ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **23**, 1511–1519
https://doi.org/10.1093/ehjci/jeab198

ORIGINAL PAPER

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

Kristian Tækker Madsen [1]*, Karsten Tange Veien[2], Pia Larsen[3], Majed Husain[1], Lone Deibjerg[1], Anders Junker[2], Martin Weber Kusk[4], Kristian Korsgaard Thomsen[1], Allan Rohold[1], Lisette Okkels Jensen[2], and Niels Peter Rønnow Sand[1,5]

[1]Department of Cardiology, University Hospital of Southern Denmark, Finsensgade 35, Esbjerg DK-6700, Denmark; [2]Department of Cardiology, Odense University Hospital, Odense, Denmark; [3]Department of Mental Health Services, Region of Southern Denmark, Odense, Denmark; [4]Department of Radiology, University Hospital of Southern Denmark, Esbjerg, Denmark; and [5]Department of Regional Health Research, University of Southern Denmark, Esbjerg, Denmark

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 cm-FFR_{CT} ≤0.80; (ii) d-FFR_{CT} ≤0.80; and (iii) a combination in which both a d-FFR_{CT} ≤0.80 and a ΔFFR_{CT} ≥0.06 must be present in the same vessel (c-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-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-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.

*Corresponding author. Tel: +45 40572733. E-mail: kristian.taekker.madsen2@rsyd.dk

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

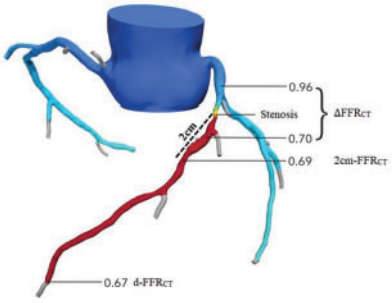
Interpretation of FFR_{CT} analysis performed blinded

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 ΔFFR_{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	1.85 (1.04-3.29)	0.035
Abnormal	30		
CRN	20	2.20 (1.18-4.10)	0.013
IR	35		
d-FFR_{CT}			
Normal	14	2.32 (1.18-4.54)	0.015
Abnormal	28		
CRN	14	2.94 (1.59-5.44)	<0.001
IR	32		
c-FFR_{CT}			
Normal	11	3.81 (1.95-7.44)	<0.0005
Abnormal	32		
CRN	12	4.96 (2.69-9.13)	<0.0001
IR	41		

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 years[5] 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 SAP[8] 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}-value[21] 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 criterium for abnormality also includes the presence of a focal trans-lesion FFR_{CT} gradient (ΔFFR_{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 ΔFFR_{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/m^2, 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%, ≥90%, or non-evaluable due to a high extent of coronary artery calcification (CAC). Location of lesions was reported using a 17-segment model[25] 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 (ΔFFR_{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 ΔFFR_{CT} ≥0.06 must be present in the same vessel (c-FFR_{CT}).[23]

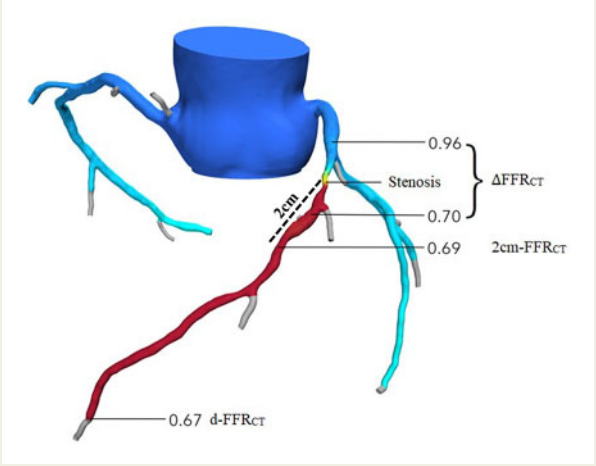


Figure 1 Schematic presentation of FFR_{CT} registrations—patient with a stenosis in the proximal left anterior descending coronary artery. FFR_{CT}, coronary computed tomography angiography-derived fractional flow reserve; ΔFFR_{CT}, the difference of FFR_{CT}-values immediately proximal and 10 mm distal 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 administrated 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 ΔFFR_{CT} threshold used in the c-FFR_{CT} interpretation algorithm was derived as the ΔFFR_{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).

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.
[a]Per-patient most severe stenosis.

