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Clinical Use of Coronary CTA–Derived FFR for Decision-Making in Stable CAD

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ABSTRACT

OBJECTIVES The goal of this study was to assess the real-world clinical utility of fractional flow reserve (FFR) derived from coronary computed tomography angiography (FFR_{CT}) for decision-making in patients with stable coronary artery disease (CAD).

BACKGROUND FFR_{CT} has shown promising results in identifying lesion-specific ischemia. The real-world feasibility and influence on the diagnostic work-up of FFR_{CT} testing in patients suspected of having CAD are unknown.

METHODS We reviewed the complete diagnostic work-up of nonemergent patients referred for coronary computed tomography angiography over a 12-month period at Aarhus University Hospital, Denmark, including all patients with new-onset chest pain with no known CAD and with intermediate-range coronary lesions (lumen reduction, 30% to 70%) referred for FFR_{CT}. The study evaluated the consequences on downstream diagnostic testing, the agreement between FFR_{CT} and invasively measured FFR or instantaneous wave-free ratio (iFR), and the short-term clinical outcome after FFR_{CT} testing.

RESULTS Among 1,248 patients referred for computed tomography angiography, 189 patients (mean age 59 years; 59% male) were referred for FFR_{CT}, with a conclusive FFR_{CT} result obtained in 185 (98%). FFR_{CT} was ≤0.80 in 31% of patients and 10% of vessels. After FFR_{CT} testing, invasive angiography was performed in 29%, with FFR measured in 19% and iFR in 1% of patients (with a tendency toward declining FFR-iFR guidance during the study period). FFR_{CT} ≤0.80 correctly classified 73% (27 of 37) of patients and 70% (37 of 53) of vessels using FFR ≤0.80 or iFR ≤0.90 as the reference standard. In patients with FFR_{CT} >0.80 being deferred from invasive coronary angiography, no adverse cardiac events occurred during a median follow-up period of 12 (range 6 to 18 months) months.

CONCLUSIONS FFR_{CT} testing is feasible in real-world symptomatic patients with intermediate-range stenosis determined by coronary computed tomography angiography. Implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow of patients. Patients with an FFR_{CT} value >0.80 being deferred from invasive coronary angiography have a favorable short-term prognosis. (J Am Coll Cardiol Img 2017;10:541–50)

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CTA = computed tomography angiography

FFR = fractional flow reserve

FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve

ICA = invasive coronary angiography

iFR = instantaneous wave-free ratio

LAD = left anterior descending artery

LCx = left circumflex artery

MPI = myocardial perfusion imaging

RCA = right coronary artery

Current guidelines recommend noninvasive functional imaging testing as the first-line strategy in patients with suspected stable coronary artery disease (CAD) (1). However, shortcomings of current noninvasive diagnostic strategies are apparent from the frequent inaccurate selection of patients for invasive coronary angiography (ICA) (2). Randomized trials have shown that a fractional flow reserve (FFR) threshold of 0.80 distinguishes patients and lesions that will (3–5) and will not (4–6) benefit from coronary revascularization. FFR has therefore emerged as the reference standard for guiding coronary revascularization in intermediate-range lesions (7,8). Noninvasive anatomic assessment using coronary computed tomography angiography (CTA) reveals high diagnostic performance for detection or exclusion of CAD. However, coronary CTA tends to overestimate obstructive CAD, and the correlation of stenoses to downstream myocardial ischemia is poor (9). Consequently, guidelines recommend additional stress testing in ambiguously symptomatic patients with suspected obstructive CAD determined by coronary CTA (1).

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Recent advances in computational fluid dynamics and individual image-based modeling permit calculation of coronary blood flow and pressure from standard acquired coronary CTA datasets (10–12). This technique allows for noninvasive calculation of FFR (coronary computed tomography angiography-derived fractional flow reserve [FFR_{CT}]). In 3 prospective multicenter trials that included 609 patients (1,050 vessels) with known or suspected CAD and blinded comparison to FFR, FFR_{CT} exhibited a high and superior diagnostic performance compared with stenosis assessment according to coronary CTA (10–12). However, because of the potential selection bias in these studies, concerns have been raised regarding to what extent FFR_{CT} in stable CAD can be translated into clinical practice (13,14). We report the first real-world experience of coronary CTA with FFR_{CT} as gatekeeper to the catheterization laboratory in nonemergent symptomatic patients with intermediate-range coronary lesions.

METHODS

This single-center, observational all-comers study was conducted in symptomatic patients with suspected CAD referred to coronary CTA at Aarhus University Hospital between May 1, 2014, and April 30, 2015. In this institution, coronary CTA testing is the preferred initial diagnostic modality in patients with new-onset chest pain with no known CAD and low-intermediate pre-test probability of disease (1). Patients were referred to nonemergent ambulatory coronary CTA from our outpatient clinic, 2 community hospitals, and 2 private cardiologist practices. Before performance of the coronary CTA, all patients underwent 12-lead electrocardiogram and routine biochemistry, echocardiography, and clinical evaluation by a cardiovascular physician; noninvasive ischemia testing (using exercise electrocardiography) was performed only in patients being referred from private cardiologist practices. Demographic and clinical characteristics, data on downstream diagnostic testing, and clinical follow-up were obtained from patient files and registries (15). The study was approved by the Danish Data Protection Agency (1-16-02-414-15) with a waiver for individual informed consent by the regional ethical committee.

