JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 24, 2018

PUBLISHED BY ELSEVIER

Fractional Flow Reserve Derived From Computed Tomographic Angiography in Patients With Multivessel CAD

Carlos Collet, MD,[a,b] Yosuke Miyazaki, MD, PhD,[c] Nicola Ryan, MB, BCh,[d] Taku Asano, MD,[a] Erhan Tenekecioglu, MD,[c] Jeroen Sonck, MD,[b] Daniele Andreini, MD, PhD,[e] Manel Sabate, MD, PhD,[f] Salvatore Brugaletta, MD, PhD,[f] Rodney H. Stables, MD,[g] Antonio Bartorelli, MD, PhD,[e] Robbert J. de Winter, MD,[a] Yuki Katagiri, MD,[a] Ply Chichareon, MD,[a] Giovanni Luigi De Maria, MD,[h] Pannipa Suwannasom, MD, PhD,[a] Rafael Cavalcante, MD, PhD,[c] Hans Jonker, BSc,[i] Marie-angèle Morel, BSc,[i] Bernard Cosyns, MD, PhD,[b] Arie P. Kappetein, MD, PhD,[b] David T. Taggart, MD, PhD,[h] Vasim Farooq, MD, PhD,[j] Javier Escaned, MD, PhD,[c] Adrian Banning, MD, PhD,[h] Yoshinobu Onuma, MD, PhD,[b,i] Patrick W. Serruys, MD, PhD[k]

ABSTRACT

BACKGROUND The functional SYNTAX score (FSS) has been shown to improve the discrimination for major adverse cardiac events compared with the anatomic SYNTAX score (SS) while reducing interobserver variability. However, evidence supporting the noninvasive FSS in patients with multivessel coronary artery disease (CAD) is scarce.

OBJECTIVES The purpose of this study was to assess the feasibility of and validate the noninvasive FSS derived from coronary computed tomography angiography (CTA) with fractional flow reserve (FFR_{CT}) in patients with 3-vessel CAD.

METHODS The CTA-SS was calculated in patients with 3-vessel CAD included in the SYNTAX II (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery II) study. The noninvasive FSS was determined by including only ischemia-producing lesions ($FFR_{CT} \leq 0.80$). SS derived from different imaging modalities were compared using the Bland-Altman and Passing-Bablok method, and the agreement on the SS tertiles was investigated with Cohen's Kappa. The risk reclassification was compared between the noninvasive and invasive physiological assessment, and the diagnostic accuracy of FFR_{CT} was assessed by the area under the receiver-operating characteristic curve using instantaneous wave-free ratio as a reference.

RESULTS The CTA-SS was feasible in 86% of patients (66 of 77), whereas the noninvasive FSS was feasible in 80% (53 of 66). The anatomic SS was overestimated by CTA compared with conventional angiography (27.6 ± 6.4 vs. 25.3 ± 6.9; $p < 0.0001$) whereas the calculation of the FSS yielded similar results between the noninvasive and invasive imaging modalities (21.6 ± 7.8 vs. 21.2 ± 8.8; $p = 0.589$). The noninvasive FSS reclassified 30% of patients from the high- and intermediate-SS tertiles to the low-risk tertile, whereas invasive FSS reclassified 23% of patients from the high- and intermediate-SS tertiles to the low-risk tertile. The agreement on the classic SS tertiles based on Kappa statistics was slight for the anatomic SS (Kappa = 0.19) and fair for the FSS (Kappa = 0.32). The diagnostic accuracy of FFR_{CT} to detect functional significant stenosis based on an instantaneous wave-free ratio ≤0.89 revealed an area under the receiver-operating characteristics curve of 0.85 (95% CI: 0.79 to 0.90) with a sensitivity of 95% (95% CI: 89% to 98%), specificity of 61% (95% CI: 48% to 73%), positive predictive value of 81% (95% CI: 76% to 86%), and negative predictive value of 87% (95% CI: 74% to 94%).

CONCLUSIONS Calculation of the noninvasive FSS is feasible and yielded similar results to those obtained with invasive pressure-wire assessment. The agreement on the SYNTAX score tertile classification improved with the inclusion of the functional component from slight to fair agreement. FFR_{CT} has good accuracy in detecting functionally significant lesions in patients with 3-vessel CAD. (A Trial to Evaluate a New Strategy in the Functional Assessment of 3-Vessel Disease Using SYNTAX II Score in Patients Treated With PCI; NCT02015832) (J Am Coll Cardiol 2018;71:2756-69) © 2018 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.02.053

Coronary physiology has emerged as the gatekeeper for coronary revascularization (1). In the SYNTAX II (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery II) study, 83% of the patients had anatomical (diameter stenosis >50%) 3-vessel coronary artery disease (CAD); the use of instantaneous wave-free ratio (iFR) reduced the number of patients with functionally significant 3-vessel disease to 37% (2). The functional SYNTAX score (FSS), a correction of the SYNTAX score (SS) using fractional flow reserve (FFR), reclassified 34% of patients from high- and moderate-risk SS tertiles to the low-risk tertile in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (3). Furthermore, the FSS improved discrimination for major adverse cardiac events while reducing interobserver variability (3).

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In patients with 3-vessel CAD, risk prediction models have been shown to be useful in stratifying risk and guiding treatment (4). The SS objectively assesses the severity of CAD, aiding the heart team in decision making between coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) (5). Both American and European guidelines (Class IIa and I recommendations, respectively) advocate the use of the anatomic SS to guide treatment recommendations in patients with multivessel and complex CAD (6,7). In the landmark SYNTAX trial, patients with a low-risk SS (≤22) were shown to have similar outcomes with CABG and PCI. However, among patients with an SS ≥23, CABG was associated with better outcomes at 5-year follow-up (8). Limitations of the anatomic SS include the moderate interobserver reproducibility and the fact that recent trials have not confirmed the prognostic performance of the SS despite a robust body of evidence supporting its utility (9,10).

The advent of blood flow simulation derived from coronary computed tomography angiography (CTA) has allowed the exploration of noninvasive physiological assessment in patients with complex CAD. Fractional flow reserve derived from computed tomography angiography (FFR_{CT},) can be used to calculate the noninvasive FSS. The noninvasive FSS has the potential to individualize risk assessment, assist the heart team in the decision-making process prior to invasive angiography, and guide treatment planning in the noninvasive setting. However, to date there is no data supporting the accuracy of this technology in patients with complex CAD.

In the present study, we sought to assess the feasibility and validate the noninvasive FSS in patients with 3-vessel CAD compared with coronary angiography and iFR. The primary objective was to assess the feasibility of and to validate the noninvasive FSS with invasive FSS as a clinical reference in patients with 3-vessel CAD. The secondary objective was to assess the diagnostic accuracy of FFR_{CT} with iFR as a clinical reference.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAD = coronary artery disease

FFR = fractional flow reserve

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

FSS = functional SYNTAX score(s)

iFR = instantaneous-wave free ratio

PCI = percutaneous coronary intervention

SS = SYNTAX score(s)

SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery

METHODS

STUDY DESIGN. The present study is a pre-defined analysis of the SYNTAX II study (11). SYNTAX II was a multicenter, all-comers, open-label, single-arm study that included patients with de novo 3-vessel disease without left main involvement. Patients were enrolled in 22 interventional cardiology centers from 4 European countries between February 2014 and November 2015. All site-reported SS were eligible for initial

