Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions

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Aims	Coronary plaque characteristics are associated with ischaemia. Differences in plaque volumes and composition may explain the discordance between coronary stenosis severity and ischaemia. We evaluated the association between coronary stenosis severity, plaque characteristics, coronary computed tomography angiography (CTA)-derived fractional flow reserve (FFR_{CT}), and lesion-specific ischaemia identified by FFR in a substudy of the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps).
Methods and results	Coronary CTA stenosis, plaque volumes, FFR_{CT}, and FFR were assessed in 484 vessels from 254 patients. Stenosis >50% was considered obstructive. Plaque volumes (non-calcified plaque [NCP], low-density NCP [LD-NCP], and calcified plaque [CP]) were quantified using semi-automated software. Optimal thresholds of quantitative plaque variables were defined by area under the receiver-operating characteristics curve (AUC) analysis. Ischaemia was defined by FFR or FFR_{CT} ≤0.80. Plaque volumes were inversely related to FFR irrespective of stenosis severity. Relative risk (95% confidence interval) for prediction of ischaemia for stenosis >50%, NCP ≥185 mm³, LD-NCP ≥30 mm³, CP ≥9 mm³, and FFR_{CT} ≤0.80 were 5.0 (3.0–8.3), 3.7 (2.4–5.6), 4.6 (2.9–7.4), 1.4 (1.0–2.0), and 13.6 (8.4–21.9), respectively. Low-density NCP predicted ischaemia independent of other plaque characteristics. Low-density NCP and FFR_{CT} yielded diagnostic improvement over stenosis assessment with AUCs increasing from 0.71 by stenosis >50% to 0.79 and 0.90 when adding LD-NCP ≥30 mm³ and LD-NCP ≥30 mm³ + FFR_{CT} ≤0.80, respectively.
Conclusion	Stenosis severity, plaque characteristics, and FFR_{CT} predict lesion-specific ischaemia. Plaque assessment and FFR_{CT} provide improved discrimination of ischaemia compared with stenosis assessment alone.
Keywords	Coronary plaque • Computed tomography angiography • Computational fluid dynamics • Fractional flow reserve • Ischaemia

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Introduction

Traditionally, the presence of severe coronary stenosis has been interpreted as indicative of myocardial ischaemia. However, it is increasingly recognized that disconnect between stenosis severity and the presence of ischaemia is common. Approximately half of obstructive lesions by coronary computed tomography angiography (CTA) or invasive coronary angiography (ICA) cause ischaemia.[1,2] On the other hand, also non-obstructive lesions may be ischaemia-causing.[3–5] Recently, it has been demonstrated by coronary CTA, applying elaborate manual segmentation, and by intravascular ultrasound, that atherosclerotic plaque characteristics, such as necrotic core, spotty calcification, or positive remodelling, are associated with the presence of ischaemia independent of the degree of luminal stenosis.[5–10] Therefore, composition of coronary atherosclerotic plaques has been proposed as a potential missing link between stenosis and ischaemia.[11]

Fractional flow reserve (FFR) derived from coronary CTA (FFR$_{CT}$) is a promising non-invasive maker of coronary physiology.[12–15] The diagnostic performance of FFR$_{CT}$ is high and superior to coronary stenosis assessment alone when compared with measured FFR. Like ICA and FFR, FFR$_{CT}$ is coupled with coronary CTA, and thus represents a hybrid anatomical–physiological diagnostic strategy. Moreover, coronary CTA can assess plaque burden and composition comparable with intravascular ultrasound.[16] Thus, added to non-invasive, semi-automated plaque assessment, potentially allowing for rapid and reproducible segmentation, we hypothesized that non-invasive physiological assessment with FFR$_{CT}$ would contribute with valuable diagnostic information. Accordingly, the aim of this study was to investigate the associations between coronary stenosis severity, semi-automated assessment of atherosclerotic plaques, FFR$_{CT}$, and lesion-specific ischaemia using FFR as the reference standard.

Methods

Study population

This was a pre-specified *post hoc* substudy comprising all patients from the *HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps* (NXT) trial (NCT01757678).[15,17] Patients suspected of stable coronary artery disease (CAD) were included. Coronary CTA was performed ≤60 days prior to clinically indicated non-emergent ICA. Exclusion criteria included prior stent implantation or coronary bypass surgery, contraindications to beta-blockers, nitrates or adenosine, suspicion of acute coronary syndrome, significant arrhythmia, and body mass index >35 kg/m^2.[15,17] The study complied with the Declaration of Helsinki. The local ethics committees approved the study protocol. All patients provided written informed consent.

Invasive coronary angiography and fractional flow reserve measurements

Angiography and FFR were performed according to standard practice.[15,17] The FFR pressure-wire was positioned minimum 20 mm distal to the stenosis in vessel segments ≥2 mm. Hyperaemia was induced by intravenous adenosine (140–180 µg/kg/min). Fractional flow reserve ≤0.80 defined lesion-specific ischaemia.

