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Published in:
European Heart Journal Cardiovascular Imaging

DOI:
[10.1093/ehjci/jeab198](https://doi.org/10.1093/ehjci/jeab198)

Publication date:
2022

Document version:
Final published version

Document license:
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Citation for pulished version (APA):
Tækker Madsen, K., Veien, K. T., Larsen, P., Husain, M., Deibjerg, L., Junker, A., Kusk, M. W., Thomsen, K. K., Rohold, A., Jensen, L. O., & Sand, N. P. R. (2022). Coronary CT angiography-derived fractional flow reserve in-stable angina: association with recurrent chest pain. *European Heart Journal Cardiovascular Imaging*, 23(11), 1511-1519. <https://doi.org/10.1093/ehjci/jeab198>

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Coronary CT angiography-derived fractional flow reserve in-stable angina: association with recurrent chest pain

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Received 12 March 2021; editorial decision 14 September 2021; accepted 19 September 2021; online publish-ahead-of-print 18 October 2021

Aims

The aim of this study was to evaluate the association between coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) and recurrent chest pain (CP) at 1-year follow-up in patients with stable angina pectoris (SAP).

Methods and results

Study of patients ($n = 267$) with SAP who underwent CCTA and FFR_{CT} testing; 236 (88%) underwent invasive coronary angiography; and 87 (33%) were revascularized. Symptomatic status at 1-year follow-up was gathered by a structured interview. Three different FFR_{CT} algorithms were applied using the following criteria for abnormality: (i) $2\text{ cm-FFR}_{CT} \leq 0.80$; (ii) $d\text{-FFR}_{CT} \leq 0.80$; and (iii) a combination in which both a $d\text{-FFR}_{CT} \leq 0.80$ and a $\Delta\text{FFR}_{CT} \geq 0.06$ must be present in the same vessel ($c\text{-FFR}_{CT}$). Patients were classified into two groups based on the FFR_{CT} test result and revascularization: completely revascularized/normal (CRN), patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with completely normal FFR_{CT} test results, and incompletely revascularized (IR), patients in whom ≥ 1 coronary artery with an abnormal FFR_{CT} test result was not revascularized. Recurrent CP was present in 62 (23%) patients. Classification of patients (CRN or IR) was significantly associated with recurrent CP for all applied FFR_{CT} interpretation algorithms. When applying the $c\text{-FFR}_{CT}$ algorithm, the association with recurrent CP was found, irrespective of the extent of coronary calcification and the degree of coronary stenosis. A negative association between per-patient minimal $d\text{-FFR}_{CT}$ and recurrent CP was demonstrated, $P < 0.005$.

Conclusion

An abnormal FFR_{CT} test result is associated with an increased risk of recurrent CP in patients with new-onset SAP.

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Graphical Abstract

FFR_{CT} and Recurrent Chest Pain in Stable Angina

Cohort and Methods

Patients with new onset stable angina pectoris who underwent coronary CTA and subsequent FFR_{CT} analysis (n = 267).

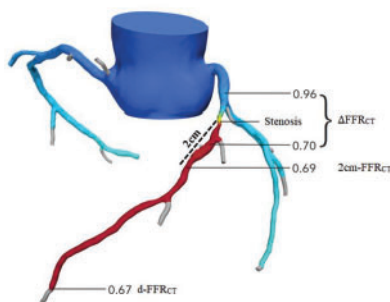
Interview on chest pain at one year follow-up

Interpretation of FFR_{CT} analysis performed blinded

FFR_{CT} categorized as normal or abnormal

Based on revascularization and FFR_{CT} interpretation patients were classified as either:

- 1) Completely revascularized/normal (CRN), all coronary arteries with an abnormal FFR_{CT} test result were revascularized or completely normal FFR_{CT}
- 2) Incompletely revascularized (IR), ≥ 1 coronary artery with an abnormal FFR_{CT} test result was not revascularized.

FFR_{CT} analysis and interpretation

Three different FFR_{CT} interpretation algorithms using the following criteria for abnormality were applied:

- 1) 2cm-FFR_{CT} ≤ 0.80
- 2) d-FFR_{CT} ≤ 0.80
- 3) A combination in which both a d-FFR_{CT} ≤ 0.80 and a Δ FFR_{CT} ≥ 0.06 must be present in the same vessel (c-FFR_{CT}).

Chest pain at one year follow-up

| FFR _{CT} algorithm | Chest pain (%) | OR (95% CI) | p-value |
|-----------------------------|----------------|------------------|---------|
| 2cm-FFR_{CT} | | | |
| Normal | 19 | | |
| Abnormal | 30 | 1.85 (1.04-3.29) | 0.035 |
| CRN | | | |
| IR | 35 | 2.20 (1.18-4.10) | 0.013 |
| d-FFR_{CT} | | | |
| Normal | 14 | | |
| Abnormal | 28 | 2.32 (1.18-4.54) | 0.015 |
| CRN | | | |
| IR | 32 | 2.94 (1.59-5.44) | <0.001 |
| c-FFR_{CT} | | | |
| Normal | 11 | | |
| Abnormal | 32 | 3.81 (1.95-7.44) | <0.0005 |
| CRN | | | |
| IR | 41 | 4.96 (2.69-9.13) | <0.0001 |

Conclusion: An abnormal FFR_{CT} test result is associated with an increased risk of recurrent chest pain in patients with new onset stable angina pectoris one year after standard-of-care guided treatment. Large-scale studies are required to validate the results of the present study.

