HOKKAIDO UNIVERSITY

Title	Effects of coronary revascularization on global coronary flow reserve in stable coronary artery disease
Author(s)	Aikawa, Tadao; Naya, Masanao; Obara, Masahiko et al.
Citation	Cardiovascular Research, 115(1), 119-129 https://doi.org/10.1093/cvr/cvy169
Issue Date	2019-01-01
Doc URL	https://hdl.handle.net/2115/72289
Rights(URL)	https://creativecommons.org/licenses/by-nc/4.0/
Type	journal article
File Information	cvy169.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

ESC European Society of Cardiology

Cardiovascular Research (2019) **115**, 119–129
doi:10.1093/cvr/cvy169

Effects of coronary revascularization on global coronary flow reserve in stable coronary artery disease

Tadao Aikawa[1], Masanao Naya[1]*, Masahiko Obara[1], Osamu Manabe[2], Keiichi Magota[3], Kazuhiro Koyanagawa[1], Naoya Asakawa[1], Yoichi M. Ito[4], Tohru Shiga[2], Chietsugu Katoh[5], Toshihisa Anzai[1], Hiroyuki Tsutsui[6], Venkatesh L. Murthy[7], and Nagara Tamaki[8]

[1]Department of Cardiovascular Medicine, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [2]Department of Nuclear Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [3]Division of Medical Imaging and Technology, Hokkaido University Hospital, Sapporo, Japan, Kita-14, Nishi-5, Kita-ku, Sapporo 060-8648, Japan; [4]Department of Biostatistics, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan; [5]Department of Biomedical Science and Engineering, Faculty of Health Sciences, Hokkaido University, Kita-12, Nishi-5, Kita-ku, Sapporo 060-0812, Japan; [6]Department of Cardiovascular Medicine, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan; [7]Divisions of Nuclear Medicine, Cardiothoracic Imaging, and Cardiovascular Medicine, Departments of Medicine and Radiology, University of Michigan, 1500 E Medical Center, Ann Arbor, MI 48109, USA; and [8]Department of Radiology, Kyoto Prefectural University of Medicine, Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

Received 11 April 2018; revised 14 June 2018; editorial decision 28 June 2018; accepted 9 July 2018; online publish-ahead-of-print 10 July 2018

Time for primary review: 27 days

Aims Coronary flow reserve (CFR) is an integrated measure of the entire coronary vasculature, and is a powerful prognostic marker in coronary artery disease (CAD). The extent to which coronary revascularization can improve CFR is unclear. This study aimed to evaluate the impact of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) on CFR in patients with stable CAD.

Methods and results In a prospective, multicentre observational study, CFR was measured by ^{15}O-water positron emission tomography as the ratio of stress to rest myocardial blood flow at baseline and 6 months after optimal medical therapy (OMT) alone, PCI, or CABG. Changes in the SYNTAX and Leaman scores were angiographically evaluated as indicators of completeness of revascularization. Follow-up was completed by 75 (25 OMT alone, 28 PCI, and 22 CABG) out of 82 patients. The median SYNTAX and Leaman scores, and baseline CFR were 14.5 [interquartile range (IQR): 8–24.5], 5.5 (IQR: 2.5–12.5), and 1.94 (IQR: 1.67–2.66), respectively. Baseline CFR was negatively correlated with the SYNTAX (ρ = -0.40, $P < 0.001$) and Leaman scores (ρ = -0.33, $P = 0.004$). Overall, only CABG was associated with a significant increase in CFR [1.67 (IQR: 1.14–1.96) vs. 1.98 (IQR: 1.60–2.39), $P < 0.001$]. Among patients with CFR <2.0 ($n = 41$), CFR significantly increased in the PCI [1.70 (IQR: 1.42–1.79) vs. 2.21 (IQR: 1.78–2.49), $P = 0.002$, $P < 0.001$ for interaction between time and CFR] and CABG groups [1.28 (IQR: 1.13–1.80) vs. 1.86 (IQR: 1.57–2.22), $P < 0.001$]. The reduction in SYNTAX or Leaman scores after PCI or CABG was independently associated with the percent increase in CFR after adjusting for baseline characteristics ($P = 0.012$ and $P = 0.011$, respectively).

