Comparison of the Diagnostic Performance of Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve in Patients With Versus Without Diabetes Mellitus (from the MACHINE Consortium)

Fay M.A. Nous, MD[a,b,*], Adriaan Coenen, MD[a,b], Eric Boersma, MSc, PhD[b], Young-Hak Kim, MD, PhD[c], Mariusz B.P. Kruk, MD, PhD[d], Christian Tesche, MD[e], Jakob de Geer, MD, PhD[f], Dong Hyun Yang, MD, PhD[g], Cezary Kepka, MD, PhD[d], U. Joseph Schoepf, MD[e], Anders Persson, MD, PhD[f], Akira Kurata, MD, PhD[a,h], Ricardo P.J. Budde, MD, PhD[a,b], and Koen Nieman, MD, PhD[a,b,i]

Coronary computed tomography angiography-derived fractional flow reserve (CT-FFR) is a noninvasive application to evaluate the hemodynamic impact of coronary artery disease by simulating invasively measured FFR based on CT data. CT-FFR is based on the assumption of a normal coronary microvascular response. We assessed the diagnostic performance of a machine-learning based application for on-site computation of CT-FFR in patients with and without diabetes mellitus with suspected coronary artery disease. The study population included 75 diabetic and 276 nondiabetic patients who were enrolled in the MACHINE consortium. The overall diagnostic performance of coronary CT angiography alone and in combination with CT-FFR were analyzed with direct invasive FFR comparison in 110 coronary vessels of the diabetic group and in 415 coronary vessels of the nondiabetic group. Per-vessel discrimination of lesion-specific ischemia by CT-FFR was assessed by the area under the receiver operating characteristic curves. The overall diagnostic accuracy of CT-FFR in diabetic patients was 83% and in nondiabetic patients 75% (p = 0.088), showing improvement over the diagnostic accuracy of coronary CT angiography, which was 58% and 65% (p = 0.223), respectively. In addition, the diagnostic accuracy of CT-FFR was similar between diabetic and nondiabetic patients per stratified CT-FFR group (CT-FFR < 0.6, 0.6 to 0.69, 0.7 to 0.79, 0.8 to 0.89, ≥0.9). The area under the curves for diabetic and nondiabetic patients were also comparable, 0.88 and 0.82 (p = 0.113), respectively. In conclusion, on-site machine-learning CT-FFR analysis improved the diagnostic performance of coronary CT angiography and accurately discriminated lesion-specific ischemia in both diabetic and nondiabetic patients suspected of coronary artery disease. **(Am J Cardiol 2019;123:537−543)**

Diabetic patients are approximately 2 times more likely to develop coronary artery disease (CAD) than nondiabetic patients, whereas the evaluation and management of CAD in these patients has proven to be more challenging.[1−3] Due to chronic hyperglycemia, diabetic patients are at risk of developing a more diffuse atherosclerosis, a more profound microvascular dysfunction, an increased vascular resistance, and a reduced vasodilation capacity.[4,5] The clinical reference standard to assess CAD is invasive coronary angiography with invasively measured fractional flow reserve (FFR).[6,7] To avoid unnecessary use of invasive modalities, alternatives such as coronary computed tomography (CT) angiography with simulated FFR (CT-FFR) are under development.[8] Novel machine-learning based CT-FFR applications, based on pattern recognition and computational learning, have been recently shown to be as accurate as the more established, on-site performed, computational fluid dynamics based CT-FFR, and furthermore, they have been able to calculate CT-FFR much faster.[9,10] All CT-FFR applications, however, are based on a computational

[a]Department of Radiology & Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands; [b]Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands; [c]Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [d]Coronary Disease and Structural Heart Diseases Department, Institute of Cardiology, Warsaw, Poland; [e]Department of Radiology and Radiological Science, Heart & Vascular Center, Medical University of South Carolina, Charleston, South Carolina; [f]Department of Radiology and Department of Medical and Health Sciences, Center for Medical Image Science and Visualization, CMIV, Linköping University, Linköping, Sweden; [g]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [h]Department of Radiology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan; and [i]Stanford University School of Medicine, Cardiovascular Institute, Stanford, California. Manuscript received July 19, 2018; revised manuscript received and accepted November 1, 2018.