From the [a]Department of Cardiology, Academic Medical Center of Amsterdam, Cardiology, Amsterdam, the Netherlands; [b]Department of Cardiology, Universitair Ziekenhuis Brussel, Brussels, Belgium; [c]Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; [d]Hospital Clínico San Carlos IDISSC and Universidad Complutense de Madrid, Madrid, Spain; [e]Centro Cardiologico Monzino, University of Milan, Milan, Italy; [f]Hospital Clinic I Provincial de Barcelona, Barcelona, Spain; [g]Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; [h]John Radcliffe Hospital, Cardiology, Oxford, United Kingdom; [i]Cardialysis BV, Rotterdam, the Netherlands; [j]Manchester Heart Centre, Manchester Royal Infirmary, Central Manchester University Hospitals, Manchester, United Kingdom; and the [k]Department of Cardiology, Imperial College London, London, United Kingdom. The European Cardiovascular Research Institute sponsored this study with unrestricted research grants from Volcano and Boston Scientific. Dr. Collet has received grant support from Heart Flow Inc. Dr. Cavalcante is an employee of Boston Scientific. Dr. Sabate has received consulting fees from Abbott Vascular. Dr. Kappetein is an employee of Medtronic. Dr. Escaned has received consulting fees from Philips Volcano, Boston Scientific, and Abbott/St. Jude Medical. Dr. Banning has received lecture fees from Abbott Vascular, Medtronic, and Boston Scientific; and has received grant support from Boston Scientific. Drs. Onuma and Serruys are members of the advisory board of Abbott Vascular. Dr. Serruys has served as a consultant for Abbott, Biosensors, Medtronic, Micell Technologies, Qualimed, St. Jude Medical, Stentys, Svelte, Philips/Volcano, and Xeltis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 21, 2017; revised manuscript received February 18, 2018, accepted February 19, 2018.

TABLE 1 Baseline Clinical Characteristics

	SYNTAX II (n = 454)	CTA Cohort (n = 77)	Non-CTA Cohort (n = 377)	p Value
Age, yrs	66.7 ± 9.7 (454)	65.8 ± 9.7	66.9 ± 9.7	0.985
Male	93.2 (423/454)	94.8 (73)	92.8 (350)	0.195
Body mass index, kg/m^2	28.9 ± 4.7 (449)	28.0 ± 3.7	29.1 ± 4.8	0.071
Diabetes mellitus type I or II	30.3 (135/446)	32.3 (21)	29.9 (114)	0.699
Current smoker	14.7 (64/435)	7.8 (6)	30.8 (116)	<0.0001
Previous MI	12.5 (56/447)	3.1 (2)	14.1 (54)	0.013
Hypertension	77.0 (344/447)	75.5 (51)	76.7 (293)	0.755
Hyperlipidemia	77.3 (341/441)	75.8 (41)	44.6 (294)	0.758
Clinical presentation				
Stable angina/silent ischemia	75.5 (339/449)	87.0 (67)	73.8 (267)	0.01
Unstable angina	25.6 (118/449)	12.9 (10)	29.0 (105)	0.004
Creatinine clearance, ml/min	82.0 ± 26.9 (454)	79.5 ± 25.2	82.4 ± 21.2	0.742
Ejection fraction, %	58.1 ± 8.3 (454)	59.0 ± 8.0	58.0 ± 8.3	0.487
EuroSCORE, %	3.5 ± 2.5	2.4 ± 2.4	3.7 ± 4.4	0.599
SYNTAX score II PCI	30.2 ± 8.6	29.1 ± 7.5	30.4 ± 8.9	0.208
Predicted 4-yr mortality with PCI, %	8.9 ± 8.8	7.6 ± 5.7	9.3 ± 9.4	0.618
SYNTAX score II CABG	29.1 ± 10.4	27.8 ± 9.7	29.3 ± 10.6	0.229
Predicted 4-yr mortality with CABG, %	9.0 ± 9.3	7.7 ± 7.7	9.3 ± 9.6	0.639
Coronary CTA acquisition				
Heart rate	–	57.4 ± 11.8	–	–
Nitrates	–	89.7 (52)*	–	
Beta-blockers	–	78.0 (47)†	–	
Prospective acquisition	–	64.0 (49)	–	
Radiation dose, CTDIvol	–	18.3 ± 20.5	–	–
Effective dose, mSv		1.9 (0.81–6.0)		
Time between coronary CTA and coronary angiography, days	–	12 (4–28)	–	–
Time between coronary CTA and invasive physiological assessment, days	–	7.5 (3–22)	–	–

Values are mean ± SD (N), mean ± SD, % (n/N), % (n), or median (interquartile range). *Information on the use of nitrates was not available for 19 patients. †Information on the use of beta-blockers was not available for 17 patients.

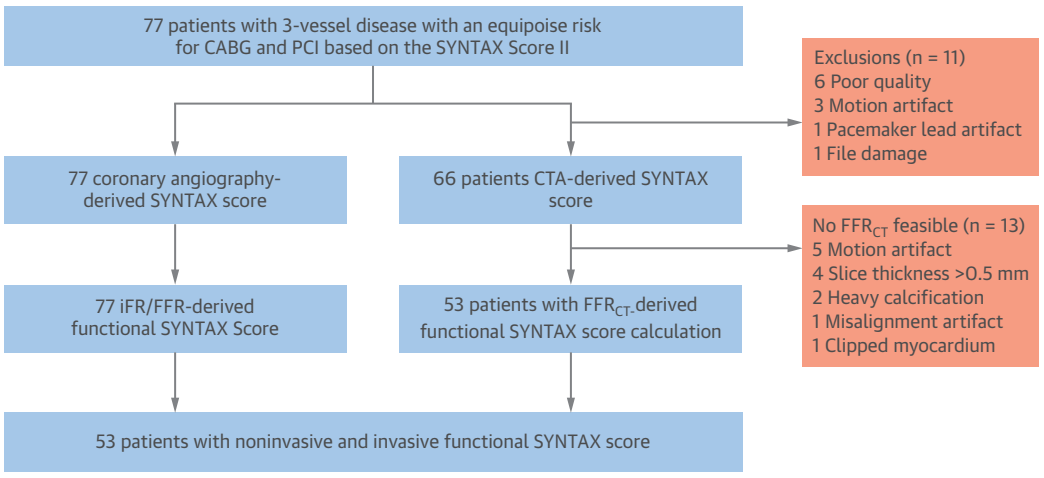
CABG = coronary artery bypass graft; CAD = coronary artery disease; CTA = computed tomographic angiography; CTDIvol = computed tomography dose index volume; FFR = fractional flow reserve; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

screening. Patients were screened using the SYNTAX score II, which combines anatomical and clinical characteristics and provides a treatment recommendation based on predicted 4-year mortality. Patients with an equipoise risk for CABG and PCI were assessed by the heart team (interventional cardiologist and cardiac surgeon), who confirmed the appropriateness of percutaneous-based revascularization provided that a similar degree of anatomical revascularization could be achieved with either treatment. After the heart team consensus, but prior to PCI, a coronary CTA was obtained (documentary only). Participation in the coronary CTA substudy was voluntary. Patients underwent physiology-guided PCI using a hybrid iFR/FFR strategy and implantation of the thin-strut, biodegradable polymer drug-eluting stent (Synergy, Boston Scientific, Natick, Massachusetts) in functionally significant lesions. Post-implantation intravascular ultrasound evaluation was mandatory. Guideline-directed medical therapy was recommended, which included mandatory dual-antiplatelet therapy (aspirin and clopidogrel or ticagrelor or prasugrel) for at least 6 months, while aspirin was recommended indefinitely as per current European Society of Cardiology/American Heart Association/American College of Cardiology guidelines (7,12). SYNTAX II was an investigator-initiated study, sponsored by the European Cardiovascular Research Institute (Rotterdam, the Netherlands), with unrestricted research grants from Volcano and Boston Scientific.

