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Feasibility and validity of CT-derived fractional flow reserve in patients with severe aortic stenosis: the CAST-FFR study

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Abstract

Background—Coronary artery disease (CAD) is common in patients with severe aortic stenosis (AS). Computed tomography-derived fractional flow reserve (CT-FFR) is a clinically-utilized modality for assessing CAD, however its use has not been validated in patients with severe AS. This study assesses the safety, feasibility and validity of CT-FFR in patients with severe AS.

Methods—Prospectively-recruited patients underwent standard-protocol invasive FFR and coronary CT angiography (CTA). CTA images were analyzed by central core laboratory (HeartFlow, Inc., US) for independent evaluation of CT-FFR. CT-FFR data were compared with FFR (ischaemia defined as FFR<0.80).

Results—42 patients (68 vessels) underwent FFR and CTA; 39 patients (92.3%) and 60 vessels (88.2%) had interpretable CTA enabling CT-FFR computation. Mean age was 76.2±6.7 years (71.8% male). No patients incurred complications relating to pre-medication, CTA or FFR protocol. Mean FFR and CT-FFR were 0.83±0.10 and 0.77±0.14, respectively. CT calcium score was 1373.3±1392.9. On per vessel analysis, there was strong positive correlation between FFR and CT-FFR (Pearson's correlation coefficient R=0.64, p<0.0001). Sensitivity, specificity, positive predictive and negative predictive values were 73.9%, 78.4%, 68.0% and 82.9%, respectively with 76.7% diagnostic accuracy. The area under the receiver-operating characteristic curve (ROC AUC) for CT-FFR was 0.83 (0.72-0.93, p<0.0001), which was higher than that of CTA and QCA (p=0.01 and p<0.001, respectively). Bland-Altman plot showed mean bias between FFR and CT-FFR as

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0.059±0.110. On per patient analysis, the sensitivity, specificity, positive predictive and negative predictive values were 76.5%, 77.3%, 72.2% and 81.0% with 76.9% diagnostic accuracy. The per-patient ROC AUC was 0.81 (0.67-0.95, $p < 0.0001$).

Conclusions—CT-FFR is safe and feasible in patients with severe AS. Our data suggests that the diagnostic accuracy of CT-FFR in this cohort potentially enables its use in clinical practice and provides the foundation for future research into the use of CT-FFR for coronary evaluation pre-AVR.

Keywords

FFR; CT-FFR; FFRct; TAVR; AS

Subject terms

Coronary Artery Disease; Aortic Valve Replacement/Transcatheter Aortic Valve Implantation; Computerized Tomography (CT); Valvular Heart Disease

Introduction

Approximately 25-50% of patients with severe aortic stenosis (AS) have concomitant coronary artery disease (CAD)¹⁻⁴. Current guidelines recommend revascularization for patients undergoing transcatheter aortic valve replacement (TAVR) with >70% diameter stenosis in proximal coronary segments and it is therefore common practice to perform prior invasive coronary angiography (ICA)⁵. In addition to revascularization decisions, ICA also serves as a means for procedural risk stratification. However, pre-TAVR ICA is associated with inherent risks, particularly in patients with severe AS whom are usually elderly and with comorbidities⁶. Additionally, ICA provides no information on the functional impact of coronary stenosis, which may be important further guiding revascularization decisions prior to TAVR⁷. Given the recognized limitations of ICA in this higher risk cohort, there remains an unmet need for a valid non-invasive alternative that identifies lesion-specific ischaemia.

Coronary computed tomography angiography (CTA) is a well-established non-invasive modality which is used in the diagnosis and management of patients with chest pain of recent onset. Its excellent negative predictive value makes it particularly useful in the assessment of patients with low to intermediate pre-test probability for CAD. Whilst it can provide clinically useful anatomical information regarding the presence and extent of CAD, it does not provide any data on the functional impact of coronary stenosis⁸. CT-derived fractional flow reserve (CT-FFR) is a more recent development which uses computational flow dynamics to simulate invasive fractional flow reserve (FFR) from a standard CTA acquisition⁹. CT-FFR now provides a mean for deriving both anatomy and function from a standard CTA and its high diagnostic performance has led to its adoption in clinical guidelines¹⁰.

The use of coronary CTA has previously been explored in patients with severe AS^{11, 12}. However, the application of this technology has been limited by the higher burden of calcium within the coronary vasculature in addition to clinicians' reluctance to use pre-scan

medications to optimize image quality (such as nitroglycerin and beta-blockers). However, recent advances and refinements in image-processing techniques have enabled the use of CTA in patients with higher burden of calcium. Improved imaging acquisition in this cohort also permits the possibility of CT-FFR modelling, which provides incremental functional data. However, CT-FFR has not been previously evaluated in the coronary assessment of patients with severe AS.

