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Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve for Therapeutic Decision Making

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This study investigated the performance of coronary computed tomography angiography (cCTA) with cCTA-derived fractional flow reserve (CT-FFR) compared with invasive coronary angiography (ICA) with fractional flow reserve (FFR) for therapeutic decision making in patients with suspected coronary artery disease (CAD). Seventy-four patients (62 ± 11 years, 62% men) with at least 1 coronary stenosis of ≥50% on clinically indicated dual-source cCTA, who had subsequently undergone ICA with FFR measurement, were retrospectively evaluated. CT-FFR values were computed using an on-site machine-learning algorithm to assess the functional significance of CAD. The therapeutic strategy (optimal medical therapy alone vs revascularization) and the appropriate revascularization procedure (percutaneous coronary intervention vs coronary artery bypass grafting) were selected using cCTA-CT-FFR. Thirty-six patients (49%) had a functionally significant CAD based on ICA-FFR. cCTA-CT-FFR correctly identified a functionally significant CAD and the need of revascularization in 35 of 36 patients (97%). When revascularization was deemed indicated, the same revascularization procedure (32 percutaneous coronary interventions and 3 coronary artery bypass grafting) was chosen in 35 of 35 patients (100%). Overall, identical management strategies were selected in 73 of the 74 patients (99%). cCTA-CT-FFR shows excellent performance to identify patients with and without the need for revascularization and to select the appropriate revascularization strategy. cCTA-CT-FFR as a noninvasive "one-stop shop" has the potential to change diagnostic workflows and to directly inform therapeutic decision making in patients with suspected CAD. **(Am J Cardiol 2017;120:2121–2127)**

Coronary computed tomography angiography (cCTA) is a robust method to safely rule out obstructive coronary stenosis in the workup of patients suspected of having coronary artery disease (CAD).[1,2] However, a purely anatomic evaluation has been shown to be a poor predictor in identifying the functional significance of a coronary lesion.[3] This has driven an interest in the addition of add-on approaches based on computed tomography (CT), which may yield a more comprehensive noninvasive imaging test for CAD. The recently introduced cCTA-derived fractional flow reserve (CT-FFR) has been validated in previous multicenter trials as a reliable method for the noninvasive detection of functionally significant stenosis in comparison with invasive fractional flow reserve (FFR).[4–6] We sought to investigate the performance of cCTA combined with machine–learning-based CT-FFR for therapeutic decision making in patients suspected of CAD, compared with invasive coronary angiography (ICA) with invasive FFR.

Methods

The present study was approved by the local Institutional Review Board with a waiver of informed consent and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A retrospective analysis was performed on a patient cohort with suspected CAD who had undergone dual-source cCTA as part of their diagnostic workup followed by ICA with invasive FFR within 3 months for the assessment of CAD from November 2009 to December 2014. Indications for cCTA were

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See page 2126 for disclosure information.

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abnormal exercise testing (n = 14), abnormal nuclear stress testing (n = 23), or chest pain (n = 37). The decision to perform ICA was based on clinical parameters, cCTA data, as well as other noninvasive functional test results, in accordance with clinical guidelines.[7] All CT-FFR values were computed as a procedure of this retrospective investigation and were not available to the patient's cardiologist at the time of treatment. All patients in the present study had at least 1 coronary stenosis of ≥50% on cCTA. Patients who previously underwent percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or cCTA datasets with nondiagnostic image quality were excluded from this analysis. Furthermore, patients with renal insufficiency (glomerular filtration rate <30 ml/min/1.73 m^2) or an allergy to iodine contrast media were excluded. Covariates, including cardiac risk factors and patient baseline characteristics, were obtained from medical records. Imaging was performed using a first- or a second-generation dual-source CT system (SOMATOM Definition or SOMATOM Definition Flash; Siemens Healthineers, Forchheim, Germany). All patients initially underwent a non–contrast-enhanced calcium scoring study. For the subsequent contrast-enhanced cCTA, scan parameters were a retrospectively electrocardiography-gated protocol for the first-generation dual-source CT scanner and a prospectively electrocardiography-triggered sequential scan protocol with a padding window for the second-generation dual-source CT scanner; a tube voltage of 100 to 120 kV, a tube current of 320 to 412 mA, a temporal resolution of 83 or 75 ms, and a $2 \times 32 \times 0.6$ mm or $2 \times 64 \times 0.6$ mm collimation with a z-flying focal spot. Fifty to eighty milliliters of iopromide (Ultravist 370 mgI/ml; Bayer, Wayne, New Jersey) was injected at 4 to 6 ml/s followed by a 30 ml saline bolus chaser at the same flow rate to provide contrast enhancement. The attending physician of the day individually determined the use of β blockers and nitroglycerin. A total of 47 patients (64%) were administered nitroglycerin and 24 patients (32%) were administered β blockers. Weighted filtered back-projection image reconstruction was performed in the cardiac phase with the least motion: a section thickness of 0.75 mm, a reconstruction increment of 0.5 mm, and a smooth convolution kernel (B26f). The mean dose-length product was 474 ± 52.8 mGy·cm. The effective radiation dose was estimated by multiplying the dose-length product with a standard conversion factor of 0.014 mSv/mGy·cm,[8] resulting in a mean effective radiation dose equivalent of 6.5 ± 0.7 mSv.