Conclusion Coronary revascularization ameliorated reduced CFR in patients with obstructive CAD. The degree of improvement in angiographic CAD burden by revascularization was correlated with magnitude of improvement in CFR.

Keywords Coronary artery disease • Coronary flow reserve • Percutaneous coronary intervention • Coronary artery bypass grafting • ^{15}O-water positron emission tomography

* Corresponding author. Tel: +81 11 706 6973; fax: +81 11 706 7874, E-mail: naya@med.hokudai.ac.jp

© The Author(s) 2018. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

1. Introduction

Quantitative coronary flow reserve (CFR), calculated as the ratio of hyperaemic to resting myocardial blood flow (MBF) estimated using dynamic positron emission tomography (PET) data, has emerged as a powerful marker of the risk for adverse cardiovascular outcomes, including death.[1–3] However, the extent to which CFR can be used to select appropriate patients with coronary artery disease (CAD) for optimal medical therapy (OMT), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG), remains unclear. Since CFR is an integrated measure of the entire coronary vasculature, reflecting epicardial coronary anatomy, and microvascular dysfunction,[4] both coronary revascularization and medical therapy may increase CFR. Importantly, several studies have demonstrated that coronary revascularization for CAD is associated with early post-procedural improvements in regional CFR.[5–8] Conversely, in one single-centre retrospective study, a prognostic difference seen between CABG and PCI was seen only among patients with very low CFR.[3] Importantly, the intermediate and long-term effects of PCI or CABG on global CFR and their effects on outcomes have not been well explored. Therefore, we conducted a prospective, multicentre observational study to determine the effects of OMT, PCI, and CABG on global CFR over 6 months in patients with CAD.

2. Methods

Between July 2015 and August 2017, patients diagnosed with obstructive CAD, defined as a ≥50% diameter stenosis in at least one coronary artery with a reference diameter of ≥1.5 mm by visual estimation on invasive coronary angiography, were prospectively identified and recruited at four centres in Japan. Patients with acute coronary syndrome, second- or third-degree atrioventricular block, bronchial asthma, or known or suspected pregnancy were excluded. The study protocol was approved by the ethics committee of each institution and registered with the University Hospital Medical Information Network clinical trials registry (UMIN000018160; http://www.umin.ac.jp/ctr/index.htm). Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

All patients received guideline-directed OMT[9] for patients with obstructive CAD. Stress myocardial perfusion imaging or invasive assessment of fractional flow reserve was performed at the cardiologist's discretion based on standards of care using previously described methods.[10] Patients with evidence of ischaemia, determined by fractional flow reserve ≤0.8 or reversible perfusion defects on stress myocardial perfusion imaging, were considered for coronary revascularization. Indications for PCI and CABG were determined based on a heart-team approach at each institution, blinded to the results of MBF and CFR assessments. Patients undergoing PCI were premedicated with dual antiplatelet therapy and treated according to standard practice, primarily with drug-eluting stents. Patients undergoing CABG received mainly internal mammary artery grafts with cardiopulmonary bypass ($n = 5$) or off-pump ($n = 21$). All CABG patients were given post-operative aspirin indefinitely.

The primary aim of the study was to assess changes in CFR on PET before and 6 months after treatment across treatment groups of OMT alone, PCI, and CABG in the entire cohort. The secondary aim was to identify significant predictors of change in CFR among baseline characteristics and revascularized CAD burden.