We therefore designed and conducted a prospective study to assess the clinical safety, feasibility and diagnostic performance of CT-FFR in patients with severe AS, compared against invasively derived FFR.

Methods

Patient selection

This was a prospective, single-center study carried out at Monash Medical Centre, Melbourne between November 2018 and November 2019. The study protocol was approved by the institutional research ethics committee (Human Research Ethics Committees Australia reference: HREC/43524/MonH-2018-67705v1). All recruited patients provided written informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients with severe AS with an indication for TAVR as per international guidelines⁵ and underwent pre-procedural ICA were screened for participation. Inclusion criteria were: (1) aged >18 years and <90 years old and, (2) patients with >30% visual stenosis in at least one coronary artery identified at time of ICA. Exclusion criteria were: (1) severe asthma or resting bradycardia precluding use of adenosine, (2) left ventricular ejection fraction <30%, (3) chronic renal impairment, defined by estimated glomerular filtration rate <30ml/min/1.73m², (4) myocardial infarction within last 3 months, (5) previous coronary artery bypass surgery (CABG), (6) percutaneous coronary intervention (PCI) in the vessel of interest, (7) >90% visual stenosis in the vessel of interest (8) chronic total occlusions and (9) significant left main coronary disease

Invasive FFR protocol

Cardiac catheterization was performed in accordance to standard practice, via the transfemoral or transradial approach. All patients were anticoagulated using 70-100 IU/kg of unfractionated heparin. Orthogonal plane angiography were acquired at 15 frames per second. Pressure wire assessment was then performed if there was at least one vessel (>2 mm ivabradine to achieve a pre-scan heart rate of <60 beats/min (protocol adopted from with

Statistical analysis

The primary endpoint of this study was per vessel diagnostic performance of CT-FFR to predict ischemia, as defined by invasive FFR <0.80 using the area under the receiveroperating characteristic curve analysis (ROC AUC). Secondary endpoints included diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for CT-FFR (<0.80), using FFR <0.80 as reference standard.

Additional outcomes included the diagnostic performance on a per patient basis, whereby the lowest values of FFR and CT-FFR were used in patients with complete data in more than one vessel. Diagnostic accuracy was also evaluated based on a median split of CT calcium scores to determine the validity of this approach in patients with high calcium scores. The Shapiro-Wilk test was used to assess normality of continuous variables. Continuous variables are expressed as mean \pm standard deviation (SD) or median \pm interquartile range. Categorical variables are provided as frequencies (percentages). The correlation between CT-FFR and invasive FFR was assessed with Pearson's correlation coefficient. Agreement between the two indices was assessed with a Bland-Altman technique. Statistical analyses were performed with Stata v.14.1 (StataCorp, College Station, TX, USA) and GraphPad Prism v.8.1.2 (La Jolla, CA, USA).

Results

42 patients (68 vessels) underwent invasive FFR and CTA assessment (Figure 1). Of those, 39 patients (92.3%) and 60 vessels (88.2%) had interpretable CTA data enabling CT-FFR computation. Three patients (6 vessels) were not suitable for CT-FFR calculation due to motion artefact on CTA as adjudicated by the central core laboratory. Additionally, 2 vessels were excluded as they could not be co-registered as the angiographic pressure wire sensor location was distal to the 3D modelled segment. The patient and echocardiographic characteristics are presented in Table 1. The mean age was 76.2 ± 6.7 years of whom 71.8% were male, 69.2% had hypertension, 53.8% had diabetes mellitus and 12.8% had previous myocardial infarction. Mean aortic valve gradient, aortic valve area and left ventricular ejection fraction were 45.1 ± 9.5 mmHg, 0.89 ± 0.25 cm² and $62.9 \pm 10.7\%$, respectively. Mean patient CT calcium score was 1373.3 ± 1392.9 Agatston units.

The CT scanning characteristics are presented in Table 2. All patients received 0.4mg sublingual glyceryl trinitrate. Two-thirds of patients received additional pre-scan medications in order to optimize their heart rate. Mean pre-CTA scan heart rate was 54.2 ± 6.6 beats/min. No patients incurred complications relating to the pre-medication, CTA or invasive FFR protocol.

The vessel characteristics are presented in Table 3. Of the vessels assessed, 36 were left anterior descending arteries, 5 were diagonal, 13 were circumflex or obtuse marginal, 1 was a ramus and 5 were right coronary arteries. On quantitative coronary angiography (QCA), 10.0% of vessels and 15.4% of patients had diameter stenosis $\geq 50\%$. On coronary CTA analysis, 35.0% of vessels and 41.0% of patients had CTA diameter stenosis $\geq 50\%$. Mean FFR and CT-FFR were 0.83 ± 0.10 and 0.77 ± 0.14 , respectively. 38.3% of vessels had an FFR < 0.80 whilst 41.7% of vessels had CT-FFR < 0.80 .