cCTA datasets were transferred to a postprocessing workstation (syngo.via VB10, Siemens, Forchheim, Germany) for further analysis. Transverse sections and automatically generated curved multiplanar reformations were assessed. Two observers independently evaluated all datasets for the presence of CAD and stenosis severity using the Coronary Artery Disease Reporting and Data System (CAD-RADS) classification: 1, none (0%) or minimal (1% to 24%); 2, mild (25% to 49% stenosis); 3, moderate (50% to 69% stenosis); 4, severe (70% to 99% stenosis); and 5, total occlusion (100%). Nondiagnostic studies (CAD-RADS N classification) were excluded from further analysis.[9] Obstructive CAD was defined as ≥50% luminal narrowing (CAD-RADS classification ≥3). All discordant cases were resolved by a consensus reading. Functional stenosis severity assessment was performed in all lesions with ≥50% luminal narrowing on cCTA (CAD-RADS classification ≥3). For the CT-FFR analysis, an artificial intelligence research prototype (Siemens cFFR, version 2.1, Siemens; not currently commercially available) was used as previously described.[10,11] The software resides on-site on a regular workstation and allows for the physician-driven creation of a patient-specific anatomic model of the coronary tree using a semiautomatic approach. CT-FFR values were computed using a recently introduced machine-learning algorithm.[12] This approach is based on a deep learning framework to determine the functional severity of the lesion. The deep learning algorithm employs a multilayer neural network architecture that was trained offline to learn the complex relation between the anatomy of the coronary tree and its corresponding hemodynamics. Model training utilized a large database of synthetically generated coronary anatomies and their corresponding hemodynamic conditions from a computational fluid dynamics simulation. Based on the geometric features of the patient's coronary anatomy on cCTA, such as the vessel radius, the degree of tapering, and the branch length, the algorithm uses the learned relation to calculate the machine–learning-based CT-FFR values. This relation is based on input data, for example, the anatomy of a vascular tree. The quantity of interest (e.g., FFR) is represented by a model built from a database of samples with known characteristics and outcome derived from the computational fluid dynamic approach. For any point available within the coronary tree, CT-FFR was generated by computing the ratio of the average local pressure over a cardiac cycle to the average aortic pressure, resulting in a color-coded 3-dimensional mesh allowing for the determination of the CT-FFR value at arbitrary locations. Functionally significant CAD was defined as a CT-FFR of ≤0.80.[10] Both observers independently decided whether functionally significant stenosis was present for each coronary lesion based on cCTA-CT-FFR (≥50% stenosis on cCTA + CT-FFR ≤0.80). Furthermore, the observers determined whether optimal medical treatment or revascularization was indicated for each patient and, in cases of revascularization, the appropriate revascularization procedure (PCI or CABG) according to societal guidelines.[13] Briefly, patients with a functionally significant 1- or 2-vessel disease without ostial left anterior descending coronary artery involvement were considered for PCI. Patients with an isolated left main disease or left main disease and additional stenosis elsewhere and patients with 3-vessel disease were considered for CABG. A consensus was reached between reviewers in all discordant cases.

