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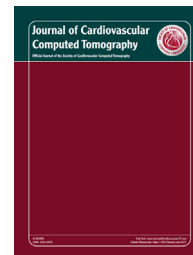**Publication Date**

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Diagnostic accuracy and discrimination of ischemia by fractional flow reserve CT using a clinical use rule: Results from the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography study

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ABSTRACT

Background: Fractional flow reserve (FFR) is the gold standard for determining lesion-specific ischemia. Computed FFR_{CT} derived from coronary CT angiography (coronary CTA) correlates well with invasive FFR and accurately differentiates between ischemia-producing and nonischemic lesions. The diagnostic performance of FFR_{CT} when applied in a clinically relevant way to all vessels $\geq$ 2 mm in diameter stratified by sex and age has not been previously examined.

Methods: Two hundred fifty-two patients and 407 vessels underwent coronary CTA, FFR_{CT}, invasive coronary angiography, and invasive FFR. FFR_{CT} and FFR $\leq$0.80 were considered ischemic, whereas CT stenosis $\geq$50% was considered obstructive. The diagnostic performance of FFR_{CT} was assessed following a prespecified clinical use rule which included all vessels $\geq$2 mm in diameter, not just those assessed by invasive FFR measurements.

Stenoses <30% were assigned an FFR of 0.90, and stenoses >90% were assigned an FFR of 0.50. Diagnostic performance of FFR_{CT} was stratified by vessel diameter, sex, and age.

Results: By FFR, ischemia was identified in 129 of 252 patients (51%) and in 151 of 407 vessels (31%). Mean age (±standard deviation) was 62.9 ± 9 years, and women were older (65.5 vs 61.9 years; P = .003). Per-patient diagnostic accuracy (83% vs 72%; P < .005) and specificity (54% vs 82%, P < .001) improved significantly after application of the clinical use tool. These were significantly improved over standard coronary CTA values before application of the clinical use rule. Discriminatory power of FFR_{CT} also increased compared with baseline (area under the receiver operating characteristics curve [AUC]: 0.93 vs 0.81, P < .001). Diagnostic performance improved in both sexes with no significant differences between the sexes (AUC: 0.93 vs 0.90, P = .43). There were no differences in the discrimination of FFR_{CT} after application of the clinical use rule when stratified by age ≥65 or <65 years (AUC: 0.95 vs 0.90, P = .10).

Conclusions: The diagnostic accuracy and discriminatory power of FFR_{CT} improve significantly after the application of a clinical use rule which includes all clinically relevant vessels >2 mm in diameter. FFR_{CT} has similar diagnostic accuracy and discriminatory power for ischemia detection in men and women irrespective of age using a cut point of 65 years.

1. Introduction

Coronary CT angiography (coronary CTA) has been demonstrated to accurately detect obstructive coronary artery disease (CAD) when compared to invasive coronary angiography (ICA).[1] However, because coronary CTA cannot define the hemodynamic significance of CAD, there is a poor positive predictive value of coronary CTA–defined coronary stenosis for detection of lesion-associated ischemia, especially if a low threshold for stenosis severity (eg, 50%) is used to define "relevant" lesions.[2,3] Fractional flow reserve (FFR) derived from standard coronary CTA scans (FFR_{CT}) is a new method for determining the functional significance of coronary lesions. The diagnostic accuracy of FFR_{CT} for the detection of lesion-specific ischemia has recently been compared with that of coronary CTA alone using invasive FFR as the reference standard.[4] The DISCOVER-FLOW trial demonstrated improved diagnostic accuracy of FFR_{CT} vs coronary CTA stenosis at a per-vessel level when compared to invasive FFR.[5] The Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study also demonstrated improved diagnostic accuracy and improved discriminatory power of FFR_{CT} compared to coronary CTA alone for the diagnosis of ischemia in stable patients with CAD at a lesion-specific level, including those with intermediate stenosis.[6,7] In addition, in the DeFACTO study not all vessels were interrogated with invasive FFR owing to safety concerns leaving only the vessels in which FFR was measured to serve as the reference standard for FFR_{CT}. Although this design was necessary for trial performance, this is not how FFR_{CT} is likely to be used in clinical practice because FFR_{CT} values are computed for the entire coronary tree and will be provided for each coronary vessel. Furthermore, only vessels of suitable diameter would be considered for revascularization, whereas all vessels would require noninvasive assessment because exclusion of vessels introduces pretest bias.[8] As such, the prespecified clinical use rule included all vessels assessed by FFR_{CT} including those that were not measured by invasive FFR. As per the trial protocol, invasive FFR was measured only in

