

CLINICAL RESEARCH

Clinical Trials

# Diagnostic Performance of Noninvasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography in Suspected Coronary Artery Disease



## The NXT Trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps)

Bjarne L. Nørgaard, MD, PhD,\* Jonathon Leipsic, MD, PhD,† Sara Gaur, MD,\*  
Sujith Seneviratne, MBBS,‡ Brian S. Ko, MBBS, PhD,‡ Hiroshi Ito, MD, PhD,§  
Jesper M. Jensen, MD, PhD,\* Laura Mauri, MD, PhD,|| Bernard De Bruyne, MD, PhD,¶  
Hiram Bezerra, MD, PhD,# Kazuhiro Osawa, MD,§ Mohamed Marwan, MD, PhD,\*\*  
Christoph Naber, MD, PhD,†† Andrejs Erglis, MD, PhD,‡‡ Seung-Jung Park, MD, PhD,§§  
Evald H. Christiansen, MD, PhD,\* Anne Kaltoft, MD, PhD,\* Jens F. Lassen, MD, PhD,\*  
Hans Erik Bøtker, MD, DMSci,\* Stephan Achenbach, MD, PhD,\*\*  
on behalf of the NXT Trial Study Group

*Aarhus, Denmark; Vancouver, British Columbia, Canada; Victoria, Australia; Okayama, Japan;  
Boston, Massachusetts; Aalst, Belgium; Cleveland, Ohio; Erlangen and Essen, Germany; Riga, Latvia;  
and Seoul, South Korea*

- Objectives** The goal of this study was to determine the diagnostic performance of noninvasive fractional flow reserve (FFR) derived from standard acquired coronary computed tomography angiography (CTA) datasets (FFR<sub>CT</sub>) for the diagnosis of myocardial ischemia in patients with suspected stable coronary artery disease (CAD).
- Background** FFR measured during invasive coronary angiography (ICA) is the gold standard for lesion-specific coronary revascularization decisions in patients with stable CAD. The potential for FFR<sub>CT</sub> to noninvasively identify ischemia in patients with suspected CAD has not been sufficiently investigated.
- Methods** This prospective multicenter trial included 254 patients scheduled to undergo clinically indicated ICA for suspected CAD. Coronary CTA was performed before ICA. Evaluation of stenosis (>50% lumen reduction) in coronary CTA was performed by local investigators and in ICA by an independent core laboratory. FFR<sub>CT</sub> was calculated and interpreted in a blinded fashion by an independent core laboratory. Results were compared with invasively measured FFR, with ischemia defined as FFR<sub>CT</sub> or FFR ≤ 0.80.
- Results** The area under the receiver-operating characteristic curve for FFR<sub>CT</sub> was 0.90 (95% confidence interval [CI]: 0.87 to 0.94) versus 0.81 (95% CI: 0.76 to 0.87) for coronary CTA (p = 0.0008). Per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia were 86% (95% CI: 77% to 92%) and 79% (95% CI: 72% to 84%) for FFR<sub>CT</sub> versus 94% (86 to 97) and 34% (95% CI: 27% to 41%) for coronary CTA, and 64% (95% CI: 53% to 74%) and 83% (95% CI: 77% to 88%) for ICA, respectively. In patients (n = 235) with intermediate stenosis (95% CI: 30% to 70%), the diagnostic accuracy of FFR<sub>CT</sub> remained high.
- Conclusions** FFR<sub>CT</sub> provides high diagnostic accuracy and discrimination for the diagnosis of hemodynamically significant CAD with invasive FFR as the reference standard. When compared with anatomic testing by using coronary CTA, FFR<sub>CT</sub> led to a marked increase in specificity. (HeartFlowNXT—HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography [HFNXT]; [NCT01757678](https://doi.org/10.1016/j.jacc.2013.11.043)) (J Am Coll Cardiol 2014;63:1145–55) © 2014 by the American College of Cardiology Foundation

From the \*Department of Cardiology, Aarhus University Hospital Skejby, Aarhus, Denmark; †Department of Radiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ‡MonashHeart, Monash Medical

Center and Monash University, Victoria, Australia; §Department of Cardiology, Okayama University Hospital, Okayama, Japan; ||Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; ¶Cardiovascular

**Abbreviations  
and Acronyms**

- AUC** = area under the receiver-operating characteristic curve
- CAD** = coronary artery disease
- CI** = confidence interval
- CT** = computed tomography
- CTA** = computed tomography angiography
- cMR** = cardiac magnetic resonance
- FFR** = fractional flow reserve
- FFR<sub>CT</sub>** = fractional flow reserve derived from coronary computed tomography angiography datasets
- ICA** = invasive coronary angiography
- NPV** = negative predictive value
- PPV** = positive predictive value

Invasive coronary angiography (ICA) is the established clinical standard for detecting coronary artery disease (CAD). The correlation between angiographic and physiological stenosis severity, however, is poor (1,2). Because coronary physiology trumps anatomy for clinical outcome (3,4), current guidelines for the management of stable CAD recom-

mend documenting ischemia by using a noninvasive functional test (e.g., single photon emission computed tomography, stress echocardiography, cardiac magnetic resonance [cMR]) before considering ICA or coronary revascularization (4,5). Shortcomings of current noninvasive diagnostic strategies in CAD, however, are apparent from the frequently

inaccurate selection of patients for ICA (6). Fractional flow reserve (FFR), which assesses the ratio of flow across a stenosis to putative flow in the absence of a stenosis, has been shown to be a powerful tool for detecting lesion-specific myocardial ischemia. Several randomized trials have shown that an FFR threshold of 0.80 distinguishes patients and coronary lesions that will benefit from coronary revascularization (7) from those that will not (8). Consequently, FFR is the accepted reference standard for assessing the functional significance of CAD in a lesion-specific manner (4). Noninvasive anatomic assessment by coronary computed tomography angiography (CTA) is being increasingly used as an accurate tool for detecting or excluding CAD (9–12). Although the absence of coronary stenoses according to coronary CTA is associated with an excellent prognosis and obviates the need for any further diagnostic evaluation (11), the correlation of stenoses detected by using coronary CTA to downstream myocardial ischemia is poor (13). Recently, a method using computational fluid dynamics to calculate coronary blood flow, pressure, and FFR based on routinely acquired coronary

CTA datasets at rest (FFR<sub>CT</sub>) has been described (14–16). FFR<sub>CT</sub> combines anatomic and functional information to enable appropriate therapeutic decision making. This method has tremendous potential because noninvasive determination of FFR may be a unique, useful test to differentiate individuals who will or will not benefit from revascularization, and thus FFR<sub>CT</sub> has the potential of being a reliable gatekeeper to the pathway of ICA.

The aim of the present study was to assess the diagnostic performance of FFR<sub>CT</sub> by using invasive FFR as the reference standard. Compared with previous studies (15,16), a substantially refined version of the FFR<sub>CT</sub> technology was used, and the emphasis on coronary CTA acquisition quality was strengthened.