2.1 Positron emission tomography

All patients were imaged on a whole-body PET/computed tomography (CT) scanner (Gemini TF 64; Philips Healthcare, Cleveland, OH, USA) at Hokkaido University Hospital before and after treatment. MBF was measured at rest and during hyperaemia, as described previously.[11] In brief, patients were instructed to fast for at least 4 h and to refrain from caffeine- and methylxanthine-containing products for at least 24 h. Routine antianginal medications were continued. A prospectively electrocardiographically gated CT scan for coronary artery calcium scoring was performed before the PET scan. After a low-dose CT scan to correct for attenuation and scatter, a 6-min list-mode acquisition was started with concomitant administration of 500 MBq of ^{15}O-water. After a 10-min interval for tracer decay, an identical scan was repeated during adenosine triphosphate infusion (0.16 mg/kg/min). Adenosine triphosphate was initiated 3 min before the scan and tracer infusion. Heart rate, blood pressure, and 12-lead electrocardiography were recorded at baseline and every minute during pharmacological stress. The emission data were reconstructed using a 3D row-action-maximum-likelihood algorithm into 24 frames (18 × 10-s and 6 × 30-s). The estimated radiation exposure per examination was 4.2 mSv, including <0.1 mSv for the scout scan, 1.2 mSv for the CT for coronary artery calcium scoring, 0.7 mSv for the CT for attenuation correction, and 1.1 mSv for each PET scan. PET images were analysed using in-house developed software[11,12] in a blinded fashion. MBF (mL/g/min) was calculated using a single tissue compartment model with correction for spillover from the myocardium to the blood. CFR was calculated as the ratio of hyperaemic to resting MBF. Global CFR <2.0 was considered reduced, which has been reported as an indicator of high-risk CAD patients.[1,2] This value is lower than another cut-off point of 2.5 for detecting haemodynamically significant CAD.[13] Regional CFR was assessed in the three main coronary arteries using the American Heart Association 17-segment model to evaluate CFR in the culprit coronary artery. A segment was considered to have ischaemia when the regional hyperaemic MBF was <2.3, which is more diagnostically accurate than using regional CFR <2.5 as the criterion.[13] The extent of myocardial ischaemia was expressed as the percentage of the left ventricle (%LV). In addition, relative flow reserve, defined as the ratio of hyperaemic MBF in a stenotic area (lesion diameter stenosis ≥50%) to hyperaemic MBF in a remote area, was also calculated in patients with one- or two-vessel disease to minimize the impact of microvascular dysfunction on perfusion values.[14,15]

2.2 Angiographic assessment

The SYNTAX score[16] at baseline was calculated in a blinded fashion. Since the SYNTAX score was developed for patients without CABG, the CABG SYNTAX score[17] was used in patients with CABG. An angiographically successful PCI was defined as <50% residual stenosis of the target lesion after the procedure. The residual SYNTAX score[18] or CABG SYNTAX score after revascularization was calculated from follow-up angiography. If patients did not undergo follow-up angiography, we calculated the residual SYNTAX score from angiography during PCI and the CABG SYNTAX score from the surgical report in conjunction with the baseline angiogram before CABG. The pre- and post-procedure anatomical Leaman score was also calculated as previously described.[19]

2.3 Assessment of left ventricular systolic function

Echocardiography was performed by experienced sonographers who were blinded to the PET results. Left ventricular ejection fraction was

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

calculated using the biplane method of disks. Interpretation was performed by cardiologists blinded to the PET results.

2.4 Assessment of cardiovascular risk factor control

Cardiovascular risk factor control for hypertension, diabetes, hyperlipidaemia, and smoking were performed and assessed on the basis of the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial protocol.[20]