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*Corresponding author: Tel: +31 10 7032055.

E-mail address: f.nous@erasmusmc.nl (F.M.A. Nous).

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simulation of normal coronary hyperemia, which is not the case in diabetic patients.[11,12] This study assessed the diagnostic performance of an on-site machine-learning based CT-FFR application in diabetic patients compared with nondiabetic patients using invasive FFR as the reference standard.

Methods

The study population was part of the MACHINE consortium, which has been described in detail previously.[10] In brief, the MACHINE consortium is a collaboration between 5 institutions in Europe, USA, and Korea, that investigated the diagnostic performance of machine-learning based CT-FFR software (clinicaltrials.gov identifier: 02805621). Patients were identified retrospectively at 4 sites and prospectively in 1 site on the availability of coronary CT angiography and invasive FFR measurements. The studies were conducted in accordance with the Declaration of Helsinki and with research ethics committee approval at each of the sites.

All coronary CT angiograms were performed on first and second generation dual-source CT scanners (Somatom Definition or Definition Flash; Siemens Healthineers, Forchheim, Germany) using a retrospectively ECG-gated spiral (78%), prospectively ECG-triggered axial (20%) or prospectively ECG-triggered high-pitch spiral (2%) scan mode. Patients received sublingual nitroglycerin before the examination and β blockers in case of high heart rates. Stenosis severity was classified per segment following the Society of Cardiovascular Computed Tomography criteria[13]: normal: 0% stenosis; minimal: <25% stenosis; mild: 25% to 49% stenosis; moderate 50% to 69% stenosis; severe: 70% to 99%; and occluded: 100% by observers with extensive previous experience in cardiac imaging. Stenosis ≥50% was considered angiographically significant. Coronary CT angiography image quality was evaluated based on a 4-point Likert scale: 1 nondiagnostic; 2 impaired image quality, differentiation of coronary arty wall possible with reduced confidence; 3 adequate, reduced image quality due to artifacts without limiting coronary artery wall differentiation; 4 excellent, no artifacts present and clear differentiation of the coronary artery wall.

A machine-learning based CT-FFR software prototype (cFFR version 2.1, Siemens Healthineers, Forchheim, Germany; not currently commercially available) was used, as previously described.[8] A 3D coronary artery tree was semiautomatically created and the left ventricular myocardial mass was automatically determined based on the coronary CT angiography data. Each point on the coronary artery tree was analyzed and CT-FFR was derived based on a combination of pattern recognition and computational learning. CT-FFR ≤0.80 was considered hemodynamically significant.

Invasive coronary angiography was performed after local standards and invasive FFR measurements were either performed for clinical reasons or for research purposes. An FFR pressure wire was positioned distal to the stenosis of interest and an FFR was measured during hyperemia by intravenous infusion of adenosine at 140 μg/kg/min. FFR ≤0.80 was considered hemodynamically significant.

Absolute variables are represented as totals and percentages and continuous variables as median and 25th to 75th percentiles. Chi-square, Fisher's exact, and Mann-Whitney U tests were used to check for differences in categorical and continuous variables between the diabetic and nondiabetic group. The correlation between CT-FFR and invasive FFR in diabetic and nondiabetic patients was assessed with a Bland-Altman plot. The diagnostic performances of coronary CT angiography and CT-FFR in diabetic and nondiabetic patients were analyzed with direct comparison of invasive FFR and were reported on a per-vessel basis as sensitivity, specificity, positive predictive value, negative predictive value, and accuracy with 95% limits of agreement. A multivariable logistic regression analysis was performed to determine whether the presence of diabetes mellitus affected the diagnostic performance after adjusting for known differences in patient characteristics. Additionally, the diagnostic accuracy of CT-FFR was reported per stratified CT-FFR group (CT-FFR < 0.6, 0.6 to 0.69, 0.7 to 0.79, 0.8 to 0.89, ≥0.9) with 95% limits of agreement. Per-vessel discrimination of lesion-specific ischemia by CT-FFR was assessed by the area under curve with 95% limits of agreement using FFR ≤0.80 as the reference standard. C-statistics were calculated for CT-FFR in diabetic and nondiabetic patients, and compared by using the method of DeLong et al.[14] Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk, New York). MedCalc (version 13.0; MedCalc Software, Ostend, Belgium) was used to compare the area under the curves.