**Methods**

**Study design.** The rationale and design of the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) study have been described previously (17). The study was designed to characterize FFR<sub>CT</sub> diagnostic accuracy in patients suspected of having CAD by using invasive FFR as the reference standard, and it reflects improvements in FFR<sub>CT</sub> technology (updated proprietary software with quantitative image quality analysis, improved image segmentation, refined physiological models, and increased automation), as well as emphasis on the coronary CTA image acquisition protocol to reflect current guidelines (18). The study protocol was approved at each of the 10 participating centers (Online Appendix) by the local institutional review board. All study subjects provided written informed consent.

**Study population.** Coronary CTA performed <60 days before scheduled nonemergent ICA was required for inclusion. As pre-specified (17), the first 100 patients included in the study had no requirements with regard to coronary stenosis severity. Beginning with patient 101, at least 1 stenosis with luminal diameter reduction between 30% and 90% in a vessel segment ≥2 mm in diameter according to coronary CTA was required. Exclusion criteria included previous coronary intervention or coronary bypass surgery; contraindications to beta-blocking agents, nitroglycerin, or adenosine; suspected acute coronary syndrome; previous myocardial infarction <30 days before coronary CTA or between coronary CTA and ICA; and body mass index >35 kg/m<sup>2</sup>.

See page 1156

Center Aalst, OLV-Clinic, Aalst, Belgium; #Department of Cardiology, Harrington Heart and Vascular Institute, University Hospitals, Cleveland, Ohio; \*\*Department of Cardiology, Erlangen University Hospital, Erlangen, Germany; ††Department of Cardiology and Angiology, Elisabeth-Krankenhaus Essen, Essen, Germany; ‡‡Latvian Centre of Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia; and the §§Heart Institute, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea. Funding for the study was provided by HeartFlow, Inc. Dr. Mauri has received research grants from Abbott Vascular, Boston Scientific, Cordis, Medtronic, HeartFlow, Eli Lilly, Bristol-Myers Squibb, Daiichi Sankyo, and Sanofi-aventis; and serves as a consultant for St. Jude Medical,

Biotronik, and Medtronic. Dr. Achenbach has received research grants from Siemens, Guerbet, and Abbott; and is a consultant for Siemens, Biotronik, and HeartFlow. Dr. Christiansen has received research grants from St. Jude Medical, Boston Scientific, Radi, Terumo, and Volcano. Dr. Leipsic has received research grants from GE Healthcare; and serves as a consultant for Edwards Lifesciences and HeartFlow. Dr. Seneviratne has given lectures at meetings organized by Toshiba. Dr. Nørgaard has received research grants from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 18, 2013; revised manuscript received November 21, 2013, accepted November 27, 2013.

**Coronary CTA acquisition and analysis.** Coronary CTA was performed by using single- or dual-source computed tomography (CT) scanners with a minimum of 64 detector rows (temporal resolution 75 to 175 ms). Both prospective triggering and retrospective gating were used for scan acquisitions. Filtered back-projection was used for image reconstruction to ensure the broadest applicability of our findings given that this is the current clinical standard of care. Laboratories followed quality standards as defined in guidelines (18). Oral and/or intravenous beta-blockers were administered targeting a heart rate of <60 beats/min, and sublingual nitrates were administered to ensure coronary vasodilation. Data acquisition was performed with 100-kV tube voltage in patients weighing  $\leq 70$  kg and 120 kV in subjects weighing  $>70$  kg. Coronary CTA images were transmitted to a central FFR<sub>CT</sub> core laboratory (HeartFlow, Inc., Redwood City, California), where image artifacts (e.g., motion, noise, contrast, blooming) were independently evaluated by using a predefined scoring system for selection of cases appropriate for FFR<sub>CT</sub> analysis (17,19). Experienced local investigators evaluated luminal diameter stenosis in each coronary artery segment  $\geq 2$  mm in diameter by using an 18-segment coronary model before ICA (18). The strategy of stenosis quantification was at the discretion of the local investigator. Significant obstruction was defined as stenosis  $>50\%$  in a major epicardial coronary artery segment  $\geq 2$  mm in diameter.

**ICA and FFR measurement.** ICA was performed according to standard practice (20). Angiograms were transferred to the angiography/FFR core laboratory (Harrington Heart and Vascular Institute, University Hospitals, Cleveland, Ohio) for quantitative angiography analysis by independent, blinded readers. Per protocol, measurement of FFR (PressureWire, St. Jude Medical, St. Paul, Minnesota) was performed during ICA in at least 1 vessel segment with diameter  $\geq 2$  mm and stenosis  $\geq 30\%$  (17). Consistent with previous studies (1), segments showing angiographic total or subtotal occlusion were assigned an FFR value of 0.50. The angiography/FFR core laboratory evaluated the complete FFR tracings for achievement of steady-state maximal hyperemia, pressure drift, and other artifacts that could compromise FFR interpretation.

**FFR<sub>CT</sub> computation.** Using the most recent generation of FFR<sub>CT</sub> analysis software, analysis was performed in a blinded fashion at HeartFlow (Fig. 1) (14,17). For each patient, a quantitative 3-dimensional anatomic model of the aortic root and epicardial coronary arteries was generated from coronary CTA images. Coronary blood flow and pressure were computed under conditions simulating maximal hyperemia. The results provide FFR<sub>CT</sub> throughout the coronary arterial tree. Occluded arteries were assigned FFR<sub>CT</sub> values of 0.50 (1). The FFR<sub>CT</sub> analysis required 1 to 4 h per examination depending on the CT image quality and atherosclerotic disease burden.

