 (27%)	90 (32%)	103 (24%)
Ex-smoker	225 (32%)	91 (32%)	134 (32%)
Non-smoker	286 (41%)	102 (36%)	184 (44%)
Hypertension	351 (50%)	119 (42%)	232 (55%)
Hypercholesterolaemia	398 (57%)	162 (58%)	236 (56%)
Diabetes mellitus	118 (17%)	40 (14%)	78 (19%)
Prior cardiovascular disease			
Coronary artery disease	139 (20%)	41 (14%)	98 (23%)
Myocardial infarction	102 (14%)	36 (13%)	66 (16%)
Percutaneous coronary intervention	100 (14%)	28 (10%)	72 (17%)
Coronary artery bypass graft surgery	31 (4%)	12 (4%)	19 (5%)
Peripheral vascular disease	21 (3%)	12 (4%)	9 (2%)
Cerebrovascular disease	33 (5%)	10 (4%)	23 (5%)

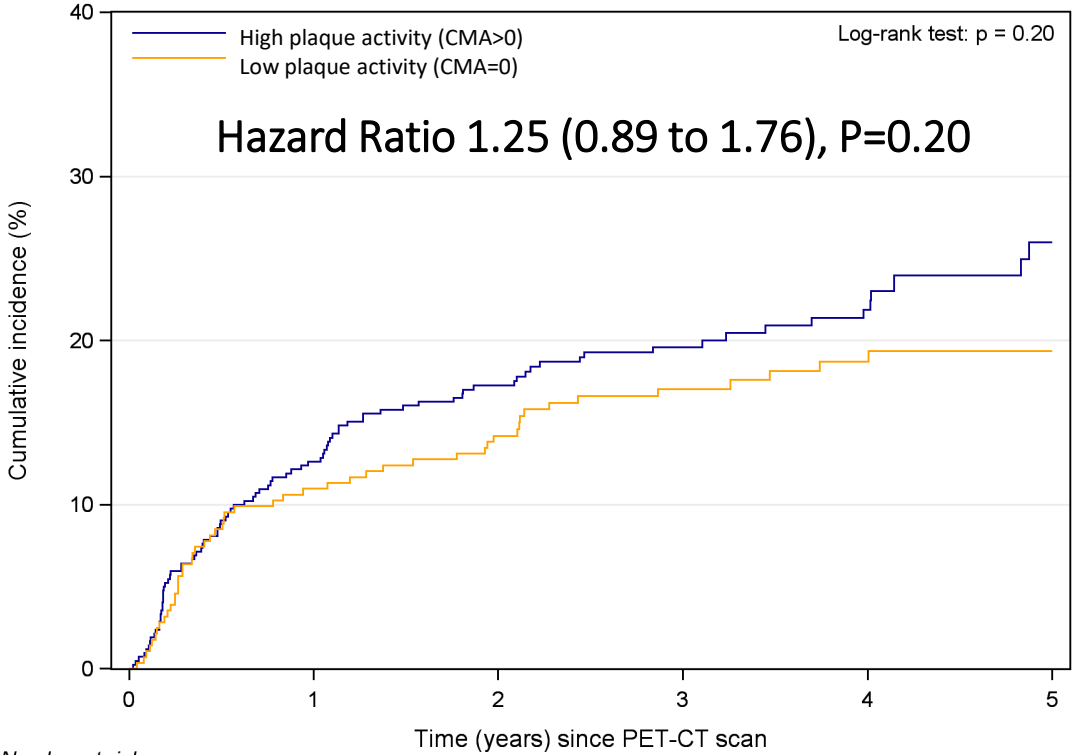
The PRE FFIR Study

Trial Population Characteristics

	Total Population	Low coronary atherosclerotic plaque activity CMA = 0	High coronary atherosclerotic plaque activity CMA > 0
Number	704	283	421
Presentation electrocardiogram			
ST-Segment elevation myocardial infarction	463 (66%)	189 (67%)	274 (65%)
Non-ST-Segment elevation myocardial infarction	239 (34%)	94 (33%)	145 (35%)
GRACE score	118±25	113±22	121±26
Severity of obstructive coronary artery disease			