vessels with ICA stenoses of 30% to 90%. Thus, the clinical use rule included predefined required assignment of an FFR value of 0.90 for vessels with stenoses <30% and assignment of an FFR value of 0.50 for vessels with stenoses >90%,[7] in accordance with prior invasive FFR trials, and inclusion of all vessels of diameter ≥2 mm as per expected clinical use. This clinical use rule was meant to emulate the expected use of FFR_{CT} and to eliminate ascertainment bias inherent in single-vessel FFR which was necessary for trial safety in use of invasive FFR.

In addition, it is well known that there are differences in the diagnosis and treatment of men and women with CAD.[9-11] Disparities in CAD outcomes by sex remain despite less obstructive CAD being detected by ICA and higher overall left ventricular function in women compared with men.[12] Recent studies have also demonstrated that there are differences in invasive FFR measurements after adenosine administration between men and women, although there are no differences in baseline characteristics or coronary lesion features.[13] Furthermore, men tend to have more FFR-positive lesions than women despite similar lesion severity by coronary angiography.[14] As such, differences between men and women in the evaluation of CAD remain an important focus to understand treatment disparities. To date, the impact of sex on the diagnostic performance of FFR_{CT} remains unknown. Coronary CTA has traditionally been limited in its application in older patients because of increased vessel calcification resulting in a decrease in diagnostic accuracy and, in particular, positive predictive value. As such, we assessed the diagnostic accuracy of FFR_{CT} in older vs younger patients on the basis of mean age from the FAME trial of 65 years.[15]

We therefore sought to evaluate the effect on diagnostic performance of FFR_{CT} with a prespecified clinical use rule that would optimize the likelihood of unbiased assessment similar to 3-vessel FFR and would integrate the expected clinical use of FFR_{CT} focusing on vessels ≥2 mm in diameter.[8] Given the limited knowledge regarding the diagnostic performance of FFR_{CT} when stratified by sex and age, we performed a further subanalysis of the diagnostic performance of FFR_{CT} using the

clinical use rule in men and women and in patients aged ≥65 or <65 years.

2. Materials and methods

2.1. Study design

The rationale and design of the DeFACTO study have been previously described.[8] Briefly, DeFACTO was a prospective multicenter trial, designed to evaluate the accuracy of FFR$_{CT}$ to diagnose hemodynamically significant CAD, as defined by an invasive FFR reference standard, in patients with suspected native CAD who were referred for clinically indicated nonemergent ICA within 60 days of a coronary CT scan. The DeFACTO study protocol was designed by the steering committee and approved by the institutional review board at each site. All patients provided written informed consent. The per-patient and per-vessel results of this study have recently been published.[4]

2.2. Study population

Enrolled patients were adults with suspected or known CAD who underwent clinically indicated ICA after coronary CTA with no intervening coronary event. Patients were not eligible if they had a history of Coronary artery bypass graft surgery, previous percutaneous coronary intervention with suspected in-stent restenosis, contraindication to adenosine, suspicion of or recent acute coronary syndrome, complex congenital heart disease, prior pacemaker or defibrillator, prosthetic heart valve, significant arrhythmia, serum creatinine level >1.5 mg/dL, allergy to iodinated contrast, pregnant state, body mass index (BMI) >35 (calculated as weight in kilograms divided by height in meters squared), evidence of active clinical instability or life-threatening disease, or inability to adhere to study procedures.