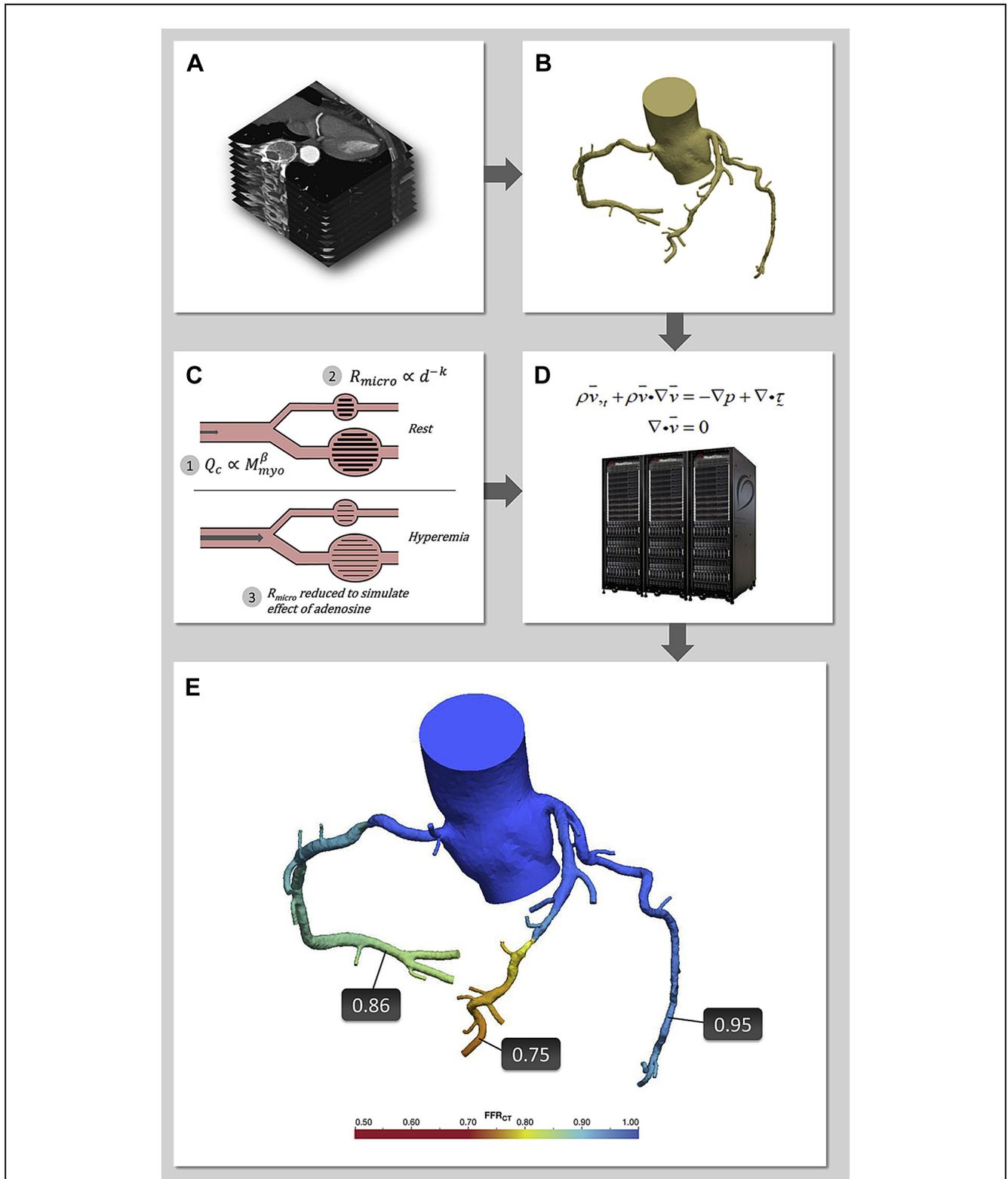
**Integration of coronary CTA and FFR data.** The angiography/FFR core laboratory received a blank 3-dimensional

computer model of the coronary anatomy from the FFR<sub>CT</sub> core laboratory; on this model, they indicated location(s) corresponding to the FFR pressure sensor location(s) at the time of FFR measurement(s). The blinded integration core laboratory (HeartFlow) received the FFR measurement location indication(s) and reported corresponding FFR<sub>CT</sub> data. Integration of FFR and FFR<sub>CT</sub> data occurred only after all FFR<sub>CT</sub> analyses for all patients were complete.

**Endpoints and statistical analysis.** The primary study endpoint was per-patient diagnostic performance as assessed by the area under the receiver-operating characteristic curve (AUC) of FFR<sub>CT</sub> ( $\leq 0.80$ ) versus coronary CTA (stenosis  $>50\%$ ) for the diagnosis of hemodynamically significant stenosis (FFR  $\leq 0.80$ ) in patients with coronary CTA stenosis of 30% to 90%. FFR  $\leq 0.80$  was the reference standard. Secondary endpoints included assessment of diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FFR<sub>CT</sub> and coronary CTA for all patients, patients with intermediate stenoses (30% to 70%), vessel-based analyses, and comparison of accuracy measures of FFR<sub>CT</sub>, coronary CTA, and ICA by using invasive FFR as the reference standard. Furthermore, diagnostic performance was assessed on a per-patient basis by using a stenosis threshold of 70% for coronary CTA and ICA and in the setting of a high Agatston score (threshold 400). Sample size calculations with assumptions have been described previously (17). Pre-test likelihood of CAD was determined by using the updated Diamond-Forrester risk score algorithm (4,21). AUC comparisons in patients with stenoses 30% to 90% were performed on per-patient and per-vessel levels according to the method described by DeLong et al. (22). Diagnostic accuracy, sensitivity, specificity, PPV, and NPV were calculated as simple proportions with 95% confidence intervals (CIs). Nonevaluable segments on coronary CTA in vessels  $>2$  mm were assumed not to be stenotic. A patient was considered positive for the presence of ischemia if any evaluable vessel  $\geq 2$  mm in diameter had an FFR value  $\leq 0.80$ . Similarly, a patient was considered negative if no vessel  $\geq 2$  mm in diameter had an FFR value  $\leq 0.80$ . The same rules applied for the assessment of FFR<sub>CT</sub>. Patient-level comparison of diagnostic performance characteristics (accuracy, sensitivity, specificity, PPV, and NPV) was performed by using the McNemar's test for paired samples or percentile bootstrap with 100,000 resamples as appropriate. To account for potential correlation between multiple vessels in the same subject, the generalized estimating equation method with an exchangeable correlation structure was used to compare paired samples at a per-vessel level. All analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

