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ORIGINAL PAPER

The impact of coronary revascularization on vessel-specific coronary flow capacity and long-term outcomes: a serial [^{15}O]H_2O positron emission tomography perfusion imaging study

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See the editorial comment for this article 'Improvement in quantitative myocardial perfusion metrics after revascularization in chronic coronary artery disease', by Teemu Maaniitty *et al.*, https://doi.org/10.1093/ehjci/jeac014.

Aims Coronary flow capacity (CFC) integrates quantitative hyperaemic myocardial blood flow (hMBF) and coronary flow reserve (CFR) to comprehensively assess physiological severity of coronary artery disease (CAD). This study evaluated the effects of revascularization on CFC as assessed by serial [^{15}O]H_2O positron emission tomography (PET) perfusion imaging.

Methods and results A total of 314 patients with stable CAD underwent [^{15}O]H_2O PET imaging at baseline and after myocardial revascularization to assess changes in hMBF, CFR, and CFC in 415 revascularized vessels. Using thresholds for ischaemia and normal perfusion, vessels were stratified in five CFC categories: myocardial steal, severely reduced CFC, moderately reduced CFC, minimally reduced CFC, and normal flow. Additionally, the association between CFC increase and the composite endpoint of death and non-fatal myocardial infarction (MI) was studied. Vessel-specific CFC improved after revascularization ($P < 0.01$). Furthermore, baseline CFC was an independent predictor of CFC increase ($P < 0.01$). The largest changes in ΔhMBF (0.90 ± 0.74, 0.93 ± 0.65, 0.79 ± 0.74, 0.48 ± 0.61, and 0.29 ± 0.66 mL/min/g) and ΔCFR (1.01 ± 0.88, 0.99 ± 0.69, 0.87 ± 0.88, 0.66 ± 0.91, and -0.01 ± 1.06) were observed in vessels with lower baseline CFC ($P < 0.01$ for both). During a median follow-up of 3.5 (95% CI 3.1–3.9) years, an increase in CFC was independently associated with lower rates of death and non-fatal MI (HR 0.43, 95% CI 0.19–0.98, $P = 0.04$).

Conclusion Successful revascularization results in an increase in CFC. Furthermore, baseline CFC was an independent predictor of change in hMBF, CFR, and subsequently CFC. In addition, an increase in CFC was associated with a favourable outcome in terms of death and non-fatal MI.

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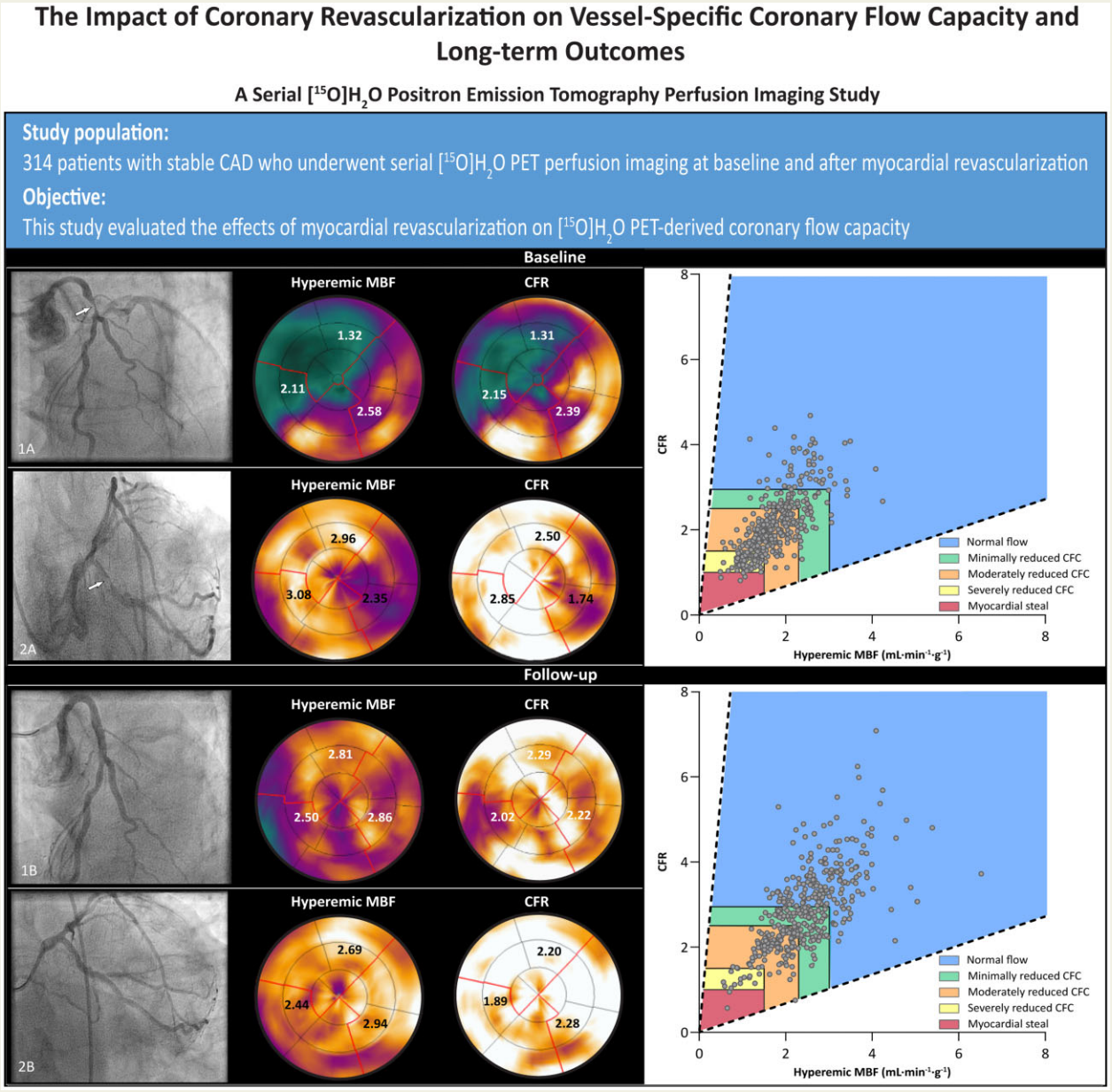
Graphical Abstract