2.5 Statistical analysis

Continuous variables are presented as medians with interquartile range (IQR). Categorical variables are presented as absolute numbers with percentages. The sample size calculation was based on the assumption that the change in CFR before and after treatment would be 0.7 with standard deviation of 1.0. To detect this change with ≥85% power and a significance level of 0.05, each group needed to comprise ≥20 patients. This sample size was calculated using Power and Sample Size Calculation version 3.1.2 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). Differences between groups were evaluated using the Wilcoxon rank sum test followed by the Steel-Dwass test for continuous data and the Fisher exact test for categorical data. Differences between paired data were evaluated using the Wilcoxon signed rank test or the McNemar test, as appropriate. A two-way analysis of variance with repeated measures was used to determine interaction effects. Bivariate Spearman's rank correlation coefficients (ρ) were calculated between baseline CFR and changes in CFR and angiographic indices and their changes. Before a multivariate regression analysis, variables were assessed for normality by the Shapiro–Wilk test and log transformation applied to correct for skewness as appropriate, such as in changes in the Leaman score between pre- and post-revascularization (ΔLeaman score). Linear regression analysis was used to examine the association between changes in CFR and revascularized CAD burden [Model 1 included changes in the SYNTAX score between pre- and post-revascularization (ΔSYNTAX score); Model 2 included log (1-ΔLeaman score)], adjusted for important covariates including the pretest likelihood of obstructive CAD, history of PCI or CABG, and the presence of left ventricular systolic dysfunction (left ventricular ejection fraction <50%) selected based on clinical relevance[3] and the CABG group. To test the relative contribution of revascularization with CABG on changes in CFR, a linear interaction term (ΔSYNTAX score × the CABG group) was added to Model 1 (Model 3). Because of the nonrandomized nature of the study, we used percent change as the dependent variable to minimize the differences in baseline CFR between groups. The pretest likelihood of obstructive CAD was estimated using the Duke clinical risk score,[21] calculated using age, sex, type of angina, history of myocardial infarction, electrocardiographic Q and ST-T wave changes, smoking, hyperlipidaemia, diabetes, and interaction terms (age × sex, history of myocardial infarction × electrocardiographic Q wave, age × smoking, age × hyperlipidaemia, and sex × smoking). The assumption of linearity for continuous covariates was evaluated by plotting the residuals against the fitted values. As an exploratory analysis, propensity score matching was used to account for differences in baseline SYNTAX scores between the PCI and CABG groups. Propensity scores were calculated using a logistic regression model including baseline SYNTAX score and the same covariates in the multivariate Model 1 (the pretest likelihood of obstructive CAD, history of PCI or CABG, and left ventricular ejection fraction <50%). A propensity score-matched cohort was generated by 1:1 nearest available matching without replacement using a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score.[22] Propensity score matching was performed using the JMP add-in program (https://www.jmp.com/ja_jp/support/technical-documents.html). A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using JMP Pro 13.1.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Patient characteristics

We prospectively recruited 82 patients to the study, of whom 30 underwent PCI, and 26 underwent CABG. Of the remaining 26 patients who were treated with OMT alone, 21 had significant comorbidities (e.g. advanced cancer or severely atheromatous aorta) or unsuitable coronary anatomy for coronary revascularization, three preferred medical therapy, and two had fixed perfusion defects in the target area on myocardial perfusion imaging. We excluded seven patients from the final analyses: one patient in the OMT group developed advanced atrioventricular block during adenosine triphosphate infusion at baseline PET and six patients (two in the PCI group and four in the CABG group) withdrew consent during the follow-up period (*Figure 1*). Thus, the final study cohort consisted of 75 patients who completed the second PET.

Baseline clinical characteristics are detailed in *Table 1*. The median age of the patients was 70 (63–75) years, 63 patients (84%) were men, and the median pretest likelihood of obstructive CAD was 94% (78–98%). Of these patients, 24 (32%) had one-vessel disease, 22 (29%) had two-vessel disease, and 29 (39%) had three-vessel or left main disease. In general, the baseline clinical characteristics were similar between the three groups. The CABG group, however, had higher SYNTAX and Leaman scores and total ischaemic burden, with lower stress MBF and CFR than the OMT and PCI groups, which reflected the non-randomized study design. *Figure 2* shows three representative cases.

Baseline CFR was negatively correlated with the SYNTAX (ρ = -0.40, P < 0.001) and Leaman scores (ρ = -0.33, P = 0.004) (*Figure 3*). Likewise, stress MBF was negatively correlated with the SYNTAX (ρ = -0.48, P < 0.001) and Leaman scores (ρ = -0.44, P < 0.001), whereas rest MBF was not significantly correlated with either angiographic score (Supplementary material online, *Figure S1*).

