Diagnostic and Clinical Value of FFRCT in Stable Chest Pain Patients With Extensive Coronary Calcification

The FACC Study

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Diagnostic and clinical value of FFR_{CT} in stable chest pain patients with extensive coronary calcification: The FACC study (Functional and Anatomical testing in intermediate risk chest pain patients with high Coronary Calcium score)

Brief title: FFR_{CT} and extensive coronary calcification

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Abstract

OBJECTIVES: Investigate the diagnostic and short-term role of coronary computed tomography angiography (CCTA) derived fractional flow reserve (FFR_{CT}) in chest pain patients with Agatston score (AS) >399.
BACKGROUND: The influence of extensive coronary calcifications on the diagnostic and prognostic value of FFR_{CT} has been scantily investigated.
METHODS: Prospective multicenter study of 260 stable patients with suspected coronary artery disease (CAD) and AS >399. FFR_{CT} was measured blinded by an independent Core Laboratory. All patients underwent invasive coronary angiography (ICA) and FFR if indicated. The agreement of FFR_{CT} ≤0.80 with hemodynamically significant CAD on ICA/FFR (≥50% left main or ≥70% epicardial artery stenosis and/or FFR ≤0.80) was assessed. Patients undergoing FFR had co-location FFR_{CT} measured, and the lowest per-patient FFR_{CT} was registered in all patients. The association between per-patient FFR_{CT}, coronary revascularization and major clinical events (all-cause mortality, myocardial infarction or unstable angina hospitalization) at 90-day follow-up was evaluated.
RESULTS: Median (IQR) age and AS were 68.5 (63-74) years and 895 (587-1513), respectively. FFR_{CT} was ≤0.80 in 204 patients (78%). Co-location FFR_{CT} (n=112) showed diagnostic accuracy, sensitivity, and specificity to identify hemodynamically significant CAD of 71%, 87%, and 54%. The area under the receiver-operating characteristics curve (AUC) was 0.75.When using the lowest FFR_{CT} (n=260) per-patient accuracy, sensitivity and specificity were 57%, 95%, and 32%, respectively. The AUC was 0.84. Eighty-five patients underwent revascularization, and FFR_{CT} was ≤0.80 in 96% of these. During follow-up major clinical events occurred in 3 patients (1.2%), all with FFR_{CT} ≤0.80.
CONCLUSIONS: Most patients with AS >399 had FFR_{CT} ≤0.80. Using ICA/FFR as the reference revealed a moderate diagnostic accuracy of co-location FFR_{CT}. Compared to the lowest per-patient FFR_{CT}, co-location FFR_{CT} measurement improved diagnostic accuracy and specificity. Ninety-day follow-up was favorable with few coronary revascularizations and no major clinical events occurring in patients with FFR_{CT} >0.80.

Clinical Trial: clinicaltrials.gov: NCT03548753

Key words: Coronary artery disease, Coronary calcification, Computed tomography angiography, Coronary angiography, Noninvasive fractional flow reserve

Abbreviations:
AS = Agatston Score
AUC = area under the receiver-operating characteristic curve
CAD = coronary artery disease
CCTA = coronary computed tomography angiography
CI = confidence interval
FACC = Functional and Anatomic testing in intermediate risk chest pain patients with high Coronary Calcium score
FFR = fractional flow reserve
FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography datasets
ICA = invasive coronary angiography
LAD = Left anterior descending artery
LCx = Left circumflex artery

NPV = negative predictive value
PPV = positive predictive value
RCA = Right coronary artery.

Introduction

In patients with suspected stable coronary artery disease (CAD) current international guidelines recommend noninvasive testing as first-line diagnostic procedure (1, 2). Despite the routine use of noninvasive diagnostic tests, less than half of patients referred for elective invasive coronary angiography (ICA) have significant CAD (3). Coronary computed tomography angiography (CCTA) has demonstrated high diagnostic performance for exclusion of CAD (4-6). However, CCTA has only modest accuracy for quantification of stenosis severity, which is further hampered by high levels of coronary calcium resulting in reduced diagnostic accuracy and specificity (7-9). Current European Society of Cardiology guidelines do not recommend CCTA for patients with extensive coronary calcium (1), and the Society of Cardiovascular Computed Tomography guidelines question the use of CCTA in patients with a high calcium score (10). Advances in computational fluid dynamics and image-based modelling allow calculation of coronary blood flow and pressure from standard CCTA permitting noninvasive estimation of fractional flow reserve (FFR), abbreviated FFR_{CT} (11-13). In patients with suspected CAD and stable ischemic chest pain/discomfort, FFR_{CT} has high diagnostic accuracy using FFR as the reference standard. The diagnostic performance of FFR_{CT} in patients with extensive coronary calcification has been scantily investigated (12,14,15). No prior study has addressed whether FFR_{CT} in the setting of patients with AS >399 can identify individuals with and without hemodynamically significant CAD, using ICA/FFR as the reference. Also, the 90-day prognostic value of FFR_{CT} in these patients is unknown.

Methods

The rationale and design of the Functional and Anatomic testing in intermediate risk chest pain patients with high Coronary Calcium score (FACC) study have been described

previously (16). In brief, patients referred for elective CCTA as first-line diagnostic test, where routine non-enhanced CT scan showed an Agatston Score (AS) >399, were eligible. An AS >399 was chosen as it represents the cut-point above which CCTA is questioned (16, 17). Exclusion criteria were prior myocardial infarction, previous coronary revascularization, atrial fibrillation, pacemaker or iodine contrast allergy. Patients were included at four hospitals in the Region of Southern Denmark (Odense University Hospital, Svendborg Hospital, Vejle Hospital, Esbjerg Hospital). The protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20160114) and is registered at clinicaltrials.gov: NCT03548753.

Interventions

CCTA was performed at inclusion. All patients subsequently underwent invasive examination (16).

Coronary computed tomography angiography.

Routine CCTA using high-end scanners (Somatom Definition Flash or Force, Siemens, Forchheim, Germany, or Revolution CT, GE HealthCare, Little Chalfont, United Kingdom) was performed in accordance with societal guidelines (10). Pre-treatment with beta-blockers or ivabradine was administrated if necessary, targeting a heart rate <60 beats/min. Sublingual nitrates were given to all patients prior to scanning. A non-enhanced CT scan for coronary calcium was performed using ECG gated high-pitch spiral or sequential scan acquisition mode with tube voltage of 120 kV. The per-patient AS was calculated by summing-up the scores from each of the lesions in the coronary arteries (18). CCTA was done after injection of 50-90 ml iodine contrast via an ante cubital vein. Experienced local site investigators assessed luminal diameter stenosis in each segment of the coronary arteries (19). Stenosis severity was classified as: 0-29%, 30-49%, 50-69%; 70-89%; 90-99%, 100% (occluded) or non-evaluable. A CCTA result was defined positive in the presence of at least 1 ≥50% left

main (LM) stenosis and/or at least 1 ≥70% stenosis in any epicardial coronary artery with a diameter ≥2 mm (20, 21). Non-evaluable coronary segments ≥2 mm were considered positive.

Fractional flow reserve derived from CCTA

FFR_{CT} analyses were performed by fee by an external Core Laboratory (HeartFlow Inc, Redwood City, California, USA). Standard CCTA datasets were transmitted anonymized through an encrypted connection to the Core Laboratory, which applied a second set of quantitative criteria to determine if the image quality was adequate for FFR_{CT} analysis. FFR_{CT} was calculated blinded to all aspects of clinical care. The FFR_{CT} results were not available to care providers. Techniques for the FFR_{CT} analysis have been detailed previously (22). In brief, the FFR_{CT} model provides computed FFR values in all vessels of the coronary tree ≥1.8 mm. Occluded vessels were assigned a value of 0.5 (12, 14). An $FFR_{CT} \leq 0.80$ was considered positive. In patients undergoing FFR, FFR_{CT} was measured at the same position as the FFR wire. Practically, co-location FFR and FFR_{CT} was performed in cooperation between one invasive and one non-invasive cardiologist, who both were blinded to measured values. On a 3D computer model of the coronary anatomy the location of the FFR pressure sensor at the time of FFR measurement was indicated. The corresponding FFR_{CT} value at the integration point was extracted in a separate process. Also the lowest per-patient FFR_{CT} value was measured in all patients (11, 12, 14, 20, 23-26).