ANGIOGRAPHIC AND PHYSIOLOGICAL ASSESSMENT. The SS was calculated offline by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands). Visual evaluation of significant lesions (diameter stenosis >50% in vessels ≥1.5 mm) was performed to obtain the anatomic SS. The online calculator (13) was used to derive the total and per-lesion SS. Target lesions were interrogated with iFR/FFR (Verrata and PrimeWire Prestige, Volcano Corp., San Diego, California). For the present analysis, a cutoff iFR ≤0.89 was used to indicate functionally significant lesions (14). In the SYNTAX II study, the revascularization decision used the hybrid iFR/FFR strategy, where FFR was performed when the iFR value was in the gray zone (i.e., 0.86 to 0.93) (11). The invasive FSS was calculated by adding the individual points of lesions with an iFR ≤0.89 (or FFR ≤0.80 if iFR was not available) and excluding functionally nonsignificant lesions. Similar to previous reports, in cases of total and subtotal coronary occlusions (visual diameter stenosis ≥90%) and in the absence of invasive physiological assessment, a default iFR value of 0.50 was imputed (15).

CORONARY CTA ANALYSIS. Coronary CTA was performed using scanners with at least 64-row detectors (256-row Somatom Definition Flash, Siemens, Munich, Germany; 320-row Aquilion One, Toshiba, Tokyo, Japan; 64-row Light Speed VCT, GE Healthcare, Little Chalfont, United Kingdom; and 64-row Brilliance, Philips, the Netherlands). Standard acquisition techniques were used, which included nitrates prior to image acquisition and beta-blockers in patients with heart rate >65 beats/min, tube settings depending on patient body mass index (80 to 140 kV), and prospective ECG triggering for patients with lower heart rates to reduce radiation doses, all at the discretion of the participating sites. Images were

FIGURE 1 Flowchart of the Study



A total of 77 patients with anatomical 3-vessel coronary artery disease underwent coronary angiography and coronary CTA. Calculation of the anatomic SYNTAX score was feasible in 77 of 77 with invasive angiography and in 66 of 77 with coronary CTA. Subsequently, the functional component of the lesions was assessed by means of pressure wire and FFR_{CT}, which was feasible in 77 and 53 patients in the invasive and noninvasive assessment, respectively. CABG = coronary artery bypass graft; CTA = computed tomographic angiography; FFR = fractional flow reserve; iFR = instantaneous-wave free ratio; PCI = percutaneous coronary intervention; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery

TABLE 2 Comparison of Lesions Assessed by Coronary CTA and Angiography

	Coronary CTA (n = 365)	Invasive Angiography (n = 359)	p Value
Lesions	365	359	NS
Vessel			
RCA	33.7 (123)	34.5 (113)	0.821
LAD	33.2 (121)	37.9 (136)	0.108
LCX	32.6 (119)	30.6 (110)	0.563
Total occlusion	5.5 (20)	6.4 (22)	0.609
Bifurcation	30.7 (111)	25.0 (132)	0.087
Medina 0.0.1	20.7 (23)	16.6 (22)	
Medina 0.1.0	15.3 (17)	12.1 (16)	
Medina 0.1.1	14.4 (16)	8.3 (11)	
Medina 1.0.0	7.2 (8)	6.8 (9)	
Medina 1.0.1	4.5 (5)	3.8 (5)	
Medina 1.1.0	18.9 (21)	6.0 (8)	
Medina 1.1.1	18.9 (21)	11.1 (15)	
Aorto-ostial	1.1 (4)	0.9 (3)	0.787
Long (>20 mm)	13.9 (50)	20.0 (72)	0.028
Heavy calcification	8.0 (29)	5.6 (20)	0.200
Points per lesion	4.97 ± 3.94	4.66 ± 3.67	0.274

Values are n, % (n), or mean ± SD.

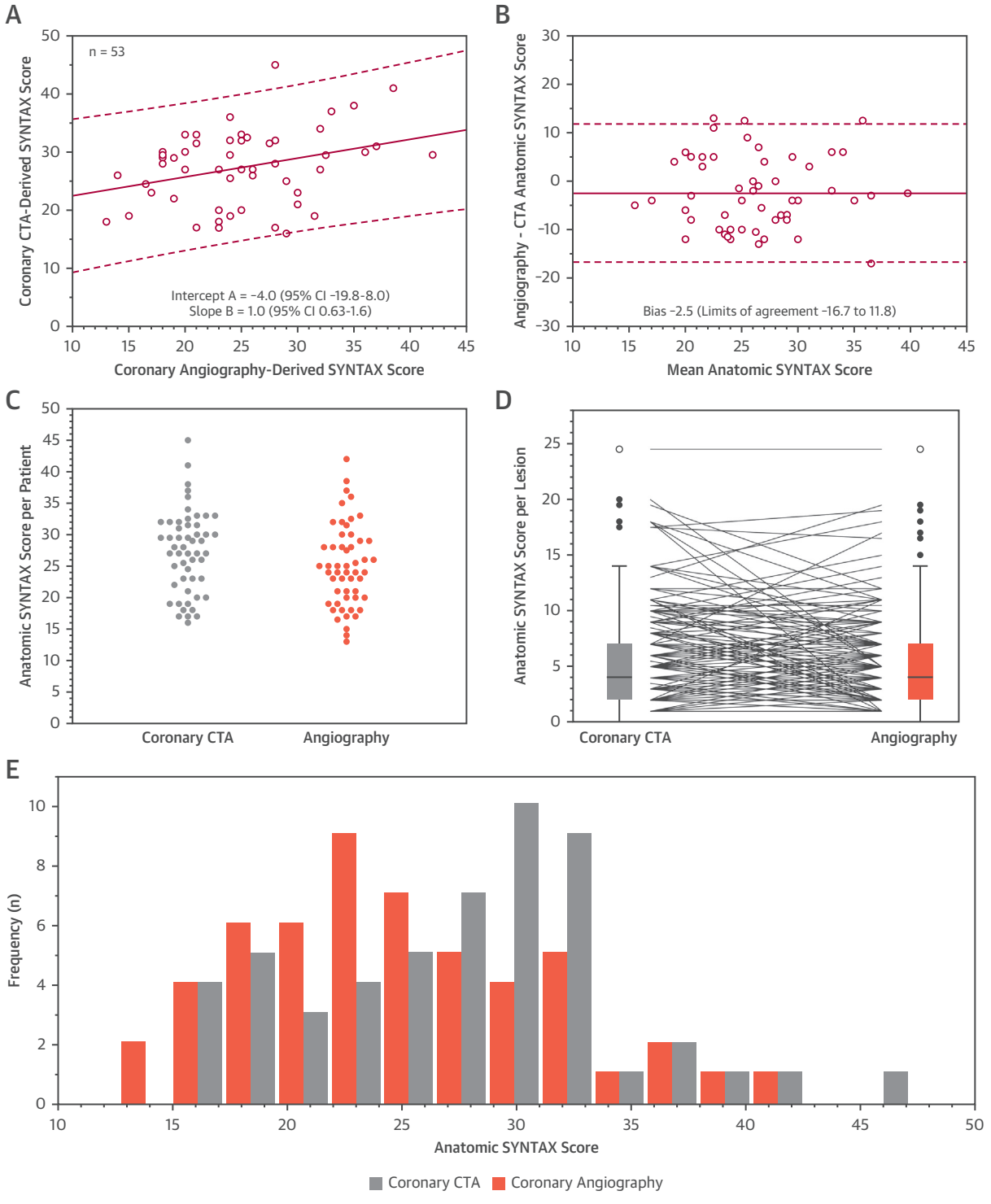
CTA = computed tomographic angiography; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery.

reconstructed using thin slices (0.50 to 0.67 mm) and medium smooth reconstruction filters in different phases. Analyses were performed offline by an independent core laboratory (Cardialysis BV) blinded to the angiographic data on a dedicated workstation (CardIQ Xpress 2.0, AW workstation, GE Healthcare). Two observers assessed the coronary CTA blinded to conventional angiography. Similar to the invasive SS, visual evaluation of lesion severity (i.e., diameter stenosis >50% in vessels ≥1.5 mm) was used to calculate the anatomic SS derived from coronary CTA (CTA-SS). Definitions of the CTA-SS component were according to previous publications (Online Table 1) (16). Visual assessment was performed using different imaging projections and adjusting window level if necessary.