2.3. Protocol for coronary CTA and coronary artery calcium scoring

Each center performed coronary CTA acquisition using a variety of different CT scanner platforms (LightSpeed VCT/Discovery; GE Healthcare, Milwaukee, WI; SOMATOM Sensation and Definition CT; Siemens, Forchheim, Germany; Brilliance 256 and 64; Philips, Surrey, United Kingdom; Aquilion ONE and 64; Toshiba, Otawara, Japan),[16] with trial recommendation to adhere to the Society of Cardiovascular Computed Tomography (SCCT) guidelines on the performance of coronary CTA. However, the exact protocol for the performance of coronary CTA was at the discretion of the site, including the use of beta blockade and nitroglycerin. Intravenous or oral metoprolol was recommended for any patient with a heart rate ≥65 beats/min. It was also recommended that before the image acquisition, 0.2-mg sublingual nitroglycerin be administered. During acquisition, 80 to 100 mL of contrast (Isovue, 370 mg/dL; Bracco, Princeton, NJ; Omnipaque, 350 mg/dL; GE Healthcare, Princeton, NJ; Visipaque, 320 mg/dL; GE Healthcare) was injected followed by a saline flush. Helical or axial scan data were obtained with retrospective gating or prospective electrocardiographic (ECG) triggering, respectively. Image acquisition was prescribed to include the coronary arteries, left ventricle, and proximal ascending aorta. The scan parameters were 64 × 0.625 or 0.750 mm collimation, tube voltage 100 or 120 mV, effective 400 to 650 mA. Radiation dose reduction strategies were used when feasible, with the BMI and heart rate as recommended factors for decisions of increasing mA or kVp or for retrospective ECG helical or prospectively ECG-triggered scan acquisition, respectively.

2.4. Noninvasive coronary artery analysis by CT

Coronay CTAs were analyzed in blinded fashion by an independent core laboratory (LA BioMed, Harbor UCLA, Los Angeles, CA) in accordance with the SCCT guidelines on CT interpretation.[17] CT images were evaluated using 3-dimensional workstations (Vital Images, Minneapolis, MN; Ziosoft, Redwood City, CA). Coronary CTA could be visualized by any postprocessing method, including axial, multiplanar reformat, maximum intensity projection, and cross-sectional analysis.

Coronary segments were scored using an 18-segment SCCT model. In each segment, atherosclerosis was defined as tissue structures >1 mm^2 that existed within the coronary artery lumen or adjacent to the coronary lumen that could be discriminated from pericardial tissue, epicardial fat, or vessel lumen itself. Coronary lesions were classified by luminal diameter stenosis severity as 0%, 1% to 29%, 30% to 49%, 50% to 69%, 70% to 90%, subtotally (90%–99%), or totally (100%) occluded.

Per-patient and per-vessel CAD stenosis were the maximal stenoses identified in all segments or in all segments within a vessel distribution, respectively. Vessel distributions were categorized for the left anterior descending (distribution including the first and second diagonal branches), left circumflex (Cx; distribution including the ramus intermediate, first and second obtuse marginal branches and left posterolateral branch if present), and right coronary artery (RCA; distribution including the posterior descending artery and right posterolateral branch if present). The diameters of all vessels were also recorded.

2.5. ICA image acquisition and FFR performance

Selective ICA was performed by standard catheterization techniques in accordance with the American College of Cardiology guidelines for coronary angiography.[18] Two projections were obtained for each major epicardial vessel, with angles of projection optimized on the basis of cardiac position. FFR was performed in vessels ≥1.5 mm as clinically indicated but was not performed for subtotal (90%–99% stenosis) lesions. After administration of nitroglycerin, a pressure-monitoring guidewire (PressureWire Certus; St. Jude Medical Systems, Uppsala, Sweden; ComboWire, Volcano Corporation, San Diego, CA) was advanced past the stenosis. Hyperemia was attained by administration of intravenous (140 mcg/kg/min) adenosine. The position of the distal pressure sensor was recorded to enable the FFR$_{CT}$ to be calculated from the same point as the measured FFR. FFR was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during hyperemia. FFR was considered diagnostic of ischemia at a threshold of ≤0.80 on a per-patient and per-vessel basis.[19]

Table 1 − Baseline characteristics of study population.