Invasive coronary angiography

ICA was performed locally, and the angiograms were visually analyzed by two experienced invasive cardiologists at the Invasive Angiographic Core Laboratory (Odense University Hospital). Stenosis severity was classified as: 0-29%, 30-49%, 50-69%, 70-89%, 90-99%, 100% (occluded) or non-evaluable. The per-patient ICA result was defined positive in the presence of at least 1 ≥50% LM stenosis and/or at least 1 ≥70% stenosis in any epicardial

coronary artery with a diameter ≥2 mm (16).

Fractional flow reserve

FFR was recommended in vessels >2 mm in diameter with a 30%-90% stenosis on ICA (16). FFR was measured distally to the most severe stenosis during maximal hyperemia induced by continuous intravenous infusion of adenosine in a central vein at a rate of 140 µg/kg/min minute for ≥2 min. A FFR value ≤0.80 was considered positive. In vessels with stenosis <30% a default FFR >0.80 was assigned, and in vessels with stenosis >90% a default FFR ≤0.80 was allocated. An occluded vessel was assigned a default value of 0.5 (12, 13).

Definition of hemodynamically significant CAD

Patients with a FFR ≤0.80 in at least 1 coronary artery were considered as having hemodynamically significant CAD (16).

Outcomes and statistical analysis

Combined primary endpoint

From the patient perspective it is important to know whether hemodynamic significant coronary stenosis is present or not. Furthermore, it is in the interest of the patient that the diagnostic evaluation is associated with the lowest risk possible. Also, from a general resource perspective it would be optimal, if the non-invasive diagnostic work-up would reduce the number of patients without significant coronary stenosis on subsequent invasive examination. To reach these goals the following 3 conditions had to be fulfilled, reflecting the combined primary endpoint (16):

1. An overall per-patient agreement between FFR_{CT} and ICA/FFR, meaning a sufficient FFR_{CT} accuracy (>80%).

2. A reduction of ≥25% in the need of ICA/FFR, if FFR_{CT} is used as gate-keeper.

3. No more than 2% of patients with a FFR_{CT} >0.80 should exhibit evidence of hemodynamically significant CAD using ICA/FFR as the reference.

Statistical analysis and secondary endpoints

Categorical variables were reported as frequencies (%), whereas continuous variables were reported as mean and standard deviation (SD) or median and inter quartile range (IQR), depending on normality distribution. All 3 parameters of primary interest, i.e. FFR_{CT} accuracy, true-negative proportion and false-negative proportion were estimated and supplemented by their respective 95% exact confidence intervals (27). Two-group comparisons were performed with unpaired t tests and Pearson's Chi-squared tests in case of continuous and categorical data, respectively. On the per-patient level diagnostic accuracy, sensitivity, specificity, positive and negative predictive values were reported for FFR_{CT} and CCTA using ICA/FFR as reference standard. For comparison of the area under the receiver-operating characteristics curve (AUC) the methods described by DeLong et al were used (28). Analyses showing the diagnostic performance across groups of increasing AS were also done. The per-vessel correlation of FFR_{CT} with FFR measurements in patients undergoing FFR was performed with Spearman's rank correlation coefficient (16) and Bland-Altman Limits of Agreement (29).

Secondary clinical endpoints included major complications from invasive diagnostic procedures <72 h, the ability of FFR_{CT} to predict coronary revascularization <90 days, and all-cause mortality, myocardial infarction or unstable angina hospitalization within 90 days of follow-up (16). These secondary endpoints were analyzed with descriptive statistics, two-group comparison and AUC analysis. A p-value <0.05 was considered significant. Statistical analysis was performed using STATA, version 15 (StataCorp LLC, College Station, Texas, USA).

Results

Study population.

From September 2016 to January 2018 totally 278 patients were enrolled: Vejle Hospital 53, Esbjerg Hospital 60, Svendborg Hospital 63 and Odense University Hospital 102. According to the external Core Laboratory 16 patients were inadequate for FFR_{CT} analysis, leaving FFR_{CT} analysis available in 262 (94%). Two patients withdraw from ICA, resulting in a study population of 260 patients (**Figure 1).**

Patient baseline characteristics, CCTA and FFR_{CT} data are shown in **Table 1**. The median age was 68.5 years, and 32% were women. The median AS was 895. In 204 patients (78%) at least one FFR_{CT} value ≤0.80 was reported. An example of test results is illustrated in **Figure 2A.**

The median (IQR) interval between CCTA and ICA was 25 days (12-35). The most severe stenosis on ICA was <30% in 92 patients and ≥90% in 53 patients (**Table 2**). FFR was measured in 112 patients (182 vessels). In 21 patients where the most severe stenosis was 30%-90%, FFR was not performed at the discretion of the invasive cardiologist (clinical judgement or technical issues e.g. vessel tortuosity and heavy calcifications). In these cases a positive ICA result was considered to define hemodynamically significant CAD. Overall, 101 patients (39%) had hemodynamically significant CAD **(Table 3).**

Combined primary endpoint (n=260)

1) Per-patient accuracy of FFR_{CT} using ICA/FFR as reference was 57% resulting from a sensitivity and specificity of 95% and 32%, respectively . The AUC was 0.84 (**Table 4)**.

2) Per-patient FFR_{CT} >0.80 was found in 56 patients **(Table 1)** translating into a potential 22% (95% CI: 16.7-27.3) reduction of referrals for ICA/FFR, if FFR_{CT} served as a gatekeeper.

3) Five of 56 (8.9%) patients with FFR_{CT} >0.80 had hemodynamically significant CAD

according to invasive evaluation (**Table 4**). One case is illustrated in **Figure 2B,** and details of all five are specified in **supplemental Table 1.**

Secondary endpoints

Per-patient diagnostic performance of CCTA (n=260)

Diagnostic values of CCTA using ICA/FFR as reference for the detection of hemodynamically significant CAD are shown in **Table 4**. No significant difference in the AUC of CCTA and FFR_{CT} was found (0.80 vs 0.84; p=0.28).

Per-patient diagnostic performance of FFR_{CT} across groups of increasing AS score (n=260)

Diagnostic values of FFR_{CT} using ICA/FFR as reference in patients with AS 400-999 vs. AS ≥1000, according to tertiles, and above or below median AS are shown in **supplemental Table 2.** The AUC decreased with increasing AS. No statistical significant difference in any of the scenarios was observed.

Diagnostic performance of co-location FFR_{CT} using FFR as reference (n=112)

In patients undergoing invasive FFR co-location FFR_{CT} measurements showed a per-patient diagnostic accuracy, sensitivity and specificity of 71%, 87% and 54%, respectively. When compared with the lowest value, no significant difference between the AUCs was found (**Table 5** and **Central Illustration A**).

Co-location FFR_{CT} showed a per-vessel FFR_{CT} accuracy, sensitivity and specificity of 78%, 82% and 75%, respectively. The per-vessel AUC was significantly higher using the co-location FFR_{CT}, as compared with the per-vessel lowest FFR_{CT} value (0.81 vs. 0.74; p=0.0078) (**Table 5** and **Central Illustration B**). In **Central Illustration C** an example of co-location and lowest FFR_{CT} measurements is shown.

The per-vessel correlation of FFR_{CT} and FFR was moderate (Spearman's rho=0.55). The agreement analysis indicated an estimated bias of 0.02 (0.003 to 0.04) with Limits of Agreement of -0.19 (-0.22 to -0.17) and 0.23 (0.21 to 0.27), respectively (**supplemental**

Figure). The per-patient diagnostic performance of co-location FFR_{CT} and CCTA using FFR as reference revealed an accuracy of 71% and 63%, respectively. The AUCs of the two modalities did not significantly differ (0.71 vs 0.75; p=0.44) (**Table 6**).

Major complications from invasive diagnostic tests <72 hours (n=260)

Four patients experienced complications (1.5%): 1 case of femoral pseudo-aneurysm requiring thrombin injection, 2 cases of bleeding requiring femoral artery surgery, and 1 patient developed gastrointestinal bleeding demanding acute hemi-colectomy because of intestinal ischemia.

All-cause mortality, myocardial infarction or unstable angina hospitalization within 90 days of follow-up (n=260)

Major clinical events occurred in three patients (1.2%): 2 cardiovascular deaths and 1 myocardial infarction. FFR_{CT} was ≤0.80 (0.54 – 0.61) in all. Two patients had a 90-99% stenosis on ICA. The third patient had a 50-70% stenosis and judged from stenosis severity and location and the clinical status of the patient, the invasive cardiologist did not find indication for FFR.

Coronary revascularization within 90 days of follow-up

Revascularization was done in 85 of 260 patients (33%). In **Figure 3** the performance of FFR_{CT} and CCTA is illustrated. The AUCs did not differ.