Graphical Abstract This study comprised 314 patients with stable CAD and evaluated the effects of revascularization on CFC as assessed by serial [^{15}O]H_2O PET perfusion imaging. Revascularization resulted in a significant increase in CFC. Furthermore, baseline CFC was an independent predictor of change in hMBF, CFR, and subsequently CFC. [^{15}O]H_2O PET-derived CFC holds the potential to identify vessels in which absolute myocardial perfusion will improve with revascularization. Our study broadens the CFC concept to [^{15}O]H_2O PET perfusion imaging and therewith expands standardization of absolute flow data interpretation. CAD, coronary artery disease; CFC, coronary flow capacity; CFR, coronary flow reserve; hMBF, hyperaemic myocardial blood flow; PET, positron emission tomography.

Keywords [^{15}O]H_2O positron emission tomography • quantitative myocardial perfusion • coronary flow capacity • coronary revascularization

Introduction

Observational studies have shown that the clinical benefit of coronary revascularization in patients with stable coronary artery disease (CAD) is dependent on the severity of myocardial perfusion impairment and the extent of ischaemia reduction.[1–3] However, randomized trials did not demonstrate a favourable prognostic effect with initial ischaemia-driven revascularization compared to optimal medical therapy. Hence the effect of revascularization in unselected patients with stable CAD remains controversial.[4,5] Therefore, more accurate diagnostic tools are needed to identify patients in whom revascularization will restore myocardial perfusion and potentially improve prognosis. The concept of coronary flow capacity (CFC), developed by Johnson and Gould[6] using ^{82}Rb positron emission tomography (PET) imaging, combines hyperaemic myocardial blood flow (hMBF) and coronary flow reserve (CFR) with thresholds for definite or possible ischaemia to comprehensively assess all relevant coronary flow characteristics. An advantage of CFC is its applicability to all modalities that measure coronary flow, which might enable standardization for physiological integration of quantitative myocardial perfusion indices. Invasively and non-invasively derived CFC have been shown to improve identification of lesions that benefit from revascularization therapy in terms of coronary flow increase, thus guiding patient selection in whom revascularization may result in improved clinical outcomes.[7–10] To date, [^{15}O]H_2O PET imaging studies evaluating the impact of revascularization on CFC in relation to traditional perfusion metrics and long-term outcomes are lacking. This study sought to evaluate the effects of revascularization on regional changes in CFC and the prognostic effect of CFC increase in patients undergoing serial [^{15}O]H_2O PET perfusion imaging.

Methods

Study population

The study comprised 314 prospectively included patients with stable CAD who underwent [^{15}O]H_2O PET perfusion imaging at baseline and after clinically driven percutaneous or surgical coronary revascularization between 2012 and 2019. The clinical indication for revascularization was based on angina, evaluation of ischaemia, viability testing when available, and invasive coronary angiography with additional interrogation of coronary lesions by fractional flow reserve (FFR) according to contemporary guidelines.[11] Vessel-specific CFC classification was performed after the indication for revascularization was established. As such, baseline CFC was not used to interpret myocardial perfusion values in order to decide for downstream referral to invasive coronary angiography and subsequent coronary revascularization after initial stress imaging. In the study cohort, 96 patients (31%) were included in an imaging study protocol and were scheduled to undergo invasive coronary angiography and revascularization, irrespective of PET results. The revascularization strategy was left at the discretion of the operator. Only successfully revascularized vessels were included in the analyses. The study was approved by the institutional Medical Ethics Committee and complied with the Declarations of Helsinki. All participants provided written informed consent.

[^{15}O]H_2O PET acquisition

[^{15}O]H_2O PET perfusion scans were acquired using a hybrid PET/computed tomography (CT) device [Gemini TF 64 (15% of patients) and Ingenuity TF 128, Philips Healthcare, Best, The Netherlands). The scanning protocol has been described in detail previously.[12] Briefly, patients underwent a 6-min dynamic scan protocol commencing simultaneously with an injection of 370 MBq [^{15}O]H_2O during resting and adenosine (140 μg/kg/min) induced hyperaemic conditions. Perfusion indices were calculated from parametric MBF images which were used for semiautomatic heart segment definition according to the standard 17-segment model of the American heart Association (Supplementary data online, *Figure S1*).[13] Quantitative analysis for each of the three coronary territories (LAD, Cx, and RCA) was performed to obtain resting MBF and hMBF in mL/min/g of perfusable tissue, using in-house developed software (Cardiac VUer).[14] CFR was defined as the ratio between hyperaemic and resting MBF. PET perfusion indices of the three vascular regions were used to calculate vessel-specific CFC before and after revascularization.