Patient Characteristics	Women (n = 74)	Men (n = 178)	P value
Age, y (mean ± SD)	65.5 ± 8.6	61.9 ± 8.6	.003
Chest pain	81.1%	75.6%	.34
BMI (mean ± SD)	26.3 ± 4.3	27.0 ± 3.5	.23
Prior CAD	32.4%	32.0%	.95
Ethnicity			
Native American	0%	0.6%	1.00
Asian	35.1%	29.2%	.35
Black	1.4%	1.7%	1.00
White	59.5%	63.5%	.55
Hispanic	4.1%	5.1%	1.00
Risk factors			
Smoking	10.8%	20.2%	.07
DM	18.9%	21.9%	.60
HTN	70.3%	71.6%	.83
HLD	78.4%	80.3%	.72
Fam Hx	21.6%	19.2%	.66
Pretest LLK CAD (mean ± SD)	58.3% ± 32.0	64.6% ± 34.6	.17

BMI, body mass index (weight in kilograms divided by height in meters squared); CAD, history of coronary artery disease; DM, diabetes mellitus; Fam Hx, family history; HLD, hyperlipidemia; HTN, hypertension; LLK, likelihood, as determined by the method of Diamond and Forrester[33]; SD, standard deviation.
P values determined by Fisher exact test.

2.6. FFR$_{CT}$ interpretation

FFR$_{CT}$ was performed in a blinded fashion by core laboratory analysts at HeartFlow, Inc (Redwood City, CA). Three-dimensional models of the coronary tree and ventricular myocardium were reconstructed using custom methods applied to blinded CT data for simulation of coronary flow and pressure[20] and as previously published.[8] FFR$_{CT}$ was modeled for conditions of adenosine-induced hyperemia; an FFR$_{CT}$ ≤0.80 was considered diagnostic of lesion-specific ischemia. For the purposes of this analysis when the clinical use rule was applied, all vessels <2 mm (as determined by Quantitative coronary angiography) in diameter were excluded. As per protocol, all vessels with a maximal stenosis (as determined by Quantitative coronary angiography) ≤30% were assigned a default value of 0.9, and vessels with a maximal stenosis ≥90% were considered positive and assigned an FFR value of 0.5 in accordance with the prespecified clinical use rule and prior multicenter randomized trials.[20]

2.7. Statistical analyses

Categorical variables are presented as frequencies and percentages, with continuous variables as mean ± standard deviations. P values for baseline characteristics were determined by the Fisher exact test. Participants were analyzed on the basis of sex and according to age, ≥65 or <65 years. Diagnostic accuracy calculations according to sex and age were performed by standard criteria. After the application of the clinical use rule and according to age and sex, diagnostic measures on a per-patient and per-vessel basis were determined, including sensitivity, specificity, accuracy, and area under the receiver operating characteristics curve (AUC). P values were calculated as determined by the 2-sample test of proportion. All analyses were performed using SAS proprietary software, version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

All 252 patients included in the DeFACTO trial comprised the study population with 407 vessels undergoing evaluation by invasive FFR. All vessels were assessed by coronary CTA and FFR$_{CT}$ to derive accuracy determination so as to reduce the effect of exclusion bias. Characteristics of the study population are listed in Table 1. Women were 3.4 years older than men (mean ± standard deviation = 65.5 ± 8.6 vs 61.9 ± 8.6 years; P = .003). Smoking was more common among male study participants, although this did not reach statistical

Table 2 − Per-patient FFR$_{CT}$ accuracy.

Data set: all patients	N	Sensitivity	Specificity	PPV	NPV	Accuracy	Accuracy P value	AUC	AUC P value
All (n = 252)	252	90	54	67	84	72		81%	
Women (n = 74)	74	90	55	60	89	70		77%	
Men (n = 178)	178	90	53	70	81	73	.61	82%	.50
Age <65 (y; n = 137)	137	89	52	66	81	71		79%	
Age ≥65 (y; n = 115)	115	91	56	68	87	74	.61	83%	.50

Data set: clinical use rule and ≥2 mm vessels	N	Sensitivity	Specificity	PPV	NPV	Accuracy	Accuracy P value	AUC	AUC P value
All (n = 252)	252	86	82	61	95	83		93%	
Women (n = 74)	74	87	81	54	96	82		90%	
Men (n = 178)	178	85	82	63	94	83	.98	93%	.43
Age <65, y, n = 137	137	81	79	58	92	80		90%	
Age ≥65, y, n = 115	115	93	84	64	97	86	.17	95%	.10