Forty-nine of the 112 patients (44%) undergoing invasive FFR had coronary revascularization. The lowest per-patient FFR_{CT} identified 47 patients (96%) compared with 44 patients (90%), if the co-location FFR measurement was used (p = 0.24). No significant difference between the AUCs of lowest vs. co-location FFR_{CT} was found, 0.79 (0.70-0.87) vs. 0.77 (0.68-0.86; p=0.48).

Discussion

In this prospective multicenter study of 260 patients with suspected stable CAD and an AS >399, the majority had a per-patient FFR_{CT} ≤0.80. Using ICA/FFR as the reference revealed a moderate diagnostic accuracy of co-location FFR_{CT}. Compared to the lowest per-patient FFR_{CT} value, co-location FFR_{CT} measurement improved the diagnostic accuracy and specificity, at the cost of a minor reduction in sensitivity. Overall a per-patient FFR_{CT} >0.80 was associated with an excellent short-term clinical outcome.

Diagnosis, comparison with earlier studies

A paucity of data on the role of FFR_{CT} in patients with AS >399 exists. In a sub-study of the NXT trial patients were classified in quartiles according to AS severity (14). The 53 patients in Q4 ("high") had per-patient AS ranging from 416 to 3599, whereas patients in Q1-Q3 ("low-mid") showed AS ≤415. Accuracy of FFR_{CT} in patients with "low-mid" vs. "high" AS was 83-85% and 74%, respectively. No statistical significant difference between the AUC of FFR_{CT} in the two patient subgroups was found (0.92 vs. 0.86; p=0.45). Recently, the MACHINE registry compared CT-FFR in vessels with AS<400 vs. AS≥400 (15). Accuracy in the two groups were 76-82% and 76%, respectively. However a significant lower AUC was observed in vessels with AS ≥400 (0.71 vs. 0.85; p=0.04). No per-patient AUC results were presented (15). In the FACC study exclusively patients with AS >399 were enrolled. In the NXT sub-trial (patients) and the MACHINE registry (vessels) less than one-third had an AS ≥400, and only 5% (25 patients) had an AS ≥1000 (14,15) compared with 43% (112 patients) in the present study. Hence, the burden of coronary calcifications is far more extensive in the FACC study than in earlier studies.

The varying study results most likely also reflect differences in design, patient selection and key definitions. In the FACC study all individuals were referred for CCTA as the initial diagnostic test and subsequently underwent invasive examination independently of the CCTA

result meaning that patients with <30% stenosis on ICA were included. In contrast, patients in the earlier trials had a clinical indication for ICA together with a 30% to 90% stenosis on CCTA (14), and most patients were retrospectively included (15). The indication for FFR ranged from a stenosis ≥30% on ICA (14) to "clinical reasons or unrelated research purposes" (15). In prior studies a ≥50% stenosis on ICA was considered obstructive (14, 15) vs. 70% in this study. Also, the methods of deriving FFR from CCTA differed. In the MACHINE registry a machine-learning–based research prototype not commercially available, was used (15), whereas FFR_{CT} in the NXT sub-trial and the present study was analyzed at the same external Core Laboratory by use of commercially available techniques (14, 16, 22).

In earlier invasive studies FFR_{CT} was calculated corresponding to the vessel locations at which FFR was measured (12,14,15). Likewise, in the present study patients undergoing FFR had co-location FFR_{CT} performed. Also the lowest per-patient FFR_{CT} was measured. Earlier clinical studies have used a similar definition, or FFR_{CT} has simply been read at the discretion of observers without any formal standardization (20, 24-26, 30-32). By using the lowest FFR_{CT} value the present study showed a low per-patient accuracy and specificity. In patients undergoing FFR co-location FFR_{CT} revealed a per-patient accuracy, sensitivity, and specificity of 71%, 87% and 54%, respectively. Hence, accuracy increased considerably, owing to a major increase in specificity and only a minor decrease in sensitivity. When using per-vessel co-location FFR_{CT} measurement accuracy, sensitivity and specificity were 78%, 82% and 75%, respectively. The resulting AUC was significantly higher than that obtained, when using the lowest FFR_{CT}. The per-patient and per-vessel diagnostic co-location based accuracies of the present study, are in line with the results reported in the AS >400 sub-groups of the NXT sub-trial (14) and the MACHINE registry (15), respectively. This observation fits well in with the fact that all patients in the FFR-subgroup (n=112) had at least one 30% to 90% stenosis on invasive angiography, and thus are comparable to patients

included in the earlier studies (14,15). The total FACC cohort (n=260) is comprised of patients with coronary artery stenosis ranging from 0% to 100%, and about half of the population did not fulfill the per-protocol indication for doing FFR. The analysis of agreement between FFR and co-location FFR_{CT} indicated a clinically negligible systematic bias, but with wider limits of agreement. When operating with a clinical cut-off of 0.80 these limits suggest a moderate agreement between FFR measurement and FFR_{CT} estimates, as reflected by a moderate diagnostic performance.

In the present study FFR_{CT} did not significantly improve the per-patient AUC for the detection of hemodynamically significant CAD over that of CCTA alone. This observation is supportive to the per-patient results found in the AS >400 group of the NXT sub-study (14). Of interest, diagnostic accuracy of CCTA was lower in patients in the FFR-subgroup vs those in the total FACC cohort. This observation probably reflects the established limitations of CCTA in diagnosing the severity of coronary artery stenosis within the 30%-90% range, particular in the presence of extensive coronary calcifications.

Clinical value of FFR_{CT}

The prognostic value of FFR_{CT} in patients with AS >399 is practically unknown. In the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE), patients with an AS >800 were excluded (32), but still 15.2% of the study cohort had an AS >399 (34). In a retrospective sub-study the lowest per-patient FFR_{CT} appeared to reduce the need for ICA and to increase the proportion of ICA leading to revascularization within 90 days (20). Also, a recent single center study showed that an FFR_{CT} <0.80 measured "anywhere along the length of the vessel" improves catheterization-laboratory efficiency and was safe for a more than 1-year of follow-up (35). Of notice, in both these studies no data of coronary calcification severity and its potential clinical role were available. In a third observational study stable patients were followed for 2.2 years. In patients with AS ≥400 the composite

endpoint of death, myocardial infarction, hospitalization for unstable angina, and unplanned coronary revascularization occurred more frequently in patients with FFR_{CT} ≤0.80 vs. those with FFR_{CT} >0.80 (9.7% vs. 4.2%; p=0.24)(32). The results of the present study support the potential good prognosis in FFR_{CT} negative patients with no major clinical events occurring in those with FFR_{CT} >0.80.

Study strengths

This is the first prospective, multicenter study to investigate whether FFR_{CT} in stable patients with suspected CAD and AS >399 can be used to identify individuals with and without hemodynamically significant CAD, when ICA/FFR serve as the standard reference. Also, no prior study has addressed the 90-day clinical value of FFR_{CT} in a cohort exclusively consisting of patients with AS>399. All patients underwent ICA regardless of CCTA stenosis severity. Local site reading of coronary CCTA stenosis was used to provide a real-world scenario and wider generalizability of the results. A conclusive FFR_{CT} analysis was available in 94% of the CCTA studies submitted to the external FFR_{CT} Core Laboratory. Both the care providers and the patients were blinded to the results of CCTA and FFR_{CT}. Hence, treatment was guided by patient symptoms in combination with the invasive diagnostic evaluation, reflecting routine guidelines at the hospitals involved.

Study limitations

The number of patients eligible for study inclusion but not recruited was not registered. Therefore, site-level selection bias cannot be excluded. Invasive FFR was not performed in 21 patients with a 30-90% stenosis. As opposed to earlier diagnostic studies (14, 15) we also included patients with stenosis <30%, and FFR_{CT} values ≤0.80 were found in the majority of these. Whether this observation represents non-lesion specific ischemia secondary to AS>399 per se or is an artifact associated with specific patterns of coronary calcification remains unknown. Also, we did not differentiate between focal, diffuse, concentric or scattered

calcifications on CCTA. We acknowledge that coronary calcification patterns may vary between patients and may influence FFR_{CT} measurements. The number of major clinical events during 90-day follow-up was low.

Conclusions

In symptomatic stable patients undergoing first-line diagnostic CCTA with an AS>399 the majority had a $FFR_{CT} \leq 0.80$. Using ICA/FFR as the reference revealed a moderate diagnostic accuracy of co-location $FFR_{CT.}$ Compared to the lowest FFR_{CT} value, co-location FFR_{CT} measurement improved diagnostic accuracy and specificity. Short-term prognosis was favorable with few revascularizations and no major events occurring in patients with FFR_{CT} >0.80.