Per vessel analysis

The diagnostic performance of QCA, coronary CTA and CT-FFR against FFR are presented in Table 4. On a per vessel basis, there was a strong positive correlation between FFR and CT-FFR (Pearson's correlation coefficient $R=0.64$, $p<0.0001$, Figure 2). Sensitivity, specificity, positive predictive and negative predictive values were 73.9%, 78.4%, 68.0% and 82.9%, respectively with overall diagnostic accuracy of 76.7%. The ROC AUC for CT-FFR

was 0.83 (95% confidence interval [CI] 0.72-0.93, $p < 0.0001$). The Bland-Altman plot showed the mean bias \pm standard deviation between FFR and CT-FFR was 0.059 ± 0.110 (Figure 3). The ROC AUC for CT-FFR to predict invasive FFR was greater than that of coronary CTA and QCA (both $p < 0.05$).

Per patient analysis

On a per patient analysis, there again was a strong positive correlation between FFR and CT-FFR (Pearson's correlation coefficient 0.70, $p < 0.0001$). Sensitivity, specificity, positive predictive and negative predictive values were 76.5%, 77.3%, 72.2% and 81.0% with overall diagnostic accuracy of 76.9%. On a per patient analysis, the ROC AUC for CT-FFR was 0.81 (CI 0.67-0.95, $p = 0.001$). The Bland-Altman plot showed the mean bias \pm standard deviation between FFR and CT-FFR was 0.064 ± 0.110 .

Subgroup analysis

A subgroup analysis was performed to look at the diagnostic performance of CT-FFR according to the magnitude of the CT-derived calcium score. This was on a per vessel and per patient basis and the results are presented in Tables S1 and S2 respectively in the Data Supplement, and in Figure 4. In the per vessel subgroup analysis, the mean vessel calcium scores in the low and high groups were 123.1 ± 94.2 and 735.3 ± 566.5 Agatston units, respectively. The correlation between CT-FFR and FFR in the low calcium score group was stronger ($r = 0.85$ vs 0.61), however there was no difference between the ROC AUC for CT-FFR between the two groups (0.83 vs 0.82 , $p = 0.94$). In the per patient subgroup analysis, the mean calcium scores in the low and high score groups were 514.8 ± 320.3 and 2277.1 ± 1518.7 , respectively. Similarly, the correlation between CT-FFR and FFR was stronger in the low calcium score group ($r = 0.85$ vs $r = 0.61$), however with no difference between the ROC AUC for CT-FFR between the two groups (0.77 vs 0.80 , $p = 0.84$).

Discussion

Our findings demonstrate, for the first time, that coronary CTA and CT-FFR is safe, feasible and has a diagnostic accuracy which potentially enables its practice in patients with severe AS. These results represent significant progress in the non-invasive assessment of the CAD in patients with severe AS. Despite the well-recognized limitations of using coronary CTA in older patient cohorts with greater burden of coronary vascular calcification, we have demonstrated that in this cohort – older and with a notably high average calcium score – a high diagnostic accuracy can be attained using CT-FFR using the protocols described. Importantly, 92% of our cohort had interpretable data highlighting the potential for future translation into clinical practice.

Several strategies were employed in order to achieve these results. Besides the use of a 320-slice detector CT scanner, we utilized CT-FFR modelling for better characterization and assessment of the vessels to overcome the inherent limitations in the diagnostic performance of CTA alone in the presence of calcified disease. Additionally, we adhered to a strict prescanning medication protocol in order to optimize image quality. This approach has traditionally been avoided in patients with severe AS due to concerns with hypotension and

circulatory collapse. In our study, we ensured all patients were well hydrated prior to drug administration. Nitroglycerin was administered both prior to coronary CTA and invasive FFR measurements. Beta-blockers and ivabradine were used pre-CTA to attain a heart rate of <60 beats/min, which was achieved in 79% of patients. During invasive FFR, intravenous adenosine was used in all patients and there were no adverse effects relating to medication protocols used in our cohort. Whilst complete atrioventricular block remains a greater risk with adenosine in this patient group, a previous report demonstrated preserved coronary hemodynamics despite systemic hypotension in a patient with severe AS¹⁴. Despite no adverse outcomes in our cohort, we are unable to quantify the risk for every patient with severe AS and this would need evaluation in further studies, comparing this strategy against the risk of invasive procedures currently used as standard of care.