AUC, area under the receiver operating characteristics curve; FFR, fractional flow reserve.
P value as determined by the 2-sample test of proportion relative to the row immediately above.
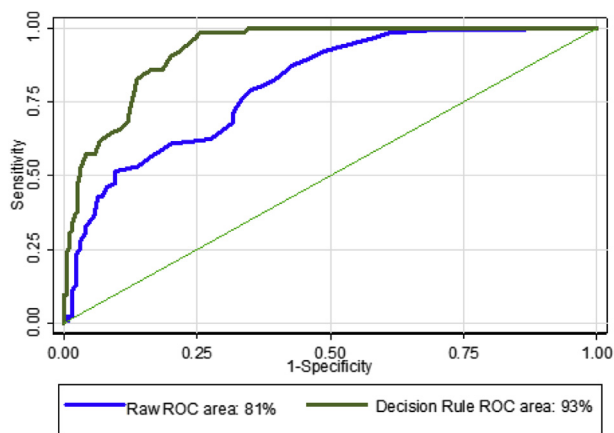
Fig. 1 – Area under the receiver operating characteristic (ROC) curve—per-patient performance of fractional flow reserve CT for all patients (raw) and after the application of the clinical use rule in vessels ≥2 mm in diameter.

significance (P = .07). There was no difference in BMI, hypertension, or diabetes (Table 1).

3.2.   Per-patient diagnostic performance and discriminatory power of FFR$_{CT}$ after application of clinical use rule

Application of the clinical use rule resulted in a significant improvement in per-patient diagnostic performance of FFR$_{CT}$

with an increase in diagnostic accuracy from 73% to 83% (P = .005). This was primarily because of a marked increase in specificity from 54% to 82% (P < .001) with little change in sensitivity (90% vs 86%; P = .78). Negative predictive value increased to 95% (Table 2). By contrast, application of the clinical use rule to anatomic CT alone resulted in a diagnostic accuracy of 70%, specificity of 61%, sensitivity of 83%, and negative predictive value of 70%. Application of the clinical use rule resulted in a significant increase in discriminatory power of FFR$_{CT}$ compared with baseline analysis (AUC: 0.93 vs 0.81; P < .001; Fig. 1; Table 2), compared with an AUC of 0.72 when the clinical use rule was applied to anatomic CT alone. Representative case examples are shown in Figure 2.