COMPETENCY IN MEDICAL KNOWLEDGE: In a multicenter study of patients with extensive coronary calcifications (AS >399) co-location FFR_{CT} provided moderate accuracy in identifying the presence of hemodynamically significant stenosis using invasive coronary angiography and FFR as the reference. Ninety-day follow-up was favorable with few coronary revascularizations and no major clinical events occurring in patients with FFR_{CT} >0.80.

TRANSLATIONAL OUTLOOK: Ischemia by FFRCT: Around one-third of the patients included in this study had <30% stenosis on invasive coronary angiography. In more than half of these cases FFR_{CT} was ≤0.80. Whether this observation reflects diffuse ischemia secondary to the extensive amount of calcifications per se or is an artifact associated with specific patterns of coronary calcification needs further research.

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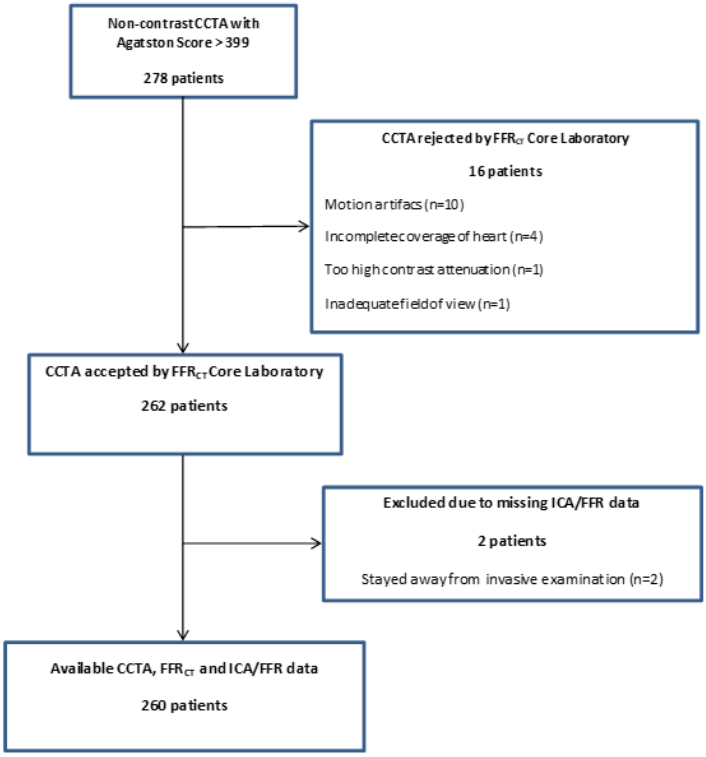
Figure legends

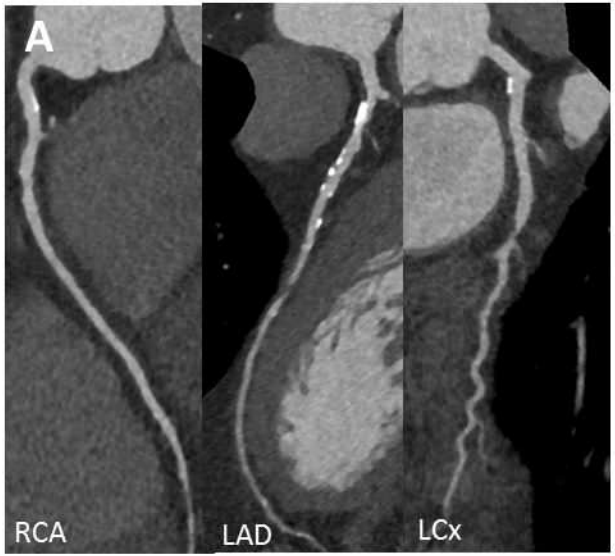
Figure 1. Study enrollment
Patient selection process.

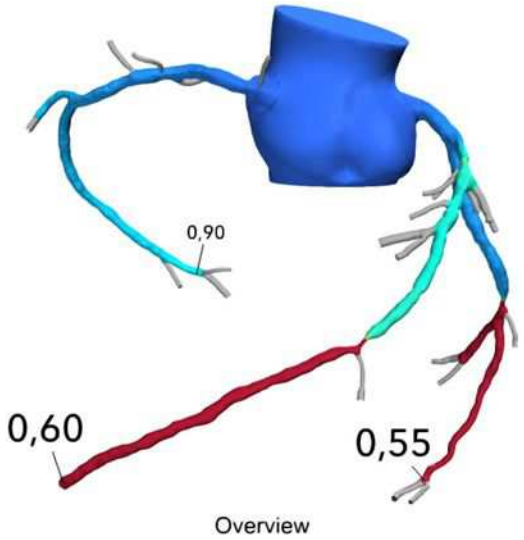
Figure 2. Examples of test results
A) 61 year old man with AS 521. CCTA demonstrated a LAD subtotal occlusion with FFR_{CT} 0.60 and LCx stenosis 90-99% with FFR_{CT} 0.55. ICA showed a 90-99% LAD stenosis and a 50-69% LCx stenosis with FFR 0.93. Percutaneous coronary angioplasty of the LAD stenosis was performed.
B) 74 year old man with AS 783. CCTA showed a 70-90% ostial RCA stenosis with FFR_{CT} 0.81. ICA demonstrated a 70-89% ostial RCA stenosis with FFR 0.58. Percutaneous coronary angioplasty of the RCA was performed.

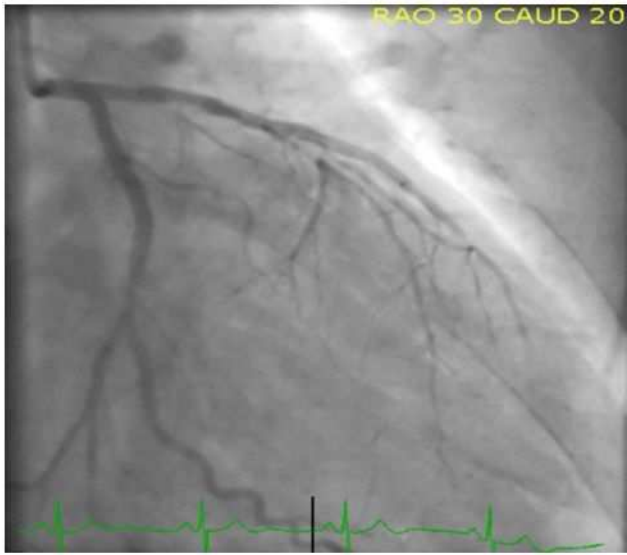
Figure 3. Performance of FFR_{CT} and CCTA in predicting coronary revascularization within 90-day follow-up.
Diagnostic values of FFR_{CT}: Accuracy 52% (46-58); sensitivity 97% (90-99); specificity 30% (24-38); PPV 40% (33-47), NPV 95% (85-99). Diagnostic values of CCTA: Accuracy 73% (68-79); sensitivity 79% (69-87); specificity 71% (64-78); PPV 57% (47-66); NPV 87% (81-92). The AUC of CCTA and FFR_{CT} were 0.82 (0.77-0.87) and 0.84 (0.78-0.89), respectively (p =0.61).

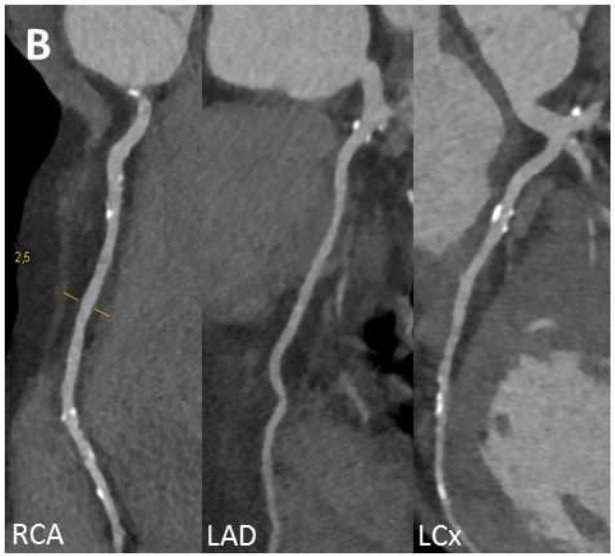
Central Illustration. Major diagnostic and clinical findings in stable patients with Agatston Score >399
Data from (A) patients (n=112) and (B) vessels (n=182) comparing co-location FFR_{CT} with lowest FFR_{CT}. Fractional flow reserve ≤0.80 was the reference standard. In both scenarios accuracy was higher using co-location measurements. At the per-patient level (A) no significant difference between AUC of lowest FFR_{CT}, 0.78 (0.69-0.86) and AUC of co-location FFR_{CT}, 0.75 (0.66-0.85) was found (p=0.4152). At the per-vessel level (B) the AUC was significantly higher using co-location FFR_{CT}, 0.81 (0.75-0.88) compared with the lowest FFR_{CT}, 0.74 (0.67-0.82) (p=0.0078). Specified diagnostic values and 95% intervals as in Table 5. In (C) FFR and co-location FFR_{CT} on mid-LAD showed values of 0.91 and 0.88, respectively. Lowest FFR_{CT} was 0.74. Clinical follow-up (D) include all study patients (n=260).