Coronary computed tomography angiography acquisition

Coronary CTA was performed using CT scanners ≥64 detector rows.[15,17] Beta-blockers were administered if necessary targeting a heart rate of <60 b.p.m. Sublingual nitrates were administered prior to scanning in all patients. Stenosis severity was categorized as 0, 1–29, 30–50, 51–70, 71–90, 91–99, or 100% in coronary segments ≥2 mm by experienced local investigators.[18] Coronary stenosis >50% was considered obstructive.

Coronary plaque analysis

Coronary segments ≥2 mm with plaque were analysed using semi-automated software (AutoPlaq version 9.7, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Two experienced readers (S.G. and K.A.Ø.) blinded to the coronary CTA readings, FFR$_{CT}$, and FFR results performed the analyses using multiplanar coronary CTA images. Scan-specific thresholds for non-calcified plaque (NCP) and calcified plaque (CP) were automatically generated.[16] Plaque components were quantified within the manually designated area using adaptive algorithms.[16] Adjustments were made if necessary. Aggregate plaque volume (APV %) was computed as (total plaque volume/vessel volume)*100%.[19] Low-density non-CP (LD-NCP) was defined as plaque with attenuation <30 Hounsfield units. Remodelling index was calculated as maximum lesion vessel area/area of a proximal normal reference point.[19] Positive remodelling was defined by remodelling index >1.1.[5] Spotty calcification was visually identified as calcifications comprising <90° of the vessel circumference and <3 mm in length.[5] Plaque analysis was performed on a per-vessel basis (detailed description provided in Supplementary Material). A case example is shown in *Figure 1*.

Computation of fractional flow reserve derived from coronary computed tomography angiography

Computation of FFR$_{CT}$ was performed centrally (HeartFlow, Inc., Redwood City, CA, USA) by independent blinded analysts (software version 1.4). The FFR$_{CT}$ computation process has previously been described.[12] FFR$_{CT}$ was computed throughout the coronary tree; however, only values corresponding anatomically to the measured FFR were included in the analysis.[15,17] FFR$_{CT}$ ≤0.80 was considered diagnostic of lesion-specific ischaemia.[13–15]

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) or medians (interquartile range) as appropriate, and categorical variables as numbers and percentages. Data were compared using Student's *t*-test, one-way ANOVA, Mann–Whitney *U*-test, Kruskal–Wallis test, or Pearson's χ^2 test as appropriate. Plaque variables were dichotomized using area under the receiver-operating characteristics curve (AUC) analysis to define the optimal thresholds for discrimination of FFR ≤0.80.[20] The thresholds were validated by bootstrapping with 10 000 samples. Relative risk of ischaemia (FFR ≤0.80) in dichotomous analysis was estimated by the log-binomial regression model or the least square method as appropriate. The latter estimates were adjusted for clustering effects by robust variance estimation. Incremental discrimination of ischaemia was assessed by AUC analysis with confidence intervals (CI) adjusted for clustering effects by bootstrapping. The AUC analyses were performed for both dichotomous and continuous variables, the latter supplemented by restricted cubic spline to adjust for non-linearity.[21] The ability to predict ischaemia in a new patient sample was assessed by enhanced bootstrapping.[21] Models comprising
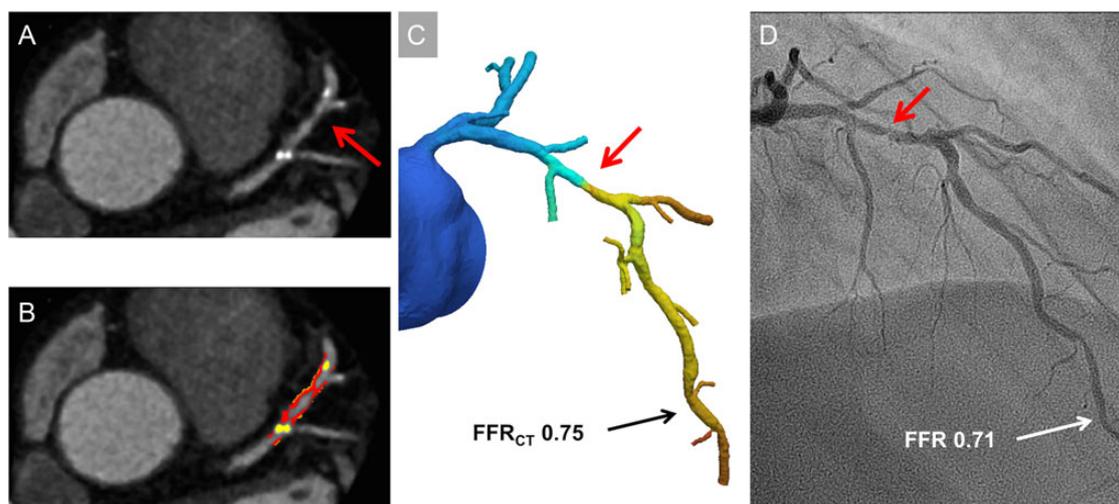
Figure 1 Case example. (*A*) Multiplanar reconstruction showing 50−70% stenosis (red arrow) in the left anterior descending artery. (*B*) Plaque analysis of the proximal portion of left anterior descending artery: non-calcified plaque 201 mm^3 (red plus orange), low-density non-calcified plaque 35 mm^3 (orange), and calcified plaque 41 mm^3 (yellow). Total per-vessel plaque volumes: non-calcified plaque 454 mm^3, low-density non-calcified plaque 85 mm^3, and calcified plaque 50 mm^3. (*C*) Fractional flow reserve derived from coronary computed tomography angiography in the distal left anterior descending artery was 0.75. (*D*) Invasive coronary angiogram with a 60% stenosis in the proximal portion of left anterior descending artery (red arrow). Measured fractional flow reserve was 0.71.