3.3.   Per-patient diagnostic performance and discriminatory power of FFR$_{CT}$ in men vs women

Patients were analyzed according to sex with FFR$_{CT}$ demonstrating similar discrimination of ischemia for both men and women at baseline (AUC: 0.82 vs 0.77; P = .50; Table 2). There was no difference between men and women in the baseline accuracy (73% vs 70%; P = .61 or AUC: 82% vs 77%) before the application of the clinical use rule (Table 2). After application of the clinical use rule, diagnostic accuracy remained similar in men and women (83% vs 82%; P = .98), as were sensitivity and specificity (85% and 82% for men and 87% and 81% for women, respectively; Table 2). There were no differences in discriminatory power between men and women (AUC: 0.93 vs 0.90; P = .43; Table 2; Fig. 3).
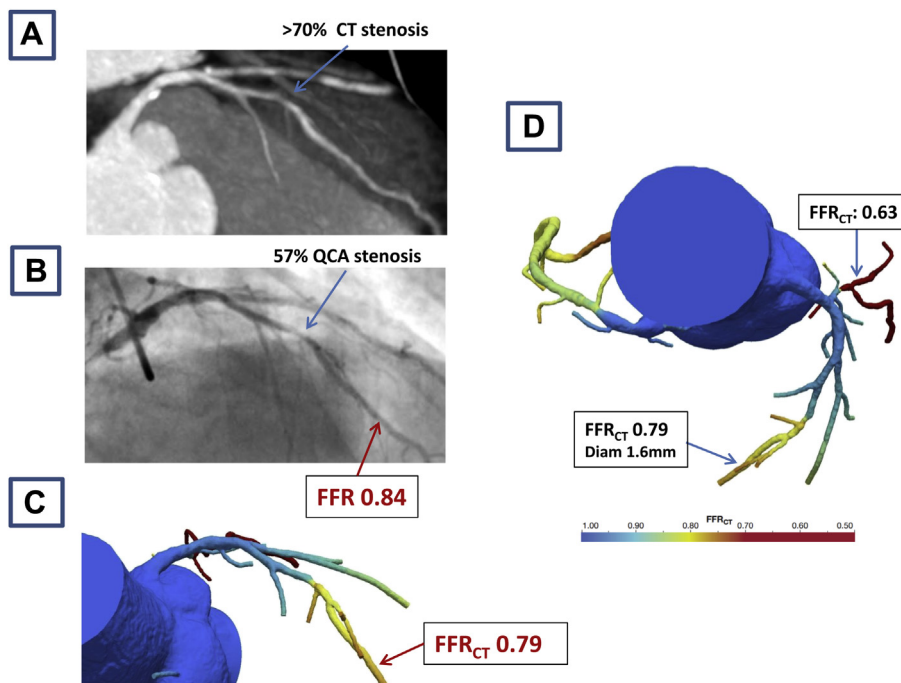
Fig. 2 – Example of false-positive fractional flow reserve CT (FFR$_{CT}$) at the per-vessel level. A left anterior descending artery, <2 mm in diameter, was determined to be positive by CCTA (A), negative by Quantitative coronary angiography and FFR (B), and false positive by FFR$_{CT}$ (C), which was however positive at the per-patient level with obstructive disease in the circumflex vessel by FFR$_{CT}$ (D).
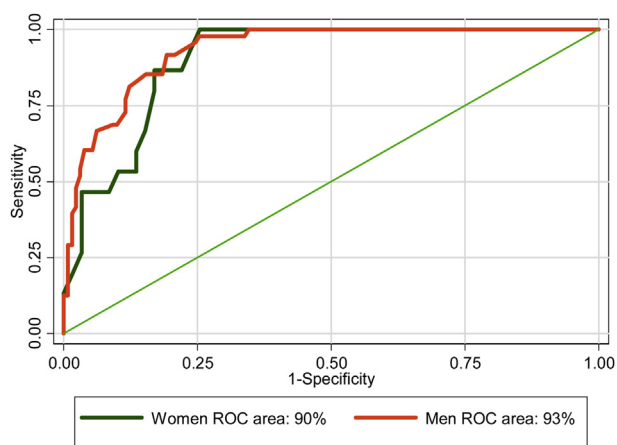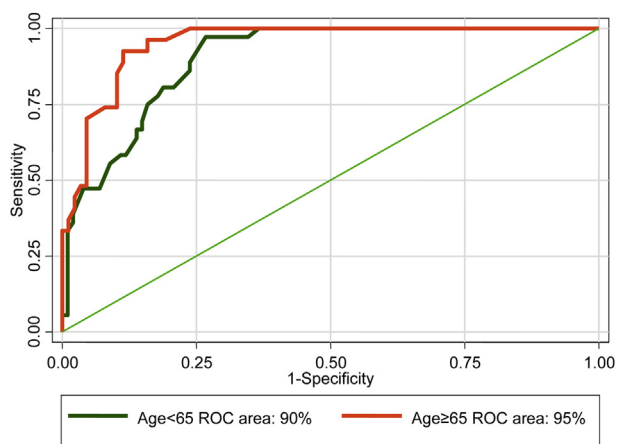
Fig. 3 — Areas under the receiver operating characteristic (ROC) curve of per-patient performance of fractional flow reserve (FFR) CT in men and women compared with invasive FFR for diagnosis of ischemia.

3.4. Per-patient diagnostic accuracy of FFR_{CT} in patients aged ≥65 or <65 years

Analysis of patients aged ≥65 and <65 years demonstrated no significant difference in the ability of FFR_{CT} to detect hemodynamically significant CAD (AUC: 0.83 vs 0.79; P = .50; Table 2; Fig. 4). Application of the clinical use rule improved AUC in all patients with no difference detected when stratified by age (0.95 vs 0.90; P = .10; Table 2). Diagnostic accuracy was similar in those aged ≥65 or <65 years overall (74% vs 71%; P = .61) and when vessels ≥2 mm only were evaluated (86% vs 80%; P = .17).