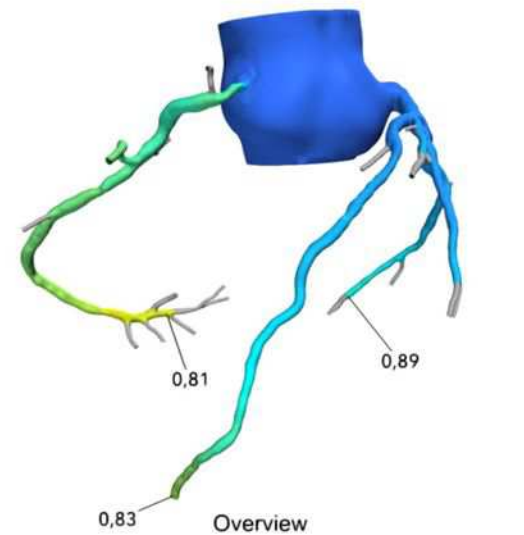

Non-contrast CCTA with Agatston Score > 399
278 patients
CCTA rejected by FFR$_{CT}$ Core Laboratory
16 patients
Motion artifacs (n=10)
Incomplete coverage of heart (n=4)
Too high contrast attenuation (n=1)
Inadequate field of view (n=1)
CCTA accepted by FFR$_{CT}$ Core Laboratory
262 patients
Excluded due to missing ICA/FFR data
2 patients
Stayed away from invasive examination (n=2)
Available CCTA, FFR$_{CT}$ and ICA/FFR data
260 patients

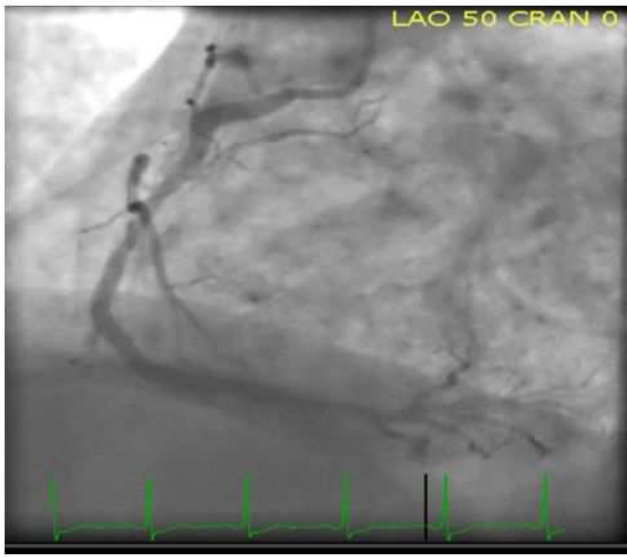

A
RCA
LAD
LCx

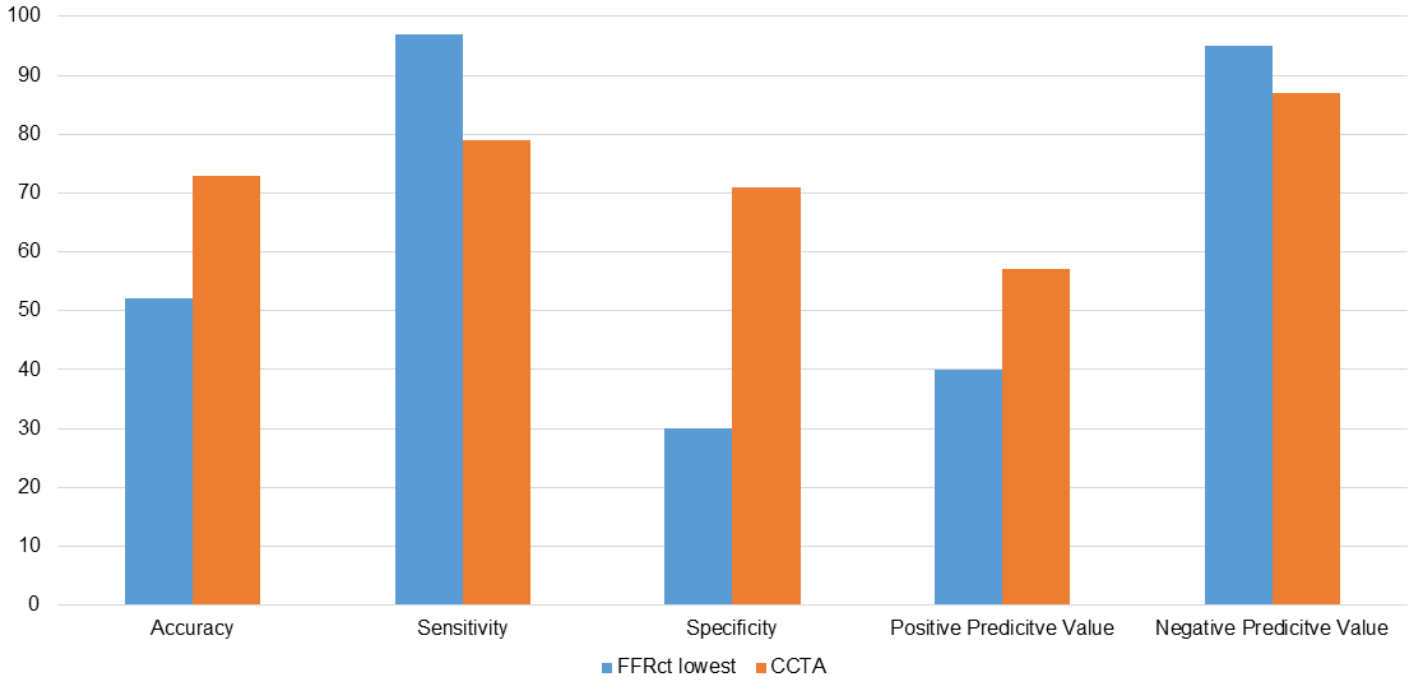

0,90
0,60
0,55
Overview


RAO 30 CAUD 20

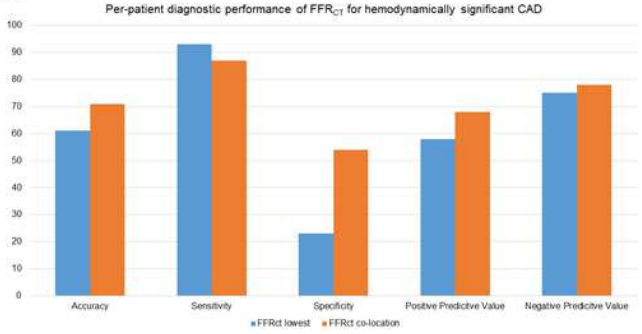

B
RCA
LAD
LCx


0,81
0,89
0,83
Overview

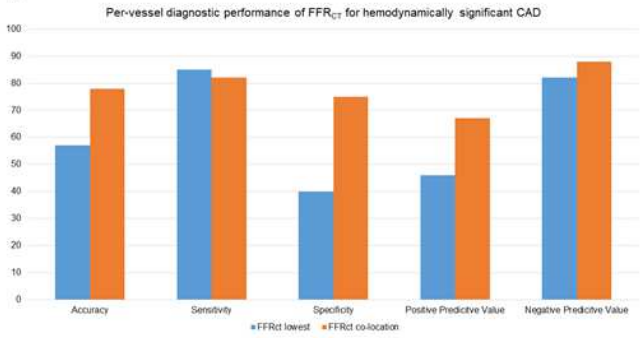

LAO 50 CRAN 0


100
90
80
70
60
50
40
30
20
10
0
Accuracy
Sensitivity
Specificity
Positive Predicitve Value
Negative Predicitve Value
FFRct lowest
CCTA