[^{15}O]H_2O PET thresholds for coronary flow capacity

Vessels were stratified into five CFC categories (myocardial steal, severely reduced CFC, moderately reduced CFC, minimally reduced CFC, and normal flow) and plotted in a 2D graph as proposed by Johnson and Gould.[6] Myocardial steal is defined as myocardium with a CFR below unity, denoting that hMBF is lower than resting MBF.[6] Danad *et al.*[12] reported thresholds associated with myocardial ischaemia as assessed by [^{15}O]H_2O PET and described optimal cut-off values of 2.3 mL/min/g and 2.5 for hMBF and CFR, respectively. Vessels within the ischaemic range with hMBF ≤1.5 mL/min/g and CFR ≤1.5 were classified as severely reduced CFC. Vessels with hMBF ≤2.3 mL/min/g and CFR ≤2.5, yet with either hMBF >1.5 mL/min/g or CFR >1.5 were classified as moderately reduced CFC. To define perfusion thresholds for [^{15}O]H_2O in patients with normal flow, we calculated the average hMBF and CFR in 155 patients from a study cohort previously described by Driessen *et al.*,[15] in whom obstructive CAD was ruled out (coronary artery calcium score 0 and CT coronary angiography showing no obstructive lesions). In these patients, mean hMBF was 3.66 ± 1.30 mL/min/g and mean CFR 3.69 ± 1.48. Vessels with hMBF and CFR >0.5 standard deviation (SD) below these normal values, yet with either hMBF or CFR above the ischaemic thresholds, were stratified to the minimally reduced CFC category. Revascularized vessels with either hMBF >3.01 mL/min/g or CFR >2.95 were defined as vessels with normal flow. Two case examples are illustrated in Supplementary data online, *Figure S2*.

Clinical follow-up

Observers blinded to PET perfusion results collected clinical follow-up using national registry databases, electronic medical patient records and standardized telephonic assessment. The occurrence of death and non-fatal myocardial infarction (MI) during follow-up was assessed and events were adjudicated according to the definitions used in current guidelines.[11] Registration of events started from the moment of successful follow-up PET perfusion imaging. We used a hierarchical end-point definition with death being considered more severe than non-fatal MI.

Statistical analysis

Categorical variables are summarized by frequencies and percentages, whereas continuous variables are displayed as mean ± SD and median (interquartile range) as appropriate. The Wilcoxon signed-rank test was used to assess changes in CFC before and after revascularization at a per-vessel level. Generalized estimating equations analysis was used to compare the proportion of vessels in which CFC increased after revascularization between baseline CFC categories, adjusting for potential confounders and accounting for correlation of regional perfusion outcomes within different revascularized territories within the same patient.

Furthermore, linear mixed model analyses were used to test whether mean changes in regional hMBF and CFR during follow-up differed between the 5 baseline CFC groups. The linear mixed models accounted for within-patient correlation of PET perfusion results by including a random effect for patient in the model. We compared mean changes in hMBF and CFR between baseline CFC groups using a Bonferroni *post hoc* correction to account for multiple testing. Additionally, a linear mixed model was fitted to assess the mean change in hMBF and CFR between vessels with concordant low perfusion values below the ischaemic cut-offs and vessels with either hMBF or CFR above the ischaemic threshold. A similar analysis was used to assess the independent predictive value of baseline CFC and quantitative stress perfusion on the absolute increase in hMBF following revascularization. The coefficient of variation (SD/mean × 100%) was calculated to evaluate test–retest repeatability. Kaplan–Meier curves with log-rank testing were used to compare event-free survival between patients whose CFC increased and the remaining patients. Those who underwent revascularization of multiple vessels were stratified in the CFC increase group if CFC augmentation of all revascularized vessels was observed. Normal flow capacity cannot increase in CFC category, thus patients with only normal flow were excluded from the survival analyses. Median follow-up time was calculated using the reverse Kaplan–Meier estimator. A multivariable Cox regression analysis was performed to determine whether CFC increase was associated with event-free survival after adjustment for clinical characteristics and CAD risk factors. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM SPSS Statistics, Armonk, NY, USA).

Results

Study population

A total of 314 patients (63 ± 10 years, 86% male) underwent [^{15}O]H_2O PET perfusion imaging before and after revascularization (*Table 1*). In 80 patients (25%), more than one vessel was revascularized, resulting in a total 415 vessels. Of these, 369 (89%) and 46 (11%) were revascularized by percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), respectively. The median interval between baseline PET imaging and revascularization was 27 (10–52) days, followed by a median interval of 96 (50–113) days until follow-up PET imaging. During this 96 day interval, no cardiac events occurred.

Table 1 Baseline characteristics

	N = 314
Demographics	
Male gender	269 (86)
Age (years)	63 ± 10
BMI (kg/m^2)	28 ± 4
Cardiovascular risk factors	
Hypertension	169 (54)
Hypercholesterolaemia	167 (53)
Diabetes mellitus	75 (24)
Smoking	76 (24)
Family history of CAD	147 (47)
Cardiac history	
No prior cardiac history	86 (27)
Prior MI	132 (42)
Prior PCI	204 (65)
Prior CABG	28 (9)
Medication	
Aspirin	270 (86)
β-Blocker	235 (75)
ACE inhibitor/ARB	171 (55)
Statin	270 (86)
Calcium channel blockers	91 (29)
Symptoms	
Typical angina	73 (23)
Atypical angina	130 (41)
Non-specific chest discomfort	60 (19)
Dyspnoea on exertion	51 (16)
Revascularization	
LAD	138 (44)
Cx	86 (27)
RCA	191 (61)
Surgical revascularization	19 (6)

Data are presented as mean ± SD/*n* (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

The impact of revascularization on regional CFC

At baseline, 4 (1%), 76 (18%), 211 (51%), 69 (17%), and 55 (13%) vessels were classified as myocardial steal, severely reduced CFC, moderately reduced CFC, minimally reduced CFC, and normal flow, respectively. In the normal flow group, 7 (2%) vessels had both hMBF and CFR above the normal CFC thresholds. After revascularization, vessel-specific CFC was classified as myocardial steal in 3 (1%), severely reduced in 13 (3%), moderately reduced in 119 (29%), minimally reduced in 100 (24%), and normal in 180 (43%) of 415 vessels. An overall increase in CFC was observed ($P < 0.01$) (*Figure 1*). After revascularization, 243 (59%) vessels increased in CFC group, whereas in 144 (35%) vessels CFC did not change and 28 (7%) vessels decreased in CFC group. *Figure 1* illustrates the impact of revascularization on vessel-specific CFC according to the five baseline CFC categories. The distribution of vessels at baseline and after revascularization according to absolute hMBF and CFR is depicted in *Figure 2*. Baseline CFC independently predicted regional CFC improvement (*Table 2*). The integration of absolute values of hMBF and CFR in a 2D plane before and after revascularization may represent a quantification of CFC improvement (Supplementary data online, *Figure S3*).

