CT acquisition and reconstruction

Three models of CT scanners, including 128-slice multidetector CT (Definition AS+, Siemens Healthineers, Germany), second generation dual source CT (SOMATOM Flash, Siemens Healthineers, Germany) and 256-slice CT scanner (Brilliance iCT, Philips Healthcare, USA), were employed for CCTA imaging. Beta-blocker (25 to 50 mg, Betaloc ZOK; AstraZeneca, China) was administered orally one hour prior to the examination in patients with baseline heart rate ≥70 bpm and scanned by 128-slice multidetector CT and 256-slice CT scanner. For patients scanned by dual source CT, beta-blocker was not used. Nitroglycerin was given sublingually in all patients from three sites. Prospective ECG-triggered sequential acquisition was used in all patients with the triggering window covering from end-systolic to mid-diastolic phase (from 35% to 75% of R-R interval). Same acquisition parameters were used for baseline and follow-up CCTA in each individuals.

For 128-slice multidetector CT, the scanning parameters were listed as follow: collimation =64×0.6 mm, reconstructed slice thickness =0.6 mm, reconstructed slice interval =0.5 mm, rotation time =300 ms and application of automated tube voltage and current modulation (CAREKv, CAREDose 4D, Siemens Healthineers, Germany). The reference tube current was set as 250 mAs and the reference tube voltage was set as 100 kVp. All CCTA data was reconstructed with a smooth kernel (B26f).

For second generation dual source CT, the scanning parameters were: collimation =64×0.6 mm, reconstructed slice thickness =0.75 mm, reconstructed slice interval =0.5 mm, rotation time =280 ms and application of automated tube voltage and current modulation (CAREKv, CAREDose 4D, Siemens Healthineers, Germany). The reference tube current was set as 350 mAs and the reference tube voltage was set as 100 kVp. All CCTA data was reconstructed with a medium soft kernel (I26f) and second generation iterative reconstruction technique (SAFIRE, strength level 3, Siemens Healthineers, Germany).

For 256-slice CT, the scanning parameters were: collimation = 128×0.625 mm, reconstructed slice thickness = 0.9 mm, reconstructed slice interval = 0.45mm, rotation time = 270 ms, tube voltage = 120 kVp, effective tube current = 210 mAs. All CCTA data was reconstructed with a smooth kernel (XCB) and hybrid iterative reconstruction technique (iDose4, Philips Healthcare, USA).

CT-based plaque and FAI analysis

Conventional qualitative and quantitative plaque parameters were evaluated via a dedicated plaque analysis software (Coronary Plaque Analysis, version 4.3, Siemens Healthineers, Germany). The following indices were measured and recorded: (I) Diameter stenosis (DS) was calculated as (reference diameter – minimal lumen diameter)/reference diameter and was measured manually with a digital caliper at the narrowest level of the lesion and the proximal reference on the cross-sectional images; (II) Remodeling index was defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter (at the site where no plaque component can be detected), with positive remodeling (PR) defined as a remodeling index ≥ 1.1; (III) Low-attenuation plaque (LAP) was defined as any voxel <30 HU within a coronary plaque; (IV) Spotty calcification (SC) was defined by an intra-lesion calcific plaque <3 mm in length that comprised <90 degrees of the lesion circumference; (V) Napkin-ring sign (NRS) was characterized by a plaque core with low attenuation areas on CT surrounded by a rim-like area of higher attenuation as previously reported. Lesions with at least two high-risk plaque features (PR, LAP, SC and NRS) were deemed high-risk plaques (HRPs).

A dedicated FAI analysis software (Coronary FAI Analysis, version 1.0.2, Siemens Healthineers, Germany) was used for quantification. The length of the lesion-based perivascular FAI was defined as the length from the proximal to the distal shoulder of the lesion, where no plaque could be detected. In brief, perivascular adipose tissue was sampled radially outward from the outer vessel wall of the plaques and measured as voxels with attenuation between –190 HU and –30 HU. FAI was defined as the mean CT attenuation of adipose tissue, which was within a radial distance from the outer vessel wall equal to the diameter of the target vessel. For the on-site processing, after CCTA data were successfully loaded, the centerline and luminal contours for whole coronary tree were automatically generated. The centerline and luminal contour are fundamental and critical information for computing FAI value. They were manually adjusted when needed. Users then identified all stenotic lesions from proximal end to distal end, where no plaque was present. After then, the radius from the outer vessel wall was input to calculate the mean density of tissue with CT attenuation between -190 HU and -30 HU within this

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volume of interest. Myocardial tissue adjacent to the vessel wall and coronary side branch originated from the vessel of interest was manually excluded in all cases when necessary.