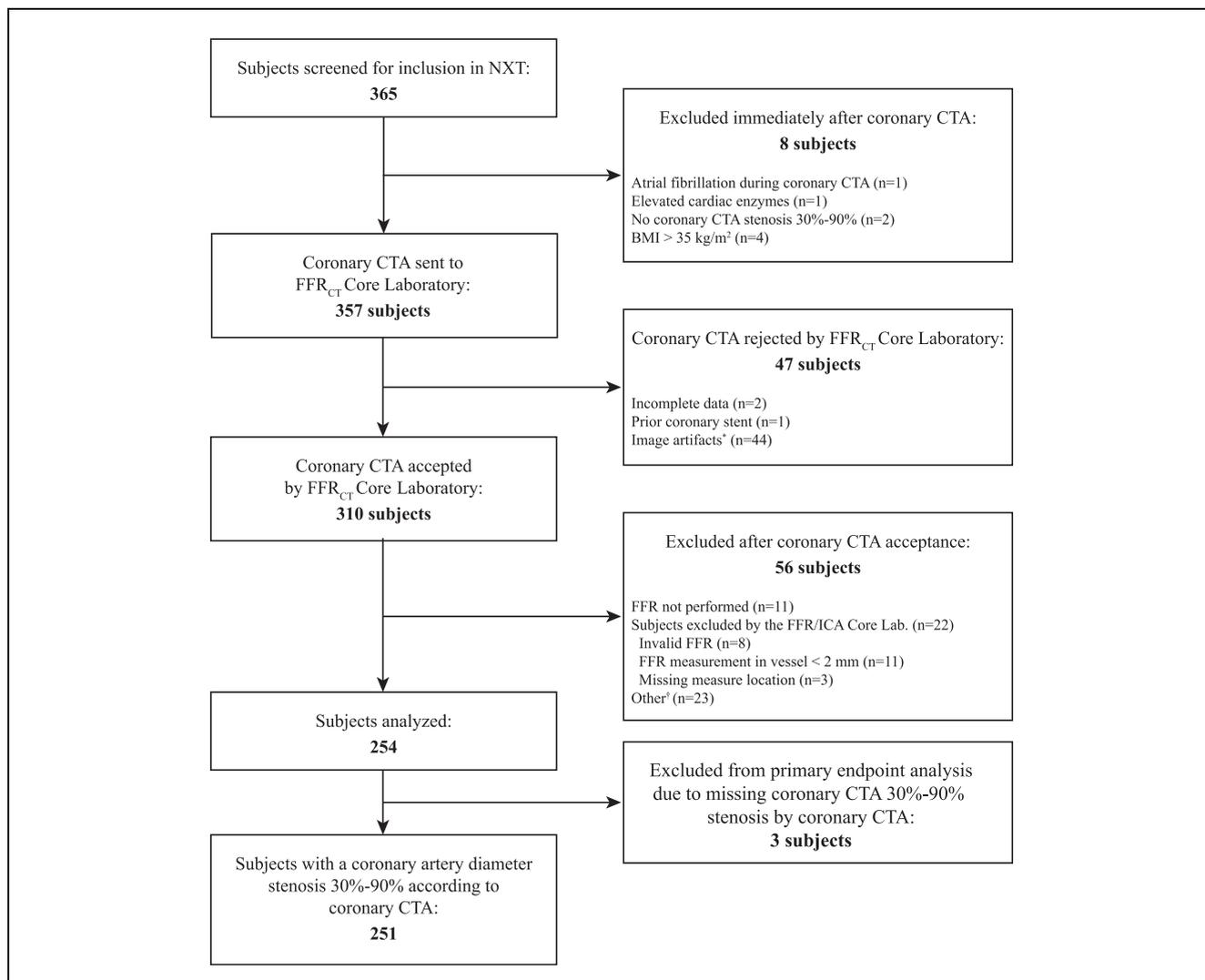
## Results

**Patient characteristics.** Among 365 patients undergoing study screening between September 2012 and August 2013,



**Figure 1** Schematic Presentation of the FFR<sub>CT</sub> Analysis

(A) Routine coronary computed tomography angiography data are received. (B) A quantitative 3-dimensional anatomic model is generated. (C) A physiological model of the coronary microcirculation is derived from patient-specific data with 3 main principles: 1) resting coronary flow proportional to myocardial mass; 2) microvascular resistance inversely proportional to vessel size; and 3) microvascular resistance reduced to simulate maximal hyperemia. (D) Physical laws of fluid dynamics are applied to compute coronary blood flow. (E) Fractional flow reserve derived from standard acquired coronary computed tomography angiography datasets (FFR<sub>CT</sub>) is calculated for each point in the coronary tree.



**Figure 2 Study Enrollment**

\*Rejected cases often had multiple artifacts. Motion/misregistration (n = 27), high image noise (n = 21), excessive calcium blooming (n = 19), and low contrast to noise ratio (n = 19). †Prior coronary stent (n = 1), severe pulmonary disease (n = 1), progressive disease (n = 1), elevated creatinine level (n = 1), withdrawal of patient consent (n = 7), invasive coronary angiography >60 days after the time of coronary computed tomography angiography (CTA) (n = 5), no coronary artery stenosis 30% to 90% according to site readings (n = 5). Adenosine not administered for fractional flow reserve (FFR) (n = 1), and unspecified (n = 1). BMI = body mass index; FFR<sub>CT</sub> = fractional flow reserve derived from coronary computed tomography angiography datasets; ICA = invasive coronary angiography; NXT = Analysis of Coronary Blood Flow Using CT Angiography: Next Steps.

a total of 8 patients were excluded immediately after coronary CTA, and 47 (13%) did not pass the CT image quality acceptance criteria (Fig. 2). After coronary CTA acceptance, 56 patients were not eligible for inclusion; Figure 2 provides the reasons for their exclusion. Thus, 254 patients were available for intention-to-diagnose analyses. Three subjects did have a coronary stenosis between 30% and 90%. Hence, 251 subjects formed the basis for the primary endpoint analysis. Comparison of FFR and FFR<sub>CT</sub> was performed in 484 vessels. FFR was directly measured in 468 vessels, and an FFR value of 0.50 was assigned to 16 occluded vessels (3%). In 22 (4.5%) vessels, a nondiagnostic segment on coronary CTA was found proximal to the segment in which the pressure wire was placed. Baseline characteristics of the

study cohort are listed in Table 1, and characteristics related to coronary CTA acquisition are provided in Table 2. The mean Agatston score (measured in 214 patients) was 302. The mean interval between coronary CTA and ICA was 18 days (range 1 to 55 days). Serious adverse events included 1 patient with coronary dissection during invasive FFR measurement requiring percutaneous coronary intervention and 2 patients with transient cerebral ischemic attacks after ICA and invasive FFR measurement. The per-patient and per-vessel characteristics of coronary CTA, ICA, FFR<sub>CT</sub>, and FFR are presented in Table 3.

**Diagnostic performance of FFR<sub>CT</sub>, coronary CTA, and ICA for diagnosis of ischemia.** Per-patient and per-vessel AUC for FFR<sub>CT</sub> were 0.90 (95% CI: 0.87 to 0.94) and 0.93

|   |           |
|---|-----------|
| Age, yrs                                |           |
| Mean ± SD                               | 64 ± 10   |
| Range                                   | 32–84     |
| Male                                    | 162 (64)  |
| Race                                    |           |
| White                                   | 163 (64)  |
| Asian                                   | 86 (34)   |
| Diabetes                                | 58 (23)   |
| Hypertension                            | 174 (69)  |
| Hyperlipidemia                          | 200 (79)  |
| Current smoker                          | 46 (18)   |
| Previous myocardial infarction          | 5 (2)     |
| Symptoms*                               |           |
| Typical angina                          | 103 (52)  |
| Atypical angina                         | 74 (37)   |
| Nonanginal chest pain                   | 9 (5)     |
| Dyspnea                                 | 12 (6)    |
| Angina within the past month            | 198 (78)  |
| Updated Diamond-Forrester risk score, % | 57.8      |
| Intermediate (20%–80%) pre-test risk    | 220 (87)  |
| Body mass index, kg/m <sup>2</sup>      | 26 ± 3    |
| Creatinine, mg/dl                       | 0.9 ± 0.2 |
| Left ventricular ejection fraction, %   | 62 ± 7    |

Values are mean ± SD, range, n (%), or %. N = 254. \*Data available in 198 patients.

(0.91 to 0.95), respectively. Diagnostic accuracy, sensitivity, specificity, PPV, and NPV for FFR<sub>CT</sub> on a per-patient basis were 81%, 86%, 79%, 65%, and 93%, respectively (Table 4). On a per-vessel basis, the values were 86%, 84%, 86%, 61%, and 95%. In analyses restricted to patients with intermediate stenoses ranging from 30% to 70% (n = 235), these values were 80%, 85%, 79%, 63%, and 92% (Table 5). There was good direct correlation of per-vessel FFR<sub>CT</sub> to FFR (Pearson’s correlation coefficient 0.82; p < 0.001), with a slight underestimation of FFR<sub>CT</sub> compared with FFR (Fig. 3). Figure 4 displays representative cases of patients with coronary obstructions without ischemia or with ischemia. Measures of diagnostic performance for coronary CTA and ICA are shown in Table 4. Raising the per-patient diameter stenosis threshold for anatomic test positivity to 70% resulted in lower sensitivity and higher specificity: 70% (95% CI: 60% to 79%) and 84% (95% CI: 79% to 90%) for

|  |            |
|--|------------|
| Heart rate, beats/min                    |            |
| Mean ± SD                                | 63 ± 10    |
| Range                                    | 37–110     |
| Pre-scan administration of nitrates      | 253 (99.6) |
| Pre-scan administration of beta-blockers | 198 (78)   |
| Prospective acquisition                  | 138 (54)   |
| Retrospective acquisition                | 116 (46)   |
| Effective CT radiation dose, mSv         |            |
| Prospective acquisition                  | 3.0 ± 2.2  |
| Retrospective acquisition                | 14.3 ± 7.0 |