One-vessel coronary artery disease	28 (4%)	12 (4%)	16 (4%)
Two-vessel coronary artery disease	387 (55%)	163 (58%)	224 (53%)
Three-vessel coronary artery disease	239 (34%)	90 (32%)	149 (35%)
Left main stem disease	50 (7%)	18 (6%)	32 (8%)
Coronary Revascularisation			
Percutaneous coronary intervention	671 (95%)	267 (94%)	404 (96%)
Medication			
Aspirin	673 (96%)	268 (95%)	405 (96%)
P2Y12 receptor antagonist	688 (98%)	299 (99%)	409 (97%)
Anticoagulant therapy	42 (6%)	17 (6%)	25 (6%)
Statin	653 (93%)	260 (92%)	393 (93%)
ACE inhibition or ARB	623 (88%)	250 (88%)	373 (89%)
Beta-adrenergic receptor antagonist	573 (82%)	233 (82%)	340 (81%)
Calcium-channel antagonist	64 (9%)	19 (7%)	45 (11%)
Nitrate	384 (55%)	158 (56%)	226 (54%)
Other anti-anginal therapy	22 (3%)	8 (3%)	14 (3%)
Mineralocorticoid receptor antagonist	42 (6%)	21 (7%)	21 (5%)
Other diuretic therapy	54 (8%)	22 (8%)	32 (8%)

The PREFFIR Study

Primary Endpoint

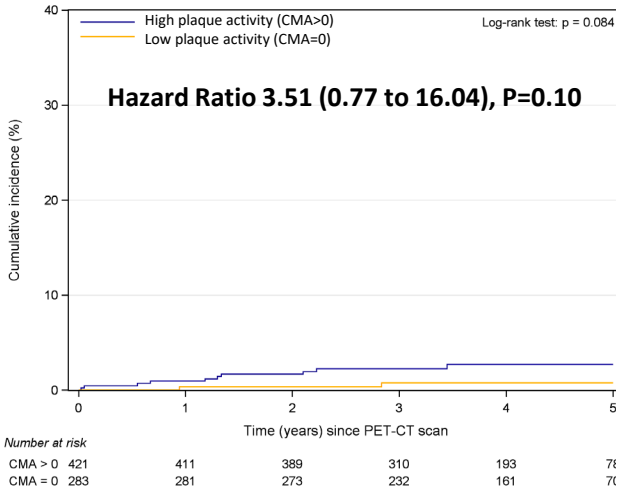


Number at risk

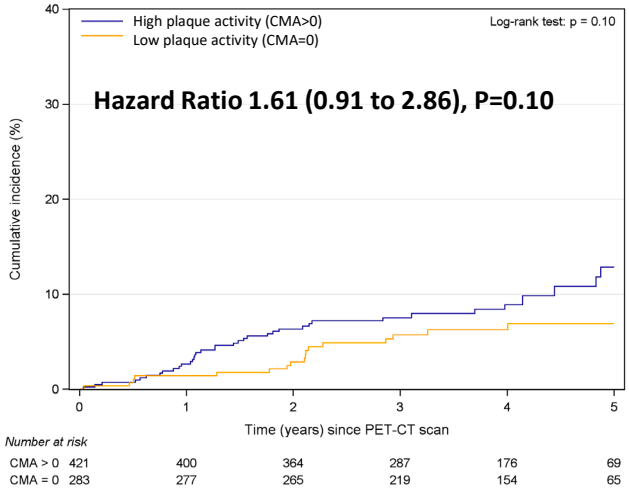
CMA > 0	421	362	326	255	152	59
CMA = 0	283	251	235	194	133	57