Keywords

stable angina pectoris • coronary computed tomography angiography • FFR_{CT} • coronary revascularization • chest pain

Introduction

Large-scale studies of patients with stable angina pectoris (SAP) have not shown any reduction in major adverse cardiovascular events by mechanical revascularization as compared with optimal medical therapy (OMT) alone.^{1,2} These data have emphasized that the purpose of treatment in the majority of patients with SAP, in addition to risk factor reduction,³ should be alleviation of symptoms.⁴ Percutaneous coronary revascularization guided by fractional flow reserve (FFR) has led to improved recovery of chest pain (CP) up to 3 years⁵ highlighting the value of physiological assessment for guiding treatment in patients with SAP.^{6,7}

Coronary computed tomography angiography (CCTA) has emerged as a recommended first-line test in SAP⁸ and has proven superior to traditional non-invasive testing algorithms in reducing the long-term incidence of fatal or non-fatal myocardial infarction.⁹ However, due to an only modest correlation between degree of stenosis by CCTA and impact on coronary flow as measured by invasive FFR,^{10,11} additional non-invasive functional testing prior to referral to invasive coronary angiography (ICA) is recommended in patients with intermediate-to-moderate stenosis.⁸ CCTA-derived FFR (FFR_{CT}) has demonstrated enhanced diagnostic performance compared with CCTA alone^{10,12} and a high agreement with invasive FFR.^{10,13} Furthermore, FFR_{CT} has demonstrated improved diagnostic sensitivity as compared with commonly applied

stress perfusion imaging modalities^{14,15} and a normal FFR_{CT}-analysis has been associated with favourable prognostic outcomes.¹⁶⁻¹⁹ Consequently, FFR_{CT} is increasingly used in clinical practice for guiding referral to ICA,²⁰ for which purpose it is recommended to apply the 2-cm distal-to-stenosis FFR_{CT}-value²¹ instead of the lowest in vessel FFR_{CT}-value.²² However, it has recently been suggested that the diagnostic performance of FFR_{CT} might be improved if the criterion for abnormality also includes the presence of a focal trans-lesion FFR_{CT} gradient (Δ FFR_{CT}).^{23,24}

It is unknown whether FFR_{CT} can be used to predict the symptomatic course of patients with SAP. Thus, in this study, we sought to evaluate if the 2-cm distal-to-stenosis value, the lowest in vessel value or a combination of the lowest in vessel value and Δ FFR_{CT} were associated with recurrent CP in patients with new-onset SAP 1 year after standard-of-care-guided treatment.

Methods

Study design and patient population

This exploratory study assessed the association between three FFR_{CT} interpretation algorithms and recurrent CP in patients with new-onset SAP. Patients were included from two research projects at

the University Hospital of Southern Denmark, Esbjerg: The ReASSESS- (PRospEctive Comparison of FFR Derived From Coronary CT Angiography with SPECT perfusion Imaging in Stable Coronary ArtEry DiSeaSe) study ($n = 124$) (14) and the ADVANCE- (Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care) Registry ($n = 143$).¹⁶ A total of 303 patients were screened for inclusion of which 36 were excluded (prior ischaemic heart disease = 1, no FFR_{CT} data available = 9, did not attend follow-up = 26) resulting in a total study population of $n = 267$. Patients with a body mass index (BMI) ≤ 40 kg/m², an estimated glomerular filtration rate ≥ 45 mL/min, no persistent atrial fibrillation, and who had not previously been revascularized were eligible for CCTA. Clinical criteria for inclusion in this study were symptoms suggestive of SAP in patients who underwent CCTA and subsequent FFR_{CT} analysis. All patients participating in the ReASSESS-study underwent ICA and measurement of FFR according to study protocol, while referral to ICA in the ADVANCE-Registry was based on standard-of-care practice. Neither PCI-operators, heart-teams responsible for decision-making on revascularization nor personnel gathering information on CP status at 1-year follow-up were informed of the results of FFR_{CT} analysis. The study was approved by the regional ethical committee of Southern Denmark (S-20150085) and the data protection registry (2008-58-0035; 1563 and 1-16-02-633-20).

Coronary computed tomography angiography

CCTA was performed using either a SOMATOM Definition Flash or a FORCE CT scanner (Siemens, Forchheim, Germany). Oral beta-blockers or ivabradine were administered, if necessary, targeting a heart rate ≤ 60 bpm. All patients received sublingual nitroglycerine. An initial non-enhanced scan for calcium scoring was performed. On-site evaluation of CCTA data sets was performed by skilled CT cardiologists (all having more than 10 years of experience in CCTA interpretation). Vessels ≥ 2 mm in diameter were evaluated and severity of stenosis was graded visually by the interpreters and classified as either 30–69%, 70–89%, $\geq 90\%$, or non-evaluable due to a high extent of coronary artery calcification (CAC). Location of lesions was reported using a 17-segment model²⁵ and classified as proximal if located in segments 1, 2, 5, 6, 7, 11, or 13; all other lesion locations were classified as distal.