Values are mean ± SD, range, or n (%). N = 254.  
CT = computed tomography; CTA = computed tomography angiography.

|   |                     |
|---|---------------------|
| Patients with coronary CTA maximum stenosis >50%    | 220 (87)            |
| Patients with coronary CTA maximum stenosis >70%    | 84 (33)             |
| Patients with intermediate-range stenoses (30%–70%) | 235 (93)            |
| Patients with FFR <sub>CT</sub> ≤0.80               | 106 (42)            |
| Vessels with FFR <sub>CT</sub> ≤0.80                | 135 (28)            |
| Agatston score*                                     | 302 ± 468 (0–3,599) |
| Patients with Agatston score >400*                  | 55 (26)             |
| Patients with ICA maximum stenosis >50%             | 81 (32)             |
| Patients with ICA maximum stenosis >70%             | 28 (11)             |
| Patients with FFR ≤0.80                             | 80 (32)             |
| Vessels with FFR ≤0.80                              | 100 (21)            |
| Patients with FFR ≤0.80 in >1 vessel                | 15 (6)              |

Values are n (%) or mean ± SD (range). N = 254 patients and 484 for vessels. \*Agatston score was measured in 214 patients.

FFR = fractional flow reserve; FFR<sub>CT</sub> = fractional flow reserve derived from standard acquired coronary computed tomography angiography datasets; ICA = invasive coronary angiography; other abbreviation as in Table 2.

coronary CTA. For ICA, the respective values were 35% (95% CI: 25% to 46%) and 100% (95% CI cannot be calculated). In patients with an Agatston score >400, accuracy, sensitivity, and specificity of FFR<sub>CT</sub> were 75% (95% CI: 62% to 84%), 88% (95% CI: 64% to 97%), and 69% (95% CI: 54% to 81%) versus 44% (95% CI: 31% to 56%), 94% (95% CI: 79% to 100%), and 23% (95% CI: 11% to 37%) for coronary CTA, respectively.

**Diagnostic performance of FFR<sub>CT</sub> versus coronary CTA for diagnosis of ischemia.** The AUC of FFR<sub>CT</sub> was higher than for coronary CTA interpretation on both a per-patient and a per-vessel level (Fig. 5). Per-patient and per-vessel diagnostic accuracy, specificity, and PPV for FFR<sub>CT</sub> were higher than for coronary CTA (Table 4). These findings were consistent also in patients with intermediate coronary stenoses (Table 5). FFR<sub>CT</sub> correctly reclassified 68% of patients with coronary CTA false-positive findings and 67% of those with coronary CTA false-positive vessels as true negative findings (Fig. 6).

## Discussion

This large study convincingly found that noninvasive determination of FFR is possible on the basis of standard coronary CTA datasets acquired under resting conditions with no additional radiation, contrast, or medication. In patients suspected of having CAD, FFR<sub>CT</sub> exhibited a very high diagnostic performance compared with invasively measured FFR. Particularly noteworthy was the high specificity of FFR<sub>CT</sub>, which was markedly better than in a previous evaluation of FFR<sub>CT</sub> (16). Moreover, compared with coronary CTA, FFR<sub>CT</sub> led to a marked reduction in false-positive results. Of note is the fact that patients with stenoses in the intermediate range (30% to 70%) comprised >90% of the overall study population. In clinical practice, such patients present a particular challenge because the relationship between angiographic stenosis severity and ischemia is poor (1,13).

**Table 4** Per-Patient and Per-Vessel Diagnostic Performance of FFR<sub>CT</sub>, Coronary CTA, and ICA

|             | Per-Patient                 |         |                          |                    | Per-Vessel                  |         |                          |                    |
|-------------|-----------------------------|---------|--------------------------|--------------------|-----------------------------|---------|--------------------------|--------------------|
|             | Coronary CTA Stenosis > 50% | p Value | FFR <sub>CT</sub> ≤ 0.80 | ICA Stenosis > 50% | Coronary CTA Stenosis > 50% | p Value | FFR <sub>CT</sub> ≤ 0.80 | ICA Stenosis > 50% |
| Accuracy    | 53 (47–57)                  | <0.001  | 81 (76–85)               | 77 (71–82)         | 65 (61–69)                  | <0.001  | 86 (83–89)               | 82 (79–86)         |
| Sensitivity | 94 (86–97)                  | 0.058   | 86 (77–92)               | 64 (53–74)         | 83 (74–89)                  | 0.91    | 84 (75–89)               | 55 (45–65)         |
| Specificity | 34 (27–41)                  | <0.001  | 79 (72–84)               | 83 (77–88)         | 60 (56–65)                  | <0.001  | 86 (82–89)               | 90 (86–93)         |
| PPV         | 40 (33–47)                  | <0.001  | 65 (56–74)               | 63 (52–73)         | 33 (27–39)                  | <0.001  | 61 (53–69)               | 58 (48–68)         |
| NPV         | 92 (83–97)                  | 0.46    | 93 (87–96)               | 83 (77–89)         | 92 (88–95)                  | 0.068   | 95 (93–97)               | 88 (85–92)         |

Values are proportion, % (95% CI). FFR ≤ 0.80 was diagnostic of lesion-specific ischemia. N = 254 subjects and 484 for vessels. NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 2 and 3.

The results of our study expand on findings and clinical implications from previous studies of FFR<sub>CT</sub> (15,16). The pilot DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) trial enrolled 103 subjects, validated against invasive FFR, and reported a per-vessel sensitivity of 88% and a specificity of 82% (15). The more recent DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) trial enrolled 252 patients, validated against FFR, and demonstrated a per-patient sensitivity of 90% but a specificity of only 54%, which did not meet the pre-specified primary endpoint of a lower 95% CI border for diagnostic accuracy of >70% (16).

The improved diagnostic performance of FFR<sub>CT</sub> in the present study, in particular with regard to specificity, importantly reflects substantial refinements in FFR<sub>CT</sub> technology and physiological modeling (14,17), as well as an increased focus on CT image quality (17) and adherence to official recommendations regarding coronary CTA acquisition (18). Refinements in technology evaluated in this study included improved automated image processing methods to more accurately identify the luminal boundary and improved physiological models to reduce the bias observed in previous studies (15,16). In particular, improvements in physiological models of microcirculatory resistance were implemented that demonstrated substantial improvement in diagnostic performance when evaluated retrospectively by using data from the DISCOVER-FLOW and DeFACTO studies. The importance of CT image quality and patient preparation in coronary CTA has been well established (18). The diagnostic performance of both coronary CTA and FFR<sub>CT</sub> have been shown to improve with adherence to established best practices for image acquisition, particularly by heart rate control and use of pre-scan nitroglycerin (23). In the DISCOVER-FLOW and DeFACTO trials, adherence to coronary CTA acquisition guidelines was neither required nor controlled. In contrast, in the present study, strict adherence to these guidelines was mandatory. Accordingly, >99% of the patients in this study received sublingual nitrates before coronary CTA compared with only 75% of patients in the DeFACTO trial (16). In addition, the present study used local site reading of coronary CTA stenosis degree to provide a real-world scenario and wider generalizability of the findings (24). Moreover, as indicated by differences in the proportion of FFR measurements ≤ 0.80 (21% of vessels in this study compared with 37% in the DeFACTO study), pre-test likelihood of CAD may have been different between the 2 studies. Notably, the pre-test probability of significant CAD in this study was intermediate (4,21) and thus reflective of the type of patients in whom noninvasive imaging is best used (4).