Results

The study population consisted of 75 diabetic patients and 276 nondiabetic patients. Direct invasive FFR comparison with CT-FFR was available in 110 vessels of diabetic patients and 415 vessels of nondiabetic patients. A detailed overview of the patient characteristics is presented in Table 1. The median age of the diabetic patients was 62 years (56 to 71 years) and 73% were men, which was similar in the nondiabetic group. Diabetic patients were more likely to smoke (44% vs 32%, $p = 0.043$) and to have a myocardial infarction in their medical history (14% vs 6%, $p = 0.035$) than nondiabetic patients. Other patient characteristics were similar in both groups.

Hemodynamically significant disease (invasive FFR ≤ 0.8) was present in 41 vessels (37%) of the diabetic patients and in 171 vessels (41%) of the nondiabetic patients ($p = 0.455$). On coronary CT angiography a ≥50% stenosis was present in 74 vessels (67%) of the diabetic patients and in 308 vessels (74%) of the nondiabetic patients ($p = 0.146$). CT-FFR classified 48 vessels (44%) as functionally obstructed in diabetic patients and 197 vessels (47%) of the nondiabetic patients ($p = 0.474$; Figure 1). The Bland-Altman plot revealed a mean difference between CT-FFR and invasive FFR of -0.034 ± 0.126 in diabetic patients and -0.034 ± 0.116 in nondiabetic patients ($p = 0.95$; Figure 2).

Because of differences in patient characteristics between the diabetic patients and nondiabetic patients, a multivariable logistic regression model was used to evaluate the effect of diabetes mellitus on the diagnostic performance of

Table 1
Patients characteristics

Variables	Diabetes mellitus*		
	No (n = 276)	Yes (n = 75)	p Value
Age (years)	63 (56-69)	62 (56-71)	0.374
Male gender (%)	203 (74%)	55 (73%)	0.970
Body mass index (kg/m^2)†	27 (25-29)	26 (24-30)	0.988
Cardiovascular risk factors (%)			
Hypertension‡	181 (66%)	51 (68%)	0.695
Dyslipidemia§	163 (59%)	47 (63%)	0.572
Family history of coronary artery disease¶	90 (33%)	29 (39%)	0.336
Smoking within the last year	87 (32%)	33 (44%)	0.043
Body mass index ≥25 (kg/m^2)†	194 (72%)	45 (63%)	0.124
Prior myocardial infarction (%)**	13 (6%)	9 (14%)	0.035
Prior percutaneous coronary intervention (%)**	43 (19%)	10 (15%)	0.526
Left ventricular mass (gram)**	161 (139-179)	165 (150-184)	0.061
Agatston coronary calcium score††	227 (39-661)	259 (32-712)	0.965
Coronary CT angiography image quality‡‡	3 (3-4)	3 (3-4)	0.585

CT = computed tomography.

Values are reported as median and twenty-fifth-seventy-fifth percentile or an absolute number n and percentage (%). Differences were tested by Mann-Whitney U tests, Chi-square tests, and Fisher's *t* tests.

* defined as a fasting glucose level of 126 mg/dl (6.99 mmol/L) and higher, HbA1c >= 6.5% or use of antidiabetic medication.

† in 9 patients.

‡ defined as blood pressure >140 mm Hg systolic, >90 mm Hg diastolic, or use of antihypertensive medication.