FFR_{CT} analysis and interpretation

Standard acquired CCTA data sets were transmitted for core laboratory analysis (HeartFlow Inc., Redwood City, CA, USA).¹⁴ Coronary arteries ≥ 2 mm in diameter were included in the analysis. The lowest in vessel FFR_{CT}-value (d-FFR_{CT}) was registered for all three major coronary arteries, including side branches. The 2 cm distal-to-stenosis FFR_{CT}-value (2 cm-FFR_{CT}) and the difference of FFR_{CT}-values immediately proximal and 10 mm distal to stenosis (Δ FFR_{CT}) were registered for every stenosis identified by CCTA, Figure 1. Interpretation of the FFR_{CT} analysis was performed by a single person, who was informed of the location of stenosis by CCTA but blinded to other patient data. The reference for defining the 2 cm measuring point was manually assigned. The 10 mm measuring point was defined as the midpoint between the 2 cm measuring point and the stenosis. Three different FFR_{CT} interpretation algorithms using the following criteria for abnormality were applied: (i) 2 cm-FFR_{CT} ≤ 0.80 ,^{10,13,22} (ii) d-FFR_{CT} ≤ 0.80 ,^{12,14,20} and (iii) a combination in which both a d-FFR_{CT} ≤ 0.80 and a Δ FFR_{CT} ≥ 0.06 must be present in the same vessel (c-FFR_{CT}).²³

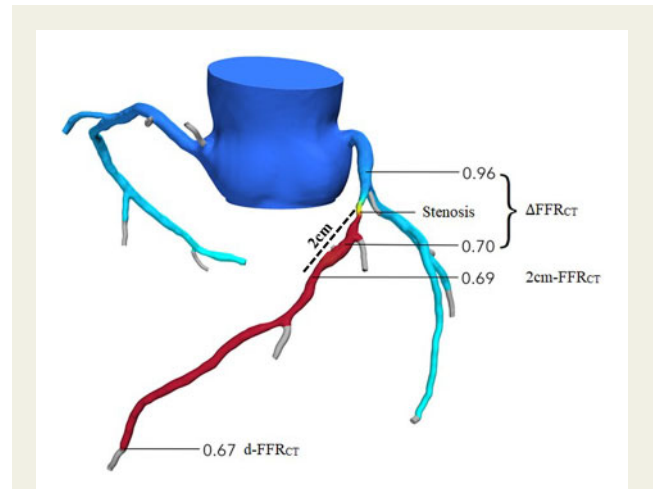


Figure 1 Schematic presentation of FFR_{CT} registrations—patient with a stenosis in the proximal left anterior descending coronary artery. FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve; Δ FFR_{CT}, the difference of FFR_{CT}-values immediately proximal and 10 mm distal to stenosis; 2 cm-FFR_{CT}, the 2-cm distal-to-stenosis FFR_{CT}-value; d-FFR_{CT}, the lowest in vessel FFR_{CT}-value.

Coronary angiography, FFR, and revascularization

Coronary angiography was performed by standard techniques. Intracoronary nitroglycerine was administered before pressure wire measurements were made. A 0.014-inch pressure wire (Verrata pressure wire, Volcano Phillips, San Diego, CA, USA) was placed distal to the coronary artery lesion. Maximal hyperaemia was induced by intravenous adenosine (140 mg/kg/min). Recordings of aortic and distal coronary pressures were obtained by manual pull-back during sustained hyperaemia (after 2 min of adenosine infusion). Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were performed according to international guidelines.^{6,8}

Revascularization status

FFR_{CT} test results were categorized according to each of the three FFR_{CT} interpretation algorithms as either normal or abnormal. Based on the FFR_{CT} test result and revascularization, patients were classified according to each of these algorithms as either: (i) completely revascularized/normal (CRN), patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with a completely normal FFR_{CT}; (ii) incompletely revascularized (IR), patients in whom ≥ 1 coronary artery with an abnormal FFR_{CT} test result was not revascularized.

Follow-up

One year after CCTA, patients were contacted by telephone or seen in the outpatient clinic. Information concerning symptoms was recorded using a structured interview. Symptoms were registered as either angina (typical, atypical, or non-specific) or dyspnoea. Data regarding use of anti-anginal medication were obtained via medical records and were confirmed during the follow-up interview. Daily intake of antianginal medication was registered.