Established noninvasive functional diagnostic tests, such as single photon emission computed tomography, cMR, or stress echocardiography, do not directly visualize the coronary arteries or assess the functional significance of individual coronary lesions; however, they do provide

Table 5

Per-Patient Diagnostic Performance of FFR<sub>CT</sub> in Patients With Intermediate Stenosis Severity (30% to 70%) According to Coronary CTA

|             | FFR <sub>CT</sub> ≤0.80 | Coronary CTA Stenosis >50% | p Value |
|-------------|-------------------------|----------------------------|---------|
| Accuracy    | 80 (75–85)              | 51 (44–57)                 | <0.0001 |
| Sensitivity | 85 (74–91)              | 93 (85–97)                 | 0.058   |
| Specificity | 79 (72–84)              | 32 (26–40)                 | <0.0001 |
| PPV         | 63 (53–72)              | 37 (31–44)                 | <0.0001 |
| NPV         | 92 (87–96)              | 91 (81–96)                 | 0.42    |

Values are proportion in % (95% confidence interval). FFR ≤0.80 was diagnostic of ischemia. N = 235.

Abbreviations as in Tables 2 through 4.

meaningful information on prognosis and thus are recommended in guidelines for the diagnostic evaluation of symptomatic patients (4). The ability of these tests to correctly identify ischemia-producing stenoses by using FFR as the reference standard has been evaluated in several 1- and 2-center studies (25–27). In 1 study, cMR was compared with FFR ≤0.80 in 103 patients with suspected angina, with high reported per-vessel diagnostic performance (i.e., sensitivity of 82% and specificity of 98%) (25). However, FFR was directly measured in only 207 vessels (or 69% of the 300 coronary segments included in this analysis). Another study compared cMR with FFR ≤0.80 in 67 patients with multivessel disease and reported a per-vessel sensitivity of 61% and a specificity of 69%, with direct measurement of FFR in 154 vessels (77%) supplying 201 vascular territories included in the analysis (26). A third study investigating the diagnostic performance of dobutamine stress echocardiography in 70 patients measured FFR in all 70 vessels included in the analysis and reported a sensitivity of 48% and a specificity of 73% (27). Inclusion of a sizable number of vessels with assigned rather than measured FFR values may introduce error because vessels with normal or minimal disease according to CT or angiography may have measured FFR ≤0.80 (2,13), and severely stenosed vessels by angiography may have measured FFR >0.80 (1,13). In the present, large, multicenter study, FFR values were directly measured in 97% of the 484 vessels included in the analysis, and per-vessel sensitivity and specificity for FFR<sub>CT</sub> were 84% and 86%, respectively.

In an era of rising healthcare costs, great attention is placed on cost-effectiveness of procedures. Current clinical algorithms for therapeutic decision making in stable CAD often require 2 separate tests for assessment of coronary anatomy and ischemia (4,5). Despite extensive use of noninvasive testing, ICA continues to play a major role in diagnostic pathways (4–6). As a result of inadequate diagnostic discrimination with the use of noninvasive tests, up to 60% of subjects suspected of having CAD and referred for ICA do not have obstructive vessel narrowing (6), and the proportion without functionally significant myocardial ischemia would be expected to be even higher. A single noninvasive test with high diagnostic performance for both anatomy and lesion-specific ischemia would provide a major advantage in

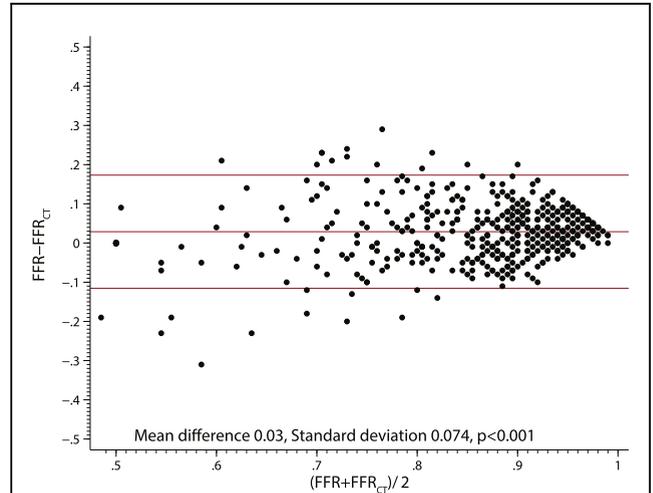
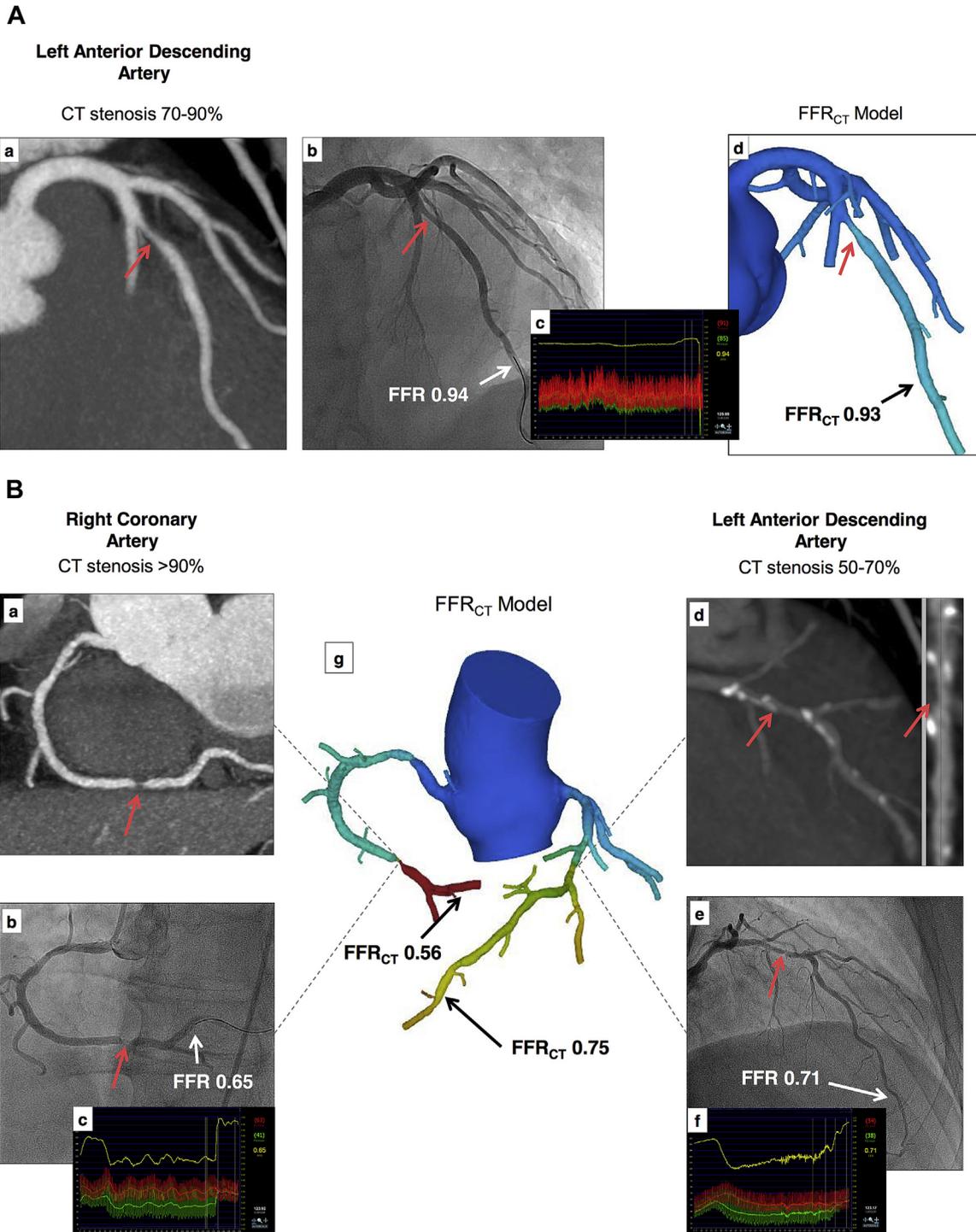