§ defined as a total cholesterol of >200 mg/dl or use of lipid-lowering therapy.

¶ included known coronary artery disease, former myocardial infarction, or any revascularizations in any first degree relative.

** in 53 patients.

†† in 37 patients.

‡‡ based on a 4-point Likert scale (1 nondiagnostic; 2 impaired image quality, differentiation of the coronary artery wall possible with reduced confidence; 3 adequate reduced image quality due to artifacts without limiting coronary artery wall differentiation; 4 excellent, no artifacts present an clear differentiation of the coronary artery wall. Data were not available.

coronary CT angiography and CT-FFR adjusted for smoking and previous myocardial infarction. The diagnostic performance of CT-FFR was similar in diabetic and nondiabetic patients and improved the diagnostic performance of coronary CT angiography (≥50% stenosis) in both groups (Table 2). No differences were found in accuracy of CT-FFR per stratified group (CT-FFR 0.6, 0.6 to 0.69, 0.7 to 0.79, 0.8 to 0.89, ≥0.9) between diabetic and nondiabetic patients (Figure 3). Additionally, the area under the curves of the diagnostic performance of CT-FFR were similar (p = 0.113; Figure 4).

Discussion

We demonstrated that CT-FFR improved the diagnostic performance of coronary CT angiography and discriminated ischemia with good accuracy in both diabetic and nondiabetic patients suspected for CAD.

The high prevalence of diabetes mellitus in the general population and its significant risk for developing cardiovascular disease emphasizes the importance of accurate anatomical and functional assessment in patients suspected for CAD.[3] Coronary CT angiography has emerged as a valuable approach in the diagnosis of CAD.[15,16] However, the interpretation of coronary CT angiography results differs in diabetic patients due to a more diffuse presentation of CAD and faster progression of the disease.[5,17] An Agatston coronary calcium score of zero has a much shorter warranty period for all-cause death in diabetic patients than in a general asymptomatic population.[18] These findings might be explained by a higher prevalence of noncalcified plaques in the population with diabetes mellitus.[19] Moreover, diabetic patients have greater plaque progression, especially of the noncalcified plaques, which are assumed to increase their risk for plaque rupture.[17] Therefore, plaque morphology assessment by coronary CT angiography has an additional value in cardiovascular risk stratification and could lead to a more focused medical therapy especially in diabetic patients.[20,21] Nevertheless, no studies have been conducted that show if this will lead to a reduction in cardiovascular events.

CT-FFR has incremental value over coronary CT angiography by ruling out the hemodynamic significance of angiographic lesions, which is especially relevant in diabetic patients due to their less typical presentation of CAD.[22] However, CT-FFR algorithms are based on the assumption that the hyperemic response to adenosine is predictable.[12] This could potentially make CT-FFR less reliable in diabetic patients due to a higher prevalence of microvascular dysfunction and higher vascular resistance.[4,5] Few studies are available on the interpretation of on-site CT-FFR analysis in diabetic patients. Coenen et al suggested that the presence of diabetes mellitus resulted in an increased discrepancy between computational fluid dynamics based CT-FFR and invasive FFR.[8] However, these results were not sufficiently powered. A study in which the diagnostic performance of the CT-FFR application commercialized by HeartFlow (HeartFlow Inc., Redwood City, California) was analyzed, showed no differences in the diagnostic accuracy of CT-FFR between diabetic patients and a control group.[23] In the present study, we confirm a similar performance of CT-FFR in diabetic and nondiabetic patients. Additionally, the diagnostic performance of CT-FFR per stratified group was comparable between diabetic and nondiabetic patients. The overall accuracy of CT-FFR did vary depending on the CT-FFR outcome, in line with the systemic review of published studies by Cook et al.[24] Overall, these findings suggest that the presence of diabetic mellitus does not negatively affect the accuracy of CT-FFR.