CORONARY CTA ACQUISITION, ANALYSIS, AND DIAGNOSTIC CONSEQUENCE. Coronary CTA was performed using a dual-source CT scanner (SOMATOM Definition Flash; Siemens, Forchheim, Germany). Contraindications were renal insufficiency, pregnancy, or allergy to contrast. Image acquisition was performed in accordance with society guidelines (16). Oral and/or intravenous beta-blockers or oral ivabradine were administered if necessary, targeting a heart rate <60 beats/min, and all patients received sublingual nitrates. An initial nonenhanced scan for calcium scoring was performed using high-pitch spiral acquisition mode and 120 kV. Coronary CTA was performed using prospective electrocardiographic triggering in all patients. In the event of a heart rate ≤65 beats/min or >65 beats/min, the recommended RR scan intervals were 65% to 75% and 40% to 70%, respectively. Data acquisition was performed with 100- or 120-kV tube voltage in patients weighing ≤70 or >70 kg. Filtered back-projection was used for image reconstruction. Scans were assessed by using axial images and multiplanar reconstructions by experienced cardiologists. Vessel segments ≥2 mm were evaluated for lumen narrowing, and the per-vessel maximum stenosis category (30% to 50%, 51% to 70%, 71% to 90%, and >90%) was reported. The strategy of stenosis quantification was at the discretion of the CT scan interpreter. The cardiologists reading the CT scans grouped patients into 1 of 3 risk categories on the basis of the coronary anatomy (1); recommendations regarding downstream patient management were based on

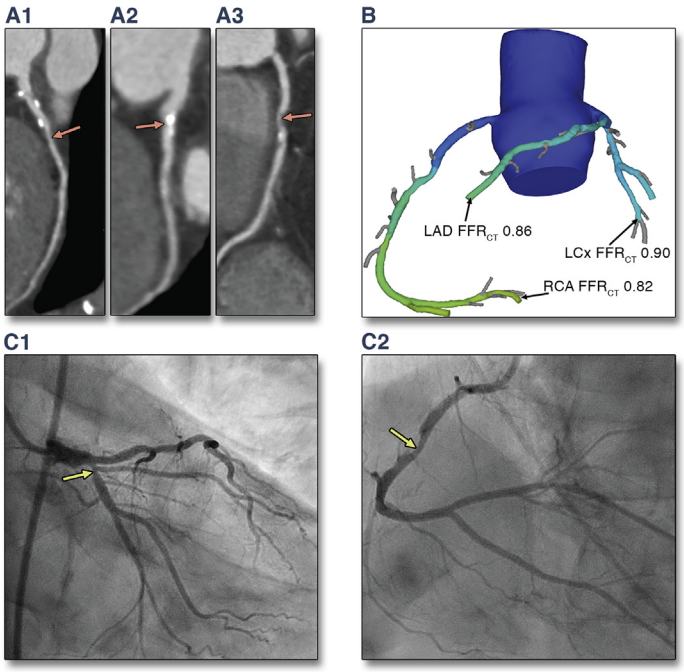
TABLE 1 Local Recommendations of Downstream Diagnostic Work-Up of Patients After Coronary CTA and FFR_{CT} Testing Between May 2014 and April 2015

	Test Outcome	Downstream Diagnostic Test
Coronary CTA		
Diagnostic conclusive	High risk*	ICA
	Intermediate risk†	FFR_{CT}
	Low risk‡	No additional testing§
Diagnostic inconclusive	–	Myocardial perfusion imaging
FFR_{CT}	≤0.80	ICA
	>0.80	No additional testing§

*Patients with left main, 3-vessel disease, and/or high-grade proximal left anterior descending artery stenosis. †Patients with 1 or 2 intermediate coronary stenoses (lumen reduction 30% to 70%). ‡Patients with no coronary disease or with maximum coronary stenosis <30%. §Optimal medical treatment was recommended. If coronary artery disease was present, statin, aspirin, and/or antianginal medication were generally prescribed or recommended via the general practitioner.

CTA = computed tomography angiography; FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve; ICA = invasive coronary angiography.

FIGURE 1 Patient Example



A 51-year-old man presented with new-onset atypical chest pain. **(A)** Coronary computed tomography angiography (curved multiplanar reconstructions) showed 50% to 70% stenoses **(pink arrows)** in the left anterior descending (LAD) **(A1)**, circumflex (LCx) **(A2)**, and right coronary (RCA) **(A3)** arteries, respectively. **(B)** Coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) indicated that lesions were not hemodynamically significant. **(C)** Invasive coronary angiography demonstrated 2 50% to 60% stenoses **(yellow arrows)** in the **(C1)** LCx and the **(C2)** RCA, and mild luminal irregularities in LAD. FFR_{CT} values in LCx and RCA were 0.92 and 0.88, respectively; distally measured FFR in the LAD was 0.88.

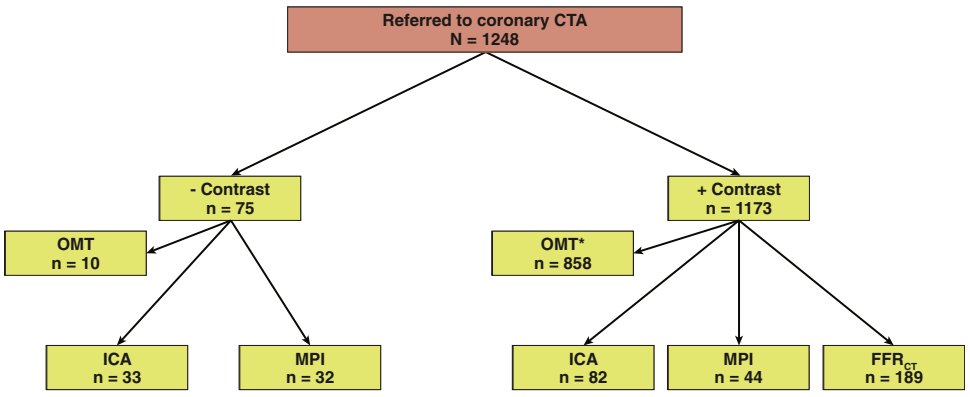
these categories (Table 1). Subsequent myocardial perfusion imaging (MPI) with rest-stress 82-rubidium positron emission tomography was recommended in patients in whom the coronary CTA interpreter deemed the result as inconclusive.