The use of coronary CTA in patients with severe AS undergoing TAVR has previously been investigated in two retrospective studies^{11,12}. In these studies, drugs for vasodilatation and chronotropic control were not used due to concerns about safety. These medications are otherwise recommended for improving the diagnostic performance of CTA, particularly in older patients with significant and calcified CAD¹⁵. In one of these studies, 18% of the patients underwent ICA as they were deemed to have significant or uninterpretable disease (excluding those who had undergone ICA for another indication)¹². Of those, more than half the patients had no significant disease on ICA with only a proportion of the remainder (4.5% of the study cohort) undergoing subsequent revascularization. In the second study, all patients underwent ICA following CTA¹¹. Whilst the diagnostic accuracy of CTA was 91% in patients with Agatston scores of <400, the overall accuracy was only 66% in those with Agatston scores >1000. These two studies concluded that the use of coronary CTA in this setting is potentially acceptable in patients with lower calcium scores, with CTA acting as a possible gatekeeper for ICA. Notably, these two studies evaluate CTA diagnostic performance against ICA rather than invasive FFR. In our study, the diagnostic performance of CTA (compared with invasive FFR) demonstrates that the use of this technology - even with strict pre-scanning medication protocols - may be inadequate, even as a gatekeeper for ICA. The use of CT-FFR modelling provides an increment in diagnostic performance and, importantly, this is maintained in both the lower and higher calcium score groups.

The use of CT-FFR also provides important data on the functional impact of coronary disease. Whilst only 10% of vessels in this study cohort had a QCA-defined lesion diameter stenosis >50%, 42% had CT-FFR <0.80 and 38% had invasive FFR <0.80. Similar to observations in non-AS patients^{16,17}, this suggests that diameter stenosis is a poor predictor of FFR <0.80. This may be due to other physiological determinants such as lesion length and the myocardial area subtended.¹⁸ The presence of abnormal physiology in the context of AS and left ventricular hypertrophy may also contribute to this apparent discrepancy.

It is key to acknowledge that the overall diagnostic performance of CT-FFR in this severe AS cohort remains lower than that in previously published literature in non-AS, stable CAD cohorts^{19, 20}. Compared to our participants, patients in previous studies were younger and with less coronary calcification. However, the performance of CT-FFR is acceptable in those with high calcium scores and this alone is unlikely to account for all the discrepancy observed. Another contributing factor may be the altered coronary and microcirculatory

pathophysiology that occurs in patients with severe AS²¹. Valvular stenosis results in pressure overload within the left ventricle and resultant left ventricular hypertrophy. The greater myocardial mass of patients with AS results in increased myocardial oxygen demand which is matched with greater resting coronary blood flow. AS patients also exhibit an impaired coronary hyperemic response. This blunted response is not currently accounted for using standard CT-FFR modelling approaches. Overall, the cumulative effect may explain the relative overestimation of translesional gradients by CT-FFR compared with invasive FFR. Further work is now required in describing the abnormal coronary physiology in differing patient cohorts, with the aim of improving the accuracy of CT-FFR and other techniques that use computational fluid dynamic approaches.

The ability to use coronary CTA and CT-FFR to appropriately delineate the anatomy opens the opportunity to using CT as a ‘one-stop-shop’ assessment for patients referred for TAVR. Currently, these patients routinely undergo CTA for pre-TAVR procedural planning for assessment of the left ventricular outflow tract, annulus, ascending and descending aorta and peripheral vasculature²². Routinely incorporating coronary assessment within this scan would permit comprehensive pre-TAVR assessment in a single scan, which has clear potential benefit for patients. This would potentially include, (1) removing the procedural risks associated with ICA, (2) reducing the risk of nephropathy associated with the additional contrast load of ICA, (3) reducing the discomfort associated with invasive procedures, and (4) potential health-economic advantages associated with fewer invasive tests. Hopefully our data acts as a stimulus for definitive clinical trials that assess the use CT-FFR in procedural planning for patients undergoing TAVR.

Limitations

This a single-center and ongoing validation in a larger, multi-center study is required. With a mean age of 76.2 years, our cohort represents a younger age group than that would currently be undergoing TAVR and it is unclear whether these results can be extrapolated into very elderly patients (>90yrs). However, with expanding indications of TAVR in low and intermediate surgical risk groups, our results may still apply in future patient cohorts. In addition, our subgroup analysis demonstrated that the diagnostic performance of this technology was maintained in patients with higher calcific burden although. Our study also excludes patients who have had previous revascularization (either by CABG or PCI) and LV dysfunction, which represent a sizeable group of patients undergoing TAVR. Finally, the results from this study relate to one commercially available CT-FFR technique and the validity of other non-invasive techniques remains unknown.