increasing numbers of predictors were compared by the Wald test. The calibration of the final model was assessed by calibration-in-the-large and calibration slope.[22] Interobserver variability of plaque characteristics was assessed by Bland−Altman analysis in a consecutive selection of 10% of patients. Two-sided *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with Stata software version 12 (StataCorp, College Station, TX, USA).

Results

The study population comprised 254 patients, in whom 484 vessels were interrogated by FFR (left anterior descending artery 41%, left circumflex artery 30%, and right coronary artery 29%). Baseline characteristics of the study population have previously been described.[15] In brief, mean (SD) age was 64 (10) years, 64% (162) were male, 87% (220) had intermediate (20−80%) pre-test risk by Diamond Forrester risk score, and mean (SD, range) Agatston score was 302 (468, 0−3599). Mean (SD) FFR was 0.87 (0.13). Fractional flow reserve was ≤0.80 in 100 (21%) vessels.

Relationship between coronary stenosis severity and lesion-specific ischaemia

The relationship between stenosis severity and FFR is illustrated in *Figure 2*. Obstructive lesions were present in 239 (49%) vessels. Fractional flow reserve was ≤0.80 in 83 (35%) vessels with obstructive lesions and in 17 (7%) vessels without obstructive lesions (*P* < 0.001; *Table 1*). In the event of >50% stenosis compared with the absence of stenosis, there was a five-fold increase in vessels with FFR ≤0.80 (*Table 2*).

Relationship between plaque characteristics and lesion-specific ischaemia

Volumes of NCP, LD-NCP, and CP were inversely related to FFR in both vessels with and without obstructive lesions (*Figure 3*). *Table 1* summarizes the different qualitative and quantitative plaque characteristics in relation to the presence or absence of coronary stenosis and FFR ≤0.80. The optimal thresholds for detection of FFR ≤0.80 for different plaque characteristics are provided in *Table 2*. Irrespective of stenosis severity, LD-NCP volume ≥30 mm^3, NCP volume ≥185 mm^3, total plaque volume ≥195 mm^3, and plaque length ≥30 mm predicted FFR ≤0.80 (*Table 2*). Low-density NCP volume ≥30 mm^3 predicted ischaemia independent of other plaque characteristics (*Table 3*).

There was good interobserver agreement in plaque analysis results (see Supplementary material, *Figure S1*).

Relationship between fractional flow reserve derived from coronary computed tomography angiography and lesion-specific ischaemia