Table 1 Baseline characteristics according to recurrent chest pain at 1-year follow-up in patients with stable angina

| Demographics | All n = 267 | No CP n = 205 | Recurrent CP n = 62 | P-value |
|--------------------------|-------------------|-------------------|------------------------|---------|
| Age | 65 ± 11 | 65 ± 10 | 67 ± 12 | 0.267 |
| Gender, male | 163 (61) | 123 (60) | 40 (65) | 0.523 |
| BMI (kg/m ²) | 27.2 ± 4.1 | 27.3 ± 4.2 | 26.9 ± 3.7 | 0.536 |
| Risk factors | | | | |
| Diabetes | 29 (11) | 25 (12) | 4 (6) | 0.211 |
| Hypertension | 154 (58) | 117 (57) | 37 (60) | 0.716 |
| Hypercholesterolaemia | 142 (53) | 107 (52) | 35 (56) | 0.556 |
| Smoking | 55 (21) | 42 (20) | 13 (21) | 0.935 |
| Symptoms | | | | |
| Typical angina | 85 (32) | 63 (31) | 22 (35) | |
| Atypical angina | 76 (28) | 60 (29) | 16 (26) | 0.706 |
| Unspecific angina | 93 (35) | 73 (36) | 20 (32) | |
| Dyspnoea | 13 (5) | 9 (4) | 4 (6) | |
| Diamond–Forrester Score | 49 (34–68) [8–93] | 49 (34–68) [8–93] | 58 (32–69) [17–89] | 0.131 |

Values are given as n (%), mean ± SD, or median (interquartile range) [range].
BMI, body mass index; CP, chest pain.

Statistical methods

Descriptive statistics were used for patient characteristics and CCTA preparation parameters and test results. Associations between recurrent CP at 1-year follow-up and age, gender, diabetes, smoking, hypertension, BMI, and Agatston Score were performed using Wilcoxon rank-sum test, Fisher's exact test or χ^2 test as appropriate. Test for trend was performed to compare proportion of patients undergoing revascularization or having recurrent CP with categories of stenosis severity by CCTA. The daily intake of antianginal medication was compared according to recurrent CP status using the Mann–Whitney test and according to FFR_{CT} classifications for each of the FFR_{CT} interpretation algorithms using two-sample t-test. Logistic regression was used to analyse associations between recurrent CP at 1-year follow-up and FFR_{CT} classifications for each of the FFR_{CT} interpretation algorithms. Comparison of areas under receiver operating characteristic (ROC) curves was performed using the algorithm by DeLong et al.²⁶ Spearman's correlation between recurrent CP and categories of per patient minimal d-FFR_{CT} categories was calculated. The Δ FFR_{CT} threshold used in the c-FFR_{CT} interpretation algorithm was derived as the Δ FFR_{CT}-value yielding the highest Youden's Index, [Supplementary data online, Figure S1](#). A P-value of <0.05 was considered statistically significant. All odds ratios (ORs) are displayed with 95% confidence intervals (CIs). All statistical analyses were performed using Stata version 16.1 software (Stata Corp, College Station, TX, USA).

Results

In total, 267 patients with SAP were included. Baseline demographics, risk factors, and symptoms according to recurrent CP at 1-year follow-up are shown in [Table 1](#). Medical therapy is illustrated in [Supplementary data online, Table S1](#). CCTA preparation parameters and findings are shown in [Table 2](#). ICA was performed in 236 (88%) patients and FFR in 132 (49%). Revascularization was performed in 87 (33%) patients, PCI in 75 (86%), and CABG in 12 (14%). Single vessel disease was present in 58 (65%) patients, 2-vessel disease in 22 (27%), and 3-vessel disease in 7 (8%). In total, 124 vessels were

Table 2 Coronary computed tomography angiography

| | |
|--|--------------------------|
| Preparation and basic information | |
| Nitroglycerine | 267 (100) |
| Medication for reduction of heart rate | 168 (63) |
| Heart rate, bpm | 58 ± 11 |
| Radiation dose (mSv) | 3.8 (2.1–7.1) [0.6–23.5] |
| Analysis | |
| Agatston score (U) | 321 (102–732) [0–6870] |
| 0–99 | 62 (23) |
| 100–399 | 92 (34) |
| ≥400 | 113 (42) |
| Stenosis severity ^a (%) | |
| 30–69 | 122 (46) |
| 70–89 | 117 (44) |
| ≥90 | 18 (7) |
| Not evaluable due to high CAC | 10 (4) |
| Stenosis location | |
| Proximal | 248 (93) |
| Distal | 19 (7) |

Values are given as n (%), mean ± SD, or median (interquartile range) [range].

Acquisition and findings.

CAC, coronary artery calcification.

^aPer-patient most severe stenosis.

revascularized: Left main coronary artery, 7 (6%); left anterior descending coronary artery, 58 (47%); left circumflex coronary artery, 14 (11%); right coronary artery, 35 (28%); side branches 3 (2%). Revascularized stenoses were located in proximal coronary segments in 109 (88%) vessels. Revascularization rates, n (%), increased with higher degree of stenosis by CCTA: 30–69%, 14 (11); 70–89%,

54 (46); $\geq 90\%$, 15 (83), respectively, (test for trend: $P < 0.0001$). The occurrence of recurrent CP, n (%), was independent of stenosis severity by CCTA: 30–69%, 23 (19); 70–89%, 30 (26); $\geq 90\%$, 4 (22), respectively, (test for trend: $P > 0.05$).