3.2 Changes in coronary risk factor control and angiographic CAD burden

Table 2 shows changes in coronary risk factor control and angiographic CAD burden during a median follow-up duration of 6.1 (5.6–6.3) months. Overall, the number of risk factors achieving the targets was high at baseline. The CABG group showed a significant increase in the percentage of patients achieving ≥5 risk factor targets, which did not differ significantly between the three groups at follow-up. Medications at follow-up are shown in Supplementary material online, *Table S1*.

During the follow-up period, none of the patients had adverse cardiac events. The symptoms disappeared after the treatment of CAD in 72 of 75 patients (96%) (*Table 2*). All 28 patients in the PCI group underwent an angiographically successful PCI. In 17 patients undergoing PCI and scheduled follow-up angiography at a median time of 251 (169–279) days after PCI, 16 had no significant restenosis and one had developed restenosis and underwent repeated PCI after the second PET. In 19 patients undergoing CABG and post-operative angiography at a median time of 9 (8–14) days after CABG, one had early saphenous vein graft

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

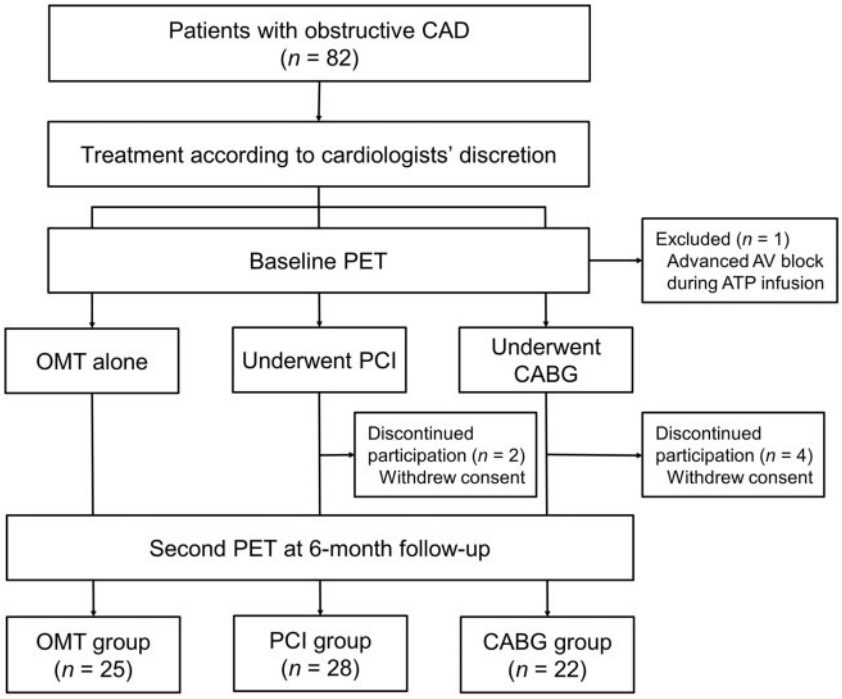

Figure 1 Study flowchart. ATP, adenosine triphosphate; AV, atrioventricular; CABG, coronary artery bypass grafting; CAD, coronary artery disease; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PET, positron emission tomography.

occlusion after CABG and underwent additional PCI in the native coronary artery before the second PET. The SYNTAX and Leaman scores in both the PCI and CABG groups significantly decreased at follow-up (*Table 2*). There was no significant difference in the proportion of patients with low post-revascularization SYNTAX scores (0–8) across the two revascularization groups and the OMT group (*Table 2*).