There was a positive relationship between FFR$_{CT}$ and FFR both in vessels with and without obstructive lesions (*Figure 3*). Mean (SD) FFR$_{CT}$ was 0.84 (0.11), and FFR$_{CT}$ was ≤0.80 in 135 (28%) vessels. Mean FFR$_{CT}$ according to the presence or absence of coronary stenosis and FFR is given in *Table 1*. Irrespective of stenosis severity, FFR$_{CT}$ ≤0.80 was associated with the presence of ischaemia (*Tables 1* and *2*).
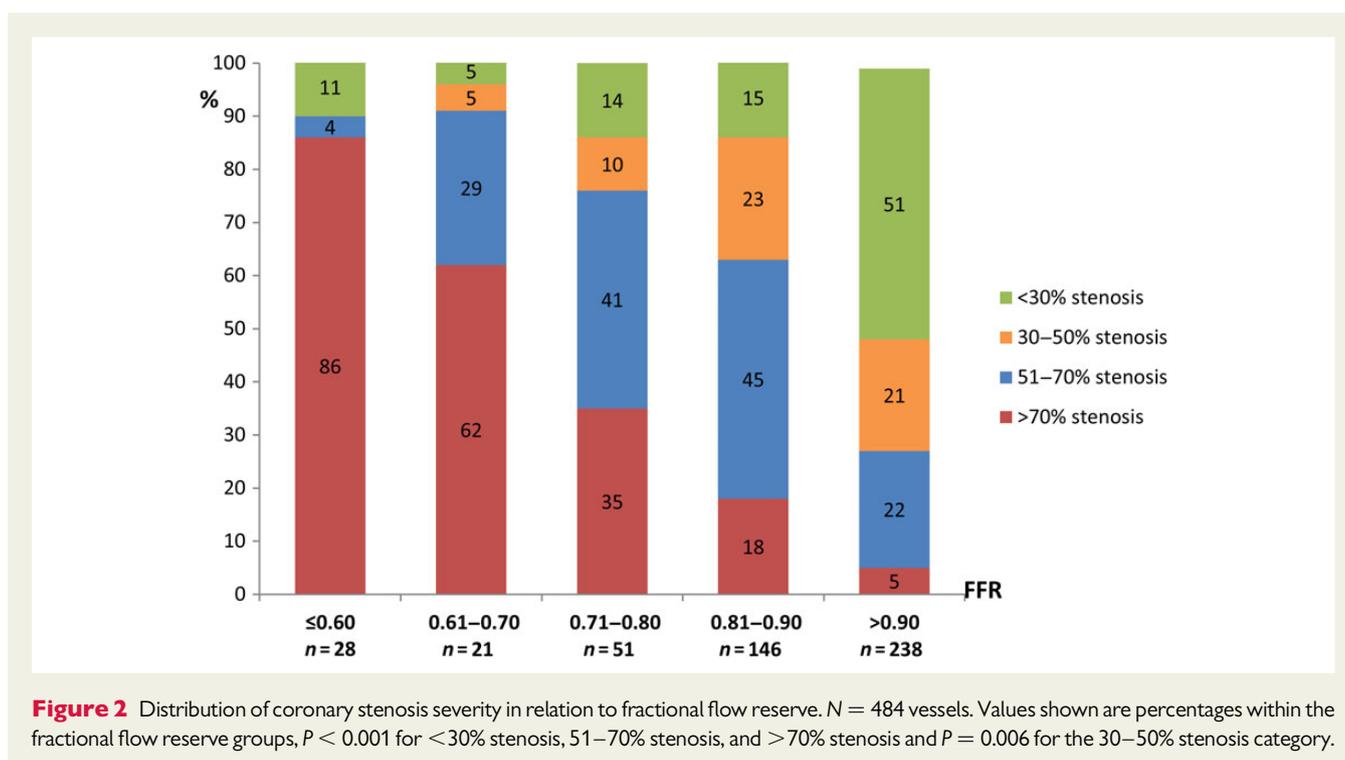
Figure 2 Distribution of coronary stenosis severity in relation to fractional flow reserve. $N = 484$ vessels. Values shown are percentages within the fractional flow reserve groups, $P < 0.001$ for <30% stenosis, 51–70% stenosis, and >70% stenosis and $P = 0.006$ for the 30–50% stenosis category.

Combined assessment of coronary stenosis severity, plaque characteristics, and fractional flow reserve derived from coronary computed tomography angiography for diagnosing ischaemia

The AUCs (95% CI) for discrimination of FFR ≤ 0.80 were 0.71 (0.67–0.76) for coronary stenosis >50%, 0.73 (0.67–0.78) for LD-NCP ≥ 30 mm^3, and 0.85 (0.82–0.89) for FFR$_{CT}$ ≤ 0.80. The addition of LD-NCP ≥ 30 mm^3 to stenosis >50% provided incremental prediction of ischaemia, with further improvement by FFR$_{CT}$ ≤ 0.80 (Table 4). The full model was well calibrated (see Supplementary material, Figure S2). In subgroup analysis, FFR$_{CT}$ ≤ 0.80 provided incremental discrimination of ischaemia over LD-NCP in both vessels without stenosis (AUC [95% CI] 0.88 [0.79–0.98] vs. 0.71 [0.57–0.84]; $P < 0.001$) and in vessels with stenosis >50% (AUC 0.84 [0.79–0.89] vs. 0.66 [0.60–0.73]; $P < 0.001$).

Model discrimination was modestly improved by the use of continuous variables for stenosis severity, LD-NCP volume, and FFR$_{CT}$ (see Supplementary material, Table S1). Applying a continuous analysis strategy, a stepwise improvement in AUC was present when information regarding LD-NCP volume and FFR$_{CT}$ were combined with stenosis severity (Figure 4). The addition of other plaque characteristics did not provide incremental risk prediction beyond stenosis severity and LD-NCP. The AUC of FFR$_{CT}$ alone (0.93 [0.91–0.95]) was not improved by the addition of stenosis severity and LD-NCP.