Recurrent CP, revascularization, and FFR_{CT}

In total, 62 (23%) patients reported recurrent CP at 1-year follow-up. Of these 14 (23%) patients had typical angina, 15 (24%) atypical angina, 20 (32%) non-specific angina, and 13 (21%) dyspnoea. Overall, there was no difference in recurrent CP at follow-up between revascularized and non-revascularized patients, 21 (24%) vs. 41 (23%), (OR 1.08, 95% CI 0.59–1.97), $P > 0.05$. In patients with an Agatston score ≥ 400 vs. Agatston score < 400 , a higher occurrence of revascularization, (OR 4.05, 95% CI 2.41–6.79), $P < 0.0001$, and of recurrent CP, (OR 1.78, 95% CI 1.00–3.15), $P < 0.05$, were observed. In non-revascularized patients, a negative association between the per-patient minimal d-FFR_{CT} value and recurrent CP was found, Figure 2. For all three FFR_{CT} interpretation algorithms 2 cm-, d-, and c-FFR_{CT}, the probability of recurrent CP was significantly higher for patients with an abnormal test result as compared with patients with a normal test result, Table 3. Correspondingly, ROC-curves revealed the largest AUC for the association with recurrent CP by the c-FFR_{CT} algorithm, Figure 3. For the d-FFR_{CT} and c-FFR_{CT} algorithms, the association with recurrent CP was demonstrated irrespective of stenosis severity, Table 4, and for the c-FFR_{CT} interpretation

algorithm both in patients with a low and a high extent of coronary calcification, Table 5.

Antianginal medication at follow-up

The number of patients, n (%), treated with antianginal medication were: beta-blockers, 98 (37); calcium antagonists, 96 (36); long-acting nitrates, 18 (7). There was no difference in the intake of antianginal medication, between patients with and without recurrent CP at 1-year follow-up, median (interquartile range), 1 (1–1) tablets and 1 (1–1) tablets, respectively, $P > 0.05$. No significant difference in daily intake of antianginal medication was registered between patients with different revascularization status (IR or CRN) for any of the applied FFR_{CT} interpretation algorithms or between patients with different degrees of flow impairment as measured by d-FFR_{CT}.

Discussion

This study is the first to indicate that an abnormal FFR_{CT} test result can be associated with recurrent CP in patients with new-onset SAP. Classification of patients based on the FFR_{CT} analysis was significantly associated with recurrent CP at 1-year follow-up. The demonstration of a negative relationship between the degree of flow impairment by the lowest in vessel FFR_{CT}-value and recurrence of symptoms in non-revascularized patients supports these findings. The combination of more than one FFR_{CT} metric improved the prediction of patient symptoms and was associated with recurrent CP irrespective of the

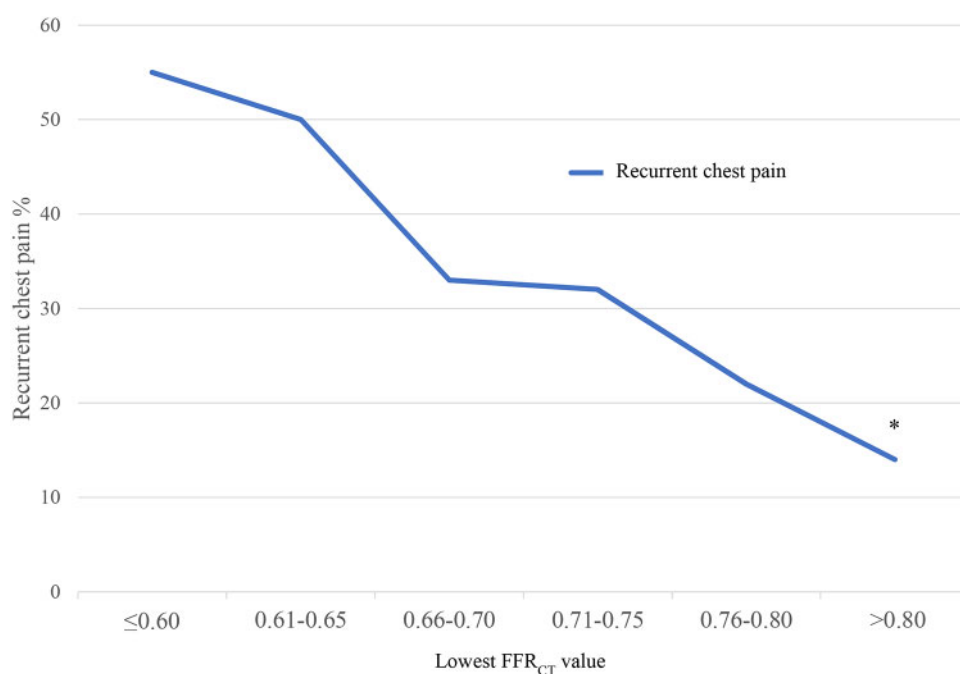


Figure 2 The per-patient lowest FFR_{CT}-value according to recurrent chest pain at 1-year follow-up in non-revascularized patients with stable angina. Non-revascularized patients were classified according to the per-patient lowest FFR_{CT}-value and categorized into groups of 0.05 increments from ≤ 0.60 to > 0.80 . * $P < 0.005$: for correlation between recurrent CP and categories of per-patient lowest FFR_{CT}-value. FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve.