Conclusions

Our results demonstrate that CT-FFR is feasible and safe in patients with severe AS. These preliminary data suggest that the diagnostic accuracy of CT-FFR potentially enables its use in clinical practice. These data should act as the foundation for future research into use of CT-FFR during procedural planning for patients with severe AS undergoing valve replacement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AS	aortic stenosis
CABG	coronary artery bypass surgery
CAD	coronary artery disease
CTA	computed tomography angiography
CT-FFR	CT-derived fractional flow reserve
FFR	fractional flow reserve
ICA	invasive coronary angiography
NPV	negative predictive value
PCI	percutaneous coronary intervention
PPV	positive predictive value
ROC AUC	area under the receiver-operating characteristic curve analysis
TAVR	transcatheter aortic valve replacement
QCA	quantitative coronary angiography

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What is Known

- It remains common practice to perform invasive coronary angiography in patients with severe AS undergoing TAVR to identify the severity and extent of CAD.
- Coronary CTA has had a limited role in this patient group due to significant coronary calcification and clinicians' reluctance to use pre-scan medications. Additionally, it provides no information on the functional impact of coronary stenosis which may be important in guiding revascularisation pre-TAVR.
- CT-FFR provides data on the functional impact of coronary stenosis, however, has not previously been validated in patients with severe AS.

What this Study ADDS

- CT-FFR is safe and feasible in patients with severe AS. CT-FFR in this cohort outperforms coronary CTA to identify FFR-significant lesions.
- Further research is required to assess the clinical utility of CT-FFR and outcomes in this patient cohort. With further validation, this may reduce the need for invasive coronary angiography in pre-TAVR assessment.