3.3 Changes in CFR and its association with angiographic CAD burden

In the CABG group, stress MBF significantly increased from baseline to follow-up [1.22 (0.95–1.48) mL/g/min vs. 1.49 (1.29–1.69) mL/g/min, $P < 0.001$], resulting in increased CFR [1.67 (1.14–1.96) vs. 1.98 (1.60–2.39), $P < 0.001$] (*Figure 4A–C*). Conversely, both stress MBF and CFR did not significantly change in the OMT and PCI groups ($P > 0.05$ for all) (*Figure 4B* and *C*). Importantly, despite baseline differences in CFR, CFR at follow-up was not significantly different between the three groups [OMT group: 2.42 (1.74–2.65) vs. PCI group: 2.23 (1.81–2.50) vs. CABG group: 1.98 (1.60–2.39); $P = 0.20$]. After excluding patients with prior myocardial infarction or coronary revascularization ($n = 34$), the CFR significantly increased only in the CABG group [$n = 13$; 1.71 (1.17–2.09) vs. 2.17 (1.63–2.42), $P = 0.002$]. Supplementary material online, *Table S2* summarizes the haemodynamic characteristics of all patients during each PET scan.

When patients with baseline CFR <2.0 ($n = 41$) were analysed, CFR was found to be significantly increased from baseline to follow-up both in the PCI group [1.70 (1.42–1.79) vs. 2.21 (1.78–2.49), $P = 0.002$] and in the CABG group [1.28 (1.13–1.80) vs. 1.86 (1.57–2.22), $P < 0.001$] (*Figure 4D*). This beneficial effect of PCI on CFR was only observed in patients with baseline CFR <2.0 ($P < 0.001$ for interaction) (*Figure 4D* and *4E*). These relationships did not change substantially when patients were stratified by CFR <2.5 and ≥2.5.

When patients with a baseline SYNTAX score ≥23 ($n = 23$) were analysed, CFR was found to be significantly increased from baseline to follow-up both in the PCI and CABG groups (*Figure 4F*), while there was no significant interaction between time and baseline SYNTAX score in the PCI and CABG groups ($P = 0.11$ and $P = 0.99$, respectively). These results did not change substantially when patients were categorised into three SYNTAX subgroups (0–22, 23–32, and ≥33) (Supplementary material online, *Table S3*).

Among 46 patients with one- or two-vessel disease in this study, 17 (37%) had regional CFR <2.0 in a remote area, reflecting coronary microvascular dysfunction. In nine patients with coronary microvascular dysfunction who underwent PCI ($n = 6$) or CABG ($n = 3$), three (one in the PCI group and two in the CABG group) had global CFR <2.0 at follow-up, indicating that their coronary microvascular dysfunction persisted after revascularization. The small number of patients with one- or two-vessel disease prevented a meaningful analysis based on relative flow reserve values.

Figure 5 shows changes in CFR and angiographic CAD burden in the PCI and CABG groups. The percent changes in CFR were negatively correlated with ΔSYNTAX score ($\rho = -0.42$, $P < 0.001$) and ΔLeaman score ($\rho = -0.44$, $P < 0.001$). The percent changes in CFR and stress MBF were not significantly correlated with coronary artery calcium scores at baseline ($P = 0.90$ and $P = 0.52$, respectively).

On a per-vessel basis, the percent change in regional CFR after treatment was significantly higher in coronary territories receiving CABG [21.3% (6.4–53.2%)] than those receiving OMT alone [<50% stenosis: -2.1% (-20.9–18.2%), $P < 0.001$; and 50–100% stenosis: -1.1% (-21.5–

