Supplementary Data

Methods

SMART score. The SMART (Second manifestations of arterial disease) risk score estimates the 10-year risk for myocardial infarction, stroke or vascular death in individual patients with previous cardiovascular disease, including coronary artery disease, cerebrovascular disease, peripheral artery disease, abdominal aortic aneurysm and polyvascular disease. The SMART risk score was developed in a population of vascular patients in the Netherlands that were included in the Secondary Manifestations of Arterial Disease (SMART)-study (1). External validation and updating were performed in pooled trial cohorts of 18,436 vascular patients from W-Europe, S-Europe, Israel, USA, Canada, Mexico, S-Africa, Australia, and N-Zealand (2). The SMART score calculators can be found at: https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/SMART-Risk-Score

^{18}F-Sodium Fluoride PET

Image reconstruction

The ECG-gated PET list mode dataset was reconstructed using a standard ordered expectation maximization algorithm with time-of-flight, and point-spread-function correction. Using 4 cardiac gates, we reconstructed the data on a 256x256 matrix (with 75 or 47 slices using 2 iterations, 21 subsets and 5-mm Gaussian smoothing for Siemens mCT data and 4 iterations, 24 subsets and 5-mm gaussian smoothing for GE Discovery data) (3). To compensate for coronary motion associated with heart contraction, we performed cardiac motion correction of the PET/CT images as described previously (4). After motion-correction, the 4 images aligned to the end diastolic gated position were summed back together to build a motion-free image containing

counts from the entire duration of PET acquisition. To offset for variation in the delay between tracer injection and the PET acquisition, we employed a recently validated correction factor to harmonize the background activity to a reference 60-min injection-to-acquisition interval (5).

Coronary Microcalcification Activity

We used a recently described measure of coronary ^{18}F-NaF uptake, coronary microcalcification activity (CMA) that quantifies PET activity across the entire coronary vasculature (6). We automatically extracted whole-vessel tubular and tortuous 3D volumes of interest which encompass all the main epicardial coronary vessels and their immediate surroundings (4-mm radius) from CT angiography datasets (Figure 1). Within such volumes of interest, we measured CMA, representing the overall disease activity in the vessel and based upon both the volume and intensity of ^{18}F-NaF PET activity within it. CMA was defined as the integrated activity in standardized uptake value (SUV) exceeding the corrected background blood-pool mean SUV + 2 standard deviations. Since CMA is based on SUV (SUV=Pixel Value (Bq/ml)) * Weight(kg) / Dose (Bq) * 1000 (g/kg), and can be considered as: SUV units x volume, the CMA unit would be g/mL x mL = g. However, given the fact that in the equation the unitless measure of activity (derived from: Pixel Bq/ml/ Dose (Bq) plays a key role to avoid confusion we refrained from reporting CMA in grams.

We measured the background activity in the right atrium, drawing cylindrical volumes of interest (10-mm radius and 5-mm thickness) at the level of the right coronary artery ostium. The per-patient CMA was defined as the sum of the per-vessel CMA values. We calculated the per vessel and per patient maximum coronary SUV and target to background ratio (TBR) as described previously (7). In brief within 3 dimensional volumes of interest which encompassed coronary

arteries the maximum standard uptake value (SUVmax) was recorded. TBR was calculated by dividing SUVmax by averaged background blood pool activity.

Machine-learning

The hyperparameters used for the XGBoost model were as follows:

Booster = gbtree

Learning rate = 0.005

Maximum depth of a tree = 1

Subsample ratio of the training instances = 0.6

Minimum sum of instance weight (hessian) needed in a child = 1

balance of positive and negative weights = 1

number of iterations = 5.000

10-fold repeated hold-out testing

The advantages of the 10-fold repeated hold-out testing over single split-sample approach are well documented and include: (1) reduction of variance in prediction error leading to a more accurate estimate of model performance; (2) maximizing the data for both training and validation, without overfitting or overlap between test and validation data; and (3) avoiding testing hypotheses suggested by arbitrarily split data (type III errors) (8,9).

Supplemental Table 1. Variables used in machine-learning.