Figure 3 Bland-Altman Plot of FFR and FFR<sub>CT</sub> on a Per-Vessel Basis

Abbreviations as in Figure 2.

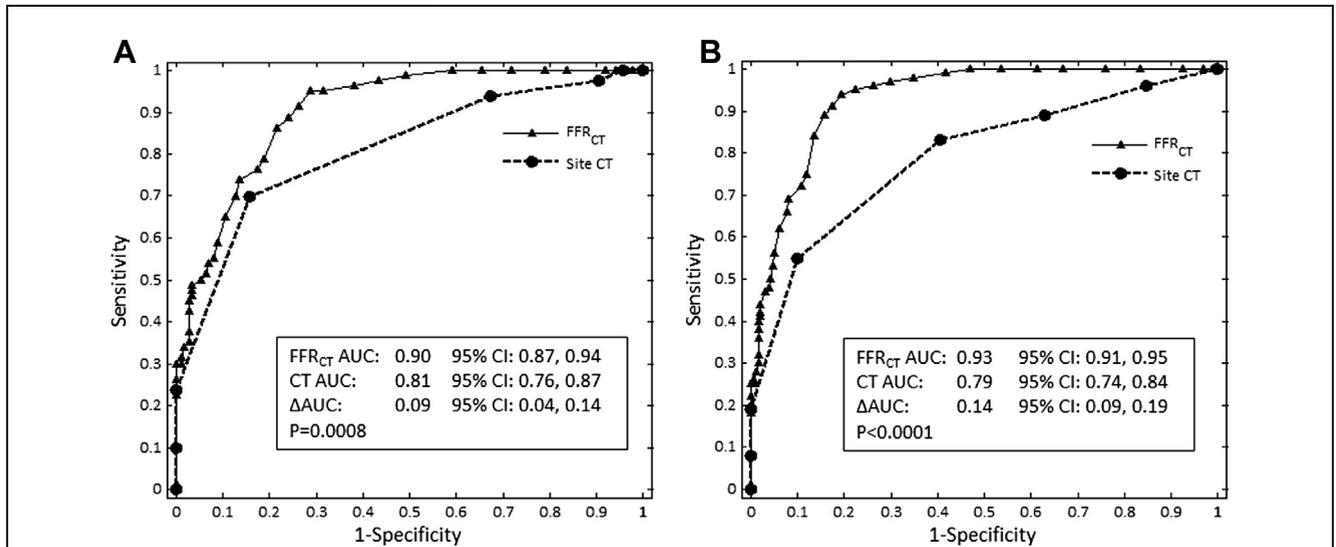
assessment of CAD. Our data firmly establish that myocardial ischemia is unlikely in patients tested negative by using FFR<sub>CT</sub> (NPV of 93%). Moreover, FFR<sub>CT</sub> revealed substantially improved specificity compared with coronary CTA. The present findings supporting the potential role of coronary CTA with FFR<sub>CT</sub> as a reliable gatekeeper to ICA and revascularization, together with the worldwide, ever-expanding access to coronary CTA (12), may have major health and economic implications. Indeed, simulation analyses based on historical data indicate that use of FFR<sub>CT</sub> to guide selection of ICA and revascularization may reduce costs and improve clinical outcomes in patients suspected of having CAD (28). The ongoing multicenter PLATFORM (Prospective Longitudinal Trial of FFR<sub>CT</sub>: Outcome and Resource Impacts; NCT01943903) trial compares the effect of FFR<sub>CT</sub>-guided testing versus standard diagnostic evaluation on clinical outcomes, resource utilization, costs, and quality of life in patients suspected of CAD.

**Study limitations.** In the present study, 13% of patients were judged to have nonevaluable coronary CTA images on the basis of a pre-defined image quality score (17,19). This proportion may diminish with further improvement of CT acquisition techniques and refinement of the FFR<sub>CT</sub> technology. The number of patients eligible for study inclusion (having ICA performed after coronary CTA) but not recruited was not recorded; therefore, site-level selection bias on the basis of coronary CTA findings cannot be excluded. However, the pre-test risk of CAD, as well as the spectrum and prevalence of disease (e.g., with regard to Agatston scores, as well as coronary CTA and FFR positive results), in this trial support the generalizability of the findings. Patients with acute coronary syndromes and previous coronary intervention or bypass surgery were excluded from the present study. Thus, generalizability of FFR<sub>CT</sub> to



**Figure 4** Representative Examples of Subjects From the NXT Study

(A) Multiplanar reformat of (a) coronary computed tomography (CT) angiogram, (b) invasive coronary angiogram, (c) invasive FFR measurement, and (d)  $FFR_{CT}$  of the left coronary artery system. Coronary CT angiogram demonstrates obstructive stenosis of the mid-portion of the left anterior descending artery (red arrow) and an  $FFR_{CT}$  value of 0.93, indicating absence of lesion-specific ischemia. Invasive coronary angiogram demonstrates obstructive stenosis of the mid-portion of the left anterior descending artery (red arrow) and a measured FFR value of 0.94, indicating no ischemia. (B) Multiplanar reformat of (a, d) coronary CT angiograms, (right side of d) straightened curved planar reformat of the coronary CT angiogram, (b, e) invasive coronary angiograms, (c, f) invasive FFR measurements, and (g)  $FFR_{CT}$  of the right coronary artery and left anterior descending artery, respectively. The coronary CT angiogram demonstrates obstructive stenosis of the distal portion of the right coronary artery and the mid-portion of the left anterior descending artery (red arrows) and  $FFR_{CT}$  values of 0.56 and 0.75 indicating ischemia. Invasive coronary angiogram demonstrates obstructive stenoses of the right coronary and left anterior descending arteries (red arrows) and measured FFR values, indicating ischemia in both vessel territories. Abbreviations as in Figures 2 and 3.