ICA was performed by an experienced interventional cardiologist according to societal guidelines.[14] The presence of at least 50% diameter stenosis was evaluated in at least 2 views of each major epicardial vessel in the same projections using the 16-segment American Heart Association coronary model used for the cCTA analysis.[15] Invasive FFR measurement was performed at the discretion of the treating physician to evaluate the functional relevance of CAD seen at angiography (≥50% stenosis). FFR measurement was performed using the QUANTIEN platform (St. Jude Medical, St. Paul, Minnesota), whereas a pressure wire (Aeris, St. Jude Medical) was used to obtain baseline pressure proximal and distal to the particular lesion. Hyperemia was induced by the continuous application of intravenous adenosine (140 μg/kg/min) and distal pressure measurement was reassessed. An FFR value

of ≤0.80 was considered diagnostic for a functionally significant CAD.[3] A combination of ICA-FFR was used to identify or to rule out a functionally significant CAD. In cases of anatomic CAD without functional significance, patients were considered for optimal medical treatment. If revascularization was indicated, the decision whether PCI or CABG was the appropriate treatment method was made according to societal guidelines.[13] All PCI procedures were performed ad hoc within the same ICA session.

MedCalc (version 15; MedCalc Software, Ostend, Belgium) and SPSS (SPSS 23.0; IBM, Chicago, Illinois) were used for all statistical analyses. Continuous variables were presented as mean ± standard deviation or median with interquartile range when not normally distributed. Student *t* test and Mann-Whitney U test were used for parametric and nonparametric data, respectively. The diagnostic performance of cCTA-CT-FFR to detect functionally significant CAD (defined as CAD-RADS classification ≥3 combined with CT-FFR value ≤0.80) was assessed on a per-patient and per-vessel level (accuracy, sensitivity, specificity, and negative and positive predictive values); the results were presented as percentages with 95% confidence intervals using invasive results (ICA-FFR) as the reference standard. A patient was considered to be positive for functionally significant CAD if any evaluable lesion of ≥50% stenosis on the cCTA study had a CT-FFR value of ≤0.80. Furthermore, the performance characteristics of cCTA-CT-FFR for therapeutic decision making (accuracy, sensitivity, specificity, and negative and positive predictive values) were calculated and presented as percentages with 95% confidence intervals using the eventual treatment strategy based on invasive results (ICA-FFR) as the reference standard. Statistical significance was assumed with a p value ≤0.05.

Results

A total of 97 patients who had undergone both clinically indicated dual-source cCTA and ICA with FFR measurement within 3 months for the assessment of CAD were retrospectively analyzed. Sixteen patients (17%) were excluded due to previous revascularization (PCI n = 11, CABG n = 5) and 7 patients (7%) for nondiagnostic cCTA image quality. Seventy-four patients (62% men, mean age 62 ± 11 years) with 220 evaluable vessels were finally included. The baseline characteristics are presented in Table 1. Based on ICA alone, 98 of 220 vessels (45%) and 58 of 74 patients (78%) demonstrated an anatomically significant CAD. Within the 98 vessels with anatomic CAD based on ICA, 19 lesions were angiographically considered hemodynamically significant. Seventy-nine vessels were evaluated with invasive FFR, of which 44 vessels showed a functionally significant CAD. Invasive assessment (ICA-FFR) showed a functionally significant CAD in 36 of 74 patients (49%). Thus, based on invasive assessment, 38 patients (51%) without a functionally significant CAD were considered for optimal medical treatment and risk factor modification, whereas revascularization was performed in all 36 patients with functionally significant coronary lesions. Of these, 33 patients (92%) underwent PCI and 3 patients (8%) were referred for CABG. Based on structural cCTA analysis, 127 of the 220 vessels (58%) in the 74 patients showed an anatomically significant CAD. Of the 127 vessels with anatomically significant CAD, 98 vessels showed a functionally significant CAD based on CT-FFR evaluation. Based on combined noninvasive cCTA-CT-FFR analysis, 35 of 36 patients (97%) with a functionally significant CAD on invasive assessment and all patients (38 of 38) with a functionally nonsignificant CAD were correctly identified. One subject (1.4%) was deemed to have a functionally nonsignificant CAD by cCTA-CT-FFR, with a CT-FFR value of 0.81, whereas the invasively measured FFR value was 0.78. Of the 21 vessels with anatomic CAD based on ICA that were angiographically considered to be hemodynamically significant and were therefore not interrogated with invasive FFR, CT-FFR assessment revealed a functionally significant CAD in 19 vessels, whereas 3 vessels showed a functionally nonsignificant CAD. The results of ICA-FFR and cCTA-CT-FFR are illustrated in Figure 1. The procedural results of ICA-FFR and cCTA-CT-FFR are displayed in Table 2. The performance of cCTA-CT-FFR for detecting a functionally significant CAD compared with ICA-FFR is listed in Table 3. Based on cCTA-CT-FFR, all patients (38 of 38) with a functionally nonsignificant CAD were considered for optimal medical therapy in perfect agreement with decisions based on ICA-FFR. One patient (1.4%) who eventually underwent PCI based on ICA-FFR findings would have been assigned to optimal medical therapy according to cCTA-CT-FFR. There was agreement of decisions on the appropriate revascularization therapy in 35 of 36 subjects (97%). cCTA-CT-FFR correctly identified the 3 patients who were referred for CABG and 32 of 33 patients who underwent PCI. Overall, the identical treatment decision was selected in 73 of 74 patients (99%) with cCTA-CT-FFR (Table 4). Examples of cCTA-CT-FFR and ICA-FFR are shown in Figures 2 and 3.