CT-FFR measurement

As introduced recently, we used a machine-learning based algorithm for CT-FFR simulation (cFFR, version 3.0, Siemens Healthineers). It's an alternative to physics-based approach and can be used on-site to calculate CT-FFR value. It's trained using a synthetically generated database of 12,000 different anatomies of coronary arteries with randomly placed stenosis among different branches and bifurcations. A computational fluid dynamics (CFD) by solving reduced-ordered Navier-Stokes equations is applied to calculate the pressure and flow distribution for each coronary tree. Quantitative features of anatomy and computed CT-FFR value were extracted for each location along the coronary tree. Then deep machine learning model is trained by using a deep neural network with four hidden layers to learn the relationship between the FFR value and quantitative anatomic features.

For the on-site processing, after CCTA data were successfully loaded, the centerline and luminal contours for whole coronary tree were automatically generated. The centerline and luminal contour are fundamental and critical information for computing CT-FFR value. They were manually adjusted when needed. Users then manually identified all stenotic lesions to extract their geometrical features required for cFFR algorithm. Finally, those data were input into the pre-learned model and cFFR was computed automatically at all locations in the coronary arterial tree, and the resulting values were visualized by color-coded 3D coronary maps.

Table S1 Interobserver reproducibility

	ICC	95% CI	P value
MLA	0.958	0.946-0.967	<0.001
Total plaque volume	0.863	0.826-0.893	<0.001
Non-calcified component volume	0.861	0.823-0.891	<0.001
LAP volume	0.853	0.816-0.883	<0.001
CT-FFR	0.979	0.967-0.986	<0.001
FAI	0.921	0.899-0.983	<0.001
	Kappa	95% CI	P value
Spotty calcium	0.944	-	<0.001
Napkin-ring sign	0.898	-	<0.001
Positive remodeling	0.926	-	<0.001
Low attenuation plaque	0.947	-	<0.001

CI, Confidence interval; CT-FFR, CT derived fractional flow reserve; FAI, fat attenuation index; ICC, Intraclass correlation coefficient; LAP, low attenuation plaque; MLA, Minimal lumen diameter

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Table S2 Intra-observer reproducibility

	ICC	95% CI	P value
MLA	0.919	0.898-0.936	<0.001
Total plaque volume	0.848	0.806-0.881	<0.001
Non-calcified component volume	0.838	0.793-0.873	<0.001
LAP volume	0.815	0.768-0.853	<0.001
CT-FFR	0.959	0.937-0.972	<0.001
FAI	0.911	0.875-0.936	<0.001
	Kappa	95% CI	P value
Spotty calcium	0.962	-	<0.001
Napkin-ring sign	0.815	-	<0.001
Positive remodeling	0.961	-	<0.001
Low attenuation plaque	0.938	-	<0.001

CI, Confidence interval; CT-FFR, CT derived fractional flow reserve; FAI, fat attenuation index; ICC, Intraclass correlation coefficient; LAP, low attenuation plaque; MLA, Minimal lumen diameter.

Table S3 Cox Regression analysis result of Model 3

Characteristics	HR	95% CI	P value
Hypertension	3.145	1.401-7.065	0.006
Decreased MLA	0.677	0.507-0.905	0.008
High-risk plaque*	2.023	0.927-4.440	0.079
Decreased CT-FFR	2.455	1.131-5.328	0.023
Before 15th month after second CCTA	0.835	0.2581-2.704	0.763
15th month to end	5.838	1.232-27.664	0.026
Increased FAI	2.956	1.472-5.934	0.002

* Defined as patients with presence of at least two high-risk plaque features. CCTA, coronary computed tomography angiography; CI, confidence interval; CT-FFR, computed tomography fractional flow reserve; FAI, fat attenuation index; HR, hazard ratio; MLA, minimal lumen area.

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Table S4 Multivariable Cox regression analysis including Diamond-Forrester score for prediction of MACE

Characteristics	HR	95% CI	P value
Clinical model			
Hypertension	2.595	1.174-5.736	0.018
Dyslipidemia	1.365	0.703-2.651	0.358
Diamond-Forrester score	1.842	0.942-3.601	0.074
Decreased CT-FFR	3.071	1.489-6.376	0.002
Before 15th month after second CCTA	1.091	0.351-3.400	0.879
15th month to end	5.555	1.173-26.309	0.031
Increased FAI	3.129	1.559-6.282	0.001

CCTA, coronary computed tomography angiography; CI, confidence interval; CT-FFR, computed tomography fractional flow reserve; FAI, fat attenuation index; HR, hazard ratio; MLA, minimal lumen area.

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