Table 3 Recurrent chest pain at 1-year follow-up according to FFR_{CT} interpretation algorithm^a and revascularization status^b in patients with stable angina

| FFR _{CT} algorithm | No CP n = 205 | Recurrent CP n = 62 | Recurrent CP (%) ^c | Odds ratio | P-value |
|------------------------------|------------------|------------------------|-------------------------------|------------------|---------|
| 2 cm-FFR_{CT} | | | | | |
| Normal | 127 (62) | 29 (47) | 19 | | |
| Abnormal | 78 (38) | 33 (53) | 30 | 1.85 (1.04–3.29) | 0.035 |
| CRN | 164 (80) | 40 (65) | 20 | | |
| IR | 41 (20) | 22 (35) | 35 | 2.20 (1.18–4.10) | 0.013 |
| d-FFR_{CT} | | | | | |
| Normal | 78 (38) | 13 (21) | 14 | | |
| Abnormal | 127 (62) | 49 (79) | 28 | 2.32 (1.18–4.54) | 0.015 |
| CRN | 112 (55) | 18 (29) | 14 | | |
| IR | 93 (45) | 44 (71) | 32 | 2.94 (1.59–5.44) | <0.001 |
| c-FFR_{CT} | | | | | |
| Normal | 103 (50) | 13 (21) | 11 | | |
| Abnormal | 102 (50) | 49 (79) | 32 | 3.81 (1.95–7.44) | <0.0005 |
| CRN | 144 (70) | 20 (32) | 12 | | |
| IR | 61 (30) | 42 (68) | 41 | 4.96 (2.69–9.13) | <0.0001 |

Values are given as n (%). Criteria for abnormality for different FFR_{CT} interpretation algorithms: 2 cm-FFR_{CT} ≤0.80; d-FFR_{CT} ≤0.80; c-FFR_{CT}, a combination in which both a d-FFR_{CT} ≤0.80 and an ΔFFR_{CT} ≥0.06 must be present in the same vessel.

CP, chest pain; FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve.

^aFFR_{CT} interpretation algorithms: 2 cm-FFR_{CT}, the 2 cm distal-to-stenosis FFR_{CT}-value; d-FFR_{CT}, the lowest in vessel FFR_{CT}-value; c-FFR_{CT}, combination of d-FFR_{CT} and a trans-lesion pressure gradient, ΔFFR_{CT} (difference of FFR_{CT}-values immediately proximal and 10 mm distal to stenosis).

^bRevascularization status: CRN, patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with a completely normal FFR_{CT}; IR, patients in whom ≥1 coronary artery with an abnormal FFR_{CT} test result was not revascularized.

^cThe percentage of patients with recurrent CP for classifications: normal/abnormal and CRN/IR.

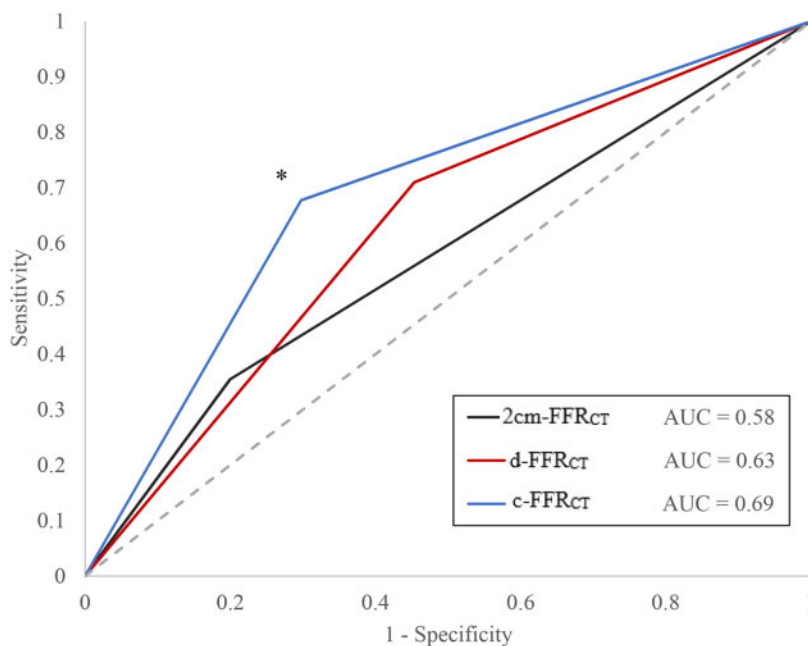


Figure 3 Association between FFR_{CT} interpretation algorithms and recurrent chest pain—ROC curves. ROC curves showing the association between classification (CRN/IR) for 2 cm-, d-, and c-FFR_{CT} interpretation algorithms and recurrent CP. Revascularization status: CRN, patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with a completely normal FFR_{CT}; IR, patients in whom ≥1 coronary artery with an abnormal FFR_{CT} test result was not revascularized. AUC, area under the curve; CP, chest pain; FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve; ROC, receiver operating characteristics. *Statistically significant difference between AUC for c-FFR_{CT} vs. d-FFR_{CT} and c-FFR_{CT} vs. 2 cm-FFR_{CT}, both $P < 0.001$.