A

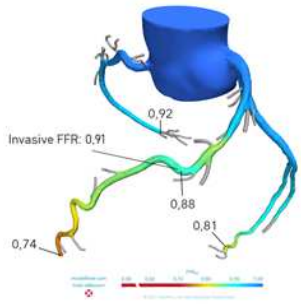


B



C

Example of co-location FFR$_{CT}$, lowest FFR$_{CT}$ and invasive FFR measurement



D

Clinical outcome at 90 days of follow-up

FFR$_{CT}$ ≤0.80 was observed in 78% of patients undergoing CCTA as first line diagnostic test

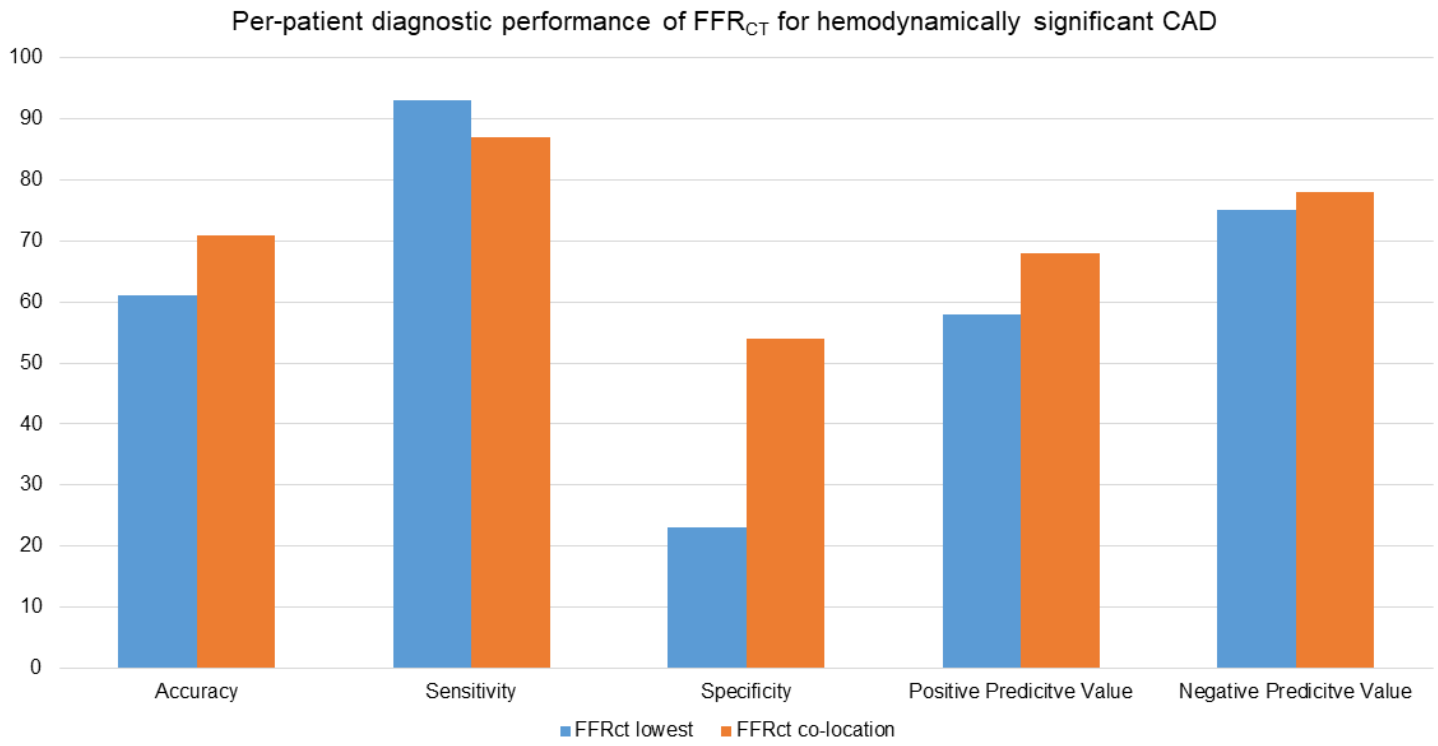
Diagnostic accuracy of FFR$_{CT}$ improved when using co-location values

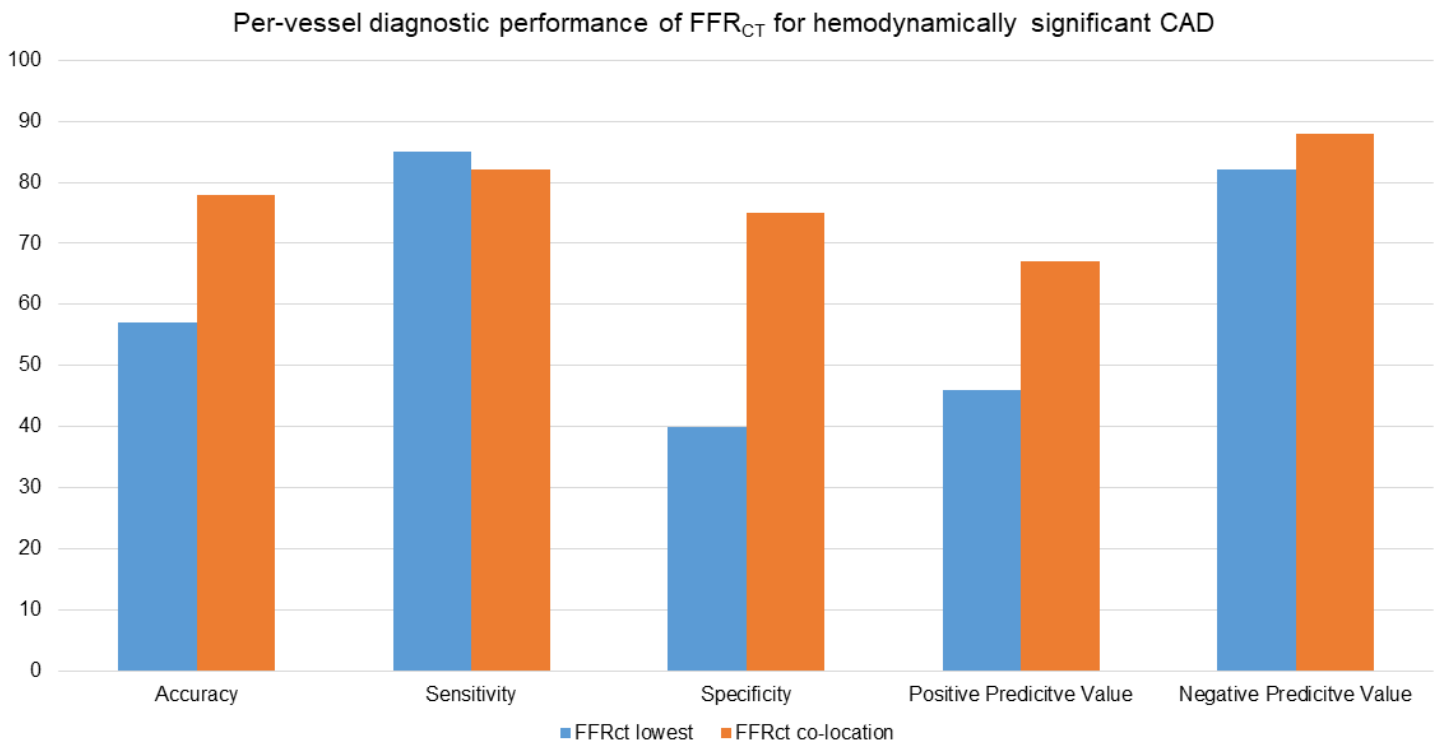
Coronary revascularization was performed in 33% of patients

Major clinical events were rare (1.2%)

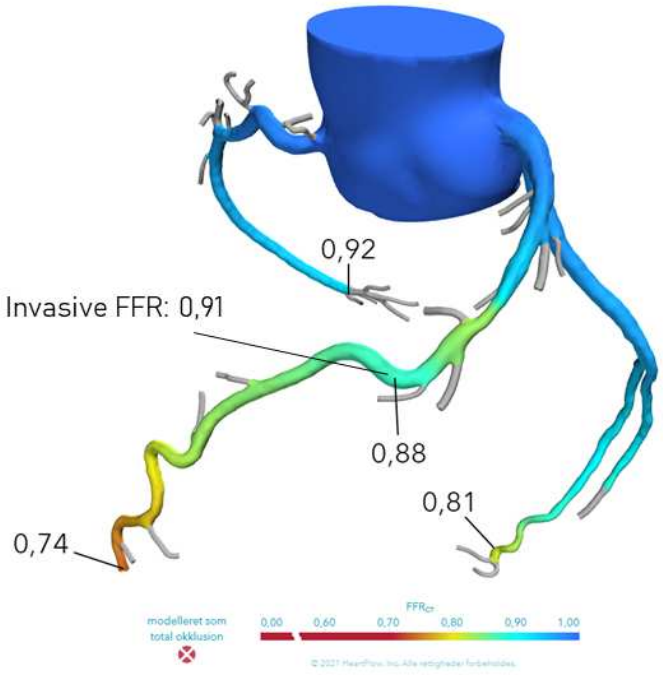
FFR$_{CT}$ >0.80 was associated with an excellent short-term outcome:

- No major clinical events
- Few coronary revascularizations (4%)


Per-patient diagnostic performance of FFR$_{CT}$ for hemodynamically significant CAD
100
90
80
70
60
50
40
30
20
10
0
Accuracy
Sensitivity
Specificity
Positive Predicitve Value
Negative Predicitve Value
FFRct lowest
FFRct co-location


Per-vessel diagnostic performance of FFR$_{CT}$ for hemodynamically significant CAD
100
90
80
70
60
50
40
30
20
10
0
Accuracy
Sensitivity
Specificity
Positive Predicitve Value
Negative Predicitve Value
FFRct lowest
FFRct co-location

Example of co-location FFR_{CT} , lowest FFR_{CT} and invasive FFR measurement



Clinical outcome at 90 days of follow-up

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- Few coronary revascularizations (4%)

Table 1. Baseline characteristics, CCTA and FFR_{CT} acquisition characteristics.

	All (n=260)	$FFR_{CT} > 0.80$ (n=56)	$FFR_{CT} \leq 0.80$ (n=204)	p-value
Median (IQR) age, yrs	68.5 (63.0-74.0)	69.5 (63.0-74.0)	68.0 (63.0-74.0)	0.85
Male,	177 (68)	32 (57)	145 (71)	0.048
Risk factors:				
Hypertension	176 (68)	40 (71)	136 (67)	0.50
Diabetes	45 (17)	9 (16)	36 (18)	0.78
Dyslipidemia	160 (62)	35 (63)	125 (61)	0.87
Family CAD history	88 (34)	20 (36)	68 (33)	0.73
Active Smoking	62 (24)	12 (21)	50 (25)	0.63
BMI, kg/m2	26.9 (24.5-30.7)	27.1 (24.5-30.8)	26.8 (24.5-30.5)	0.58
BMI ≥ 30	73 (28)	17 (30)	56 (27)	0.67
Symptoms				
Typical angina	47 (18)	10 (18)	37 (18)	0.87
Atypical angina	168 (65)	35 (63)	133 (65)	
Non-anginal	45 (17)	11 (20)	34 (17)	
Likelihood of CAD	59 (38-69)	58 (37-69)	59 (44-69)	0.10
Range	17-84	17-84	17-84	
Low (<25%)	19 (7)	6 (11)	13 (6)	0.047
Intermediate (25 to 75%)	208 (80)	48 (86)	160 (78)	
High (>75%)	33 (13)	2 (4)	31 (15)	
s-creatinin, µmol/L	82 (70-94)	78 (65-92)	82 (72-95)	0.24
CCTA				
Heart rate, bpm	57 (53-62)	56 (53-60)	57 (53-63)	0.47
DLP	191 (111-382)	195 (110-377)	191 (111-389)	0.58
AS	895 (587-1513)	787 (496-1362)	910 (613-1561)	0.078
Range	400-7070	401-2917	400-7070	
400-999	148 (57)	34 (61)	114 (56)	
≥1000	112 (43)	22 (39)	90 (44)	0.52
FFR_{CT}				
FFR_{CT}, AS ≥ 400	0.71 (0.57-0.79)	0.84 (0.83-0.87)	0.67 (0.51-0.74)	<0.0001
FFR_{CT}, AS 400-999	0.72 (0.61-0.80)	0.84 (0.83-0.87)	0.68 (0.52-0.74)	<0.0001
FFR_{CT}, AS ≥1000	0.70 (0.54-0.78)	0.83 (0.82-0.85)	0.63 (0.51-0.74)	<0.0001

Values are median (IQR) or n (%)

AS = Agatston Score; BMI = Body mass index; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DLP = Dose Length Product; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography.

Table 2. Maximum coronary artery stenosis on ICA and its association with FFR_{CT} and ICA/FFR.

ICA stenosis (n=260)	$FFR_{CT} \leq 0.80$ (%)	Hemodynamically significant CAD on ICA/FFR (%)
< 30% (n=92)	56 (61)	0
30-49% (n=58)	44 (76)	10 (17)
50-69% (n=34)	31 (91)	16 (47)
70-89% (n=23)	22 (96)	22 (96)
90-99% (n=35)	33 (94)	35 (100)
100% (n=18)	18 (100)	18 (100)

Values are n (%); CCTA = coronary CT angiography; FFR_{CT} = coronary CT angiography derived FFR; ICA/FFR = invasive coronary angiography/fractional flow reserve with hemodynamically significant CAD.

Table 3. Patient and vessel characteristics according to CCTA, FFR_{CT}, ICA and FFR

Patients with a positive CCTA result	118/260 (45)
Patients with FFR_{CT} ≤0.80	204/260 (78)
Vessels with FFR_{CT} ≤0.80	358/720 (46)
Patients with a positive ICA result	77/260 (30)
Patients with LM stenosis ≥50%	8/77 (10)
Patients with LAD stenosis ≥70%	41/77 (53)
Patients with LCX stenosis ≥70%	26/77 (34)
Patients with RCA stenosis ≥70%	37/77 (48)
Patients with 1-vessel disease	49/77 (64)
Patients with 2-vessel disease	14/77 (18)
Patients with 3-vessel and/or LM disease	14/77 (18)
Patients with FFR ≤0.80	66/112 (59)
Vessels with FFR ≤0.80	69/182 (38)
Patients with hemodynamically significant CAD on ICA/FFR	101/260 (39)

Values are n (%); CCTA = coronary CT angiography;
FFR = fractional flow ratio; FFR_{CT} = coronary CT angiography derived FFR; ICA/FFR = invasive coronary angiography/fractional flow reserve with hemodynamically significant CAD; LAD = left anterior descending; LCX = left circumflex; LM = left main; RCA = right coronary artery

Table 4. Per-patient diagnostic performance of FFR_{CT} (upper panel) and CCTA (lower panel) using ICA/FFR as reference for the detection of hemodynamically significant CAD (n=260).

Patients Prev CAD 39%	TP (n)	FN (n)	FP (n)	TN (n)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC*
FFR_{CT}	96	5	108	51	57 (50-63)	95 (89-98)	32 (25-40)	47 (40-54)	91 (80-97)	0.84 (0.79-0.89)
CCTA	73	28	45	114	72 (66-77)	72 (63-81)	72 (64-79)	70 (53-71)	80 (73-87)	0.80 (0.75-0.86)

95% confidence intervals are shown in brackets; AUC = area under the receiver-operating characteristic curve; CAD = coronary artery disease; CCTA: coronary computed tomography angiography; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; FFR = fractional flow reserve; FN = false negative; FP = false positive; ICA = invasive coronary angiography; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.
*P=0.28

Table 5. Diagnostic performance of FFR_{CT} using ICA/FFR as reference for the detection of hemodynamically significant CAD.

Per-patient	Accuracy %	Sensitivity %	Specificity %	PPV %	NPV %	AUC*
Lowest FFR_{CT} value in patients with measured FFR values (n=112)	61 (51-70)	93 (84-98)	23 (13-37)	58 (48-68)	75 (48-93)	0.78 (0.69-0.86)
Co-location FFR_{CT} value in patients with measured FFR values (n=112)	71 (62-80)	87 (75-94)	54 (40-68)	68 (57-79)	78 (61-90)	0.75 (0.66-0.85)
Per-vessel						
Lowest FFR_{CT} value in vessels with measured FFR values (n=182)	57 (49-64)	85 (75-93)	40 (30-49)	46 (37-55)	82 (69-91)	0.74 (0.67-0.82)
Co-location FFR_{CT} value in vessels with measured FFR values (n=182)	78 (71-84)	82 (71-91)	75 (67-83)	67 (56-77)	88 (80-94)	0.81 (0.75-0.88)

95% confidence intervals are shown in brackets. AS= Agatston Score; AUC = area under the receiver-operating characteristic curve; CAD = coronary artery disease; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; NPV = negative predictive value; PPV = positive predictive value.