Discussion

In this multicentre study, we demonstrated an inverse relationship between coronary plaque volumes and lesion-specific ischaemia.

Non-CP volume, plaque length, and in particular LD-NCP predicted ischaemia. These findings applied consistently to vessels with and without obstructive lesions. The assessment of LD-NCP provided incremental discrimination of ischaemia beyond stenosis severity alone, with further discrimination of ischaemia by adding information regarding FFR$_{CT}$.

Previous studies have demonstrated an association between coronary atherosclerotic plaque characteristics and ischaemia.[5–8] Similar to our findings, myocardial perfusion imaging studies have demonstrated an association between NCP volume, positive remodelling, LD-NCP, and ischaemia.[6,8] On the other hand, a study by Naya et al. ($N = 73$)[23] reported no significant association between plaque length, plaque composition, or remodelling index by coronary CTA and the presence of ischaemia. In a study by Nakazato et al. ($N = 58$),[7] it was demonstrated that APV% was superior and additive to luminal narrowing for the discrimination of ischaemia. In a recent substudy of the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy (DeFACTO) trial ($N = 252$),[5] APV%, LD-NCP, lesion length, and positive remodelling predicted ischaemia. Moreover, in contrast to the findings in this study, increasing numbers of adverse plaque characteristics were associated with improved prediction of ischaemia. Major differences in crucial determinants of study outcomes may explain the differences in results between studies. The prior studies evaluating coronary plaque characteristics in relation to FFR[5,7] investigated plaques located upstream from the measured FFR point. Plaque analysis in this study included all coronary segments ≥ 2 mm. This strategy appears clinically relevant, since evaluation of coronary CTA is independent of the location of a hypothetical FFR sensor. Moreover, plaques localized downstream from the FFR sensor location may contribute to the induction of ischaemia. In contrast to previous

Table I Plaque characteristics and FFR$_{CT}$ according to coronary stenosis severity and lesion-specific ischaemia (FFR ≤0.80)

	Overall			Stenosis >50% (N = 239)			Stenosis ≤50% (N = 245)		
	FFR >0.80 (n = 384)	FFR ≤0.80 (n = 100)	P-value	FFR >0.80 (n = 156)	FFR ≤0.80 (n = 83)	P-value	FFR >0.80 (n = 228)	FFR ≤0.80 (n = 17)	P-value
NCP, mm^3	145 ± 144	265 ± 148	<0.0001	210 ± 163	274 ± 140	0.003	101 ± 108	223 ± 181	<0.0001
LD-NCP, mm^3	23 ± 27	54 ± 46	<0.0001	35 ± 31	56 ± 47	<0.0001	15 ± 19	44 ± 41	<0.0001
CP, mm^3	23 ± 43	29 ± 41	0.011	31 ± 52	29 ± 41	0.832	17 ± 35	29 ± 41	0.040
Total plaque volume, mm^3	168 ± 170	294 ± 167	<0.0001	241 ± 194	303 ± 159	0.014	117 ± 130	252 ± 204	0.0001
APV, %	46 ± 27	55 ± 21	0.002	55 ± 21	57 ± 20	0.454	40 ± 28	47 ± 23	0.333
Remodelling index	1.3 ± 0.7	1.5 ± 0.4	0.014	1.6 ± 0.7	1.6 ± 0.4	0.698	1.2 ± 0.6	1.3 ± 0.5	0.269
Plaque length, mm	25 ± 21	42 ± 22	<0.0001	33 ± 22	42 ± 20	0.002	19 ± 18	41 ± 28	<0.0001
Spotty calcification, n (%)	228 (59)	67 (67)	0.164	93 (59)	54 (65)	0.410	135 (59)	13 (76)	0.160
Agatston score[a]	89 ± 173	123 ± 164	0.023	134 ± 227	128 ± 168	0.817	60 ± 117	92 ± 141	0.119
FFR$_{CT}$	0.88 ± 0.07	0.69 ± 0.12	<0.0001	0.85 ± 0.08	0.68 ± 0.12	<0.0001	0.91 ± 0.05	0.74 ± 0.12	<0.0001

If not otherwise stated, values are mean ± SD. N = 484 vessels.
FFR$_{CT}$, fractional flow reserve derived from coronary computed tomography angiography; FFR, fractional flow reserve; NCP, non-calcified plaque; CP, calcified plaque; LD-NCP, low-density non-calcified plaque; APV, aggregate plaque volume.
[a]Agatston score available in 214 patients (333 vessels).

studies, we provided optimal thresholds for quantitative plaque characteristics in order to increase clinical applicability of study results. Finally, the use of a semi-automated plaque segmentation algorithm potentially allows for rapid segmentation in a fashion that could conceivably be performed clinically with excellent correlation with intravascular ultrasound.[16]