FSS DERIVED FROM CORONARY CTA WITH FFR_{CT}.

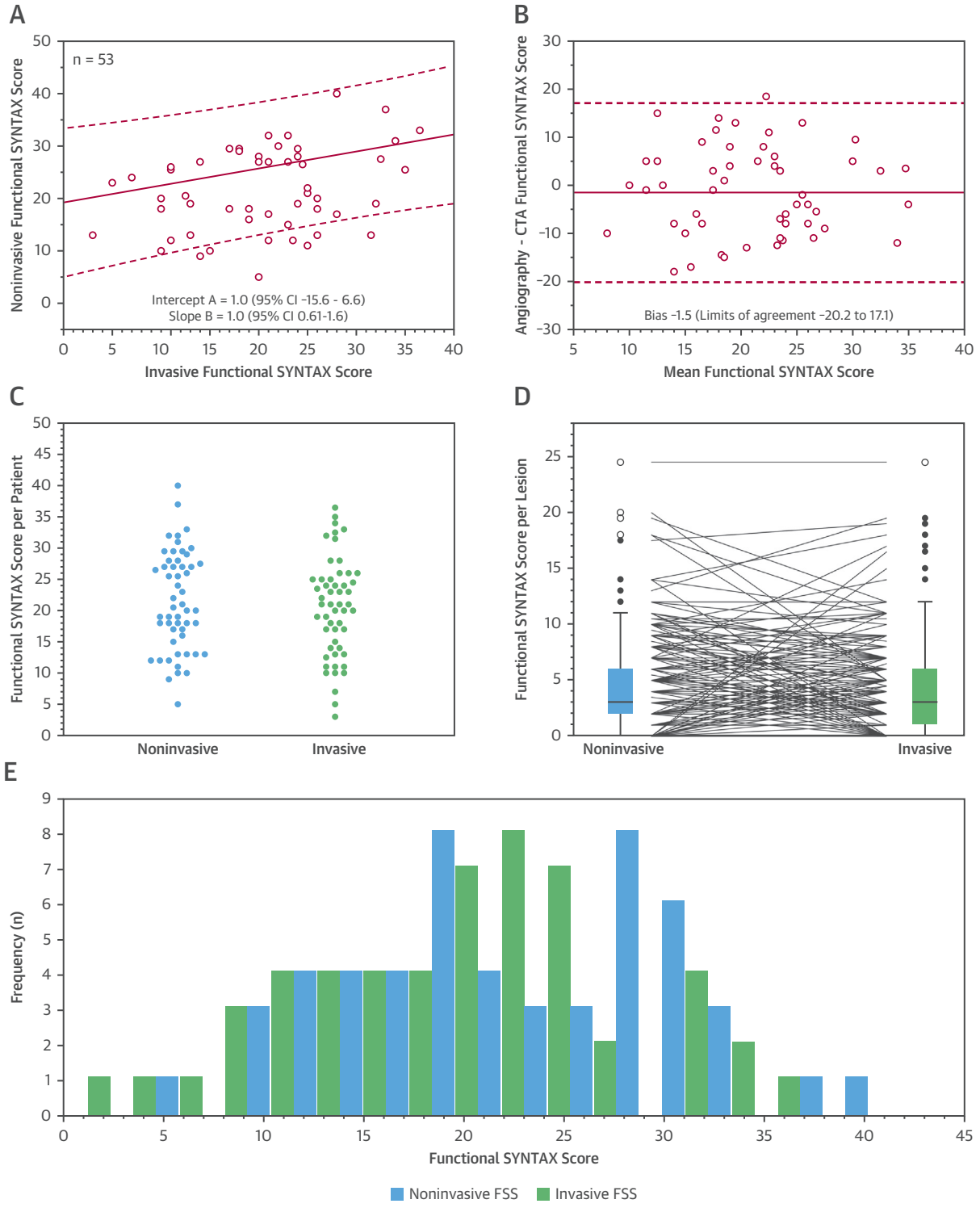
The FFR_{CT} was performed by an independent core laboratory at HeartFlow, Inc. (Redwood City, California) blinded to the angiographic and invasive physiological data. A quantitative 3-dimensional anatomic model of the aortic root and epicardial coronary arteries was generated from coronary CTA images for each patient. Coronary blood flow and pressure were computed under conditions simulating maximal hyperemia. Blood was considered a Newtonian fluid. The noninvasive FSS was calculated by

FIGURE 2 Comparison of the Anatomic SYNTAX Score Between Coronary CTA and Conventional Coronary Angiography



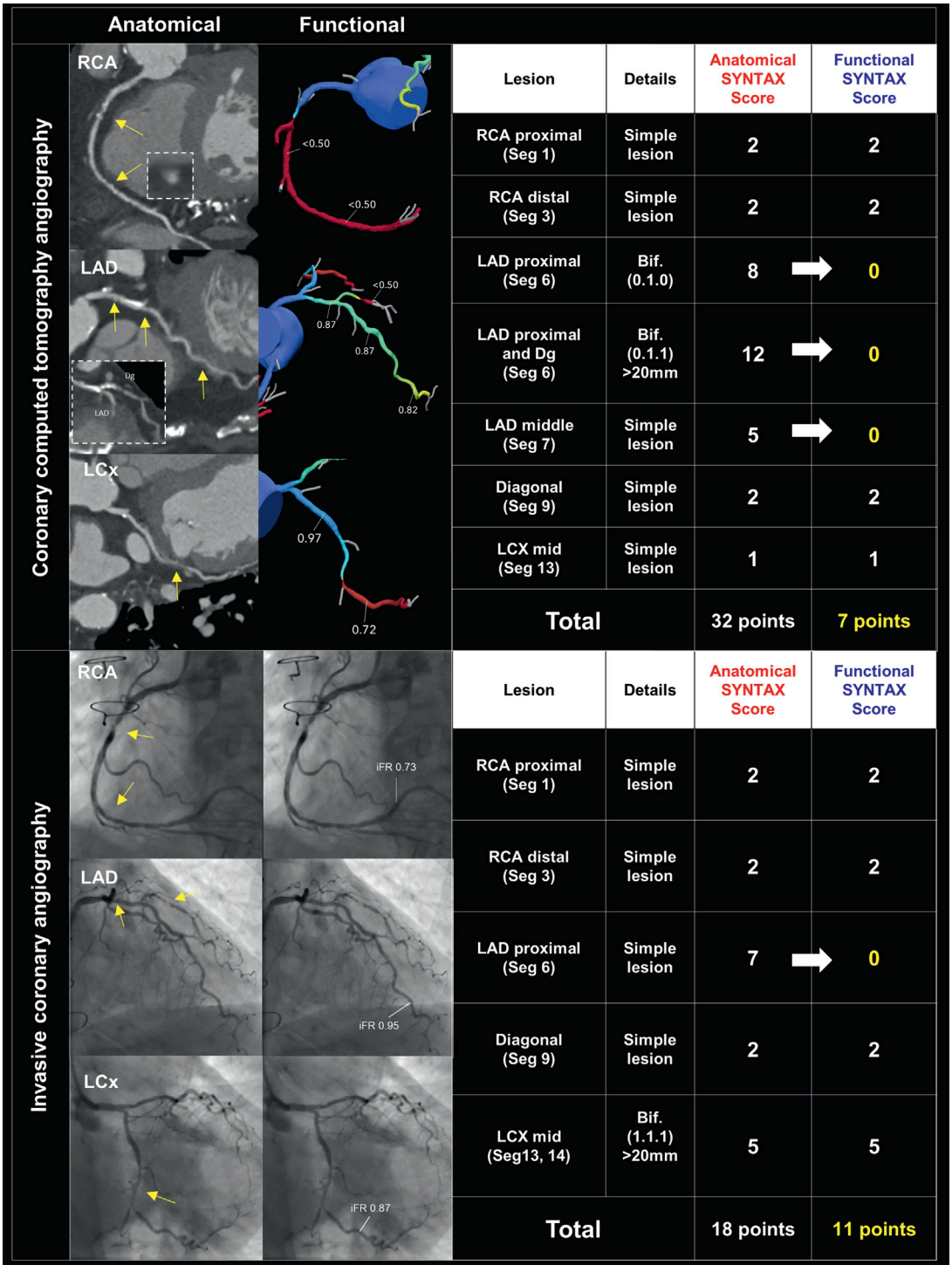
(A) Passing-Bablok regression analysis demonstrating the absence of systematic or proportional difference between the anatomic SYNTAX score (SS) derived from coronary CTA and conventional angiography. **(B)** Bland-Altman plot and mean difference between coronary CTA and conventional angiography-derived anatomic SS. **(C and D)** Comparison between coronary CTA and conventional angiography-derived SS per patient **(C)** and per lesion **(D)**. **(E)** Distribution of the coronary CTA and conventional angiography-derived anatomic SS. Abbreviations as in Figure 1.