3.5. Per-vessel diagnostic accuracy of FFR_{CT} in men vs women

Data were analyzed on a per-vessel basis for patients according to sex. There were no significant differences bet-

Fig. 4 — Areas under the receiver operating characteristic (ROC) curve of per-patient performance of fractional flow reserve CT in patients aged < 65 or > 65 years compared with invasive FFR for diagnosis of ischemia.

ween men and women on a per-vessel basis with regard to diagnostic accuracy or AUC for the left anterior descending artery (P = .45 and .09, respectively) or RCA (P = .06 and .13). Insufficient positive counts occurred in the Cx to determine statistical differences, Table 3.

3.6. Per-vessel diagnostic accuracy of FFR_{CT} in patients aged >65 or <65 years

Data were analyzed on a per-vessel basis for patients according to age, >65 or <65 years. There were no significant differences between older and younger patients with regard to diagnostic accuracy or AUC for the left anterior descending artery (P = .45 and .09, respectively). In the Cx, accuracy was no different, but AUC approached statistical significance (P = .7 and .05, respectively). The RCA demonstrated significant difference for accuracy but not AUC (P = .01 and .07, respectively; Table 3).

4. Discussion

The use of computational fluid dynamics for the calculation of FFR using anatomic data from a typically acquired coronary CTA data set provides a unique opportunity to define the physiological significance of CAD without the need for additional radiation or reliance on other functional studies.[4,21] This expands the usefulness of coronary CTA by combining anatomic and functional assessment and raises the potential of coronary CTA to help define those patients that may derive benefit from invasive angiography and possible revascularization. Furthermore, FFR_{CT} analysis provides functional information at all locations in the coronary tree adding a richness of information which may be useful in clinical decision making. This analysis, using a prespecified clinical use rule, may help further our understanding of the potential clinical usefulness of FFR_{CT}. When applied in clinical practice, FFR_{CT} may serve as a single noninvasive test that can provide a complete assessment of anatomy and lesion-specific ischemia in all vessels of suitable size for revascularization rather than just selected vessels studied with invasive FFR. Importantly, our study confirms a significant improvement in the diagnostic accuracy and discriminatory capability of FFR_{CT} when evaluated in accordance with its expected use. Importantly, these improvements hold true in men and women, as well as older and younger patients.

Coronary artery diameter is an important consideration with regard to decision making regarding revascularization. Coronary arteries larger than 3 mm are considered good candidates for revascularization, and the benefit of coronary stenting has been consistently demonstrated in coronary vessels >3 mm in diameter.[22-24] It is well known that restenosis after percutaneous coronary intervention is influenced by vessel diameter and stent occlusion is more frequent in small vessels leading to controversy regarding the utility of stenting in small vessels <3 mm in diameter.[25,26] The issue of small coronary stenting has been addressed in numerous prospective randomized trials of vessels <3 mm in diameter which were analyzed in 2 meta-analyses of the overall

Clinical use rule and vessel ≥2 mm	N	Sensitivity	Specificity	PPV	NPV	Accuracy	Accuracy P value	AUC	AUC P value
LAD									
All (n = 252: 246)	246	75	90	62	94	87		95%	
Women (n = 74: 73)	73	73	87	50	95	85		91%	
Men (n = 178: 173)	173	76	91	68	94	88	.45	97%	.09
Age <65 (y; n = 137: 135)	135	76	89	61	94	87		95%	
Age ≥65 (y; n = 115: 111)	111	74	91	64	94	88	.70	96%	.67
LCX									
All (n = 252: 216)	216	80	95	42	99	94		97%	
Women (n = 74: 66)	66	N/A	N/A	N/A	N/A	N/A	N/A	—	0 Cell counts*
Men (n = 178: 150)	150	80	94	47	99	93		97%	
Age <65 (y; n = 137: 122)	122	75	95	50	98	93		97%	
Age ≥65 (y; n = 115: 94)	94	100	95	29	100	95	.70	100%	.05
RCA									
All (n = 252: 224)	224	84	93	52	98	92		97%	
Women (n = 74: 68)	68	100	97	75	100	97		99%	
Men (n = 178: 156)	156	77	91	44	98	90	.06	96%	.13
Age <65 (y; n = 137: 122)	122	63	90	29	97	88		94%	
Age ≥65 (y; n = 115: 102)	102	100	97	79	100	97	.01	99%	.07

Table 3 – Per vessel.