Baseline CFC and regional changes in absolute myocardial perfusion

Changes in absolute myocardial perfusion after revascularization were stratified according to baseline CFC groups (*Table 3*). The increase of hMBF was higher with lower baseline CFC groups ($P < 0.01$). *Post hoc* tests revealed that mean hMBF improvement was higher in the severely reduced CFC group compared to the

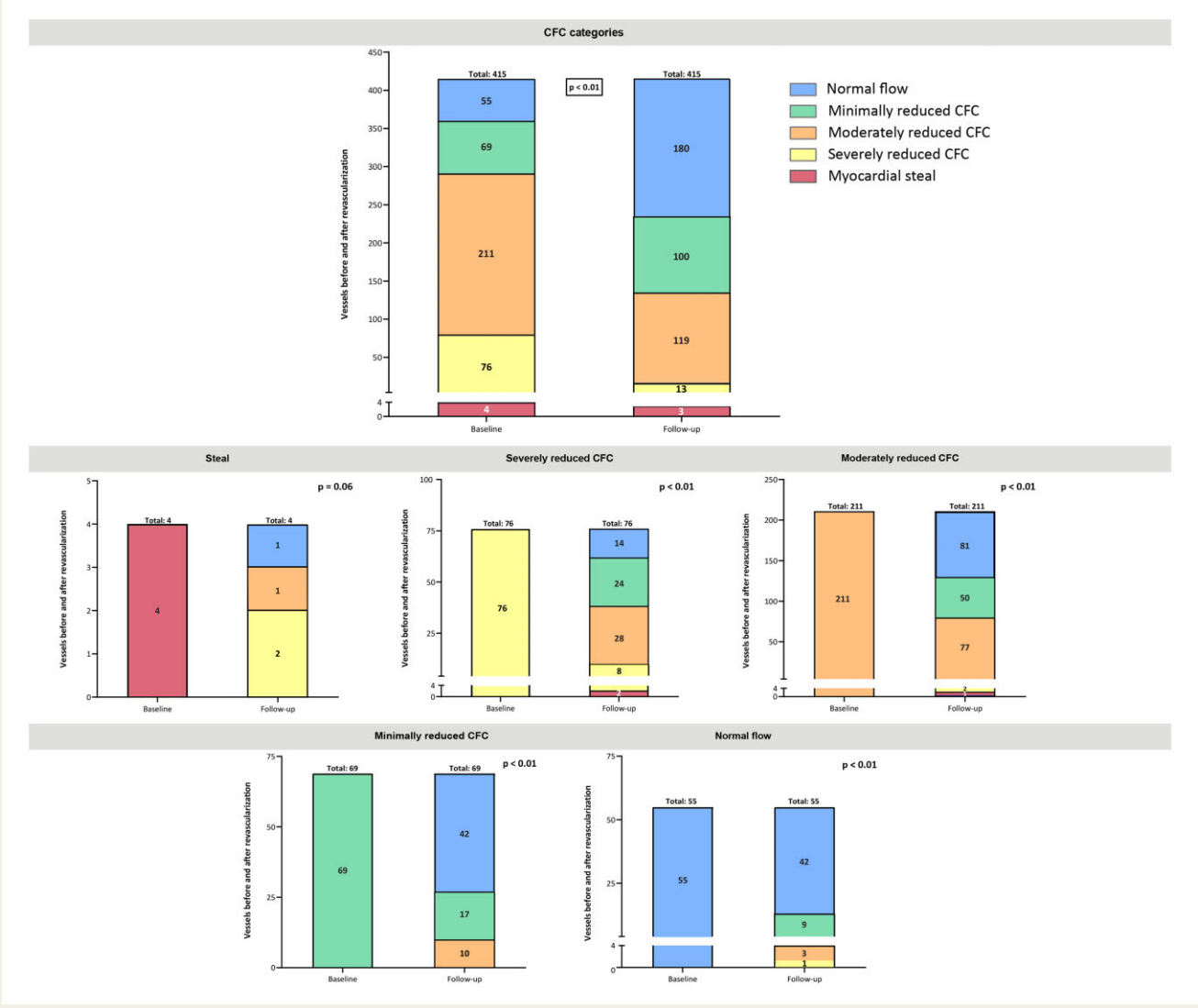


Figure 1 Vessel-specific CFC before and after revascularization. Vessel-specific changes in CFC category between baseline and follow-up are demonstrated for 415 revascularized vessels. An overall improvement in CFC can be observed. Additionally, for all five baseline CFC groups, the bar graphs indicate the vessel distribution after revascularization, showing more frequent CFC increase in vessels with lower baseline CFC. CFC, coronary flow capacity.