Our finding of a continuous relationship between plaque volumes and FFR, irrespective of the presence or absence of obstructive disease, indicates that the presence of coronary plaques *per se* is associated with ischaemia. In accordance with previous findings,[1–5] we found that although stenosis >50% was a predictor of FFR ≤0.80, ischaemia was present in 7% of vessels without obstructive lesions, and 24% of the vessels with FFR 0.71–0.80 had no obstructive lesions. Moreover, the finding in this study of LD-NCP providing incremental discrimination of ischaemia beyond stenosis severity is in accordance with previous results.[5,8] Local impaired function of the coronary endothelium caused by the presence of high LD-NCP volume is a potential explanation for the mismatch between stenosis severity and ischaemia.[11] Low-density NCP is the coronary CTA surrogate for the presence of necrotic core.[8] Plaques with necrotic cores harbour abundant oxidative stress and local inflammation, and may compromise production and bioavailability of the vasodilator nitric oxide and increase levels of vasoconstrictors such as isoprostanes.[11,24] This can lead to local endothelial dysfunction, which may cause a focal 'functional stenosis' with inability of the vessel segment to dilate adequately during stress.[25] Moreover, plaques with necrotic cores are the main cause of myocardial infarction and sudden cardiovascular death.[26–28] Findings in this and other studies of an association between the presence of LD-NCP and ischaemia may explain why revascularization may be safely deferred in the absence of FFR ≤0.80 even in lesions with severe stenosis.[29]

Over the past decades, an optimal non-invasive imaging modality combining anatomy and physiology with the ability to serve as a 'one-stop shop' for the diagnosis of ischaemia and gatekeeping to ICA has been requested.[30] FFR$_{CT}$, a novel clinical tool for non-invasive and reproducible computation of FFR from standard coronary CTA,[12,31] has been evaluated in three studies using FFR as the reference standard.[13–15] The most recent NXT trial performed with refined FFR$_{CT}$ technology demonstrated superior per-patient and per-vessel discrimination of ischaemia of FFR$_{CT}$ when compared with coronary CTA stenosis assessment.[15,17] Moreover, it was recently demonstrated that a diagnostic strategy comprising FFR$_{CT}$ vs. standard practice before ICA reduces the number of subsequent ICA and the proportion of unnecessary ICA examinations without influencing the short-term clinical outcome.[32] The present study adds to these studies by demonstrating that FFR$_{CT}$ provides incremental discrimination of lesion-specific ischaemia beyond stenosis severity and plaque assessment. In contrast to our findings, a recently published substudy of the DeFACTO trial reported improved discrimination of ischaemia by adding plaque characteristics to stenosis severity and FFR$_{CT}$.[9] However, the DeFACTO study was conducted with an earlier generation FFR$_{CT}$ analysis algorithm than in the NXT trial. Moreover, in DeFACTO, in contrast to the present trial, pre-scan administration of beta-blockers and nitroglycerine was not administered in a substantial number of patients which adversely affected CT image quality with a corresponding increase in differences between FFR$_{CT}$ and measured FFR.[33]

Table 2 Univariable analyses of coronary stenosis severity, plaque characteristics, and FFR$_{CT}$ for prediction of lesion-specific ischaemia (FFR $\leq$0.80; N = 484 vessels).

	Overall		Stenosis >50% (N = 239)		Stenosis ≤50% (N = 245)	
	RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
Stenosis >50%	5.0 (3.0−8.3)	<0.001	−	−	−	−
NCP $\geq$185 mm^3	3.7 (2.4−5.6)	<0.001	2.2 (1.4−3.4)	0.001	3.5 (1.3−9.2)	0.013
LD-NCP $\geq$30 mm^3	4.6 (2.9−7.4)	<0.001	2.6 (1.7−4.1)	<0.001	5.7 (2.1−15.6)	0.001
CP $\geq$9 mm^3	1.4 (1.0−2.0)	0.070	1.0 (0.7−1.4)	0.956	2.2 (0.8−6.0)	0.117
Total plaque volume $\geq$195 mm^3	3.4 (2.3−5.2)	<0.001	2.0 (1.3−3.0)	0.001	4.0 (1.5−10.7)	0.006
APV $\geq$50%	1.8 (1.3−2.6)	0.001	1.2 (0.9−1.8)	0.207	1.8 (0.7−5.1)	0.245
Remodelling index >1.1	3.1 (1.4−6.6)	0.004	1.7 (0.8−3.9)	0.181	2.2 (0.6−7.7)	0.224
Plaque length $\geq$30 mm	2.7 (1.8−4.0)	<0.001	1.6 (1.1−2.4)	0.016	3.5 (1.3−9.7)	0.014
Spotty calcification	1.3 (0.9−2.0)	0.211	1.2 (0.8−1.7)	0.427	2.1 (0.7−6.5)	0.182
FFR$_{CT}$ $\leq$0.80	13.6 (8.4−21.9)	<0.001	8.3 (4.5−15.1)	<0.001	17.7 (7.5−42.0)	<0.001