LAD, left anterior descending artery; LCX, left circumflex; RCA, right coronary artery.

Numbers in brackets in first column represent the total number of patients enrolled in the trial, followed after the colon by the number with complete data sets (ie, includes all patients with invasive fractional flow reserve performed on that vessel or not performed because of stenosis <30% or >90% as per protocol) sufficient for statistical analysis. P value as determined by 2-sample test of proportion relative to row immediately above.

* Zero positive counts in circumflex artery for women resulted in inability to report appropriate sensitivity and specificity and subsequent values.

results.[27,28] Vessels <2 mm in diameter are rarely considered for revascularization and are typically not interrogated with invasive FFR as they are unlikely to benefit from revascularization. Nonetheless, the DeFACTO protocol allowed FFR interrogation of vessels ≥1.5 mm. Importantly, the pre-specified clinical use rule called for the exclusion of vessels between 1.5 mm and 2 mm in diameter that were initially included in the primary DeFACTO analysis. In addition, owing to safety concerns, it was not feasible to mandate 3-vessel FFR as part of the trial design. To eliminate ascertainment bias, we used predefined criteria similar to those used in the FAME studies[20] in which mild disease is assigned a negative FFR and severe stenosis a positive one and limited vessel inclusion to clinically relevant vessels ≥2 mm in diameter. Importantly, this clinical use rule was prespecified during the trial design and is in line with other clinical trials previously performed in this field.

Although differences observed in the invasively measured FFR between men and women have previously been reported, there were no significant differences in the diagnostic performance of FFR$_{CT}$ demonstrated in this study.[13] The reason for differences in invasive FFR between men and women is not known but is felt to at least in part relate to coronary diameter and baseline coronary flow. Importantly, these issues are accounted for in FFR$_{CT}$ modeling through the anatomic model of the coronary arteries and the segmentation of the left ventricular myocardial mass.[29] Although there is evidence that the pathophysiology of CAD and angina in men and women may be different,[30] these issues remain the focus of much investigation; the relevance of lesion-specific ischemia by invasive FFR to help guide revascularization decisions is, however, well solidified. In fact, FFR-guided revascularization has recently received class 1A guideline support,[31] and therefore, a noninvasive test that accurately provides anatomy and lesion-specific ischemia would be of significant clinical value. FFR$_{CT}$ offers this opportunity without exposure to additional radiation or expensive and invasive procedures.

Older age and the associated increased likelihood of calcification have long been felt to limit the application of coronary CTA in older patients. This study confirms that the prediction of hemodynamically significant stenosis is preserved in patients aged ≥65 years compared with those aged <65 years, and thus, age should not hinder the application of this technology. These findings are of particular import as FFR$_{CT}$ may prove to be a technology with significant value in the older age group when exercise stress testing is less applicable because of mobility issues and the risk of adverse outcomes is higher with ICA.[32]

4.1. Limitations

This study is not without limitations. This study is a sub-analysis of the DeFACTO trial, and although the primary trial is significant in size and multicenter in nature, some of the presented subanalyses are limited by smaller sample size (in the analyzed subgroups) limiting power. The findings were meant as exploratory to derive important clues for optimizing FFR$_{CT}$ accuracy. As such, future studies should be performed to confirm our results in future investigations.

5. Conclusions

The diagnostic performance and discriminatory power of FFR$_{CT}$ improve significantly after the application of a prespecified clinical use rule. FFR$_{CT}$ has similar diagnostic accuracy and discriminatory power for the detection of lesion-specific ischemia in men and women and in older and younger patients.

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