FFR_{CT} ANALYSIS. A standard coronary CTA dataset was transmitted for analysis (HeartFlow, Inc., Redwood City, California) (12). Clinical information related to FFR_{CT} analysis was restricted to patient weight, height, heart rate, and blood pressure. The principles behind FFR_{CT} computation have been described previously (10–12). FFR_{CT} was displayed for each point in the coronary tree. FFR_{CT} values distally in the major epicardial (left main, left anterior descending [LAD], left circumflex [LCx], and right coronary [RCA]) arteries (including side branches) >2 mm in diameter were registered. FFR_{CT} ≤0.80 was considered diagnostic of lesion-specific ischemia (10–12). Recommendations during the study period on downstream patient management according to the FFR_{CT} result are shown in Table 1. Figure 1 displays a representative case.

FOLLOW-UP. The proportion of patients having ICA performed as a consequence of the FFR_{CT} result was registered. The proportion of patients having subsequent coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) was registered. Patients were followed up for a median of 12 (range 6 to 18 months) months during which the occurrence of cardiac events (death, acute myocardial infarction, and angina leading to hospital admission or visit in the outpatient clinic) and diagnostic procedures (ICA, coronary CTA, and MPI) were recorded. No patients were lost to follow-up.

ICA AND FFR. ICA and FFR were performed according to standard practice by experienced invasive cardiologists. All information relevant for patient management, including the FFR_{CT} result, was available for decision-making. Decisions on measuring FFR and coronary revascularization were at the discretion of the interventionalist. Measurement of FFR was performed using the PressureWire (St. Jude Medical, St. Paul, Minnesota) or the ComboWire XT guidewire (Volcano Therapeutics, Cordova, California). The pressure sensor was advanced past the most distal stenosis, and FFR was measured during intravenous infusion of adenosine (140 to 180 μg/kg/min) via the antecubital vein. Intracoronary nitroglycerin (100 to 250 μg) was given before introduction of the FFR guidewire. Instantaneous wave-free ratio (iFR)

FIGURE 2 Work-Up of Patients Referred to Coronary CTA Between May 2014 and April 2015



*Of the 858 patients discharged from the outpatient clinic without further testing, 270 (31%) had cholesterol-lowering medication, aspirin, and/or antianginal medication prescribed. CTA = computed tomography angiography; FFR_{CT} = coronary computed tomography angiography–derived fractional flow reserve; ICA = invasive coronary angiography; MPI = myocardial perfusion imaging; OMT = optimal medical treatment.

was measured in few patients (17). FFR ≤0.80 or iFR ≤0.90 was indicative of ischemia.

RADIATION EXPOSURE. Cumulative radiation exposure including all diagnostic tests are reported in millisieverts using the formula mSv = (dose length product) × 0.014 for coronary CTA, a conversion factor of 0.18 mSv/(Gy cm^2) for ICA (18), and 0.00126 MBq/mSv for MPI (19).

STATISTICAL ANALYSIS. Categorical data are presented as numbers or proportions. Continuous data are presented as mean ± SD, median (interquartile range), or median (range) as appropriate. Fisher's exact test, chi-square test, Mann-Whitney *U* test, or the Student *t* test were used for comparisons as appropriate. Correlation of per-vessel FFR_{CT} to FFR was assessed using the Pearson correlation coefficient and Bland-Altman analysis. Statistical analyses were performed using Stata version 14.0 (Stata Corp, College Station, Texas).

RESULTS

Figure 2 displays the diagnostic flow of patients referred for coronary CTA during the study period. Contrast was not administered in 75 patients because of irregular heart rhythm and/or severe coronary calcification and/or inadequate patient cooperation. In this patient group, 77% were in sinus rhythm; the mean heart rate was 72 (range 53 to 131 beats/min) beats/min; and the median Agatston score was 617 (interquartile range: 56 to 2,024; range 0 to 4,723). Because of inconclusive coronary CTA results (low contrast, severe motion, misalignment, and/or blooming artifacts), 33 (3%) patients were referred for subsequent MPI. In 11 (1%) patients with a conclusive coronary CTA result and ≥1 intermediate lesion, MPI was the preferred downstream test strategy. Baseline characteristics of patients in whom coronary CTA was performed are shown in Table 2. Before coronary CTA testing, exercise electrocardiography was performed in 12% of the patients without temporal changes in proportions during the study. Baseline characteristics of patients referred directly to ICA based on the coronary CTA result or to MPI are shown in Table 3. No proportional changes during the study period in direct referrals to ICA or MPI could be detected.

FFR_{CT}. Table 3 presents the baseline characteristics of patients scheduled for FFR_{CT} testing. A conclusive FFR_{CT} result was available within 24 h in 185 (98%) patients. In 4 patients, FFR_{CT} computation was not possible due to calcium blooming, motion, and/or low contrast (n = 3) or missing diastole reconstruction for myocardial segmentation (n = 1). The per-patient and per-vessel distribution of FFR_{CT} values are shown in Figure 3. In 31% (57 of 185) of patients and 10% (72 of 740) of vessels, FFR_{CT} was ≤0.80. Among these 185 patients, intermediate stenoses were present in 303 vessels (left main, n = 9; LAD, n = 156; LCx, n = 62; RCA, n = 76). FFR_{CT} in these vessels was 0.85 ± 0.08 (range 0.43 to 0.98) versus 0.92 ± 0.05 (range 0.78 to 1.00) in vessels without stenosis or with <30% stenosis ($p < 0.0001$). In the latter group, FFR_{CT} was ≤0.80 (range 0.78 to 0.80) in 5 (1%) vessels (LCx, n = 4; RCA, n = 1).