Validation studies of invasively measured FFR have shown contradictive results on the diagnostic accuracy in diabetes patients.[25−27] This might be explained by differences in study population, since limited data were available on the coronary vasodilation capacity and blood glucose levels of these patients. Clinical outcome studies of invasive FFR guided revascularization have shown higher event rates in diabetic patients than in nondiabetic patients.[28,29] Therefore, the diagnostic

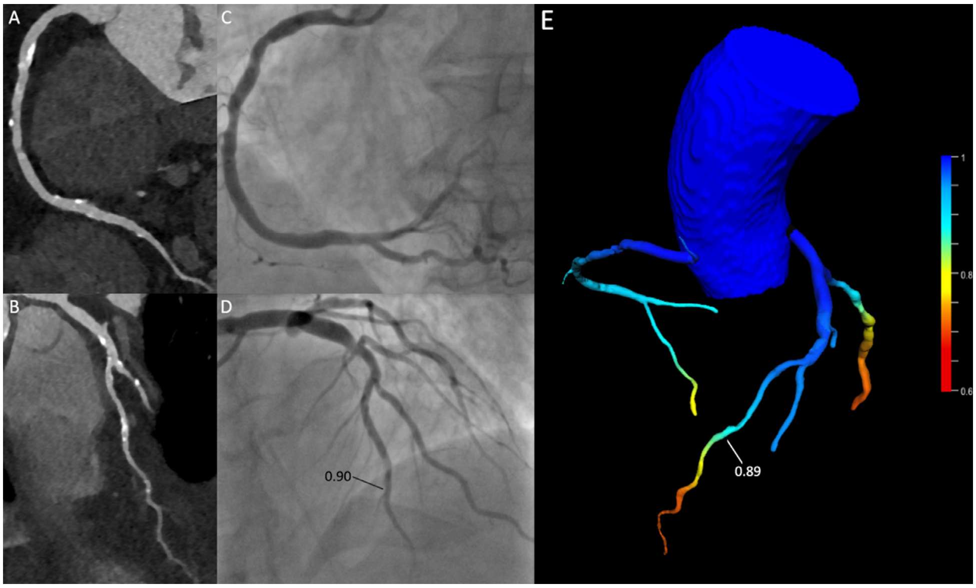

Figure 1. Coronary CT angiography, invasive coronary angiography, and CT-FFR in a single patient. The coronary CT angiography showed several moderate stenoses in the right *(A)* and left coronary artery *(B)*, but the evaluation was hampered by the amount of calcium in the coronary arteries. Invasive coronary angiography showed no significant stenoses in right coronary artery *(C)* and multiple lesions in the left anterior descending artery with a FFR of 0.90 *(D)*. The CT-FFR analysis showed comparable results with the invasively measured FFR *(E)*.

accuracy and interpretation of invasively measured FFR in diabetic patients remains ambiguous.

This study has several limitations that should be acknowledged. Given the retrospective nature of the study and the small sample size, the potential impact of other variables on the diagnostic performance cannot be excluded. Moreover, we assumed that the presence of microvascular dysfunction is based on the presence of