Components of the Primary Endpoint

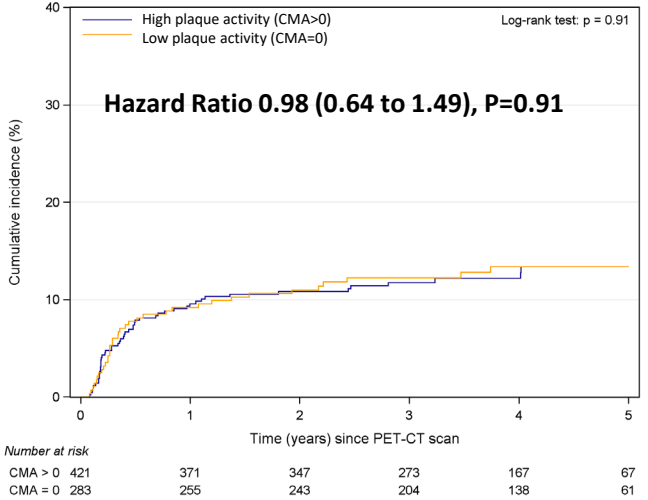
Cardiac death



Non-fatal myocardial infarction

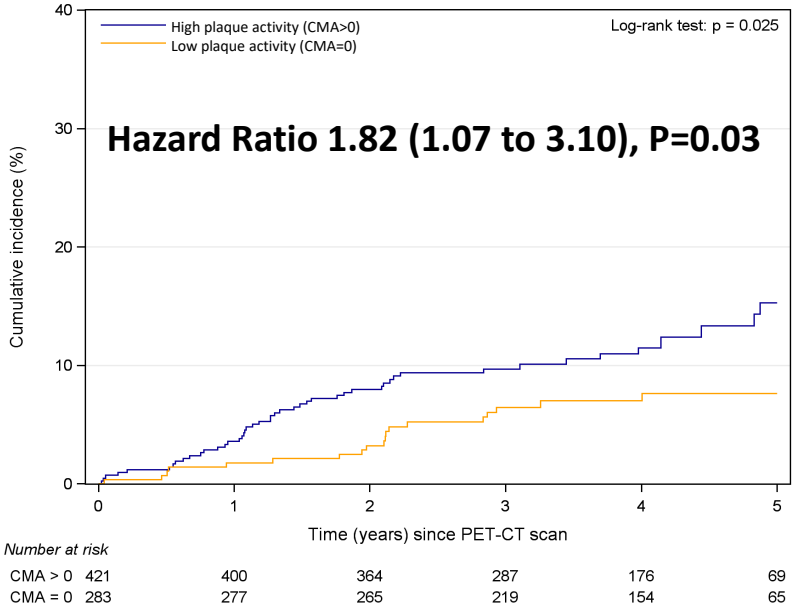


Unscheduled Coronary Revascularisation

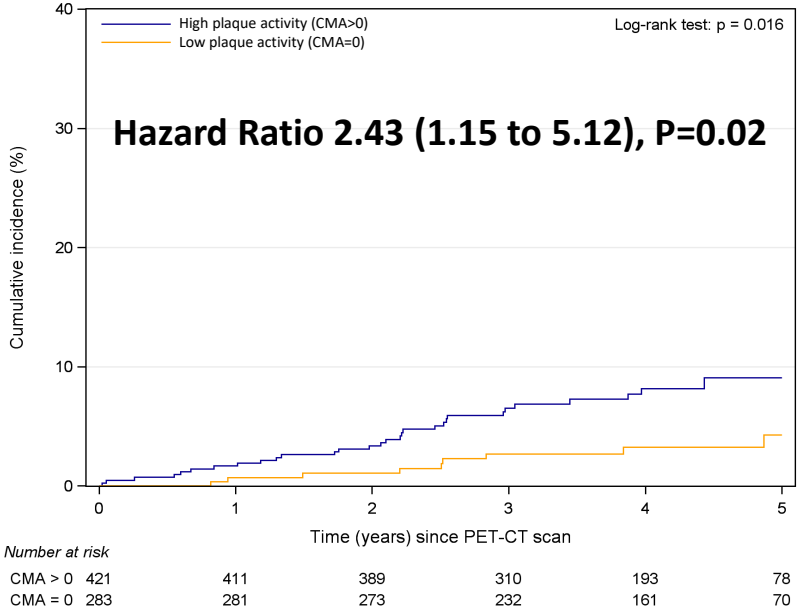


Original Primary Endpoint and All-cause Death

Cardiac death or non-fatal myocardial infarction



All-cause death



Original Primary Endpoint and All-cause Death

	Adjusted Hazard Ratio (95% Confidence Interval)	P value
Cardiac death or non-fatal myocardial infarction		
CMA > 0 versus CMA = 0 adjusting for:		
GRACE score*	1.73 (1.01 to 2.97)	0.048
Severity of obstructive coronary artery disease	1.76 (1.03 to 3.00)	0.038
GRACE score and severity of obstructive coronary artery disease	1.69 (0.98 to 2.91)	0.058
All-cause death		
CMA > 0 versus CMA = 0 adjusting for:		
GRACE score†	1.80 (0.84 to 3.86)	0.13
Severity of obstructive coronary artery disease	2.25 (1.06 to 4.74)	0.034
GRACE score and severity of obstructive coronary artery disease	1.75 (0.82 to 3.73)	0.15

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

The PREFFIR Study

Safety: Radiation Exposure

Radiotracer*:

6·0±0·3 mSv

CT attenuation correction, calcium score and angiogram†:

4·9±3·0 mSv

*conversion factor 0·024 mSv/MBq

†conversion factor 0·014 mSv/Gy·cm

Safety: Adverse Events

	POSSIBLY RELATED TO IMP	POSSIBLY RELATED TO NIMP	NUMBER OF EVENTS	NUMBER OF PATIENTS
All Adverse Events			15	15
Serious Adverse Events	0	2	2	2
Palpitation	0	1	1	1
Beta-blocker induced bradycardia	0	1	1	1
Non-serious Adverse Events	3	9	13	13
Contrast reaction*	3	7	8	8
Cannula access site	0	2	5	5

*Two reactions were felt to be possibly related to either the IMP or the NIMP