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 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); ≥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); ≥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

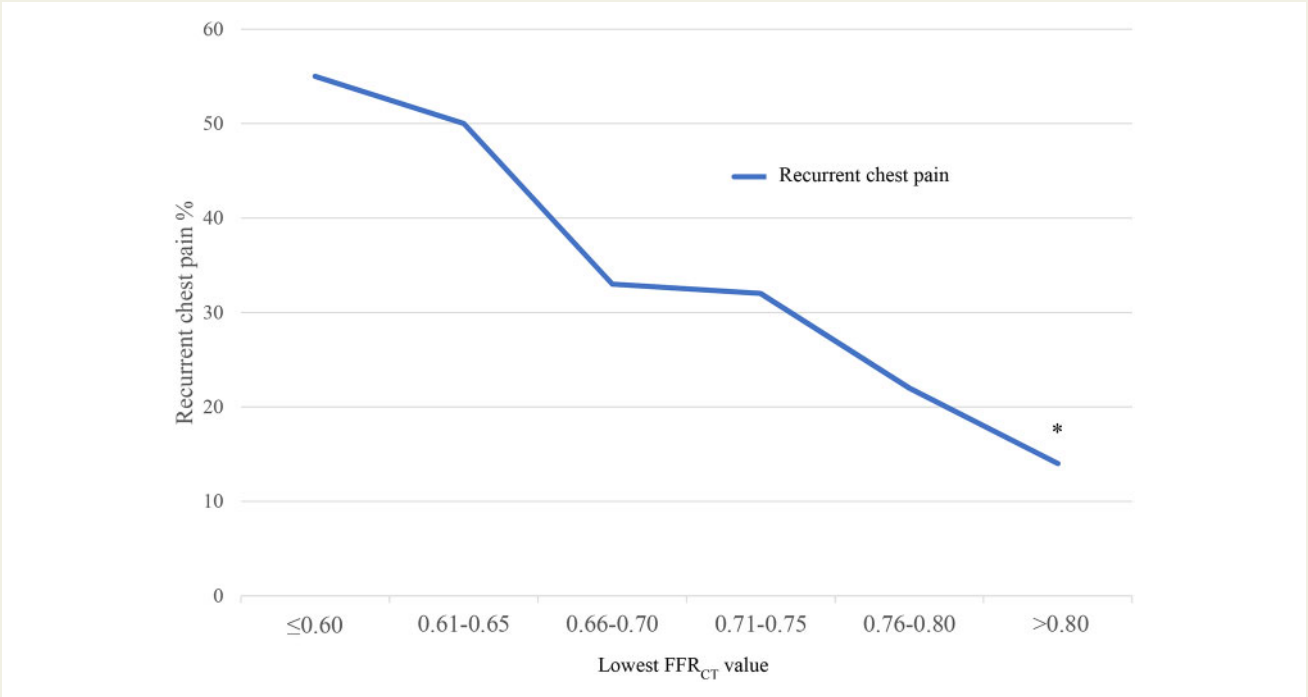


Figure 2 The per-patient lowest FFR_{CT}-value according to recurrent chest pain at 1-year follow-up in non-revascularized patients with stable angina. Non-revascularized patients were classified according to the per-patient lowest FFR_{CT}-value and categorized into groups of 0.05 increments from ≤0.60 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	1.85 (1.04–3.29)	0.035
Abnormal	78 (38)	33 (53)	30		
CRN	164 (80)	40 (65)	20	2.20 (1.18–4.10)	0.013
IR	41 (20)	22 (35)	35		
d-FFR$_{CT}$					
Normal	78 (38)	13 (21)	14	2.32 (1.18–4.54)	0.015
Abnormal	127 (62)	49 (79)	28		
CRN	112 (55)	18 (29)	14	2.94 (1.59–5.44)	<0.001
IR	93 (45)	44 (71)	32		
c-FFR$_{CT}$					
Normal	103 (50)	13 (21)	11	3.81 (1.95–7.44)	<0.0005
Abnormal	102 (50)	49 (79)	32		
CRN	144 (70)	20 (32)	12	4.96 (2.69–9.13)	<0.0001
IR	61 (30)	42 (68)	41		

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.
[a]FFR_{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).
[b]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.
[c]The percentage of patients with recurrent CP for classifications: normal/abnormal and CRN/IR.