moderately reduced ($P = 0.01$), minimally reduced ($P < 0.01$), and normal flow groups ($P < 0.01$). Furthermore, higher hMBF increases were observed for moderately reduced CFC compared to minimally reduced CFC and normal flow ($P < 0.01$ for both), and for minimally reduced CFC compared to normal flow ($P = 0.04$). Similarly, CFR changes differed between baseline CFC groups ($P < 0.01$). *Post hoc* tests showed greater CFR increase in vessels with severely reduced baseline CFC compared to vessels with minimally reduced CFC ($P = 0.04$) and normal flow ($P < 0.01$). Furthermore, CFR increase was higher in vessels with minimally reduced CFC compared to normal flow ($P < 0.01$). Higher baseline CFC group was independently associated with diminished increase in hMBF and CFR ($P < 0.01$ for both) (Supplementary data online, *Table S1*). Additionally, the increase in hMBF and CFR following revascularization was higher in vessels with concordant perfusion values below the ischaemic cut-offs, compared to vessels with either hMBF or CFR above the ischaemic threshold ($P < 0.01$ for both hMBF and CFR) (Supplementary data online, *Figure S4*). In a combined model with baseline CFC and quantitative hMBF, baseline CFC remained an independent predictor of absolute stress perfusion increase (Supplementary data online, *Table S2*). The test–retest variability for non-revascularized vessels is depicted in Supplementary data online, *Table S3*.

Prognostic value of CFC improvement

Outcome analyses were performed in 271 patients. During a median follow-up of 3.5 (95% CI 3.1–3.9) years, 26 (10%) patients experienced death or non-fatal MI, with 19 deaths (7%) and 7 non-fatal MIs (3%). Kaplan–Meier estimates, stratified by the occurrence of CFC increase are depicted in *Figure 3*. Patients in whom CFC improved had superior event-free survival ($P = 0.04$). CFC increase remained

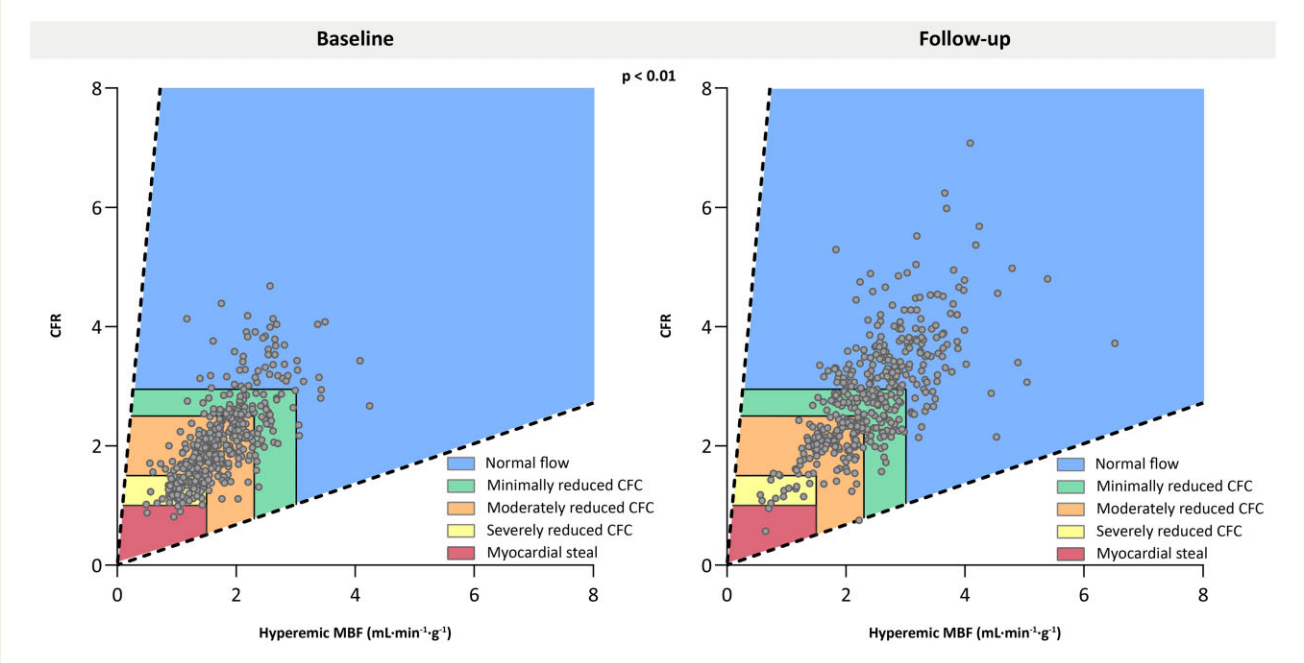


Figure 2 Scatterplots showing CFC vessel-distribution at baseline and follow-up. Each point on the colour-coded CFC scatterplot represents a vessel at baseline and after revascularization. Distribution on the *XY* graph is based on integration of vessel-specific quantitative hMBF and CFR. This graph shows the improvement in CFC. CFC, coronary flow capacity; CFR, coronary flow reserve; hMBF, hyperaemic myocardial blood flow.

independently associated with superior outcome after adjusting for clinical characteristics and CAD risk factors (HR 0.43, 95% CI 0.19–0.98, $P = 0.04$) (Supplementary data online, *Table S4*).

Discussion

CFC is an integration of hMBF and CFR providing a comprehensive assessment across the entire spectrum of myocardial ischaemia spanning from epicardial obstructive stenosis to microvascular CAD. To the best of our knowledge, our study is the first to report the concept of CFC using [^{15}O]H_2O PET perfusion imaging. Germane to this, serial [^{15}O]H_2O PET scans were performed to assess the impact of revascularization therapy on CFC. An overall increase in vessel-specific CFC was observed in patients who underwent percutaneous or surgical revascularization. Furthermore, baseline CFC was an independent predictor of change in hMBF, CFR, and subsequently CFC. In addition, an increase in flow capacity was independently associated with a favourable outcome resulting in a lower incidence of death and non-fatal MI.