The PREFFIR Study

Coronary Atherosclerotic Plaque Activity and Future Coronary Events

Coronary atherosclerotic plaque activity:

- Does not predict all coronary events.
- Has no association with subsequent coronary revascularisation.
- Predicts cardiac death or non-fatal myocardial infarction.
- Predicts all-cause death.

Long-term outcomes from acute myocardial infarction are determined by residual coronary atherosclerotic plaque activity.

Acknowledgements

All participating patients.

The PRE[18]FFIR Investigators.

Chief Investigator: David E. Newby.

Site Principal Investigators: Dana Dawson (Valerie Harries; Aberdeen), Parthiban Arumugam (Thabitha Charles, Martin Sherwood; Manchester) , Nikant Sabharwal (Rachel Bates; Oxford), John Greenwood (Kathryn Somers, Hemant Kumar Chumun; Oxford), Jon Townend (Annette Nilsson; Birmingham), Patrick Calvert (Victoria Warnes, Catherine Galloweay; Cambridge), Dan Berman (Rebekah Park; Los Angeles), Johan Verjans (Denise Healy, Adelaide).

Trial Fellows: Alastair Moss, Marwa Daghem.

Core Laboratory: Piotr Slomka, Damini Dey, Evangelos Tzolos, Mohammed Meah, Kang-Ling Wang, Anda Bularga, Philip D. Adamson, Jacek Kwiecinski, David Senyszak.

Trial Team: Alison Fletcher, Christophe Lucatelli, James Rudd, Nicholas L. Mills, Edwin J.R. van Beek, Michelle C. Williams, Marc R. Dweck

Edinburgh Clinical Trials Unit: Laura Forsyth, Lauren Murdoch, Anny Briola, Ruth Armstrong, Alix Macdonald, Gill Scott, Garry Milne, Lynsey Milne, Claire Battison, Robert Lee, Steff Lewis

Trial Steering Committee: Martin R. Wilkins (Chair), David Newby, Robert F. Storey, Reza Razavi, Marc R. Dweck, Steff Lewis, Maja Wallberg, Rodney Mycock.