Table 1
Patient characteristics. Total patient cohort ($n = 74$)

Variable	Value (mean ± SD or number (%))
Age (years)	62.2 ± 10.6
Men	46 (62%)
Height (cm)	171.4 ± 10.8
Weight (kg)	88.5 ± 19.5
Body-mass-index (kg/m^2)	30.2 ± 6.7
Hypertension*	60 (81%)
Diabetes mellitus	26 (35%)
Dyslipidemia†	62 (84%)
Tobacco abuse	39 (52%)
Family history of CAD	35 (47%)
Aspirin	53 (72%)
Statin	61 (82%)
Beta-blocker	38 (51%)
Calcium channel blocker	16 (22%)
ACE inhibitor	24 (32%)
Diuretics	13 (18%)

CAD = coronary artery disease; ACE = angiotensin-converting enzyme; SD = standard deviation.

* Defined as blood pressure >140 mmHg systolic, >90 mmHg diastolic, or use of antihypertensive medication.

† Defined as a total cholesterol of >200 mg/dl or use of anti-lipidemic medication.

Discussion

The present study demonstrates the ability of cCTA with machine–learning-based CT-FFR to differentiate patients with

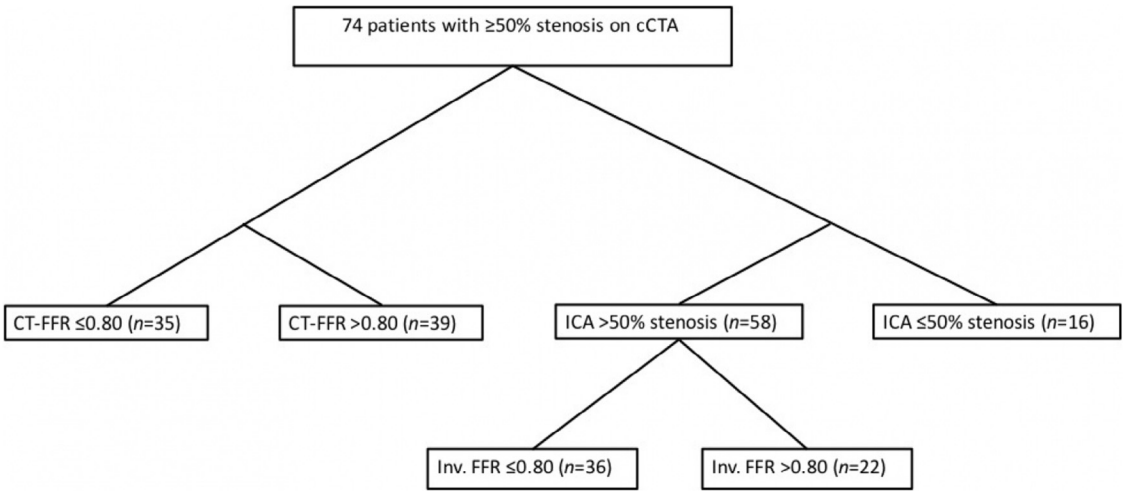

Figure 1. Findings with cCTA, computational fractional flow reserve (CT-FFR), ICA, and invasive FFR.