Table 4 Recurrent chest pain at 1-year follow-up according to FFR_{CT} interpretation algorithm^a, revascularization status^b, and degree of coronary stenosis in patients with stable angina

| Stenosis degree (%) | FFR _{CT} algorithm | No CP n = 186 | Recurrent CP n = 53 | Recurrent CP (%) ^c | Odds ratio | P-value |
|------------------------------|-----------------------------|------------------|------------------------|-------------------------------|-------------------|---------|
| 2 cm-FFR_{CT} | | | | | | |
| 30–69 | CRN | 83 (45) | 15 (28) | 15 | 2.77 (1.01–7.61) | 0.049 |
| | IR | 16 (9) | 8 (15) | 33 | | |
| 70–89 | CRN | 68 (37) | 20 (38) | 23 | 1.79 (0.72–4.46) | 0.212 |
| | IR | 19 (10) | 10 (19) | 34 | | |
| d-FFR_{CT} | | | | | | |
| 30–69 | CRN | 58 (31) | 8 (15) | 12 | 2.65 (1.03–6.84) | 0.043 |
| | IR | 41 (22) | 15 (28) | 27 | | |
| 70–89 | CRN | 46 (25) | 9 (17) | 17 | 2.62 (1.08–6.36) | 0.034 |
| | IR | 41 (22) | 21 (40) | 34 | | |
| c-FFR_{CT} | | | | | | |
| 30–69 | CRN | 77 (41) | 9 (17) | 10 | 5.44 (2.08–14.25) | <0.001 |
| | IR | 22 (12) | 14 (26) | 39 | | |
| 70–89 | CRN | 55 (30) | 9 (17) | 14 | 4.01 (1.64–9.81) | <0.005 |
| | IR | 32 (17) | 21 (40) | 40 | | |

Values are given as n (%). Criteria for abnormality for different FFR_{CT} interpretation algorithms: 2 cm-FFR_{CT} ≤0.80; d-FFR_{CT} ≤0.80; c-FFR_{CT}, a combination in which both a d-FFR_{CT} ≤0.80 and an ΔFFR_{CT} ≥0.06 must be present in the same vessel. Data not shown for 10 patients with non-evaluable stenosis severity due to high CACS and 18 patients with highest stenosis degree ≥90%.

CP, chest pain; FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve.

^aFFR_{CT} interpretation algorithms: 2 cm-FFR_{CT}, the 2 cm distal-to-stenosis FFR_{CT}-value; d-FFR_{CT}, the lowest in vessel FFR_{CT}-value; c-FFR_{CT}, combination of d-FFR_{CT} and a trans-lesion pressure gradient, ΔFFR_{CT} (difference of FFR_{CT}-values immediately proximal and 10 mm distal to stenosis).

^bRevascularization status: CRN, patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with a completely normal FFR_{CT}; IR, patients in whom ≥1 coronary artery with an abnormal FFR_{CT} test result was not revascularized.

^cThe percentage of patients with recurrent CP for classifications: normal/abnormal and CRN/IR.

Table 5 Recurrent chest pain at 1-year follow-up according to FFR_{CT}-interpretation algorithm^a, revascularization status^b, and extent of coronary calcification in patients with stable angina

| Agatston score | FFR _{CT} algorithm | No CP n = 205 | Recurrent CP n = 62 | Recurrent CP (%) ^c | Odds ratio | P-value |
|------------------------------|-----------------------------|------------------|------------------------|-------------------------------|-------------------|---------|
| 2 cm-FFR_{CT} | | | | | | |
| <400 | CRN | 106 (52) | 21 (34) | 17 | 2.13 (0.82–5.49) | 0.120 |
| | IR | 19 (9) | 8 (13) | 31 | | |
| ≥400 | CRN | 58 (28) | 19 (31) | 25 | 1.94 (0.83–4.53) | 0.124 |
| | IR | 22 (11) | 14 (23) | 39 | | |
| d-FFR_{CT} | | | | | | |
| <400 | CRN | 75 (37) | 14 (23) | 16 | 1.61 (0.71–3.62) | 0.252 |
| | IR | 50 (24) | 15 (24) | 23 | | |
| ≥400 | CRN | 37 (18) | 4 (6) | 10 | 6.24 (2.01–19.39) | <0.005 |
| | IR | 43 (21) | 29 (47) | 40 | | |
| c-FFR_{CT} | | | | | | |
| <400 | CRN | 93 (45) | 15 (24) | 14 | 2.71 (1.18–6.23) | 0.019 |
| | IR | 32 (16) | 14 (23) | 30 | | |
| ≥400 | CRN | 51 (25) | 5 (8) | 9 | 9.85 (3.43–28.29) | <0.0001 |
| | IR | 29 (14) | 28 (45) | 49 | | |

Values are given as n (%). Criteria for abnormality for different FFR_{CT} interpretation algorithms: 2 cm-FFR_{CT} ≤0.80; d-FFR_{CT} ≤0.80; c-FFR_{CT}, a combination in which both a d-FFR_{CT} ≤0.80 and an ΔFFR_{CT} ≥0.06 must be present in the same vessel.

CP, chest pain; FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve.