FFR$_{CT}$, fractional flow reserve derived from coronary computed tomography angiography; FFR, fractional flow reserve; RR, relative risk; CI, confidence interval; NCP, non-calcified plaque; LD-NCP, low-density non-calcified plaque; CP, calcified plaque; APV, aggregate plaque volume.
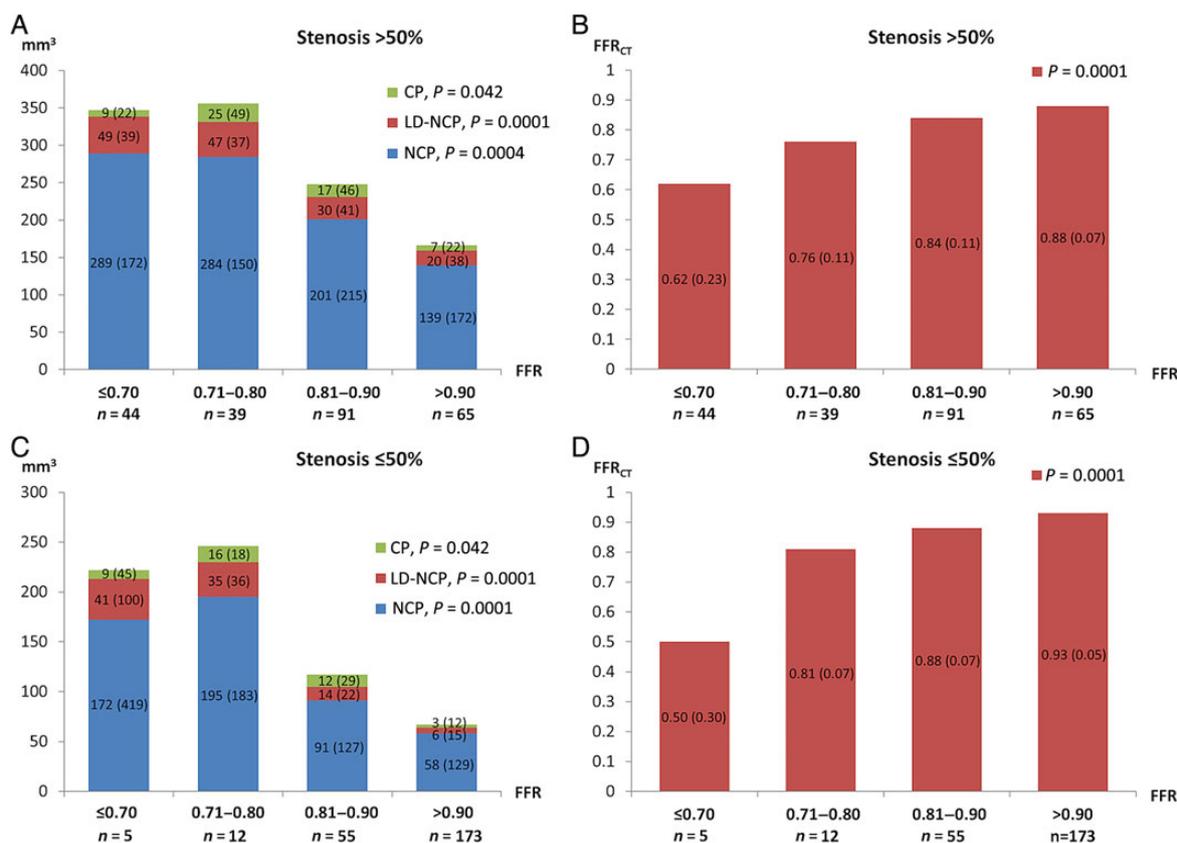

Figure 3 Distribution of coronary plaque volumes (A + C) and fractional flow reserve derived from coronary computed tomography angiography values (B + D) in relation to fractional flow reserve. N = 484 vessels. Values shown are medians (interquartile range).