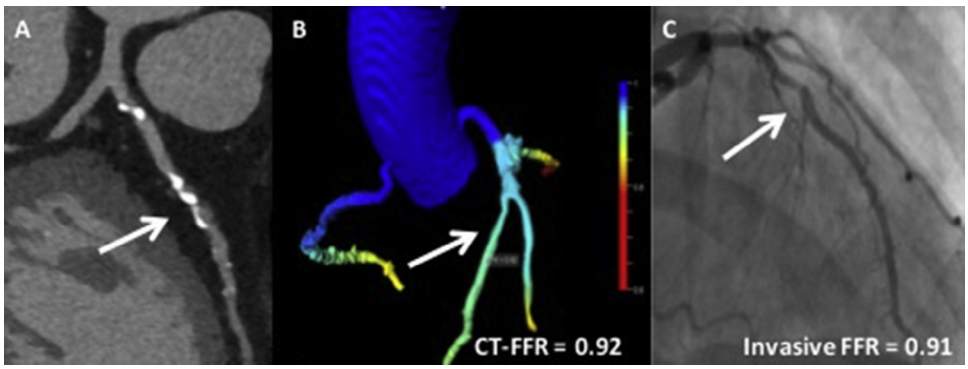

Figure 2. *(A)* cCTA demonstrates ≥50% stenosis of the medial left anterior descending artery caused by severe calcification (white arrow). *(B)* Color-coded CT-FFR calculation for the evaluation of functional stenosis significance revealed a CT-FFR value of 0.92 (white arrow). *(C)* Invasive coronary angiography shows moderate stenosis (>50% stenosis) with an invasive FFR of 0.91 (white arrow).

Table 2
Procedural results of the per patient analysis. Total patient cohort ($n = 74$)

Invasive coronary angiography with FFR	
Anatomical CAD (*≥50% stenosis)*	58 (78%)
Functionally significant CAD (*≥50% stenosis + FFR ≤0.80) n (%)*	36 (49%)
Coronary CT angiography-derived parameters with CT-FFR	
Agatston calcium score	497.2 (218.3, 1077.8)
CAD-RADS™ classification*	
CAD-RADS™ 3	43 (58%)
CAD-RADS™ 4	31 (42%)
Functionally significant CAD (*CAD-RADS™ ≥3 + CT-FFR ≤0.80) n (%)*	35 (47%)

CAD-RADS™ = Coronary Artery Disease Reporting and Data System, FFR = fractional flow reserve, CAD = coronary artery disease, CT-FFR = coronary computed tomography angiography-derived fractional flow reserve.

Data are presented as mean ± standard deviation, numbers with percentages (%), or median with interquartile range if not normally distributed.

* CAD-RADS™ classification of 0–2 was not included as we only included lesions with at least ≥50% stenosis. CAD-RADS™ classification of 5 met the exclusion criteria.

Table 3
Per patient and per vessel performance of coronary CT angiography (cCTA) with cCTA-derived fractional flow reserve (CT-FFR) for the detection of functionally significant CAD

Parameter	Per patient ($n = 74$) Value (95%CI)	Per vessel ($n = 79$) Value (95%CI)
Accuracy	99%	96%
Sensitivity	97% (86%-100%)	95% (85%-99%)
Specificity	100% (91%-100%)	97% (85%-100%)
Positive predictive value	100% (90%-100%)	98% (88%-100%)
Negative predictive value	97% (87%-100%)	94% (81%-99%)
No. of true-positive findings	35	42
No. of false-positive findings	0	1
No. of true-negative findings	38	34
No. of false-negative findings	1	2

CI = confidence interval.

The findings at invasive coronary angiography with invasive fractional flow reserve (ICA/FFR) were used as the reference standard.

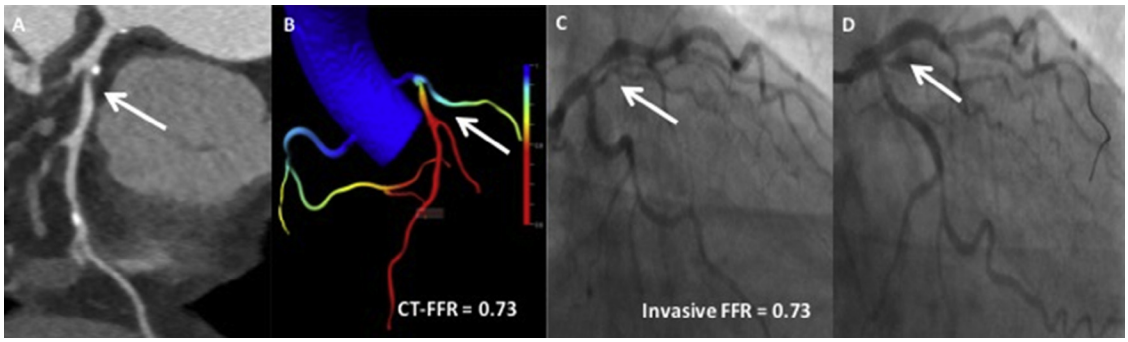

Figure 3. *(A)* cCTA demonstrates ≥50% stenosis of the proximal left anterior descending artery caused by a mixed plaque (white arrow). *(B)* Color-coded CT-FFR calculation for the evaluation of functional stenosis significance revealed a CT-FFR value of 0.73 (white arrow). *(C)* Invasive coronary angiography shows severe obstructive stenosis with an invasive FFR of 0.73 (white arrow), which was subsequently treated with stent placement *(D)* (white arrow).