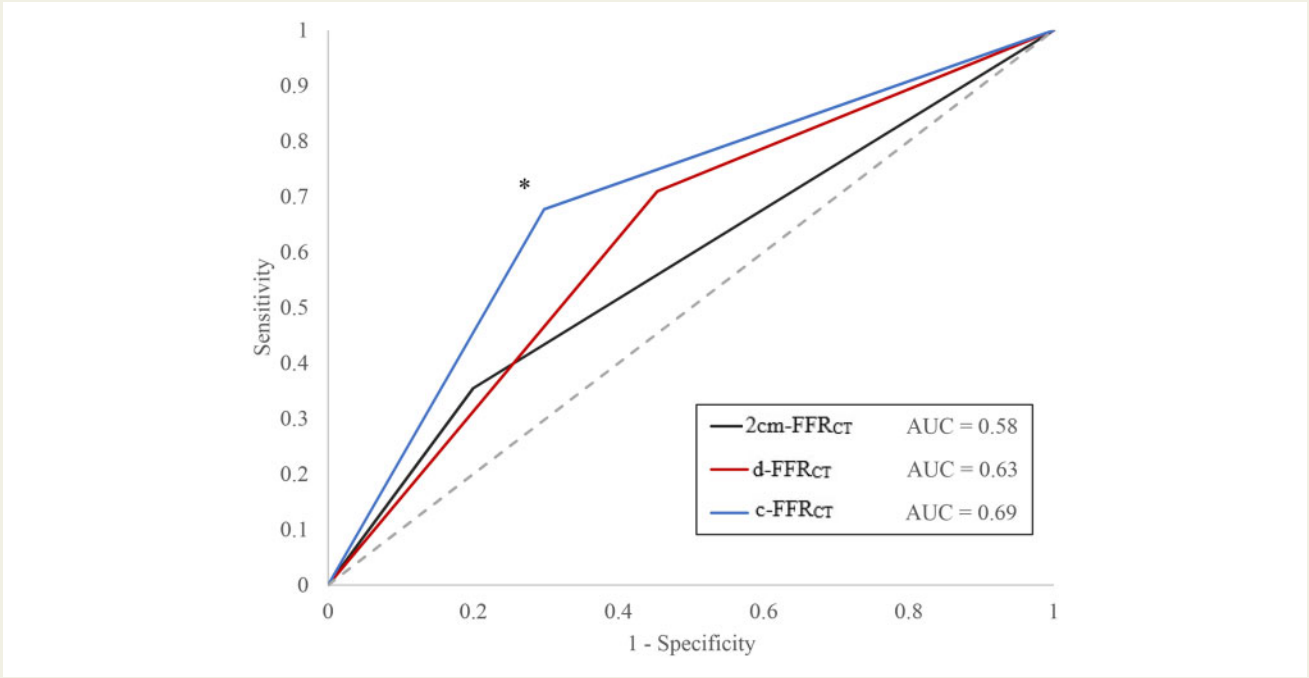


Figure 3 Association between FFR_{CT} interpretation algorithms and recurrent chest pain—ROC curves. ROC curves showing the association between classification (CRN/IR) for 2 cm-, d-, and c-FFR_{CT} interpretation algorithms and recurrent CP. Revascularization status: CRN, patients in whom all coronary 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.

[a]FFR_{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).

[b]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.

[c]The 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.

[a]FFR_{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).

[b]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.

[c]The 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 CP[27] 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 Questionnaire[33] 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-Registry[16] 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 availabilty

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

References

1. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE *et al.*; ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–407.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16.
3. Mortensen MB, Steffensen FH, Bøtker HE, Jensen JM, Rønnow Sand NP, Kragholm KH *et al.* CAD severity on cardiac CTA identifies patients with most benefit of treating LDL-cholesterol to ACC/AHA and ESC/EAS targets. *JACC Cardiovasc Imaging* 2020;**13**:1961–72.