**Figure 5** AUC of FFR<sub>CT</sub> Versus Coronary CTA for Demonstration of Ischemia (FFR ≤ 0.80) on a Per-Patient and Per-Vessel Basis

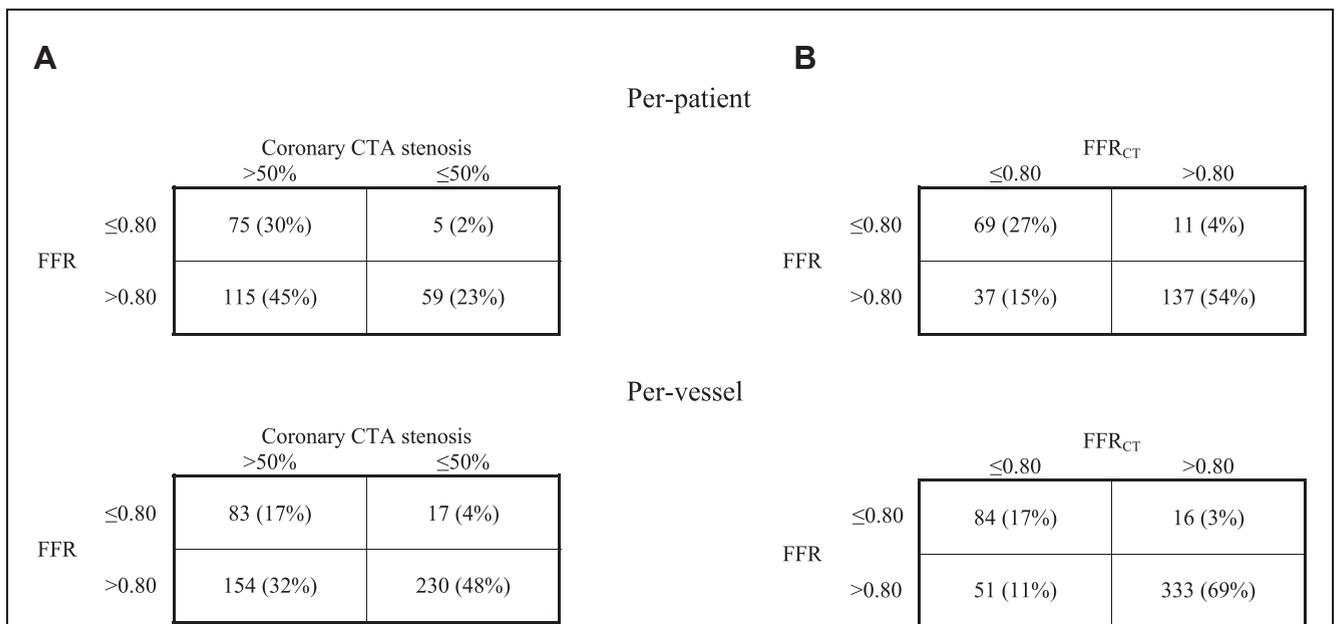
(A) Per-patient; (B) per-vessel. In the per-patient analysis, a FFR<sub>CT</sub> ≤ 0.80 was diagnostic of ischemia, and stenosis >50% at coronary CTA was anatomically obstructive. N = 251 for subjects and 484 for vessels. AUC = area under the receiver-operating characteristic curve; other abbreviations as in Figures 2 and 3.

these specific populations of patients with CAD is unknown.

**Conclusions**

This study found that FFR<sub>CT</sub> has high diagnostic performance compared with invasively measured FFR,

identifying patients with hemodynamically relevant obstructions with high sensitivity and specificity. Compared with anatomic interpretation by using coronary CTA, FFR<sub>CT</sub> led to a marked increase in diagnostic specificity. The addition of FFR<sub>CT</sub> to coronary CTA may allow for a comprehensive anatomic and functional assessment of CAD in a manner potentially promoting



**Figure 6** Agreement for Detection of Ischemia (FFR ≤ 0.80) Between Coronary CTA and FFR<sub>CT</sub> on a Per-Patient and Per-Vessel Basis

(A) Coronary CTA; (B) FFR<sub>CT</sub>. N = 254 for subjects and 484 for vessels. Abbreviations as in Figures 2 and 3.

beneficial clinical and cost outcomes, which remain to be definitively proven in appropriately designed prospective trials.

**Reprint requests and correspondence:** Dr. Bjarne Linde Nørgaard, Department of Cardiology, Aarhus University Hospital Skejby, Skejby DK-8200 Aarhus N, Denmark. E-mail: bnorgaard@dadlnet.dk.

## REFERENCES

1. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;55:2816–21.
2. De Bruyne B, Hersbach F, Pijls NH, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but “normal” coronary angiography. *Circulation* 2001;104:2401–6.
3. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900–7.
4. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949–3003.
5. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J* 2010;31:2501–55.
6. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886–95.
7. 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.
8. Muller O, Mangiacapra F, Ntalianis A, et al. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol Intv* 2011;4:1175–82.
9. Meijboom WB, Meijjs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135–44.
10. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
11. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;57:1237–47.
12. Shaw LJ, Marwick TH, Zoghbi WA, et al. Why all the focus on cardiac imaging? *J Am Coll Cardiol Img* 2010;3:789–94.
13. 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.
14. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol* 2013;61:2233–41.
15. 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.
16. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;308:1237–45.
17. Gaur S, Achenbach S, Leipsic J, et al. Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) study. *J Cardiovasc Comput Tomogr* 2013;7:279–88.
18. 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.
19. Nørgaard BL, Leipsic J, Sengupta S, et al. Quantitative assessment of image quality for determination of FFR by coronary computed tomography angiography (abstr). *J Cardiovasc Comput Tomogr (Suppl)* 2013;3:233.
20. Naidu SS, Rao SV, Blankenship J, et al. Clinical expert consensus statement on best practices in the cardiac catheterization laboratory: Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2012;80:456–64.
21. Genders TS, Steverberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;32:1316–30.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
23. Leipsic J, Yang TH, Thompson A, et al. Technical factors and patient preparation prior to coronary CT angiography and diagnostic performance of non-invasive fractional flow reserve: results from the determination of fractional flow reserve by anatomic computed angiography (DeFACTO) study. *Am J Roentgenol* 2014. In press.
24. Patel MR. Detecting obstructive coronary disease with CT angiography and noninvasive fractional flow reserve. *JAMA* 2012;308:1269–70.
25. Watkins S, McGeoch R, Lyne J, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009;120:2207–13.
26. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *J Am Coll Cardiol Intv* 2010;3:307–14.
27. Jung PH, Rieber J, Störk S, et al. Effect of contrast application on interpretability and diagnostic value of dobutamine stress echocardiography in patients with intermediate coronary lesions: comparison with myocardial fractional flow reserve. *Eur Heart J* 2008;29:2536–43.
28. Hlatky MA, Saxena A, Koo BK, Erglis A, Zarins CK, Min JK. Projected costs and consequences of computed tomography-determined fractional flow reserve. *Clin Cardiol* 2013 Oct 1 [E-pub ahead of print].

**Key Words:** computational fluid dynamics ■ coronary CT angiography ■ fractional flow reserve ■ invasive coronary angiography.

## APPENDIX

For the participating study centers, please see the online version of this article.