*n=112, 0.78 vs. 0.75, p=0.4152
*n=182, 0.74 vs. 0.81, p=0.0078

Table 6. Per-patient diagnostic performance of co-location FFR_{CT} and CCTA using FFR as reference for the detection of hemodynamically significant CAD (n=112).

	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC*
FFR_{CT}	71 (62-80)	87 (75-94)	54 (40-68)	68 (57-79)	78 (61-90)	0.75 (0.66-0.85)
CCTA	63 (53-71)	65 (52-77)	60 (45-73)	65 (52-77)	60 (45-73)	0.71 (0.62-0.80)

95% confidence intervals are shown in brackets; AUC = area under the receiver-operating characteristic curve; CAD = coronary artery disease; CCTA: coronary computed tomography angiography; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; FFR = fractional flow reserve; NPV = negative predictive value; PPV = positive predictive value; *P=0.44

Supplemental Table 1. Specification of 5 patients with FFR_{CT} >0.80 and hemodynamically significant coronary artery disease on ICA/FFR.

Patient	Vessel and segment	Per-patient FFR_{CT}	Stenosis on ICA %	Per-patient FFR	Treatment
1	LCx 11	0.83	90-99	<0.80	PCI + OMT
2	RCA 1	0.87	90-99	<0.80	PCI + OMT
3	RCA 1	0.81	70-89	0.58	PCI + OMT
4	LAD 9	0.85	30-49	0.78	OMT
5	LAD 7	0.82	50-69	0.79	OMT

Abbreviations; FFR; fractional flow reserve, LCx; left circumflex artery, LAD; left descending coronary artery, OMT; optimal medical therapy, PCI; percutaneous coronary intervention, RCA; right coronary artery. As shown a false negative FFR_{CT} was observed in 5 patients. In patient 1-3 invasive testing demonstrated clear evidence of hemodynamically significant stenosis, and coronary revascularization was done. In patient 4 and 5 ICA showed borderline stenosis only, FFR was marginally positive, and the symptoms were modest. Consequently, optimal medical treatment was chosen.

Supplemental Table 2. Per-patient diagnostic performance of FFR_{CT} using ICA/FFR as reference in patients with AS 400-999 vs. AS ≥1000, according to tertiles, and above or below median AS

Per-patient	Accuracy %	Sensitivity %	Specificity %	PPV %	NPV %	AUC
AS						
ICA/FFR AS 400-999 (n=148)	48 (40-56)	91 (79-98)	29 (21-39)	36 (27-46)	88 (73-97)	0.84 (0.76-0.92)
ICA/FFR AS ≥ 1000 (n=112)	68 (58-77)	98 (90-100)	38 (25-52)	61 (50-71)	96 (77-100)	0.83 (0.75-0.91)*
Tertiles						
ICA/FFR AS 400-670 (n=87)**	56 (45-68)	96 (80-100)	39 (27-53)	40 (28-54)	96 (80-100)	0.90 (0.82-0.97)
ICA/FFR AS 671-1278 (n=88)	42 (32-53)	90 (73-98)	19 (10-31)	35 (24-47)	79 (49-95)	0.80 (0.69-0.91)
ICA/FFR AS ≥ 1279 (n=85)	72 (61-81)	98 (89-100)	41 (26-58)	66 (54-77)	95 (71-100)	0.80 (0.70-0.90)†
Median						
ICA/FFR AS 400-895 (n=130)^	51 (42-60)	93 (80-98)	32 (23-43)	38 (28-48)	91 (75-98)	0.86 (0.78-0.94)
ICA/FFR AS ≥ 896 (n=130)	62 (53-71)	97 (89-100)	32 (21-44)	56 (46-65)	92 (73-99)	0.81 (0.73-0.88)‡

95% confidence intervals are shown in brackets. AS= Agatston Score; AUC = area under the receiver-operating characteristic curve; CAD = coronary artery disease; FFR_{CT} = fractional flow reserve derived from coronary computed tomography angiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; NPV = negative predictive value; PPV = positive predictive value;

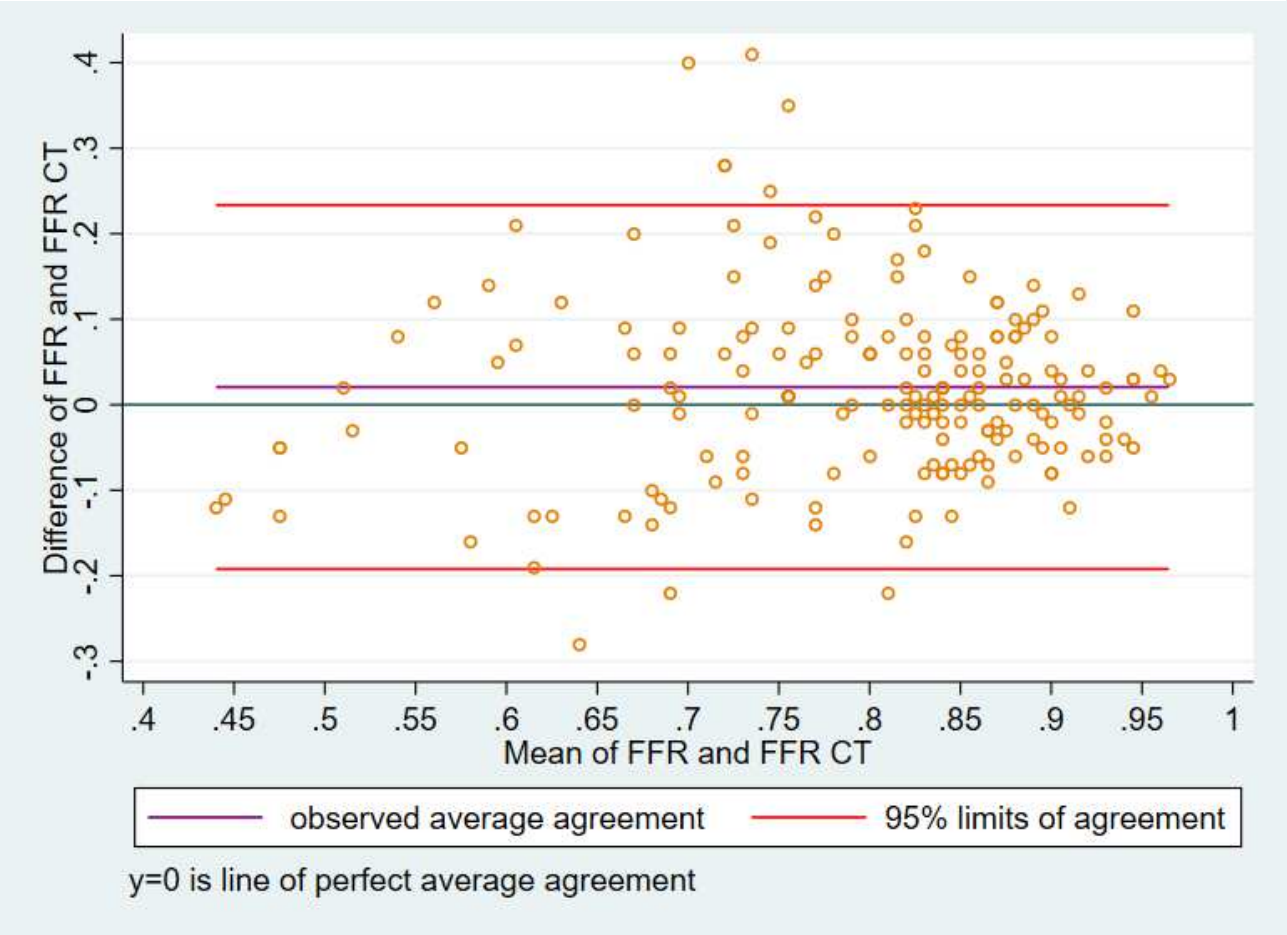
Differences between AUCs: *p= 0.89, †p = 0.19; ‡ p = 0.33

Median 895 (range 400-7070)

**Prevalence of significant CAD in tertiles (95% CI); T1: 30(21-41)%, T2: 33(23-43)%, T3: 54 (43-65)%

^Prevalence of significant CAD below and above median; 31(23-40)% vs 47(38-56)%.

Supplemental Figure. Per-vessel Bland-Altman agreement analysis of FFR_{CT} and FFR



Per-vessel correlation of FFR_{CT} and FFR was moderate (Spearman's rho=0.55). The agreement analysis indicated an estimated bias of 0.02 (0.003 to 0.04) with Limits of Agreement of -0.19 (-0.22 to -0.17) and 0.23 (0.21 to 0.27), respectively