The CFC concept, defining [^{15}O]H_2O PET-specific CFC thresholds

Vasodilator capacity is closely related to demand ischaemia and is a measure of microcirculatory autoregulation reserve. CFC was proposed to assess the mismatch between myocardial oxygen demand and the coronary vasodilator reserve by combining CFR and absolute stress perfusion, providing a physiological framework for quantitative classification of CAD severity.[6] Vessel-specific perfusion thresholds for classification of myocardial territories into CFC categories have been validated for ^{82}Rb PET and invasive coronary flow measurements.[6,8,16] For [^{15}O]H_2O PET perfusion indices, CFC categories have not been previously documented. We aimed to determine thresholds for ischaemia and normal flow to examine the application of CFC with [^{15}O]H_2O PET, according to its original concept.[6] Quantitative [^{15}O]H_2O PET thresholds for hMBF and CFR for assessment of significant CAD have been validated by relating perfusion values to invasive coronary angiography in conjunction with FFR as a reference.[12] We used these cut-offs to identify vessels with reduced CFC within the ischaemic range. The original CFC concept yields classification of severely reduced and moderately reduced ischaemia-related CFC categories. Similarly, we aimed to further categorize differences in severe and moderate perfusion defects within the ischaemic range, since myocardial perfusion improvement after revascularization may differ within these subgroups. To distinguish between severely and moderately reduced CFC, we used perfusion values <1.5 mL/min/g for hMBF and <1.5 for CFR in accordance with a Joint position paper by the Society of Nuclear Medicine and Molecular Imaging and the American Society of Nuclear Cardiology.[17] Johnson and Gould[6] established thresholds for a minimally reduced CFC category, a subgroup in which patients did not have clinically pertinent ischaemia yet with perfusion values that did not fit in the normal flow range, by subtracting 1 SD from the average perfusion indices in young, healthy volunteers. The division of CFC categories in minimally reduced CFC and normal flow may allow for additional evaluation of coronary vasodilator capacity in non-

Table 2 Predictors of CFC improvement

CFC increase	OR (95% CI)	*P*-value
Baseline CFC groups		<0.01
Severely reduced CFC vs. moderately reduced CFC	4.84 (2.12–11.09)	
Severely reduced CFC vs. minimally reduced CFC	5.77 (2.20–15.16)	
Moderately reduced CFC vs. minimally reduced CFC	1.19 (0.67–2.13)	
Demographics		
Gender (male vs. female)	0.43 (0.17–1.10)	0.08
Age (years)	0.99 (0.96–1.02)	0.37
BMI	1.00 (0.94–1.07)	0.99
Cardiovascular risk factors		
Hypertension	1.37 (0.75–2.48)	0.30
Hypercholesterolaemia	1.18 (0.61–1.84)	0.83
Diabetes mellitus	0.69 (0.38–1.25)	0.22
Family history of CAD	0.96 (0.52–1.64)	0.87
Smoking	1.55 (0.79–3.08)	0.21
Cardiac history		
History of MI	0.56 (0.31–1.00)	0.05
History of PCI	0.98 (0.51–1.89)	0.95
History of CABG	0.48 (0.21–1.08)	0.07
Medication		
Aspirin	1.07 (0.34–3.33)	0.91
β-Blocker	1.11 (0.54–2.26)	0.78
ACE inhibitor/ARB	0.72 (0.40–1.3)	0.28
Statin	0.76 (0.31–1.85)	0.54
Calcium channel blocker	0.95 (0.52–1.75)	0.87
Revascularization		
Surgical revascularization	0.86 (0.33–2.29)	0.77

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CFC, coronary flow capacity; LAD, left anterior descending coronary artery; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention.

Table 3 Comparison of change in [^{15}O]H_2O PET perfusion between baseline CFC groups

	Time point		Δ perfusion	Overall *P*-value
	Baseline	Follow-up		
Hyperaemic MBF (mL/min/g)				
Baseline CFC group				
Steal ($n = 4$)	0.88 ± 0.26	1.78 ± 0.89	0.90 ± 0.74	<0.01
Severely reduced CFC ($n = 76$)	1.12 ± 0.21	2.05 ± 0.72	0.93 ± 0.65	
Moderately reduced CFC ($n = 211$)	1.62 ± 0.34	2.41 ± 0.82	0.79 ± 0.74	
Minimally reduced CFC ($n = 69$)	2.21 ± 0.37	2.70 ± 0.62	0.48 ± 0.61	
Normal flow ($n = 55$)	2.53 ± 0.62	2.82 ± 0.83	0.29 ± 0.66	
CFR				
Steal	0.89 ± 0.07	1.91 ± 0.94	1.01 ± 0.88	<0.01
Severely reduced CFC	1.29 ± 0.13	2.28 ± 0.69	0.99 ± 0.69	
Moderately reduced CFC	1.91 ± 0.30	2.78 ± 0.86	0.87 ± 0.88	
Minimally reduced CFC	2.52 ± 0.32	3.18 ± 1.01	0.66 ± 0.91	
Normal flow	3.43 ± 0.49	3.43 ± 0.95	-0.001 ± 1.06	

Values are presented as mean ± SD.
CFC, coronary flow capacity; CFR, coronary flow reserve; Δ, delta; MBF, myocardial blood flow; PET, positron emission tomography.