Category	No.	Variable name
Clinical	1	abnormal rest ECG (0, 1)
	2	age (years)
	3	body mass index (kg/m^2)
	4	conduction disease (0, 1)
	5	current smoker (0, 1)
	6	past smoker (0, 1)
	7	diabetes mellitus (0, 1)
	8	dyslipidemia (0, 1)
	9	family history of premature coronary artery disease (0, 1)
	10	height (cm)
	11	hypertension (0, 1)
	12	past cerebrovascular accident
	13	past coronary artery bypass surgery (0, 1)
	14	past myocardial infarction (0, 1)
	15	past open-heart surgery (0, 1)
	16	past percutaneous coronary intervention (0, 1)*

17	peripheral vascular disease (0, 1)
18	coronary stent (0, 1)
19	coronary stent in LM, LAD
20	coronary stent in LCX
21	coronary stent in RCA
22	rest DBP (mmHg)
23	rest heart rate (bpm)
24	rest SBP (mmHg)
25	sex (m, f)
26	atrial fibrillation (0, 1)
27	weight (kg)
28	Aspirin (0, 1)
29	PY12_anatagonist (0, 1)
30	Statin (0, 1)
31	ACE inhibitors (0, 1)
32	ARB (0, 1)
33	Diuretic (0, 1)

34	Beta_Blocker (0, 1)
35	Calcium_Channel_Blocker (0, 1)
36	Isosorbide mononitrate (0, 1)
37	Nicorandil (0, 1)
38	Ivabradine (0, 1)
39	Warfarin/NOACS (0, 1)
40	Nitrate Spray (0, 1)
41	Metformin (0, 1)
42	Gliclazide (0, 1)
43	insulin (0, 1)
44	Proton pump inhibitors (0, 1)
45	Alpha blockers (0, 1)
46	Haemoglobin g/L
47	WBC n/dL
48	Platelets n/dL
49	Urea mmol/L
50	Sodium mmol/L

	51	Potassium mmol/L
	52	Creatinine mmol/L
	53	eGFR ml/m2
	54	Random Glucose mg/dL
	55	HbA1c %
	56	hsTnI ng/L
	57	Total Cholesterol mmol/L
	58	LDL mmol/L
	59	HDL mmol/L
	60	Triglycerides mmol/L
	61	SMART risk score (integer)
	62	Recent acute coronary syndrome (0, 1)*
Computed Tomography – qualitative and non-contrast	63	Duke coronary artery disease score (integer)
	64	Left Main Stenosis (0-5)
	65	pLAD Stenosis (0-5)
	66	mLAD Stenosis (0-5)
	67	dLAD Stenosis (0-5)

	68	Diagonal Stenosis (0-5)
	69	pLCx Stenosis (0-5)
	70	AVCx Stenosis (0-5)
	71	dLCx Stenosis (0-5)
	72	OM Stenosis (0-5)
	73	pRCA Stenosis (0-5)
	74	mRCA Stenosis (0-5)
	75	dRCA Stenosis (0-5)
	76	PDA Stenosis (0-5)
	77	Multivessel Disease (0, 1)
	78	Maximum Stenosis Grade (0-5)
	79	Obstructive coronary artery disease (0, 1)
	80	Segment Involvement Score (0-16)
	81	Coronary calcium score (integer)
	82	Coronary calcium score <1000 (0, 1)
	83	Coronary calcium score <1199 (0, 1)
	84	Total plaque volume (continuous)

Computed tomography - qualitative	85	Non-calcified plaque volume (continuous)
	86	Calcified plaque volume (continuous)
	87	Low attenuation plaque volume (continuous)
	88	Total plaque burden (continuous)
	89	Non-calcified plaque burden (continuous)
	90	Calcified plaque burden (continuous)
	91	Low attenuation plaque burden (continuous)
	92	Area stenosis (continuous)
	93	Contrast density difference (continuous)
	94	Minimal lumen area (continuous)
	95	Minimal lumen dimension (continuous)
	96	Remodelling index (continuous)
	97	Plaque length (continuous)
	98	Plaque composition LAP% (continuous)
	99	Plaque composition non-calcified plaque (continuous)
	100	Plaque composition calcified plaque (continuous)
	101	Ischemia score (continuous)

^{18}F-NaF	102	CMA (continuous)
	103	CMA LAD (continuous)
	104	CMA RCA (continuous)
	105	CMA LCX (continuous)
	106	CMA > 1.56 (0, 1)
	107	CMA < 0 (0, 1)
	108	Maximum TBR (continuous)
	109	Maximum SUV (continuous)

ACS – acute coronary syndrome, CMA – coronary microcalcificatin activity, CCS – coronary calcium score, CVA – cardiovascular accident, DG – diagonal, eGFR – estimated glomerular filtration rate, HDL – High density lipoprotein, LAD – left anterior descending, LCX – left circumflex, LMN – left main, LDL – low density lipoprotein, RCA – right coronary artery, SD – standard deviation, SIS – segment involvement score, SUV – standard uptake value, TAG – Triglicerydes, TBR – target to background ratio

*Because 61 patients in our study were subjects imaged shortly after an acute coronary syndrome for machine-learning we choose to differentiate them from subjects who had a percutaneous coronary intervention performed at a greater interval from PET imaging. These 61 patients were coded as recent ACS individuals and were considered positive for PCI only if an intervention was also conducted irrespective of the recent ACS.

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