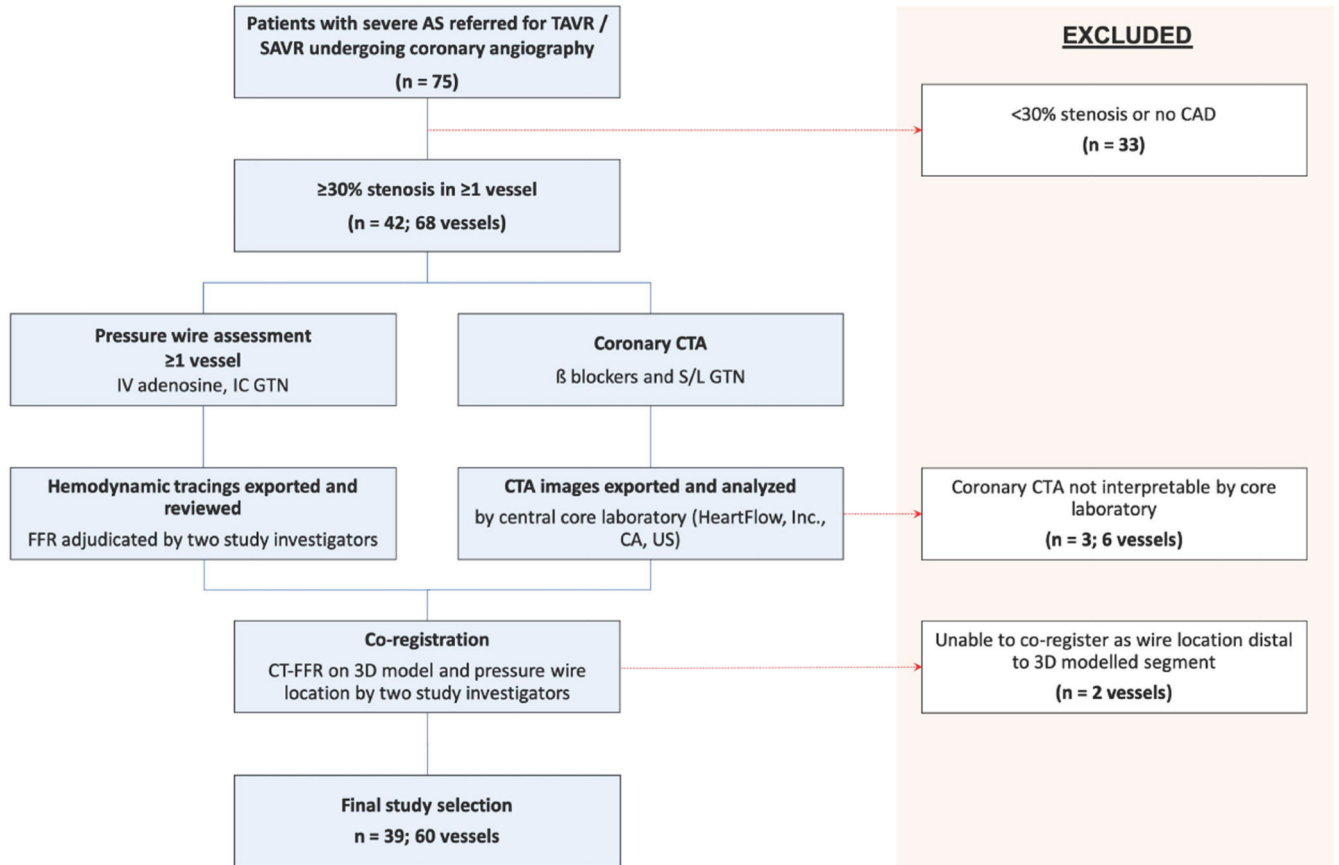


Figure 1. Study Flow Chart

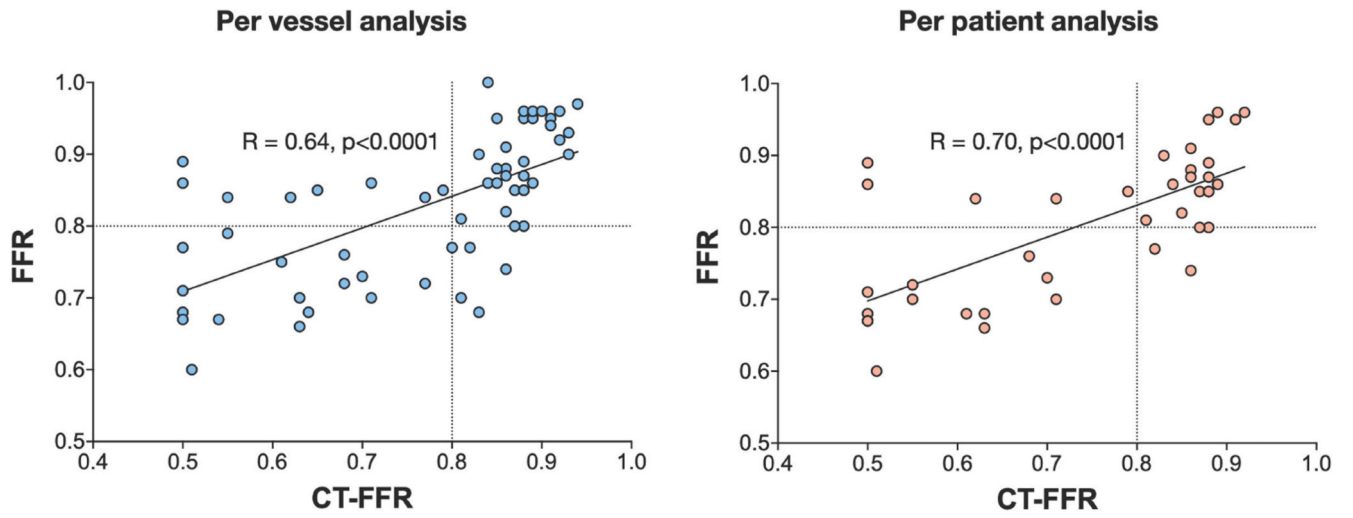


Figure 2. Correlations of CT-FFR vs FFR on A Per Vessel and Per Patient Basis

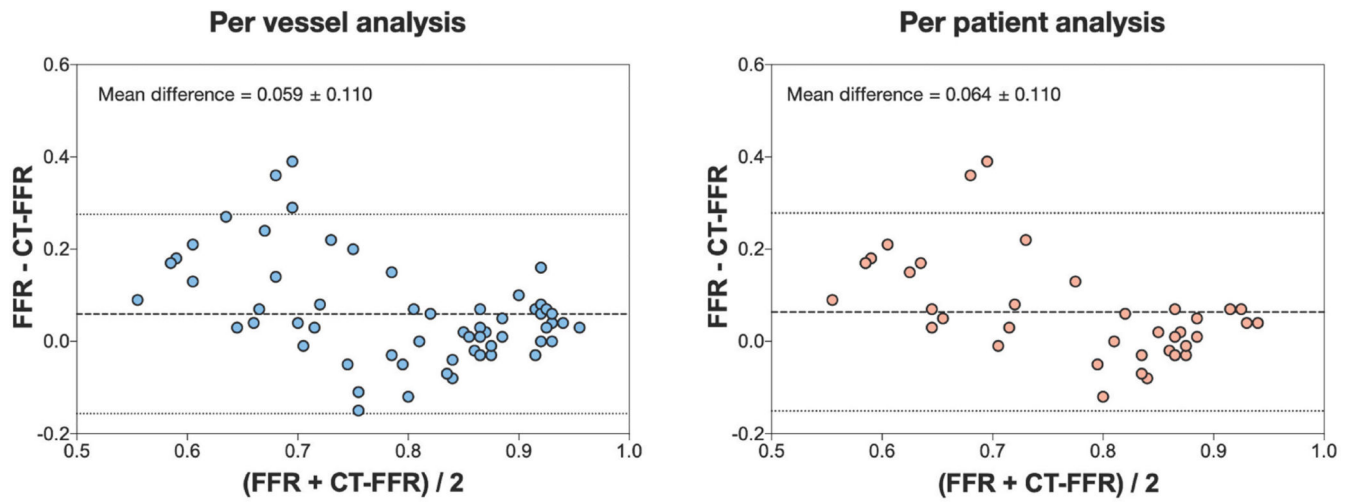