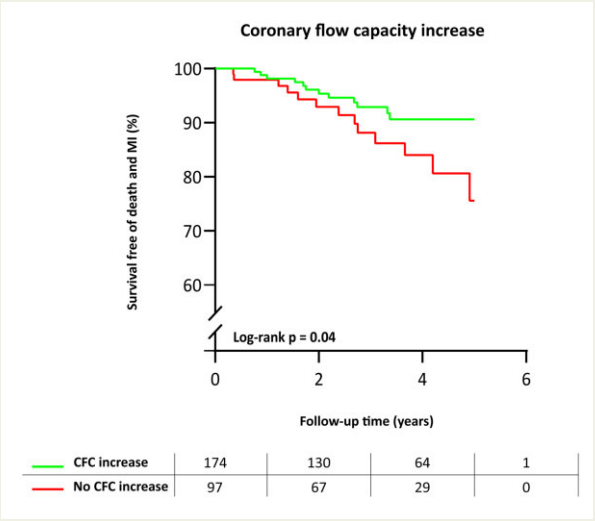


Figure 3 Kaplan–Meier curve of event-free survival. Kaplan–Meier curve of event-free survival stratified according to CFC increase. CFC, coronary flow capacity; MI, myocardial infarction.

ischaemic regions with reduced perfusion compared to vessels without atherosclerotic disease.[10] In this study, the threshold for minimally reduced CFC was calculated 0.5 SD below the average of hMBF and CFR in patients in whom significant CAD was excluded. Contrary to healthy individuals, our cohort might best represent patients without pathological impairment of coronary vasodilator capacity as encountered in daily clinical practice. The SD of our normal control group did not allow for a similar method as used by Johnson and Gould without deviating from the original CFC concept as it selects patients too close to the predefined ischaemic thresholds for [^{15}O]H_2O PET.[12] An apparent characteristic of ^{15}O-water is the wide range of MBF values it provides in both healthy volunteers and patients with cardiovascular risk factors without obstructive CAD.[18,19] As such, an SD value of 1 seems not to be feasible for [^{15}O]H_2O PET.

The effect of revascularization on myocardial perfusion

An overall increase in vessel-specific CFC was observed. Interestingly, the increase was more pronounced in vessels with lower CFC at baseline, independent of clinical CAD risk factors. Similarly, in the COURAGE nuclear substudy, a reduction in inducible ischaemia was observed with PCI added to optimal medical therapy, with greater benefit in those patients with the largest ischaemic burden at baseline.[3] A previous study by Bober *et al.*[7] using ^{82}Rb PET illustrated the value of CFC for prediction of regional improvement in hMBF, with a more pronounced restoration of perfusion in regions with reduced CFC at baseline. In addition, invasively derived CFC was shown to better detect lesions in which a restoration of coronary flow was expected in comparison to FFR, instantaneous wave-free ratio and CFR.[8] Our study confirms and extends previous observations that CFC may guide identification of lesions with the best potential for improved vessel-related outcomes after revascularization.

Clinical outcomes after revascularization

Restoration of vasodilator capacity in patients with significant ischaemic burden at baseline may identify patients that benefit most from revascularization.[1,3] In contrast, revascularization without a corresponding increase in coronary blood flow may be associated with detrimental patient outcome.[2,20] Indeed, several studies showed that improvement of FFR after revascularization is a strong independent predictor of adverse cardiovascular events.[21,22] Additionally, Driessen *et al.*[23] reported a close agreement between absolute changes in intracoronary pressure following PCI and improvement of [^{15}O]H_2O PET stress perfusion. This finding underscores that the prognostic benefit of restored post-PCI pressure may be mediated by normalization of myocardial perfusion. Recently, the ISCHEMIA trial, which randomized more than 5000 patients with stable CAD and predefined substantial ischaemic burden, did not find evidence of superior patient outcome with an initial invasive strategy.[5] ISCHEMIA showed an improvement of symptoms and quality of life in the revascularization group but did not quantify ischaemia reduction.[24] Only patients with a history of heart failure and reduced left ventricular function benefitted from an invasive approach, illustrating the need to identify patients with stable CAD most likely to benefit from coronary revascularization.[25] In this context, the cross-modality CFC concept seems promising. Using flow wires, van de Hoef *et al.*[16] found that reduced baseline CFC was associated with higher major adverse cardiovascular event rates compared to normal flow. In a study of 3774 routine diagnostic rest-stress ^{82}Rb PET scans, regional CFC before intervention was directly associated with the risk of death and non-fatal MI and a >50% risk reduction was observed after revascularization in lesions with severe CFC perfusion abnormalities.[9] Furthermore, regional severely reduced baseline CFC was associated with the highest risk of all-cause mortality, which was attenuated by restoration of myocardial perfusion.[10] Importantly, these studies used baseline CFC as a predictor for patient outcome, whereas this study extend to their findings by assessing the increase in flow capacity after revascularization in relation to prognosis. We found that an increase in vessel-specific CFC was associated with lower rates of death and non-fatal MI, independent of CAD risk factors. Notably, patients with normal flow at baseline were excluded from the survival analyses. Thus, the increased risk of unfavourable outcome relates to patients that did not benefit from revascularization in terms of CFC increase, despite a reduced CFC at baseline. The potential of CFC for integrated risk stratification in patients evaluated for ischaemic heart disease to select patients with anticipated benefit from revascularization is illustrated in this study with [^{15}O]H_2O PET.

Limitations

First, this is an observational single-centre study. Secondly, coronary microvascular function was not assessed and vessels in which revascularization was not performed were not included, hence the quantitative impact of diffuse CAD on [^{15}O]H_2O-derived flow capacity was not evaluated.[26] Thirdly, Johnson and Gould applied a regional, per-pixel (1344 pixels) combination to calculate flow capacity maps accounting for individual patient variation in coronary artery distribution.[6,27] Our study lacks this granular CFC size-severity classification and may average absolute perfusion towards higher values compared to a more advanced segmental model, possibly diluting the observed effect of revascularization on [^{15}O]H_2O PET-derived CFC. These

methodological differences likely contributed to the observed differences between our ischaemia threshold values and those of Johnson and Gould used to define CFC categories within the ischaemic range. Furthermore, Johnson and Gould evaluated electrocardiograms, perfusion defects and angina symptoms during stress testing to rigorously define clinical CFC thresholds for severely and moderately reduced flow.[6,9] In our study, such robust clinical data were not available. In the absence of documented cut-offs to define CFC categories for [^{15}O]H_2O PET, we established CFC thresholds that need to be validated in an external, larger patient cohort. Of note, differences in perfusion thresholds for severely and moderately reduced CFC between this study and previous work by Johnson and Gould may be related to the different definitions used to relate quantitative PET indices to myocardial ischaemia and severe CFC reduction. Finally, the limited event rate in this study hampers complex survival analyses and outcome data stratified to [^{15}O]H_2O PET-derived CFC values require validation in larger studies.