FIGURE 3 Comparison of the Functional SYNTAX Score Between Coronary CTA and Conventional Coronary Angiography



(A) Passing-Bablok regression analysis demonstrating the absence of systematic or proportional difference between the noninvasive and invasive functional SYNTAX score (FSS). **(B)** Bland-Altman plot and mean difference between the noninvasive and invasive FSS. **(C and D)** Comparison between noninvasive and invasive FSS per patient **(C)** and per lesion **(D)**. **(E)** Distribution of the noninvasive-derived and invasive-derived FSS. Abbreviations as in Figure 1.

FIGURE 4 Case Example of the Calculation of Noninvasive and Invasive Anatomic and Functional SYNTAX Score

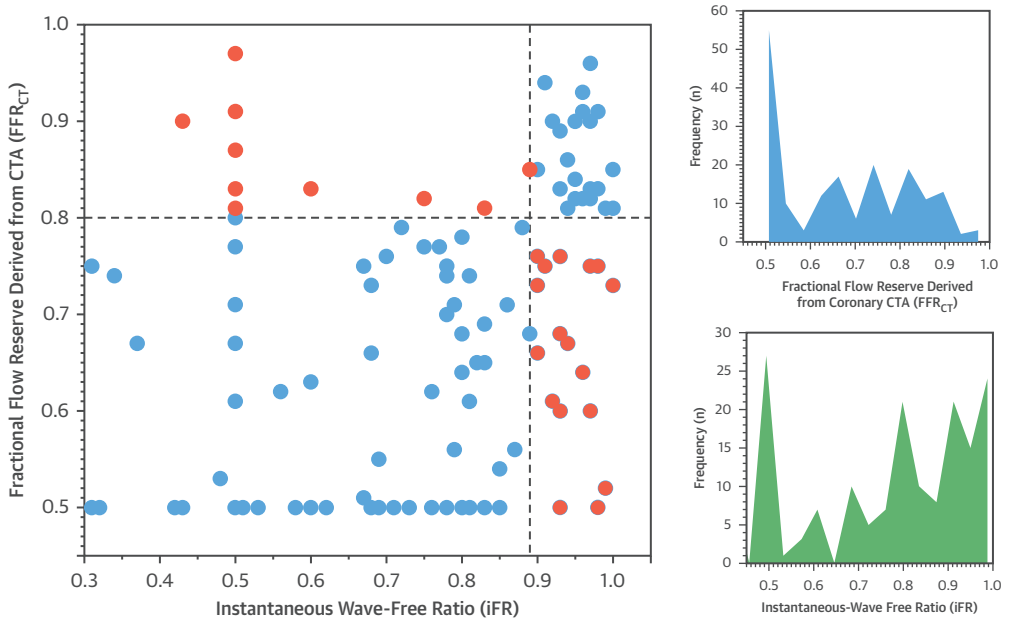


Lesion	Details	Anatomical SYNTAX Score	Functional SYNTAX Score
RCA proximal (Seg 1)	Simple lesion	2	2
RCA distal (Seg 3)	Simple lesion	2	2
LAD proximal (Seg 6)	Bif. (0.1.0)	8 →	0
LAD proximal and Dg (Seg 6)	Bif. (0.1.1) >20mm	12 →	0
LAD middle (Seg 7)	Simple lesion	5 →	0
Diagonal (Seg 9)	Simple lesion	2	2
LCX mid (Seg 13)	Simple lesion	1	1
Total		32 points	7 points

Lesion	Details	Anatomical SYNTAX Score	Functional SYNTAX Score
RCA proximal (Seg 1)	Simple lesion	2	2
RCA distal (Seg 3)	Simple lesion	2	2
LAD proximal (Seg 6)	Simple lesion	7 →	0
Diagonal (Seg 9)	Simple lesion	2	2
LCX mid (Seg13, 14)	Bif. (1.1.1) >20mm	5	5
Total		18 points	11 points

(Top) Calculation of the noninvasive SS. The anatomic CTA-SS based on the presence of lesions with diameter stenosis >50% identified 7 lesions for a total anatomic SS of 32 points. However, the lesions in the LAD (segments 6 and 7) were not functionally significant (FFR_{CT} 0.82) and were thus removed for the FSS calculation. The final noninvasive FSS was 7 points. **(Bottom)** The SS derived from invasive angiography identified 5 lesions for a total anatomic SS of 18 points. However, the lesion in the LAD was removed from the calculation due to an iFR of 0.95; thus, the pressure-wire-derived FSS was 11 points. Bif = bifurcation lesion; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; other abbreviations as in Figures 1 to 3.

FIGURE 5 Comparison of Fractional Flow Reserve Derived From Coronary CTA and iFR



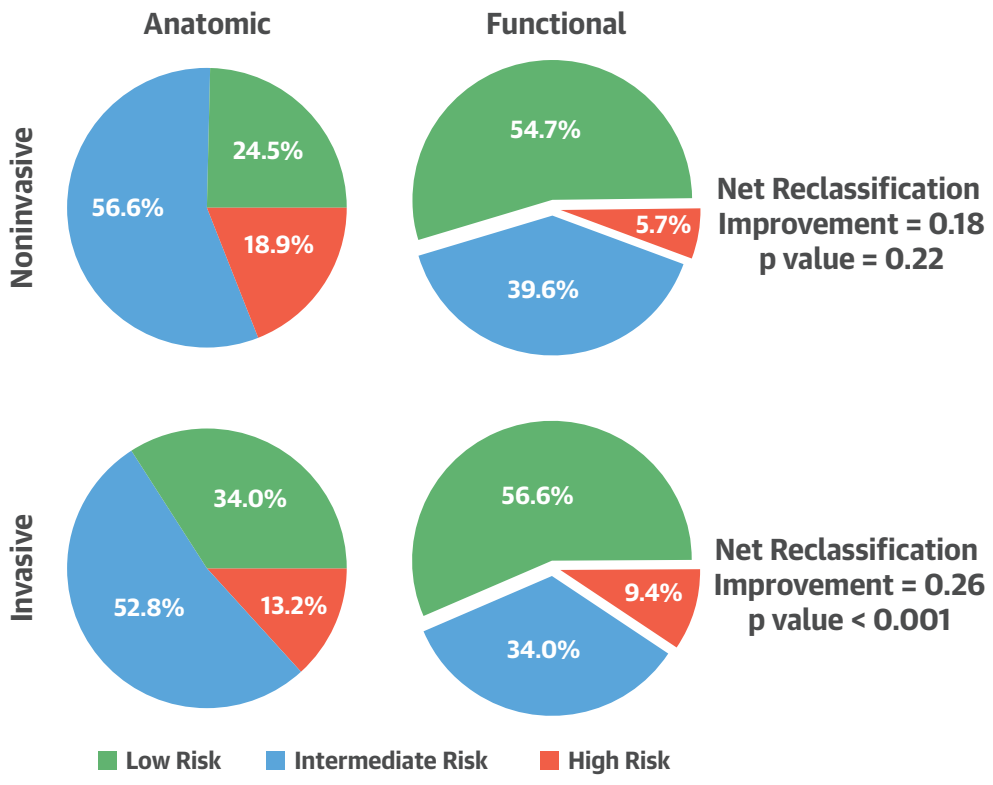
(Left) Scatter plot showing the correlation between instantaneous wave-free ratio (iFR) and fractional flow reserve derived from coronary CTA (FFR$_{CT}$). The **blue dots** represent the agreement in the physiological classification of the lesion, whereas the **orange dots** denote the lesions with disagreement (false positive and negatives). The **right panels** show the distribution of the FFR$_{CT}$ **(top)** and iFR **(bottom)** values. Abbreviations as in Figure 1.