^aFFR_{CT} interpretation algorithms: 2 cm-FFR_{CT}, the 2 cm distal-to-stenosis FFR_{CT}-value; d-FFR_{CT}, the lowest in vessel FFR_{CT}-value; c-FFR_{CT}, combination of d-FFR_{CT} and a trans-lesion pressure gradient, ΔFFR_{CT} (difference of FFR_{CT}-values immediately proximal and 10 mm distal to stenosis).

^bRevascularization status: CRN, patients in whom all coronary arteries with an abnormal FFR_{CT} test result were revascularized or patients with a completely normal FFR_{CT}; IR, patients in whom ≥1 coronary artery with an abnormal FFR_{CT} test result was not revascularized.

^cThe percentage of patients with recurrent CP for classifications: normal/abnormal and CRN/IR.

extent of coronary calcification and the degree of coronary stenosis by CCTA.

At the moment, FFR is the gold standard for decision-making on coronary revascularization in patients with stable CAD^{6,8} who are referred to ICA. However, FFR is not capable of directly quantifying the diffuse disease component that may be a cause of recurrent CP²⁷ and often associated with focal disease.²⁸ The potential impact of non-obstructive epicardial coronary stenosis on patient symptoms was demonstrated in a recent study, in which patients with non-obstructive CAD had a higher degree of symptomatic relief and improvement in quality of life, when antianginal medical treatment was guided by contemporary invasive physiological estimates of coronary impairment, as compared with standard-of-care-guided medical treatment.²⁹

The results of the present study may be supportive of diffuse disease as a cause of recurrent CP. First, the incidence of recurrent CP was similar for revascularized and non-revascularized individuals. Second, although revascularization was performed more often in patients with a high extent of coronary calcification, as compared with patients with a low degree of calcification, the former did not have a lower incidence of recurrent CP at follow-up. Third, interpretation algorithms based on distal FFR_{CT}-values reflecting the cumulative pressure loss along the entire vessel indicated an improved association with recurrent CP as compared with the 2 cm-FFR_{CT} algorithm, which solely mirrors focal disease, *Figure 3* and *Tables 3–5*. Fourth, in non-revascularized patients, the incidence of recurrent CP was highest in patients with the lowest distal FFR_{CT}-values, *Figure 2*.

The prevalence of recurrent CP at 1-year follow-up in the present study (23%) was lower than what has been observed in previous large-scale studies of stable patients, 48%² and 46%.³⁰ One potential explanation might be the relatively high proportion of patients undergoing FFR in this study, as physiological guidance of revascularization has previously been shown to reduce the prevalence of recurrent CP.⁵ The demonstrated association between FFR_{CT} and recurrent CP in the current study would probably be more pronounced in a general SAP population in which a higher prevalence of recurrent CP may be expected due to less utilization of ICA, which otherwise might lead to reduced angina complaints even amongst non-revascularized patients.³¹

In contemporary practice, the majority of patients with SAP can be securely managed by non-invasive testing modalities.^{9,16} However, revascularization compared with OMT is not associated with better prognostic outcomes in patients with invasive FFR ≤ 0.80 ⁵ or moderate-to-severe ischaemia.¹ At the same time, the number of patients with SAP experiencing recurrent CP due to inadequate antianginal medical therapy appears to be increasing.⁴ Together, these results seem to indicate that a major future treatment goal in patients with SAP, in addition to risk factor reduction,³ should be alleviation of patient symptoms. Currently, there is a lack of tools to assess and aid in the management of symptoms amongst patients with SAP.⁴ The findings in this study suggest that FFR_{CT} may be suited for this purpose, clinical case example [Supplementary data](#) online, *Figure S2*.

Limitations

It should be emphasized that prediction of recurrent symptoms is a potential new application of FFR_{CT}. The results of this study might be considered exploratory and need validation before a general

implementation. Furthermore, our data do not allow for conclusions regarding the potential effects on recurrent symptoms by intensifying antianginal medical therapy in patients with an abnormal FFR_{CT} test.

Symptoms were classified using the Diamond–Forrester (DF) Score.³² An extended angina classification tool such as the Seattle Angina Questionnaire³³ might have provided a more in-depth evaluation of the primary endpoint. However, DF classification of symptoms is broadly used in SAP and we do not believe this to impact the results of this study.

The degree of stenosis by CCTA was not core laboratory adjudicated, as CCTA data sets were analysed on-site by experienced CT cardiologists. The degree of stenosis by CCTA was based on classifications in the ADVANCE-Registry¹⁶ or the ReASSESS-study.¹⁴ In the latter, stenoses ranging from 40% to 69% were classified as intermediate, which made subdivision in categories 30–49% and 50–69% impossible. However, we do not believe this to have influenced the conclusions of this study.

Conclusion

An abnormal FFR_{CT} test result is associated with an increased risk of recurrent CP in patients with new-onset SAP 1 year after standard-of-care-guided treatment.

Large-scale studies are required to validate the results of this study.

Supplementary data

[Supplementary data](#) are available at *European Heart Journal - Cardiovascular Imaging* online.

Funding

The entire financial support for the study was delivered by participating departments. No external funding was used for coverage of expenditures.

Conflict of interest: L.O.J. has received institutional research grants from St. Jude Medical, Biosensors, and Biotronik. All other authors had no disclosures to declare.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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