Table 4
Performance of coronary CT angiography (cCTA) with cCTA-derived fractional flow reserve (CT-FFR) in determining the appropriate treatment strategy

Parameter	All patient ($n = 74$) Value (95%CI)
Accuracy	99%
Sensitivity	97% (86%-100%)
Specificity	100% (91%-100%)
Positive predictive value	100% (90%-100%)
Negative predictive value	97% (87%-100%)
No. of true-positive findings	35
No. of false-positive findings	0
No. of true-negative findings	38
No. of false-negative findings	1

Numbers in parentheses are 95% confidence intervals. The findings at invasive coronary angiography with invasive fractional flow reserve (ICA/FFR) were used as the reference standard.

and without the need for revascularization and to select the appropriate revascularization strategy among patients with at least 50% coronary stenosis compared with traditional ICA with invasive FFR.

Notably, 3 vessels that were revascularized due to angiographically determined hemodynamic significance, but not interrogated with invasive FFR at the discretion of the invasive cardiologist, were determined to be functionally nonsignificant by CT-FFR, which could potentially underline the strength of CT-FFR to inform treatment decision making. It has been demonstrated in several studies that a solely anatomic CAD assessment based on cCTA typically leads to an overestimation of stenosis severity due to severe plaque burden and coronary calcification.[16,17] Thus, controversial results on the benefit of cCTA for treatment decision making have been published with a wide range (78% to 95%) of agreement with invasive findings.[18,19] This discrepancy results in more invasive procedures and a higher confidence level for ICA in regard to diagnosis and treatment decision making.[20] Thus, due to the low predictive value of cCTA in identifying the functional significance of CAD, an appropriate ancillary tool based on CT to detect a functionally significant ischemia is needed. Recently, CT-FFR has demonstrated its ability to provide a sufficient noninvasive functional assessment of coronary stenosis.[4,6] It is well established that invasive FFR can alter and refine treatment decisions that were previously based solely on angiographic findings.[3] The authors of the FFR_{CT} RIPCORD (Does the Routine Availability of CT-Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?) study demonstrated a substantial effect on patient management using CT-FFR over cCTA alone, leading to changes in treatment strategy in 36% of the patients.[21] Our results confirm and expand on the authors' findings by showing excellent agreement between invasive results and the use of cCTA-CT-FFR for treatment decision making. Nørgaard et al evaluated the implementation and the utility of CT-FFR for decision making and downstream testing in a clinical setting.[22] Nørgaard et al showed that none of the patients with CT-FFR values of >0.80 who were deferred from ICA experienced a major adverse cardiac event during a median follow-up of 12 months. Our findings from a single-center population are in line with these results and further support the integration of CT-FFR into clinical workflows. Furthermore, our results indicate that CT-FFR provides valuable information that may better inform physicians for an appropriate therapeutic management decision.

Several limitations of this proof-of-concept study need to be addressed. We performed a retrospective single-center study that included a relatively small patient cohort, which could influence the validity of our results and might be affected by selection bias. Large-scale multicenter trials will be necessary to validate our findings. Invasive FFR was not performed in all lesions as this was at the discretion of the interventional cardiologists. Two different scanner systems were used for the cCTA acquisition, which may have affected the accuracy of the subsequent CT-FFR determination. Because the present study investigated a cohort that underwent ICA with FFR measurement, a high prevalence of CAD is present in the population. The indication to perform ICA was mainly driven by cCTA results, which may have induced selection bias. Because CT-FFR measurements require a relatively normal relation between myocardial mass and the patient's hemodynamic status regarding resting blood flow, patients with previous myocardial infarction, PCI, and CABG were excluded, which could induce a selection bias.

Disclosures

Dr. Schoepf receives institutional research support from Astellas, Bayer, GE, and Siemens. Dr. De Cecco receives institutional research support from Siemens. Dr. Schoepf has received consulting fees from Bayer and Guerbet. Drs. De Cecco and Varga-Szemes have received consulting fees from Guerbet. The other authors have no conflict of interest to disclose. Workstation-based flow computations of coronary blood flow were not carried out in the United States and are not currently approved by the Food and Drug Administration.

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