adding the individual scores of lesions with an FFR$_{CT}$ ≤0.80 distal to the stenosis, excluding lesions with FFR$_{CT}$ >0.80. In the case of sequential lesions, the FFR$_{CT}$ distal to the most distal lesion was used to assess lesion significance. Similar to the invasive methodology, a default FFR$_{CT}$ value of 0.50 was imputed when the FFR$_{CT}$ model identified a lesion as totally occluded. When a lesion was included in the anatomical SYNTAX score but an FFR$_{CT}$ value could not be calculated (e.g., small vessels, distal segments with reference vessel diameter <1.8 mm), the points from the anatomic CTA-derived SS were included in the calculation of the noninvasive FSS. To compare pressure-wire (iFR/FFR) and FFR$_{CT}$ values, the position of the pressure wire sensor and the noninvasive model were colocalized.

CLINICAL ENDPOINTS. Major adverse (patient-oriented) cardiac events at 1-year follow-up were defined as the composite of all-cause death, any myocardial infarction (MI), or any revascularization. The Society for Cardiovascular Angiography and Interventions definition was used for periprocedural MI (17). Spontaneous MI was defined as new Q waves or 1 plasma level of creatine kinase-MB 5× the upper limit of normal (or troponin ≥35× upper limit of normal if creatine kinase-MB was not available) in the clinical context of acute coronary syndrome. An independent clinical event committee adjudicated adverse events.

STATISTICAL ANALYSIS. Binary variables are presented as percentages, and continuous variables as mean ± SD or median (interquartile range [IQR]), depending on the distribution. Continuous variables with normal distribution were compared with the Student's *t*-test. Proportions were compared with the chi-square test. The agreement in the SS between imaging modalities was assessed using the Passing-Bablok and Bland-Altman methods. Cohen's kappa was used to assess the agreement of the SS components between imaging modalities (18). The risk reclassification of the SS tertiles from the anatomical to the functional model was assessed by net reclassification improvement with 2 categories (i.e., low SS ≤22 and intermediate/high SS ≥23). The area under the receiver-operating characteristics curve (AUC) was used to assess the diagnostic accuracy of FFR$_{CT}$. The interobserver reproducibility of the anatomical SS and FSS was evaluated at the per-lesion level using intraclass correlation coefficient (ICC) for single measures and the Bland-Altman method. Agreement on the SS tertiles (0 to 22, 23 to 32, and ≥33) was

CENTRAL ILLUSTRATION **Noninvasive Functional SYNTAX Score: Comparison of Risk Reclassification Between the Noninvasive and Invasive Functional SYNTAX Score**



Collet, C. et al. J Am Coll Cardiol. 2018;71(24):2756-69.

(Top) Risk reclassification based on the noninvasive SYNTAX score risk tertiles. With the use of noninvasive imaging and fractional flow reserve derived from computed tomography angiography, 30% of patients were reclassified to the low-risk tertile. **(Bottom)** Conventional angiography and pressure wire assessment reclassified 23% to the low-risk tertile. Net reclassification improvement is based on 2 categories of the SYNTAX score (i.e., low 0 to 22, and intermediate/high ≥23). Net reclassification improvement with 3 categories is shown in Online Table 4. SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery.

investigated using weighted Cohen's kappa. All statistical analyses were performed with SPSS software version 23.0 (IBM Corp., Armonk, New York) and MedCalc Software version 14.12 (Ostend, Belgium).

RESULTS

A total of 77 patients with 3-vessel CAD underwent coronary CTA prior to physiology-guided PCI and were included in this study. Baseline patient characteristics are shown in **Table 1**. Radiation dose from conventional coronary angiography was significantly higher compared with noninvasive CTA (9.6 mSv [4.7 to 11.9 mSv] in 22 of 77 patients vs. 1.9 mSv [0.81 to 6.00 mSv] in 77 of 77 patients; $p < 0.0001$). The feasibility of the CTA-SS was 86% (66 of 77) whereas the FFR_{CT} computation was feasible in 80% (53 of 66) of patients. The study flowchart is presented in **Figure 1**.

ANATOMIC SS. Using coronary CTA, 365 obstructive lesions (5.5 ± 1.5 per patient) were observed. The mean CTA-SS was 27.6 ± 6.4 points (**Table 2**). Invasive coronary angiography identified 359 lesions (5.4 ± 1.6 per patient) with a mean SS of 25.3 ± 6.9 points. The mean difference between coronary angiography and CTA-derived SS was −2.5 points (limits of agreement −16.7 to 11.8); CTA overestimated the SS by 10.5% (95% CI: 3% to 18%; $p < 0.0001$) using coronary angiography as reference. The Passing-Bablok regression analysis did not reveal a systematic or proportional difference between the CTA and angiography (**Figure 2**). The agreement in the components of the SS between coronary CTA and conventional coronary angiography is shown in Online Figure 1. The ICC of

interobserver reproducibility for the CTA-SS calculation was 0.52 (95% CI: 0.35 to 0.66) (Online Table 2).

FUNCTIONAL SYNTAX SCORE. The FFR_{CT} value was available for 78% (283 of 365) of lesions, whereas the invasive pressure-wire assessment was feasible in 74% (220 of 296) of lesions assessed by the operator at the PCI session. The main reason for not calculating FFR_{CT} was related to small vessel diameter impairing the FFR_{CT} calculation, whereas invasive physiology assessment was not performed due to total occlusion lesions (n = 22), operator decision (visual DS ≥90% or small vessel; n = 35), attempted but unable to cross the lesion (n = 12), and technical failure of the pressure-wire system (n = 7).

FFR_{CT} >0.80 was observed in 73 lesions, whereas an iFR >0.89 was obtained in 78 lesions (Online Figure 2). The functional component of the coronary lesions led to reduction of the noninvasive and invasive FSS to 21.6 ± 7.8 and 21.2 ± 8.8, respectively (p = 0.589). The mean difference between the noninvasive and invasive FSS was −1.5 points (limits of agreement −20.2 to 17.1) without systematic or proportional difference (**Figure 3**). The ICC for interobserver reproducibility of the noninvasive FSS was 0.78 (95% CI: 0.67 to 0.85). A representative example of the calculation of the noninvasive and invasive FSS is shown in **Figure 4**.

ACCURACY OF FFR_{CT} IN PATIENTS WITH 3-VESSEL DISEASE. In 178 lesions, both FFR_{CT} and iFR measurements were available (**Figure 5**). The diagnostic discrimination of FFR_{CT} to detect functionally significant stenosis based on an iFR ≤0.89 revealed an AUC of 0.85 (95% CI: 0.79 to 0.90) with a disease prevalence of 64% (Online Figure 3, Online Table 3). The best cut-off value for FFR_{CT} was 0.80 with a sensitivity of 95% (95% CI: 89% to 98%) and specificity of 61% (95% CI: 48% to 73%). Positive predictive value and negative predictive value were 81% (95% CI: 76% to 86%) and 87% (95% CI: 74% to 94%), respectively.