TABLE 2 Baseline Characteristics of Patients in Whom Coronary CTA Was Performed (N = 1,173)

Age, yrs	57 ± 11, 25-85
Male	551 (47)
Diabetes	117 (10)
Hypertension	399 (34)
Hyperlipidemia	340 (29)
Current smoker	205 (17)
Family history of CAD	538 (46)
Symptoms	
Typical angina	152 (13)
Atypical angina	763 (65)
Nonanginal chest pain	176 (15)
Dyspnea	82 (7)
Updated Diamond-Forrester risk score, %	34
Intermediate (20%-80%) pre-test risk	844 (72)
Noninvasive ischemia testing performed before coronary CTA	141 (12)
Body mass index, kg/m^2	26 ± 4
Serum creatinine, μmol/l	74 ± 15
Heart rate, beats/min	58 ± 9, 37-122
Sinus rhythm	1,152 (98)
Agatston score	0 (0-54; 0-4,830)
Effective CT radiation dose	3.2 ± 1.4*

Values are mean ± SD, range, n (%), %, or median (IQR; range). *Includes both the noncontrast and contrast-enhanced scan.

CAD = coronary artery disease; CT = computed tomography; CTA = computed tomography angiography; IQR = interquartile range.

TABLE 3 Baseline Characteristics of Patients Referred to FFR_{CT}, Invasive Coronary Angiography, or Myocardial Perfusion Imaging Testing on the Basis of Coronary CTA Outcome

	ICA* (n = 82)	FFR_{CT}† (n = 189)	MPI‡ (n = 44)
Age, yrs	58 ± 10, 37-78	59 ± 9, 34-78	61 ± 9, 42-78
Male	51 (62)	111 (59)	24 (55)
Diabetes	10 (12)	24 (13)	7 (16)
Hypertension	36 (44)	82 (43)	19 (43)
Hyperlipidemia	32 (39)	73 (39)	18 (41)
Current smoker	18 (22)	43 (23)	11 (25)
Family history of CAD	41 (50)	96 (51)	24 (55)
Symptoms			
Typical angina	46 (56)	29 (15)§	6 (14)
Atypical angina	32 (39)	117 (62)§	28 (64)
Nonanginal chest pain	1 (1)	17 (9)§	6 (14)
Dyspnea	3 (4)	26 (14)§	4 (9)
Updated Diamond-Forrester risk score, %	53	41§	40
Intermediate (20%-80%) pre-test risk	72 (88)	162 (86)	38 (86)
Noninvasive ischemia testing performed before coronary CTA	14 (17)	19 (10)	3 (7)
Body mass index, kg/m^2	28 ± 3	26 ± 4	26 ± 4
Serum creatinine, μmol/l	79 ± 19	77 ± 16	73 ± 16
Heart rate, beats/min	60 ± 13, 41-122	58 ± 8, 40-93	59 ± 9, 41-87
Sinus rhythm	78 (95)	189 (100)§	42 (95)‖
Agatston score	79 (16-259; 0-4,830)	61 (9-209; 0-1,277)§	89 (6-268; 0-1,390)
Maximum coronary CTA stenosis severity¶			
30%-49%	22 (18)	110 (36)§	0§
50%-69%	49 (41)	165 (54)§	10 (83)§
70%-89%	49 (41)	28 (9)§	2 (17)
>90%	0 (0)	0 (0)	0 (0)
Cumulative radiation exposure, mSv‖	8.8 ± 6.6	3.2 ± 1.1§	7.0 ± 1.2§

Values are mean ± SD, range, n (%), % or median (IQR; range). *Patients with high-risk anatomy (i.e., left main, 3-vessel disease, and/or high-grade proximal left anterior descending artery stenosis) preferably were referred for ICA. †FFR_{CT} testing was recommended in patients with 1 or 2 intermediate coronary stenosis (lumen reduction 30% to 70%). ‡MPI was performed due to an inconclusive coronary CTA result (n = 33) or because of the presence of intermediate stenosis (n = 11). §Indicates $p < 0.05$ compared with the group on its left. ‖For ICA and MPI, the radiation dose associated with the preceding coronary CTA examination is included. Both the noncontrast and contrast-enhanced CT scans are included in the estimate. ¶A total of 303 vessels were tested in the FFR_{CT} assessment group, 120 vessels in the ICA group, and 12 vessels in the MPI group.

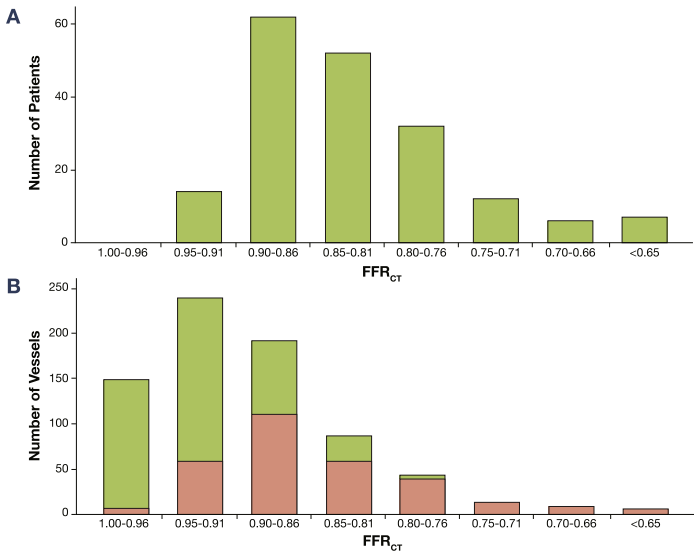
MPI = myocardial perfusion imaging; other abbreviations as in Tables 1 and 2.

The diagnostic work-up of patients after FFR_{CT} testing is shown in Figure 4. Median time between CT scan and catheterization was 30 (range 1 to 121) days. In 37 patients, FFR (n = 35) or iFR interrogation was performed. The proportion of patients having FFR or iFR measured in the first two-thirds versus the last one-third of the study period was 77% (27 of 35) and 53% (10 of 19), respectively ($p = 0.08$). FFR was measured in 51 vessels and iFR in 2 vessels (LAD, n = 34; LCx, n = 8; RCA, n = 11).