Our findings suggest that a comprehensive anatomical−physiological approach combining coronary CTA anatomical stenosis assessment with semi-automated quantification of plaque volumes and FFR$_{CT}$ computation may be a valuable strategy for non-invasive assessment of stable CAD and potentially efficient gatekeeping to the catheterization laboratory. In addition, the results in this study

Table 3 Multivariable analysis of coronary plaque characteristics for prediction of lesion-specific ischaemia (FFR ≤0.80; *N* = 484 vessels)

	RR (95% CI) adjusted for age and gender	*P*-value
NCP ≥185 mm^3	1.2 (0.6–2.5)	0.610
LD-NCP ≥30 mm^3	4.3 (2.0–9.2)	<0.001
Total plaque volume ≥195 mm^3	0.9 (0.4–2.1)	0.834
APV ≥50%	1.0 (0.7–1.5)	0.861
Remodelling index >1.1	1.5 (0.7–3.5)	0.295
Plaque length ≥30 mm	0.8 (0.5–1.3)	0.298

FFR, fractional flow reserve; RR, relative risk; CI, confidence interval; NCP, non-calcified plaque; LD-NCP, low-density non-calcified plaque; APV, aggregate plaque volume.

Table 4 Comparison of different models for discrimination of ischaemia (FFR ≤0.80; *N* = 484 vessels)

Model	Wald test, *P*-value	AUC (95% CI)
Model 1: Stenosis >50%	Comparison with no effect, <0.001	0.71 (0.67–0.76)
Model 2: Stenosis >50% + LD-NCP ≥30 mm^3	Comparison with Model 1, <0.001	0.79 (0.74–0.84)
Model 3: Stenosis >50% + LD-NCP ≥30 mm^3 + FFR$_{CT}$ ≤0.80	Comparison with Model 2, <0.001	0.90 (0.87–0.93)

FFR, fractional flow reserve; AUC, area under the receiver-operating characteristics curve; CI, confidence interval; LD-NCP, low-density non-calcified plaque; FFR$_{CT}$, fractional flow reserve derived from coronary computed tomography angiography.

Figure 4 AUCs for discrimination of fractional flow reserve ≤0.80. AUC, area under the receiver-operating characteristics curve; CI, confidence interval; CTA, stenosis severity by coronary CTA; FFR$_{CT}$, fractional flow reserve derived from coronary computed tomography angiography; LD-NCP, low-density non-calcified plaque.

Conclusions

In patients suspected of CAD, coronary stenosis severity, plaque characteristics, and FFR$_{CT}$ predict lesion-specific ischaemia. The addition of coronary atherosclerotic plaque and FFR$_{CT}$ assessment improve the discrimination of ischaemia compared with stenosis evaluation alone.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

S.G., K.A.Ø.: performed statistical analysis; S.G., K.A.Ø., H.E.B., J.M.J., E.H.C, A.K.K., H.B., J.F.L., B.S.K., B.L.I.: acquired the data; H.E.B., S.A., J.F.L., B.L.N.: handled funding and supervision; S.G., K.A.Ø., D.D., J.L., H.E.B., J.M.J., D.S.B., J.N., A.A., B.L.N.: conceived and designed the research; S.G., K.A.Ø., B.L.N.: drafted the manuscript; D.D., J.L., H.E.B., J.M.J., E.H.C., J.N., A.A., S.A., B.S.K., A.K.K., J.F.L., D.S.B., B.L.N.: made critical revision of the manuscript for key intellectual content.

indicate that coronary CTA plaque assessment, by a simple and reproducible metric such as LD-NCP volume, may be beneficial for selection of patients for further diagnostic testing.

Limitations

We did not confirm plaque findings by intravascular ultrasound. However, plaque assessment by coronary CTA has been shown to highly correlate with the findings by intravascular ultrasound.[16] The relationship between stenosis severity and plaque characteristics is dose-dependent, and thus, collinearity may exist. However, coexistence of various plaque features is likely to represent CAD at high risk of producing ischeamia.[5] The pre-specified selection criteria for inclusion in this study resulted in a higher proportion of patients with obstructive CAD than in a non-selected coronary CTA population.[15,17] The thresholds for plaque characteristics were generated from the present study data. Optimal thresholds may differ in populations with lower prevalence of disease. Patients with acute coronary syndromes or previous revascularization were excluded in this study. Thus, generalizability of results to these patient categories needs further delineation.
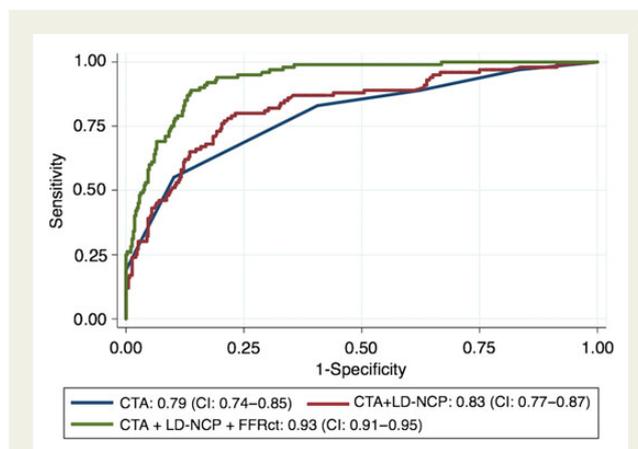
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