Four sensitivity analyses were performed: 1) removing 13 lesions with imputed iFR/FFR_{CT} values showed a similar AUC of 0.85 (95% CI: 0.79 to 0.90) with a sensitivity and specificity of 95% (95% CI: 89% to 98%) and 62% (95% CI: 49% to 74%), respectively; 2) excluding lesions with an iFR in the gray zone (i.e., 0.86 to 0.93; n = 17) also yielded a similar diagnostic accuracy AUC of 0.85 (95% CI: 0.78 to 0.90), sensitivity of 93% (95% CI: 26% to 97%), and specificity of 65% (95% CI: 50% to 78%); 3) excluding the patients without nitrate administration before the computed tomography acquisition (n = 6), which yielded similar diagnostic accuracy AUC of 0.83 (95% CI: 0.75 to 0.90), sensitivity of 96% (95% CI: 88% to 99%), and a slight improvement in specificity of 71% (95% CI: 52% to 86%); and 4) excluding the lesion without precise colocalization (n = 66) between the pressure wire position and FFR_{CT} yielded comparable diagnostic accuracy AUC of 0.75 (95% CI: 0.66 to 0.82), sensitivity of 94% (95% CI: 87% to 98%), and specificity of 55% (95% CI: 38% to 71%).

CLINICAL OUTCOMES. All patients were treated using physiology-guided PCI that reduced the number of treated lesions per patient to 2.56 ± 0.99. The use of coronary physiology deferred stenting in one-third of the lesions (30.5%, n = 72). Patient reclassification based on SS tertiles is shown in the **Central Illustration**. The noninvasive FSS reclassified 30% of patients from the high/intermediate-SS tertiles to the low-risk tertile, whereas invasive FSS reclassified 23% of patients from the intermediate/high-SS tertiles to

TABLE 3 Net Reclassification Improvement Between Anatomical SYNTAX Score Derived From CTA and Coronary Angiography

		Functional SYNTAX Score			
Anatomic SYNTAX Score	**Events**	**Low**	**Intermediate**	**High**	**Total**
Coronary CTA					
Low	Nonevents	12	0	0	12
	Events	1	0	0	1
Intermediate	Nonevents	11	15	0	26
	Events	1	3	0	4
High	Nonevents	4	1	3	8
	Events	0	2	0	2
Total	Nonevents	27	16	3	
	Events*	2	5	0	
Coronary angiography					
Low	Nonevents	14	0	0	14
	Events	4	0	0	4
Intermediate	Nonevents	12	14	0	26
	Events	0	2	0	2
High	Nonevents	0	1	5	7
	Events	0	0	1	1
Total	Nonevents	26	14	6	
	Events*	4	2	1	

*Two patients with target lesion revascularization were not included because the FFR_{CT} computation was not feasible.

Abbreviations as in Table 1.

TABLE 4 Agreement Between Anatomic Noninvasive and Invasive Imaging According to the SYNTAX Score Tertiles

		Angiography-Derived Anatomic SYNTAX Score			
		0–22	**23–32**	**>32**	**Total**
Coronary CTA-Derived Anatomic SYNTAX	**0–22**	4	9	0	13 (24.5)
	23–32	12	14	4	30 (56.6)
	>32	2	5	3	10 (18.9)
	Total	18 (34.0)	28 (53.0)	7 (13.0)	53
		Weighted Kappa 0.19			

Values are n or n (%). **Shaded cells** indicate the cases of agreement on the risk category.

Abbreviations as in Table 1.

TABLE 5 Agreement Between Functional Noninvasive and Invasive Imaging According to the SYNTAX Score Tertiles

		Pressure Wire-Derived Functional SYNTAX Score			
		0–22	23–32	>32	Total
FFRCT-Derived Functional SYNTAX Score	0–22	17	12	0	29 (54.7)
	23–32	13	5	3	21 (39.6)
	>32	0	1	2	3 (5.7)
		30 (56.6)	18 (34.0)	5 (9.4)	53
		Weighted Kappa 0.32			

Values are n or n (%). **Shaded cells** indicate the cases of agreement on the risk category.
Abbreviations as in Table 1.

the low-risk tertile; however, the risk reclassification using the noninvasive FFS was not statistically significant. The difference in risk reclassification was driven by a greater reduction of the high-SS tertile by FFR_{CT} compared with the iFR/FFR (**Table 3**). The noninvasive FSS reclassified 2 patients with adverse events (i.e., target lesion revascularization) from the high-SS to the intermediate-SS tertile. PCI was deferred in 32 lesions with FFR_{CT} >0.80 and negative iFR/FFR; none of these lesions required intervention at 1 year. The agreement on risk classification based on the classic SS tertiles was slight (Kappa = 0.19) for the anatomic SS and fair (Kappa = 0.32) for the FSS (**Table 4 and 5**).

At 1-year follow-up, the major adverse cardiac event rate was 13.6% (9 of 66 patients): 1 patient died (1.5%) from a noncardiovascular cause, 1 patient had a periprocedural MI (1.5%), and 7 patients underwent revascularization (10.6%; 5 re-PCI and 2 CABG) (Online Table 5).

DISCUSSION

The main findings of the present study can be summarized as follows: 1) in patients with 3-vessel disease, the CTA-SS overestimates the SS derived from coronary angiography; 2) the calculation of noninvasive FSS was feasible and yielded similar FSS compared with the invasive FSS; 3) the integration of the functional component with the CTA-SS improved the reproducibility of the score and the agreement on the classic SS tertile classification between imaging modalities; and 4) FFR_{CT} showed good diagnostic accuracy in patients with 3-vessel disease.

Coronary CTA is a highly sensitive method to detect CAD and has been recommended as a tool to exclude obstructive CAD in noncomplex patients (19). Several studies have compared the anatomic SS derived from coronary CTA and invasive angiography (16,20). A recent meta-analysis (7 studies comprising 1,100 patients) comparing the anatomic SS derived from coronary CTA versus invasive angiography in noncomplex patients (mean SS: 13.5 points) showed a nonsignificant difference between imaging modalities (mean difference 0.6 points; 95% CI: −1.4 to 2.7 points; p = 0.553), suggesting that coronary CTA is accurate in the calculation of the anatomic SS (21). In contrast, the present study, with a mean anatomic SS of 25.3 ± 6.9 points, showed that coronary CTA overestimated the SS by 10.5% compared with invasive coronary angiography. The difference between these findings can be explained by the different complexity of CAD and mean SS between studies. In addition, moderate agreement was observed when assessing the components of the anatomic SS (Online Figure 1). Visual inspection of coronary CTA images in the presence of calcified plaques has shown to overestimate stenosis severity and reduce the agreement between CTA and invasive angiography (22).

In the present study, the use of physiology had a greater effect on the noninvasive FSS. FFR_{CT} reduced the SS by −5.8 points (95% CI: −7.62 to −3.90 points) whereas iFR reduced the SS by −4.5 points (95% CI: −5.79 to −3.21 points). The overestimation of the CTA-SS was corrected by FFR_{CT}, resulting in a similar FSS to that derived from invasive assessment with iFR. In the FAME trial, a similar reduction of the SS was observed with FFR: the SS was reduced from 14.8 ± 6.0 points to 11.3 ± 6.9 points (1). Furthermore, Nam et al. (3) showed that, compared with the anatomic SS, the FSS had a better prognostic value to discriminate risk for adverse clinical events; in their study, the FSS reclassified 32% of patients to a lower-risk SS tertile. Similarly, we found that 30% and 23% of the patients were reclassified to the low-risk tertile with noninvasive and invasive FSS, respectively; however, with noninvasive imaging, the net reclassification improvement did not achieve statistical significance. Consistently, the FAME, FAME II, and SYNTAX II trials have shown a risk reclassification in approximately 25% to 30% of patients with multivessel disease who are undergoing coronary physiology evaluation. Furthermore, the approach of deferring nonhemodynamically significant lesions has been shown to be safe in very late follow-up (23).