There was good direct correlation of per-vessel FFR_{CT} to FFR, with a slight systematic underestimation of FFR_{CT} compared with FFR (Figure 5). Overall, FFR_{CT} ≤0.80 correctly classified 73% (27 of 37) of patients and 70% (37 of 53) of vessels by using FFR ≤0.80 or iFR ≤0.90 as the reference standard. There was an inverse continuous relationship between the FFR_{CT} numerical value and the probability of detecting ischemia (Table 4). The diagnostic agreement of FFR_{CT} ≤0.80 according to coronary stenosis severity using FFR or iFR as the reference standard, as well as median (interquartile range; range) FFR_{CT} in vessels with "true or false-positive" or "true or false-negative" FFR_{CT} test results are shown in Table 5. FFR_{CT} values in 3 "false-negative" vessels ranged between 0.81 and 0.83, all with a corresponding FFR value of 0.79. On a patient level, no FFR_{CT} "false-negative" outcomes were observed.

CORONARY REVASCULARIZATION AND FOLLOW-UP. In patients with FFR_{CT} ≤0.80 being referred to ICA, 45% (22 of 49) underwent coronary revascularization (PCI, n = 12; CABG, n = 10). In 23 patients with FFR_{CT} ≤0.75 being referred to ICA (FFR or iFR measured, n = 13), revascularization was performed in 70% (PCI, n = 10; CABG, n = 6). In patients referred from coronary CTA directly to ICA, FFR or iFR was measured in 20% without temporal proportional changes during the study, and 65% (53 of 82)

FIGURE 3 Distribution of FFR_{CT} Values



(A) Per-patient minimum coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) values (n = 185). **(B)** Total per-vessel FFR_{CT} (n = 740) values and values in vessels giving rise to FFR_{CT} analysis (n = 303) **(pink)**.

underwent revascularization (PCI, n = 42; CABG, n = 11). No patients having FFR_{CT}, ICA, or MPI performed experienced a serious adverse cardiac event during follow-up, including the 123 (66%) patients with FFR_{CT} >0.80 in whom ICA was deferred. In 1 patient with the lowest FFR_{CT} value of 0.88 (LAD) and 1 patient with FFR_{CT} = 0.78 (LAD) in whom ICA originally was deferred, subsequent ICAs were performed after 4 and 6 months of follow-up, respectively, because of continuing chest pain. ICA revealed minor vessel irregularities (no FFR interrogation) in the former patient, and diffuse nonobstructive disease (measured FFR = 0.84) in the other patient. In the MPI group, ICA was performed in 2 patients during follow-up (normal test results).

DISCUSSION

This report demonstrates for the first time the real-world feasibility of FFR_{CT} testing in consecutive patients with intermediate-range coronary stenosis. We made several important observations: 1) conclusive FFR_{CT} results were obtained in 98% of patients who had CT scans referred for FFR_{CT} testing; 2) implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow; 3) in the event of FFR_{CT} ≤0.75, the risk of a false-positive result using FFR as the reference standard is very low (<10%), whereas in patients with FFR_{CT} ranging between 0.76 and 0.80, a non-negligible number of false-positive results may be expected; and 4) patients with FFR_{CT} >0.80 being deferred from ICA have a favorable short-term prognosis.

In the most recent trial (NXT [Analysis of Coronary Blood Flow Using CT Angiography: Next Steps]) investigating the diagnostic performance of FFR_{CT} in stable CAD, 13% of the patients had nonevaluable coronary CTA images (12). In this real-world report, we found that only 2% of patients failed to meet the image quality requirements for FFR_{CT} analysis. Taking into account those patients in whom contrast was not administered because of an anticipated nondiagnostic CT image quality and those with an inconclusive test outcome, a conclusive CT scan-based anatomic or anatomic-physiological result was available in >90% of all patients referred to coronary CTA testing. These findings most likely reflect that CT image acquisition in this report was performed in accordance with guidelines, with careful attention to heart rate control and use of nitroglycerin (16,20). Of note, it was recently shown that FFR_{CT} also provides high and superior diagnostic performance compared with coronary CTA alone in patients with high calcium scores (21). This outcome, together with future improvements in CT spatial resolution, may expand the eligibility of coronary CTA to patients in whom a nondiagnostic CT image quality is anticipated and to those with an inconclusive test result due to severe coronary calcification. Accordingly, MPI may potentially be avoided in a substantial proportion of patients in the diagnostic pathway of coronary CTA.

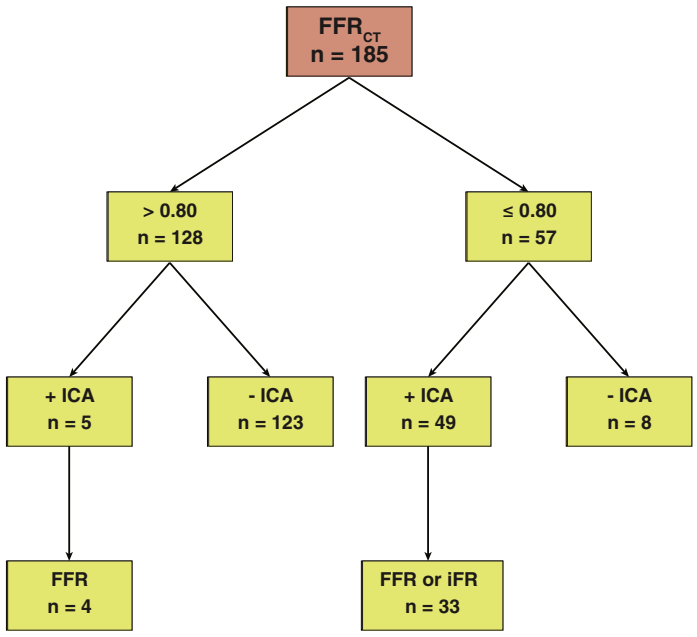
The recent multicenter PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts) trial demonstrated, in patients referred to ICA, that a diagnostic strategy of coronary CTA and FFR_{CT} resulted in safe cancellation of planned ICAs in 61% of the patients (22). Similarly, in the present study that includes a contemporary coronary CTA cohort, a "normal" FFR_{CT} result was present in 69% of the patients, among whom ICA was successfully deferred. On the other hand, the coronary revascularization rate in patients with FFR_{CT} ≤0.80 in this study was surprisingly low (45%). This finding is partially explained by the high proportion of false-positive results in patents with FFR_{CT} between 0.75 and 0.80. Accordingly, the revascularization rate increased to 70% in patients with FFR_{CT} ≤0.75. Moreover, decisions on revascularization, especially in the FFR range between 0.75 and 0.80, are often influenced by factors other than FFR (e.g., severity