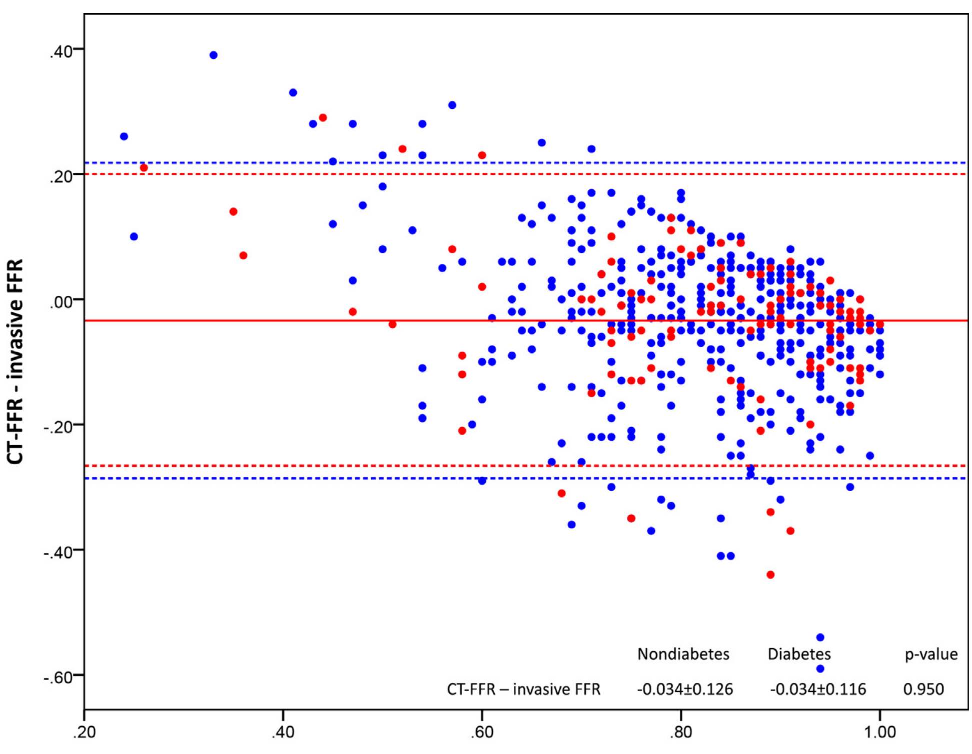

Figure 2. A Bland-Altman plot of CT-FFR and invasive FFR in vessels of diabetic (red) and nondiabetic patients (blue). A horizontal line is placed at the mean difference between CT-FFR and invasive FFR. The dotted lines are placed at the limits of agreement: mean ± 1.96 standard deviation. CT-FFR: computed tomography based fractional flow reserve. (Color version available online.)

Table 2
Per-vessel diagnostic performance

		Sensitivity	Specificity	PPV	NPV	Accuracy
Coronary CT angiography ≥50%	Nondiabetes	87% (82-93%)	37% (30-43%)	50% (44-56%)	80% (72-88%)	58% (53-63%)
	Diabetes	90% (80-100%)	48% (35-61%)	54% (41-66%)	88% (76-100%)	65% (55-75%)
	p-value	0.532	0.271	0.687	0.271	0.223
CT-FFR ≤ 0.80	Nondiabetes	79% (73-86%)	72% (66-78%)	67% (60-74%)	83% (77-88%)	75% (71-80%)
	Diabetes	88% (77-98%)	80% (70-90%)	74% (62-87%)	91% (82-99%)	83% (76-90%)
	p value	0.234	0.190	0.350	0.151	0.088

CT = computed tomography; CT-FFR = computed tomography based fractional flow reserve; NPV = negative predictive value; PPV = positive predictive value.

Values are reported as percentage with 95% confidence interval. Differences are conducted by a multivariable logistic regression model including diabetes, smoking, and prior myocardial infarction.

diabetes mellitus. Our study is limited by the unavailability of directly measured microvascular circulation and vascular resistance and therefore we do not know the impact of microvascular dysfunction in our population. Vasodilatory dysfunction could also have been reversed when patients were optimally treated.[30] Therefore, further studies are needed with extensive information on long-term glucose control of diabetic patients and the extent of microvascular dysfunction to fully evaluate the diagnostic performance of CT-FFR and its effect on clinical outcome of diabetic patient with CAD.

In conclusion, CT-FFR was able to accurately identify functionally significant CAD in both diabetic and nondiabetic patients and improved the diagnostic performance of coronary CT angiography.