Figure 3. Bland-Altman (Difference Versus Average) of FFR vs CTFFR

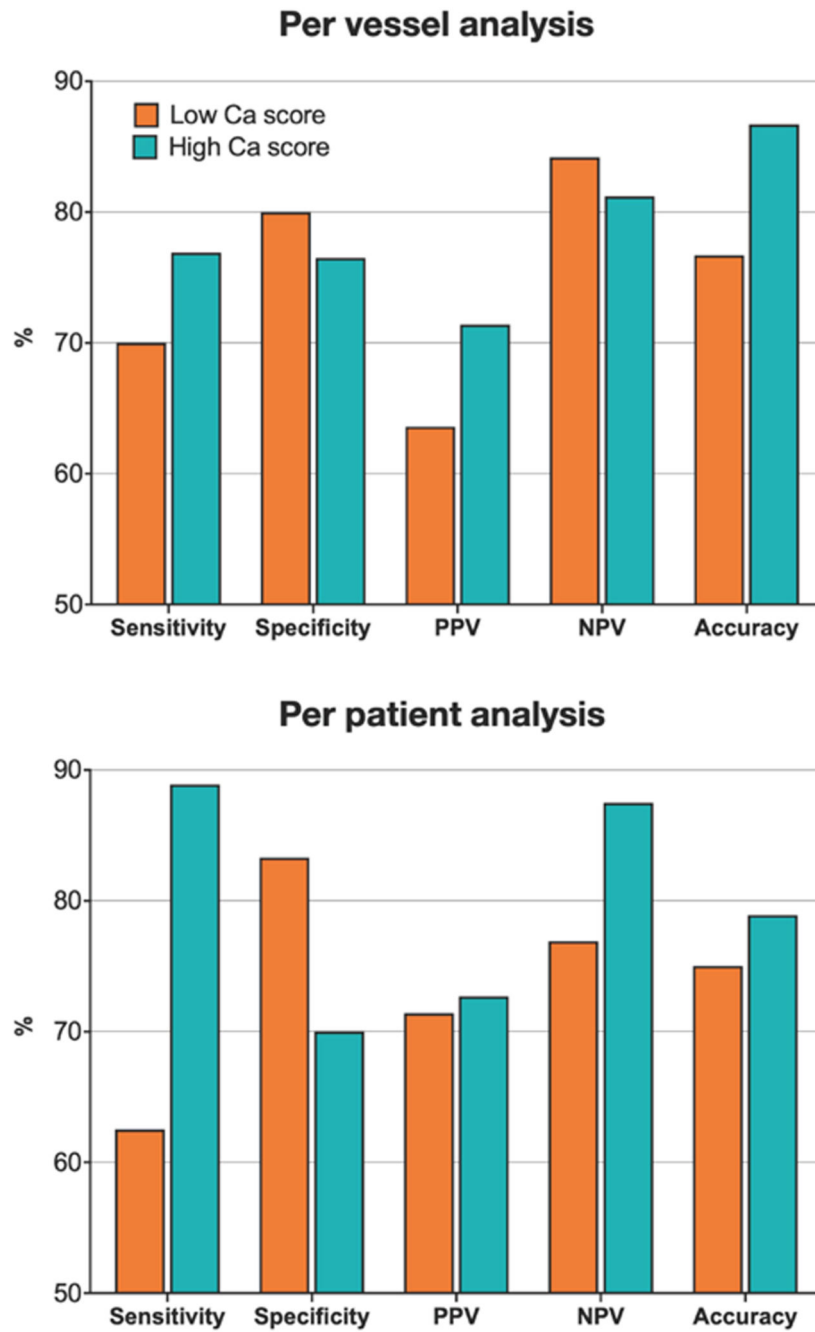


Figure 4. Subgroup Analysis of Diagnostic Performance of CT-FFR According to CT Calcium Score