4. Camm AJ, Manolis A, Ambrosio G, Daly C, Komajda M, Lopez De Sa E *et al.* Unresolved issues in the management of chronic stable angina. *Int J Cardiol* 2015; **201**:200–7.
5. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL *et al.* Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med* 2018;**379**:250–9.
6. Franz-Josef N, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization the task force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2019; **40**:87–165.
7. Ali ZA, Horst J, Gaba P, Shaw LJ, Bangalore S, Hochman JS *et al.* Standardizing the definition and analysis revascularization. *J Am Heart Assoc* 2021;**10**:1–10.
8. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019;**41**:407–77.
9. Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M *et al.*; SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33.
10. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H *et al.*; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: next Steps). *J Am Coll Cardiol* 2014;**63**:1145–55.
11. Budoff MJ, Nakazato R, Mancini GBJ, Gransar H, Leipsic J, Berman DS *et al.* CT angiography for the prediction of hemodynamic significance in intermediate and severe lesions head-to-head comparison with quantitative coronary angiography using fractional flow reserve as the reference standard. *JACC Cardiovasc Imaging* 2016;**9**:559–64.
12. Driessen RS, Danad I, Stuijfzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA *et al.* Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. *J Am Coll Cardiol* 2019;**73**:161–73.
13. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS *et al.* Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noni). *J Am Coll Cardiol* 2011;**58**:1989–97.
14. Sand NPR, Veien KT, Nielsen SS, Nørgaard BL, Larsen P, Johansen A *et al.* Prospective comparison of FFR derived from coronary CT angiography with SPECT perfusion imaging in stable coronary artery disease: the ReASSESS study. *JACC Cardiovasc Imaging* 2018;**11**:1640–50.
15. Sand NPR, Nissen L, Winther S, Petersen SE, Westra J, Christiansen EH *et al.* Prediction of coronary revascularization in stable angina: comparison of FFRCT with CMR stress perfusion imaging. *JACC Cardiovasc Imaging* 2020;**13**:994–1004.
16. Patel MR, Nørgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS *et al.* 1-year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE registry. *JACC Cardiovasc Imaging* 2020;**13**:97–105.
17. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA *et al.* 1-year outcomes of FFRct-guided care in patients with suspected coronary disease. *J Am Coll Cardiol* 2016;**68**:435–45.
18. Nørgaard BL, Hjort J, Gaur S, Hansson N, Bøtker HE, Leipsic J *et al.* Clinical use of coronary CTA-derived FFR for decision-making in stable CAD. *JACC Cardiovasc Imaging* 2017;**10**:541–50.
19. Ihdayhid AR, Norgaard BL, Gaur S, Leipsic J, Nerlekar N, Osawa K *et al.* Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. *Radiology* 2019;**292**:343–51.
20. Fairbairn TA, Nieman K, Akasaka T, Nørgaard BL, Berman DS, Raff G *et al.* Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE registry. *Eur Heart J* 2018;**39**:3701–11.
21. Nørgaard BL, Fairbairn TA, Safian RD, Rabbat MG, Ko B, Jensen JM *et al.* Coronary CT angiography-derived fractional flow reserve testing in patients with stable coronary artery disease: recommendations on interpretation and reporting. *Radiol Cardiothorac Imaging* 2019;**1**:e190050.
22. Kueh SH, Mooney J, Ohana M, Kim U, Blanke P, Grover R *et al.* Fractional flow reserve derived from coronary computed tomography angiography reclassification rate using value distal to lesion compared to lowest value. *J Cardiovasc Comput Tomogr* 2017;**11**:462–7.
23. Madsen KT, Veien KT, Nørgaard BL, Larsen P, Deibjerg L, Husain M *et al.* Prediction of coronary revascularization by coronary computed tomography angiography derived fractional flow reserve—different algorithms for interpretation. *Eur Heart J* 2019;**40**(Suppl. 1):DOI: 10.1093/eurheartj/ehz746.0781.
24. Takagi H, Ishikawa Y, Orii M, Ota H, Niiyama M, Tanaka R *et al.* Optimized interpretation of fractional flow reserve derived from computed tomography: comparison of three interpretation methods. *J Cardiovasc Comput Tomogr* 2019;**13**: 134–41.
25. Habets J, Van Den Brink RBA, Uijlings R, Spijkerboer AM, Mali WPTM, Chamuleau SAJ *et al.* Coronary artery assessment by multidetector computed tomography in patients with prosthetic heart valves. *Eur Radiol* 2012;**22**:1278–86.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837–45.
27. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP *et al.* A diamond approach to personalized treatment of angina. *Nat Rev Cardiol* 2018;**15**:120–32.
28. Gould KL, Johnson NP. Physiologic severity of diffuse coronary artery disease hidden high risk. *Circulation* 2015;**131**:4–6.
29. Ford TJ, Stanley B, Sidik N, Good R, Rocchiccioli P, McEntegart M *et al.* 1-year outcomes of angina management guided by invasive coronary function testing (CorMicA). *JACC Cardiovasc Interv* 2020;**13**:33–45.
30. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C *et al.* Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 2008;**359**:677–96.
31. Al-Lamee R, Thompson D, Dehbi H, Sen S, Tang K, Davies J *et al.*; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;**391**:31–40.
32. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–8.
33. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonnell M *et al.* Development and evaluation of the Seattle angina questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995;**25**:333–41.