Conclusion

CFC combines absolute stress flow, flow reserve and ischaemic thresholds into a physiological measure for quantitative classification of CAD severity. Revascularization resulted in a significant increase in CFC. Furthermore, baseline CFC was an independent predictor of change in hMBF, CFR, and subsequently CFC. CFC measured with serial [^{15}O]H_2O PET perfusion imaging holds the potential to identify vessels in which absolute myocardial perfusion will improve with revascularization. Finally, improvement of flow capacity following revascularization may affect clinical outcomes. These findings extend the potential application of CFC to [^{15}O]H_2O PET perfusion imaging and expand standardization of absolute flow data interpretation.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

Data supporting the findings of this study are available upon reasonable request to the corresponding author (Paul Knaapen).

References

1. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–7.
2. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P *et al.* Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;**64**:1641–54.
3. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM *et al.* Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;**117**:1283–91.
4. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ *et al.*; COURAGE Trial Research Group. Optimal medical therapy with or without pci for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16.
5. 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.
6. Johnson NP, Gould KL. Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging* 2012;**5**:430–40.
7. Bober RM, Milani RV, Oktay AA, Javed F, Polin NM, Morin DP. The impact of revascularization on myocardial blood flow as assessed by positron emission tomography. *Eur J Nucl Med Mol Imaging* 2019;**46**:1226–39.
8. Murai T, Stegehuis VE, van de Hoef TP, Wijntjens GWM, Hoshino M, Kanaji Y *et al.* Coronary flow capacity to identify stenosis associated with coronary flow improvement after revascularization: a combined analysis from DEFINE FLOW and IDEAL. *J Am Heart Assoc* 2020;e016130.
9. Gould KL, Johnson NP, Roby AE, Nguyen T, Kirkeeide R, Haynie M *et al.* Regional, artery-specific thresholds of quantitative myocardial perfusion by PET associated with reduced myocardial infarction and death after revascularization in stable coronary artery disease. *J Nucl Med* 2019;**60**:410–7.
10. Gould KL, Kitkungvan D, Johnson NP, Nguyen T, Kirkeeide R, Bui L *et al.* Mortality prediction by quantitative pet perfusion expressed as coronary flow capacity with and without revascularization. *JACC: Cardiovasc Imaging* 2021;**14**:1020–34.
11. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.*; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
12. Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA *et al.* Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. *J Am Coll Cardiol* 2014;**64**:1464–75.
13. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK *et al.*; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539–42.
14. Harms HJ, Knaapen P, de Haan S, Halbmeijer R, Lammertsma AA, Lubberink M. Automatic generation of absolute myocardial blood flow images using [15O]H2O and a clinical PET/CT scanner. *Eur J Nucl Med Mol Imaging* 2011;**38**:930–9.
15. Driessen RS, Bom MJ, van Diemen PA, Schumacher SP, Leonora RM, Everaars H *et al.* Incremental prognostic value of hybrid [15O]H2O positron emission tomography-computed tomography: combining myocardial blood flow, coronary stenosis severity, and high-risk plaque morphology. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1105–13.
16. van de Hoef TP, Echavarria-Pinto M, van Lavieren MA, Meuwissen M, Serruys PW, Tijssen JG *et al.* Diagnostic and prognostic implications of coronary flow capacity: a comprehensive cross-modality physiological concept in ischemic heart disease. *JACC Cardiovasc Interv* 2015;**8**:1670–80.
17. Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P *et al.*; ASNC Board of Directors. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI Cardiovascular Council and the ASNC. *J Nucl Med* 2018;**59**:273–93.
18. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res* 2001;**50**:151–61.
19. Danad I, Raijmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever ML *et al.* Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: a quantitative [15O]H2O PET/CT study. *Eur J Nucl Med Mol Imaging* 2012;**39**:102–12.
20. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P *et al.* Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015;**36**:3182–8.
21. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF *et al.* Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation* 2002;**105**:2950–4.

22. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N *et al.* Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. *Circ Cardiovasc Interv* 2017;**10**:e005233.
23. Driessen RS, Danad I, Stuijfzand WJ, Schumacher SP, Knuuti J, Mäki M *et al.* Impact of revascularization on absolute myocardial blood flow as assessed by serial [(15)O]H(2)O positron emission tomography imaging: a comparison with fractional flow reserve. *Circ Cardiovasc Imaging* 2018;**11**:e007417.
24. Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y *et al.*; ISCHEMIA Research Group. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020;**382**:1408–19.
25. Lopes RD, Alexander KP, Stevens SR, Reynolds HR, Stone GW, Piña IL *et al.* Initial invasive versus conservative management of stable ischemic heart disease in patients with a history of heart failure or left ventricular dysfunction. *Circulation* 2020;**142**:1725–35.
26. van de Hoef TP, Nolte F, Echavarría-Pinto M, van Lavieren MA, Damman P, Chamuleau SA *et al.* Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment. *Heart* 2014;**100**:951–9.
27. Bui L, Kitkungvan D, Roby AE, Nguyen TT, Gould KL. Pitfalls in quantitative myocardial PET perfusion II: arterial input function. *J Nucl Cardiol* 2020;**27**:397–409.