of angina) (4,5). Finally, it should be acknowledged that "thresholds" by individual CT operators in prescribing subsequent FFR_{CT} testing govern the proportion of normal and abnormal results. In the present study, this decision was recommended primarily on the basis of coronary anatomy; however, integration to a varying degree of other factors (including preference of downstream testing modality and information on pre-test risk of CAD and symptoms) naturally may have influenced decision-making regarding downstream patient management.

The high negative predictive value of FFR_{CT} for the prediction of ischemia (10–12), as well as the findings in the PLATFORM trial (22) and in this report of a favorable short-term clinical outcome in patients with FFR_{CT} >0.80, may encourage confidence for clinicians that such patients can safely be deferred for subsequent ICA. However, in the NXT trial, using an FFR_{CT} dichotomous interpretation approach, despite diagnostic superiority compared with coronary CTA stenosis assessment alone, the FFR_{CT} per-patient specificity and positive predictive value in predicting ischemia were modest (79% and 65%, respectively) (12). Thus, a substantial rate of false-positive results remained. After our initial clinical experiences with FFR_{CT} testing as described in this report, our institution recently implemented an FFR_{CT} testing decision-rule algorithm (**Figure 6**). We recommend in patients with FFR_{CT} ranging between 0.75 and 0.80 that decisions on referral to ICA should be based on all available information, in particular regarding the severity of angina (i.e., the main target of PCI), whereas in patients with FFR_{CT} >0.80 or ≤0.75, we propose a dichotomous interpretation strategy. Several factors support the relevance of this approach. First, in accordance with this report, the overall prognosis in patients with stable chest pain in contemporary practice is favorable (22,23), and the annual risk of cardiac death or myocardial infarction after deferral of coronary revascularization in intermediate-range lesions with FFR ≥0.75 is very low (<1%) (6). Moreover, it should be acknowledged that FFR exhibits a continuous relationship between its numerical value and the clinical outcome, with the largest benefit of revascularization being obtained at lower FFR values (5). In this study, the lower limit of FFR_{CT} values among patients with a false-positive result was modestly low (0.74), and, in the event of FFR_{CT} ≤0.75, the probability of having ischemia was high (92%), whereas if FFR_{CT} ranged between 0.76 and 0.80, ischemia was present in only 55% of the patients. Accordingly, it has been shown that the variation in repeated FFR (24) measurements and FFR_{CT} calculations (25) has the largest impact on interpretation of results when approaching the established cutpoint of 0.80. The finding in this study and in previous studies of a slight systematic underestimation of FFR_{CT} compared with measured FFR (10–12) support the proposed FFR_{CT} guidance algorithm. Safety and cost-efficiency of this FFR_{CT} guidance diagnostic workflow in symptomatic patients with intermediate-range coronary lesions need delineation in future studies.

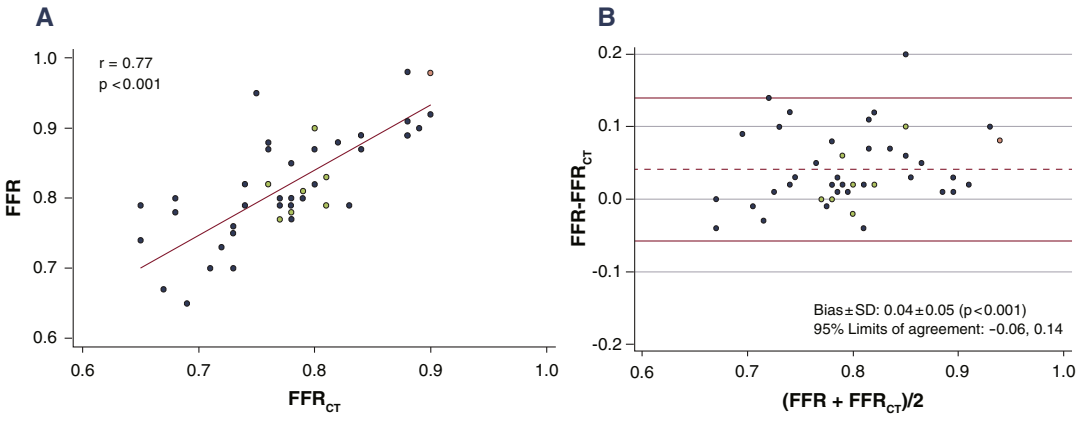
We observed a higher proportion of FFR guidance (69% vs. 20%) and lower revascularization rate (45% vs. 65%) in patients being referred to ICA based on FFR_{CT} assessment compared with patients being referred directly from coronary CTA. These findings may reflect the higher severity in risk, symptoms, and CAD in the latter group, thus encouraging direct PCI in the majority of patients. In addition, the extensive use of FFR testing in patients being referred to ICA based on the FFR_{CT} result may reflect an FFR_{CT} diagnostic uncertainty among the interventionalists, thus prompting "reassurance" FFR measurements.