Despite the absence of significant differences in the FSS derived from noninvasive and invasive imaging, the agreement on the FSS risk tertile classification was only fair (Kappa = 0.32). The noninvasive FSS accurately classified 45% of the cases into low, intermediate, and high risk compared with invasive FSS. Interestingly, misclassifications in the FSS tertile occurred only in 1 category and were mainly due to the disagreement in physiological assessment between FFR_{CT} and iFR (**Tables 4 and 5**). It is worth

mentioning that the clinical decision-making process for revascularization is enhanced by the inclusion of patients' clinical characteristics and comorbidities. The SYNTAX score II, which combines patients' clinical characteristics and comorbidities with the angiographic complexity assessed by the SS, has been shown to assist the heart team in the decision between CABG and PCI based on an individualized prediction of 4-year mortality. Use of the noninvasive FSS and SYNTAX score II to guide the heart team in the decision-making process is being investigated in the randomized SYNTAX III REVOLUTION trial (24).

The diagnostic accuracy of FFR_{CT} has been investigated in patients with suspected CAD (25). The median FFR_{CT} value reported in these studies was 0.86 (IQR: 0.76 to 0.91), with an overall diagnostic accuracy of 82% (95% CI: 79.4% to 84.4%) (26). In contrast, SYNTAX II included patients with known 3-vessel CAD. The median FFR_{CT} value was 0.67 (IQR: 0.50 to 0.81) and the diagnostic accuracy assessed by the AUC was 0.85 (95% CI: 0.79 to 0.90) using iFR as a reference. Cook et al. (26) combined different FFR_{CT} technologies and observed a V-shaped curve relationship between the FFR_{CT} value (x-axis) and diagnostic accuracy (y-axis), suggesting a higher accuracy of FFR_{CT} to detect physiologically significant lesions with values <0.63 or >0.83. However, we observed a higher accuracy of FFR_{CT} than that predicted by the V-shape curve (26). Yet, Cook et al. (26) included various FFR_{CT} methodologies and used FFR as a reference, as opposed to the present study, which used 1 FFR_{CT} technology and iFR as a reference. At 1 year, clinical outcomes have been similar between patients undergoing PCI guided by iFR and FFR; however, iFR has been found to reduce the number of functionally significant lesions compared with FFR (14). This may partially explain the lower specificity reported in the SYNTAX II trial compared with previous FFR_{CT} publications; nonetheless, the small number of "false negatives" is reassuring in the noninvasive setting. Other factors that should be taken into consideration are the anatomical complexity of the SYNTAX II population and the absence of nitrates before computed tomography image acquisition that occurred in 10% of the patients. The advance stage of CAD and presence of multiple lesions (5.5 ± 1.5 per patient) challenges the accuracy of the noninvasive coronary reconstruction, and thus of FFR_{CT}. In the present analysis, despite a complex anatomical scenario, the accuracy of the FFR_{CT} remained high.

In the 2017 American and 2014 European revascularization guidelines (6,7), the recommendation for CABG or PCI is based on the extent and complexity of the CAD assessed by the anatomic SS. In patients with 3-vessel CAD and SS >22 points, CABG is the preferred strategy, whereas in patients with SS <22, both CABG (Class I) and PCI (Class IIb for the American guideline and Class I for the European guideline) can be recommended (6,7). However, refining risk stratification with the FSS can reclassify 25% to 30% of patients into a lower-risk category and potentially an alternative revascularization strategy can be offered (3). Computational fluid dynamic modeling utilizing CTA images has the potential to reclassify an individual patient's risk, determine the optimal revascularization strategy, and assist in treatment planning with virtual PCI prior to an invasive procedure. A prospective, blinded, randomized clinical trial is currently ongoing assessing the agreement between heart teams in the decision-making process between CABG and PCI using either coronary CTA with FFR_{CT} or conventional angiography in patients with multivessel CAD (24). This trial will set the foundation for an outcome trial that should assess whether a noninvasive anatomical and functional stratification is superior to the current standard of care.

Coronary physiology has refined the assessment of patients with CAD by identifying patients who benefit from revascularization. Invasive physiological assessment has several limitations, such as cost, time, and associated risk; a noninvasive physiological investigation could guide the physician to lesions that require invasive assessment. Although invasive pressure-wire evaluation is steadily increasing, the National Institute for Health and Care Excellence guidelines have advocated the use of coronary CTA (with FFR_{CT}) as the first-line test for patients with suspected anginal pain (27). In the next decade, the use of coronary CTA is expected to increase 700% (27,28). The widespread adoption of these technologies brings the potential to change the clinical practice would be changed by refining the management of patients with CAD.

STUDY LIMITATIONS. First, although pre-defined in the protocol, the present study is a post hoc analysis of the SYNTAX II study. Second, the relatively small number of included patients precludes addressing the clinical discrimination of the noninvasive FSS, and the study is also underpowered to investigate clinical outcomes. Third, inclusion in the SYNTAX II study relied on an equipoise SYNTAX score II recommendation; therefore, patients with a clear benefit from CABG, such as young female patients and those with the most complex CAD, could have been underrepresented. Fourth, although the FFR_{CT} was feasible in 80% of the cases with CTA analysis, 24 of 77 patients could not be analyzed for noninvasive FSS; however, the CT scanners used were neither uniform nor of the latest technology (Online Table 6).

Fifth, the Agatston score was not calculated in the present study, which limits the comparability with previous publications regarding calcium burden. Sixth, the method used for the FSS calculation does not address the effect of an individual lesion in cases of diffuse disease or sequential lesions. Seventh, though the iFR and FFR_{CT} were assessed distal to the coronary lesions, the pressure-wire position was recorded in 63% of the lesions (29). Eighth, a potential selection bias may exist because not all patients undergoing physiology-guided PCI underwent coronary CTA before the invasive procedure. Ninth, although the radiation dose from coronary angiography was higher compared with coronary CTA, this reduction should be interpreted with caution because the calculation of ED with invasive coronary angiography was feasible in a limited number of patients. Tenth, the safety of deferring lesions based on FFR_{CT} in the context of multivessel disease requires further investigation. However, previous studies have demonstrated the safety of deferring lesions based on FFR and FFR_{CT} (23,30). Eleventh, although computed tomography readers were blinded to the invasive angiogram, they might have been aware that patients had 3-vessel disease as this was an inclusion criterion for the SYNTAX II study.

CONCLUSIONS

The calculation of the noninvasive FSS is feasible and the results are similar to those obtained by coronary angiography with invasive pressure-wire assessment. The agreement on the SYNTAX score tertile classification improved with the inclusion of the functional component from slight to fair agreement. FFR_{CT} showed good accuracy in detecting functionally significant lesions in patients with 3-vessel CAD.

ADDRESS FOR CORRESPONDENCE: Dr. Patrick W. Serruys, Imperial College London, Cardiology, Westblaak 98, 3012 KM, Rotterdam, the Netherlands. E-mail: patrick.w.j.c.serruys@gmail.com.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The anatomic SS is used to grade the severity and complexity of multivessel CAD and guide the choice of revascularization technique. A refined physiological assessment, the FSS incorporates ischemia to improve discrimination for clinical events and increase reproducibility. Both anatomic SS and FSS can be derived from coronary CTA and FFR_{CT}.

TRANSLATIONAL OUTLOOK: Further developments in cardiac computed tomography and FFR_{CT} have the potential to enhance the accuracy and clinical utility of the technology, even for patients with complex coronary disease.

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KEY WORDS coronary artery bypass graft, coronary computed tomography angiography, coronary physiology, drug-eluting stents, functional SYNTAX score, multivessel disease, percutaneous coronary intervention, SYNTAX score

APPENDIX For supplemental figures and tables, please see the online version of this paper.