Table 1
Patient and Echocardiographic Characteristics

Patient characteristics (n = 39)	
Age, yrs	76.2 ± 6.7
Male	28 (71.8)
Body mass index	28.6 ± 6.7
Diabetes mellitus	21 (53.8)
Hypertension	27 (69.2)
Atrial fibrillation	4 (10.3)
Previous MI	5 (12.8)
Dyslipidemia	26 (66.7)
Previous CVA or TIA	5 (12.8)
Smoking	
Current smoker	2 (5.1)
Former smoker	14 (35.9)
Creatinine (mmol/L)	90.5 ± 27.2
Total patient calcium score (Agatston units)	
Mean ± SD	1373.3 ± 1392.9
Median	1027
Pre-procedural echocardiographic parameters	
LVEF, %	62.9 ± 10.7
Peak gradient, mmHg	75.3 ± 15.9
Mean gradient, mmHg	45.1 ± 9.5
Valve Area, cm ²	0.89 ± 0.25
Dimensionless index	0.23 ± 0.04

Values are presented as n (%) or mean ± SD; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Table 2
CT Scan Acquisition Characteristics

CT characteristics	(n = 39)
Heart rate, beats/min	54.2 ± 6.6
Nitrates administered	39 (100)
Pre-scan beta-blocker use	
Oral	26 (66.7)
Intravenous	1 (2.6)
Beta-blocker dose, mg (SD)	
Oral metoprolol	78.8 ± 49.3
Intravenous metoprolol	20 ± 0
Ivabradine (10 mg) use	16 (41.0)
Tube voltage, kV	
100	12 (30.8)
120	27 (69.2)
Tube current, mA	663.3 ± 123.1
Radiation exposure (mSv), (SD)	13.1 ± 8.3
CT protocol A (n=23)	17.1 ± 6.7
CT protocol B (n=16)	7.3 ± 6.8

Values are presented as n (%) or mean ± SD

Table 3
Vessel Characteristics

Variable	
Vessels studied	
LAD or diagonal	41 (68.3)
Cx or OM	13 (21.7)
Ramus intermedius	1 (1.7)
RCA, PDA or R-PLV	5 (8.3)
QCA	
Mean diameter stenosis, %	33.8 ± 12.0
Number of vessels with diameter stenosis ≥ 50%	6/60 (10.0)
Number of patients with diameter stenosis ≥ 50	6/39 (15.4)
Coronary CTA	
Number of vessels with CTA maximum stenosis ≥ 50%	21 (35.0)
Number of patients with CTA maximum stenosis ≥ 50%	16 (41.0)
Mean FFR	0.83 ± 0.10
Vessels with FFR < 0.80	23/60 (38.3)
Patients with FFR < 0.80	17/39 (43.6)
Mean CT-FFR	0.77 ± 0.14
Vessels with CT-FFR < 0.80	25/60 (41.7)
Patients with CT-FFR < 0.80	18/39 (46.1)

Values are presented as n (%) or mean ± SD; CTA, CT computed tomography angiography; CT-derived fractional flow reserve; Cx, circumflex; FFR, fractional flow reserve; LAD, left anterior descending; OM, obtuse marginal; PDA, posterior descending artery; QCA, quantitative coronary angiography; RCA, right coronary artery; R-PLV, right posterior left ventricular.

Table 4
Diagnostic Performance of CT-FFR, Coronary CTA and QCA against Invasive FFR

	Per vessel analysis			Per patient analysis
	CT-FFR	CCTA (>50%)	QCA (>50%)	CT-FFR
Pearson's correlation coefficient	0.64, p<0.0001	N/A	N/A	0.70, p<0.0001
True positive	17	12	4	13
False positive	8	9	2	5
True negative	29	28	35	17
False negative	6	11	19	4
Sensitivity %	73.9	52.2	17.4	76.5
Specificity %	78.4	75.7	94.6	77.3
PPV %	68.0	57.1	66.7	72.2
NPV %	82.9	71.8	64.8	81.0
Accuracy %	76.7	66.7	65.0	76.9
ROC AUC (95% CI) Comparison against ROC AUC for CT-FFR to predict FFR	0.83 (0.72-0.93)	0.64 (0.51-.0.76) p = 0.01	0.56 (0.47-0.65) p <0.001	0.81 (0.67 to 0.95)
Bland-Altman analysis (mean bias ± SD)	0.059 ± 0.110 (-0.16-0.27)	N/A	N/A	0.064 ± 0.110 (-0.15-0.28)

Values are presented as n (%) or mean ± SD. CCTA, coronary computed tomography angiography; NPV, negative predictive value; PPV, positive predictive value; ROC AUC, area under the receiver-operating characteristic curve.