FIGURE 4 Diagnostic Work-Up of Patients After FFR_{CT} Testing



Instantaneous wave-free ratio (iFR) was measured in 2 patients. In patients referred for ICA (n = 54), fractional flow reserve (FFR) was not measured in 19 patients (angiographic minor changes, n = 9; high-grade stenosis, n = 5; technical reasons, n = 3; contraindication to adenosine, in which case iFR was performed, n = 2). Mean (range) FFR_{CT} in vessels with minor angiographic changes or high-grade stenosis were 0.79 (0.74 to 0.84) and 0.63 (0.43 to 0.77), respectively. In 4 patients with FFR_{CT} >0.80, measured FFR mirrored the FFR_{CT} results. Abbreviations as in **Figure 2**.

FIGURE 5 Correlation and Bland-Altman Plots of FFR and FFR_{CT} in Vessels Having FFR Measured (n = 51)



Green represents 2 overlying data points and **pink** represents 3 overlying data points. Abbreviations as in Figures 3 and 4.

TABLE 4 Per-Patient and Per-Vessel Agreement for Detection of Ischemia According to FFR_{CT} at Different Thresholds ≤0.80

	Patients (n = 33)	Vessels (n = 37)
≤0.80	70 (23/33)	65 (24/37)
0.76–0.80*	55 (11/20)	50 (11/22)
0.71–0.75*	83 (5/6)†	75 (6/8)†
≤0.70*	100 (7/7)†	100 (7/7)†

Values are % (n/N). Fractional flow reserve ≤0.80 was used as reference. *When comparing per-patient and per-vessel agreement estimates between the lower 3 FFR_{CT} range categories, p values were 0.06 and 0.04, respectively. †Two patients (vessels) in whom instantaneous wave-free ratio ≤0.90 was used as the reference standard.

FFR_{CT} = coronary computed tomography angiography–derived fractional flow reserve.

This scenario is supported by the observation that FFR guidance in this group was reduced by 30% during the study period. Finally, in accordance with previous trials and real-world observations (3–5,26), the lower revascularization rate in this group may at least partially reflect the more extensive use of FFR testing per se. It can be speculated that the implementation of FFR_{CT} and the extensive use of FFR in patients referred to ICA after FFR_{CT} testing may stimulate the overall institutional adoption of FFR. However, in this study, FFR guidance in patients being referred directly from coronary CTA to ICA was relatively infrequent throughout the study period. We cannot exclude that the use of uncaptured PCI guidance procedures such as intravascular ultrasound and optical coherence tomography may have influenced the PCI operators' overall threshold for FFR testing (26).

STUDY LIMITATIONS. This study was a single-center, observational trial with inherent limitations. Data were collected in a nonselected cohort of patients and involved multiple CT and PCI operators unblinded to the FFR_{CT} results. However, it included all patients encountered in a defined time period and represents consecutive data from a relevant study cohort in a real-world setting. FFR_{CT}-FFR agreement estimates were based on few observations and most likely were

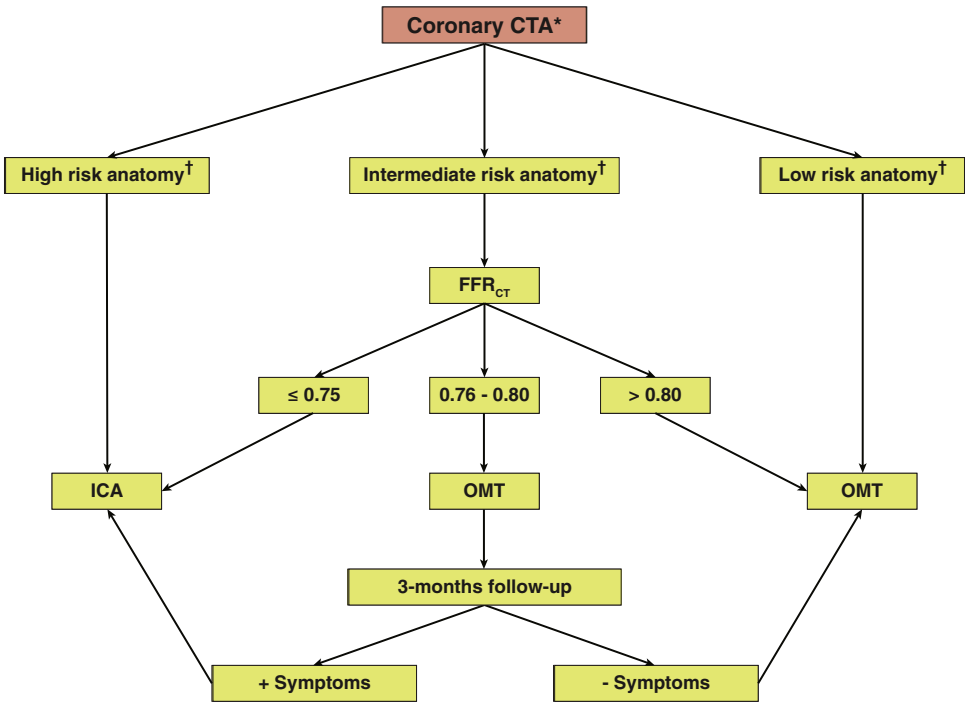
TABLE 5 Per-Vessel FFR_{CT} Test Outcome According to Coronary Stenosis Severity

	True Positive	False Positive	True Negative	False Negative
Coronary stenosis severity				
30%–50%	4 (22)	3 (17)	10 (56)	1 (6)
51%–70%	15 (56)	8 (30)	2 (7)	2 (7)
71%–90%	5 (63)*	2 (25)	1 (13)	0
FFR_{CT}	0.74 (0.69–0.78; 0.65–0.80)	0.78 (0.76–0.80; 0.74–0.80)	0.88 (0.84–0.88; 0.81–0.90)	0.81 (0.81–0.83)†

Values are n (%) or median (IQR; range). FFR_{CT} ≤0.80 was diagnostic of ischemia. Reference standard was fractional flow reserve ≤0.80 (n = 51). *Instantaneous wave-free ratio ≤0.90 (n = 2) was used as reference. †Range (IQR) not shown because of low number of observations.