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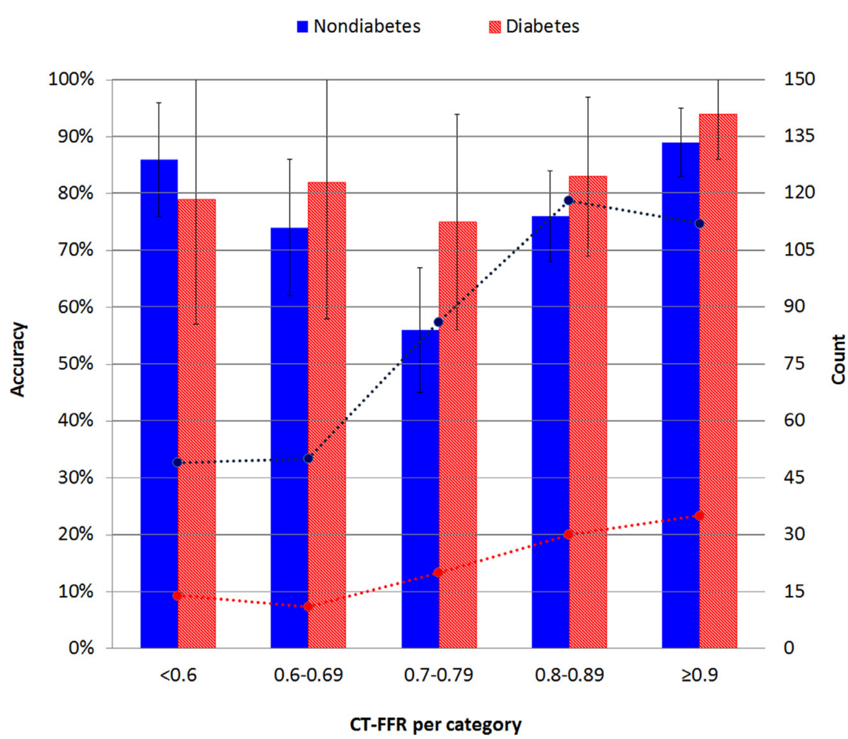

Figure 3. Per-vessel diagnostic accuracy of CT-FFR per stratified group in diabetic (red) and nondiabetic patients (blue). Error bars represent the standard error in each group. On the right y-axis the number of vessels with an invasive FFR value corresponding to each interval of diabetic (red) and nondiabetic patients (blue). CT-FFR = computed tomography based fractional flow reserve. (Color version available online.)

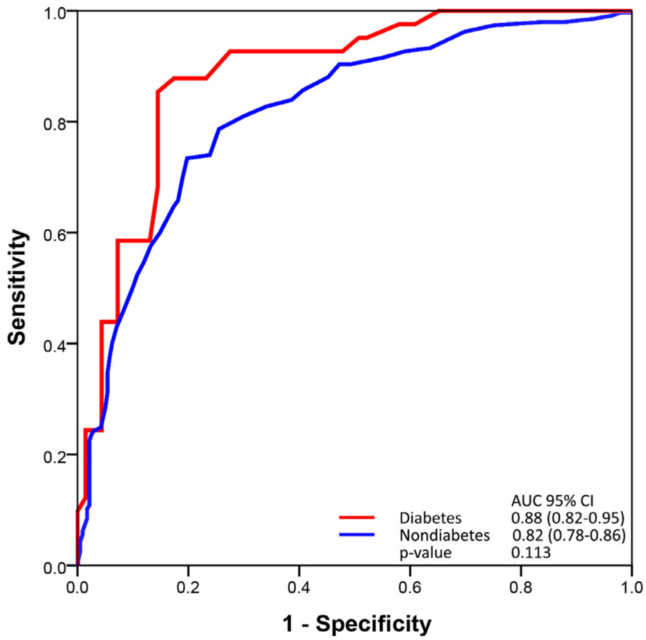

Figure 4. Per-vessel receiver operating characteristics the curves displaying the diagnostic performance of CT-FFR in diabetic (red) and nondiabetic patients (blue). AUC = area under curve; CI = confidence interval; CT-FFR = computed tomography based fractional flow reserve. (Color version available online.)

GE Healthcare, Bayer Healthcare. Other authors declare that they have no competing interests.

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