Abbreviations as in Tables 1 and 2.

FIGURE 6 The "Aarhus" FFR_{CT} Decision-Rule Algorithm



*Patients with new-onset chest pain without known coronary artery disease, low to intermediate pre-test probability of disease, and in whom a diagnostic coronary CTA result can be expected. †"High risk anatomy" is defined as the presence of left main, 3-vessel and/or high-grade left anterior descending artery stenosis; "intermediate risk anatomy" as 1 or 2 intermediate stenoses (30% to 70%); and "low risk anatomy" as normal or stenosis <30%. Abbreviations as in Figures 2 and 4.

influenced by selection bias. However, measurement of FFR in more low- or high-grade lesions may have resulted in higher agreement estimates (27). No current guidelines provide recommendations about the clinical use of FFR_{CT} testing and its interpretation. Thus, in this study, FFR_{CT} testing was recommended in patients with intermediate-range lesions in whom coronary CTA interpretation is most challenging and for whom guidelines recommend performance of additional ischemia testing (1). We did not consider the reduction in angina. However, during 12 months of follow-up, the rate of symptom-driven ICA was low. No information on the downstream primary physician contact was obtainable, leaving questions about changes in medication unanswered. The implementation of a "standard diagnostic testing" comparison group and a longer follow-up period would have added valuable information. Patients with emergent chest pain were not included in this study. FFR_{CT} testing requires offsite computer processing, with a current 3- to 6-h turnaround time. A reduced order model for on-site (<1 h) CT scan-based derivation of FFR, which may be relevant in the acute setting, was recently introduced (28). However, further investigations in prospective multicenter trials are needed to determine the diagnostic performance of this technique.

CONCLUSIONS

FFR_{CT} testing is feasible in real-world patients with intermediate-range coronary stenosis determined by coronary CTA. Implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow of patients. Patients with FFR_{CT} >0.80 being deferred from ICA have a favorable short-term prognosis. We propose an "FFR_{CT} guidance algorithm" to be evaluated in future studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: FFR_{CT} is feasible in real-world symptomatic patients with intermediate-range coronary stenosis. Real-world implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow of patients. Patients being deferred from ICA based on an FFR_{CT} value >0.80 have a favorable short-term prognosis.

TRANSLATIONAL OUTLOOK: FFR_{CT} is a promising gatekeeper to the catheterization laboratory in patients with intermediate-range coronary stenosis. In this scenario, future studies are needed to evaluate the safety and cost-efficiency of FFR_{CT} relative to conventional noninvasive ischemia-testing modalities. We propose an "FFR_{CT} guidance algorithm" to be evaluated in future studies.

REFERENCES

1. Montalescot G, Sechtem U, Achenbach S, et al. The task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.

2. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–995.

3. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

4. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

5. Johnson NP, Tóth GG, Lai D, et al. Prognostic value of fractional flow reserve. Linking physiologic severity to clinical outcomes. J Am Coll Cardiol 2014;64:1641–54.

6. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol 2007;49:2105–11.

7. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;3:789–94.

8. Levine GN, Bates ER, Blankenship JC, et al. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58. e44–22.

9. Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.

10. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.

11. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237–45.

12. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial. J Am Coll Cardiol 2014;63:1145–55.

13. Hecht HS. The game changer? J Am Coll Cardiol 2014;63:1156–8.

14. Schoenhagen P, Desai MY. Computed tomography-based fractional flow reserve (FFR-CT)—an attractive concept, but still lacking proof of clinical utility. Circ J 2015;79:300–2.

15. Nielsen LH, Nørgaard BL, Tilsted HH, et al. The western Denmark cardiac computed tomography registry: a review and validation study. Clin Epidemiol 2014;7:53–64.

16. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2009;3:190–204.

17. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59. 1392–2.

18. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation 2007;116:1290–305.

19. Senthamizhchelvan S, Bravo PE, Esaias C, et al. Human biodistribution and radiation dosimetry of ^{82}Rb. J Nucl Med 2010;51:1592–9.

20. Leipsic J, Yang TH, Thompson A, et al. CT angiography (CTA) and diagnostic performance of noninvasive fractional flow reserve: results from the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) study. AJR Am J Roentgenol 2014;202:989–94.

21. Nørgaard BL, Gaur S, Leipsic J, et al. Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: a substudy of the NXT trial. J Am Coll Cardiol Img 2015;8:1045–55.

22. Douglas PS, Pontone G, Hlatky MA, et al., PLATFORM Investigators. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRCT: outcome and resource impacts study. Eur Heart J 2015;36:3359–67.

23. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

24. Petraco R, Sen S, Nijjer S, et al. Fractional flow reserve-guided revascularization. Practical implications of a diagnostic grey zone and measurement variability on clinical decisions. J Am Coll Cardiol Intv 2013;6:222–5.

25. Gaur S, Bezerra HG, Lassen JF, et al. Fractional flow reserve derived from coronary CT angiography: variation of repeated analyses. J Cardiovasc Comput Tomogr 2014;8:307–14.

26. Park SJ, Ahn JM, Park GM, et al. Trends in the outcomes of percutaneous coronary intervention with the routine incorporation of fractional flow reserve in real practice. Eur Heart J 2013;34:3353–61.

27. Martus P, Schueler S, Dewey M. Fractional flow reserve estimation by coronary computed angiography. J Am Coll Cardiol 2012;59:1410–1.

28. Coenen A, Lubbers MM, Kurata A, et al. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. Radiology 2015;274:674–83.

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