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

Table 1 Baseline characteristics of the study patients

Variables	OMT (*n* = 25)	PCI (*n* = 28)	CABG (*n* = 22)	*P*-value
Age (years)	71 (64–79)	71 (65–78)	66 (55–74)	0.09
Male	23 (92)	23 (82)	17 (77)	0.35
Body mass index (kg/m^2)	23.4 (20.1–26.7)	23.6 (22.4–24.4)	26.5 (22.3–29.0)	0.10
Pretest likelihood of obstructive CAD (%)	95 (81–99)	90 (78–97)	94 (76–98)	0.43
Anginal symptoms				0.33
Typical angina	13 (52)	13 (46)	11 (50)	
Atypical angina	6 (24)	2 (7)	2 (9)	
Non-anginal chest pain	1 (4)	1 (4)	0 (0)	
Hypertension	19 (76)	20 (71)	19 (86)	0.48
Diabetes	10 (40)	16 (57)	16 (73)	0.08
Hyperlipidaemia	18 (72)	22 (79)	18 (82)	0.78
Family history of CAD	2 (8)	2 (7)	1 (5)	1.00
Current smoker	4 (16)	4 (14)	5 (23)	0.74
Prior myocardial infarction	12 (48)	7 (25)	6 (27)	0.18
Prior PCI	10 (40)	9 (32)	4 (18)	0.26
Prior CABG	2 (8)	4 (14)	0 (0)	0.23
Systolic blood pressure (mmHg)	118 (106–136)	126 (112–137)	120 (108–132)	0.43
Diastolic blood pressure (mmHg)	60 (55–75)	64 (58–73)	64 (58–73)	0.56
Laboratory data				
Total cholesterol (mg/dL)	160 (133–186)	162 (136–184)	161 (138–178)	0.98
HDL cholesterol (mg/dL)	52 (42–63)	45 (36–49)	44 (37–54)	0.13
LDL cholesterol (mg/dL)	76 (58–110)	89 (68–111)	81 (74–115)	0.67
Triglycerides (mg/dL)	111 (87–150)	122 (87–184)	113 (78–172)	0.86
Non-HDL cholesterol (mg/dL)	102 (87–134)	116 (99–140)	107 (95–139)	0.59
Haemoglobin A_{1c} (%)	6.0 (5.6–6.5)	6.0 (5.7–7.6)	6.9 (6.0–7.4)	0.24
Echocardiographic LV ejection fraction (%)	57 (47–64)	62 (51–67)	59 (34–64)	0.09
Vessels involved				<0.001
1-vessel disease	15 (60)	8 (29)	1 (5)	
2-vessel disease	7 (28)	12 (43)	3 (14)	
3-vessel disease	3 (12)	7 (25)	13 (59)	
Left main disease	0 (0)	1 (4)	5 (23)	
SYNTAX score	9 (5–15)	14 (7–22)	29 (23–34)*,**	<0.001
Leaman score	4 (2–7)	4 (2–8)	14 (7–19)*,**	<0.001
Coronary artery calcium score (*n* = 50), 0/1–400/>400	0/5/10	0/4/13	0/7/11	0.69
Rest myocardial blood flow (mL/g/min)	0.86 (0.67–1.01)	0.80 (0.60–1.12)	0.76 (0.65–0.88)	0.38
Stress myocardial blood flow (mL/g/min)	1.86 (1.72–2.35)	1.74(1.31–2.14)	1.22 (0.95–1.48)*,**	<0.001
Coronary flow reserve	2.38 (1.83–2.80)	2.03 (1.70–2.78)	1.67 (1.14–1.96)*,**	0.002
Myocardial ischaemia extent (%LV)	94 (47–100)	94 (65–100)	100 (100–100)*,**	0.005
Medications				
Antiplatelet agents	23 (92)	27 (96)	18 (82)	0.24
Angiotensin inhibitors	16 (64)	18 (64)	14 (64)	1.00
Beta-blockers	18 (72)	15 (54)	13 (59)	0.37
Calcium-channel blockers	13 (52)	13 (46)	9 (41)	0.77
Statins	24 (96)	25 (89)	19 (86)	0.54
Nitrates	11 (44)	7 (25)	11 (50)	0.15
Diuretics	8 (32)	6 (21)	8 (36)	0.51
Insulin	2 (8)	7 (25)	4 (18)	0.27
Warfarin	2 (8)	2 (7)	1 (5)	1.00

Data are represented median (interquartile range) or *n* (%).
CABG, coronary artery bypass grafting; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.
*$P < 0.05$ vs. the OMT group.
**$P < 0.05$ vs. the PCI group.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

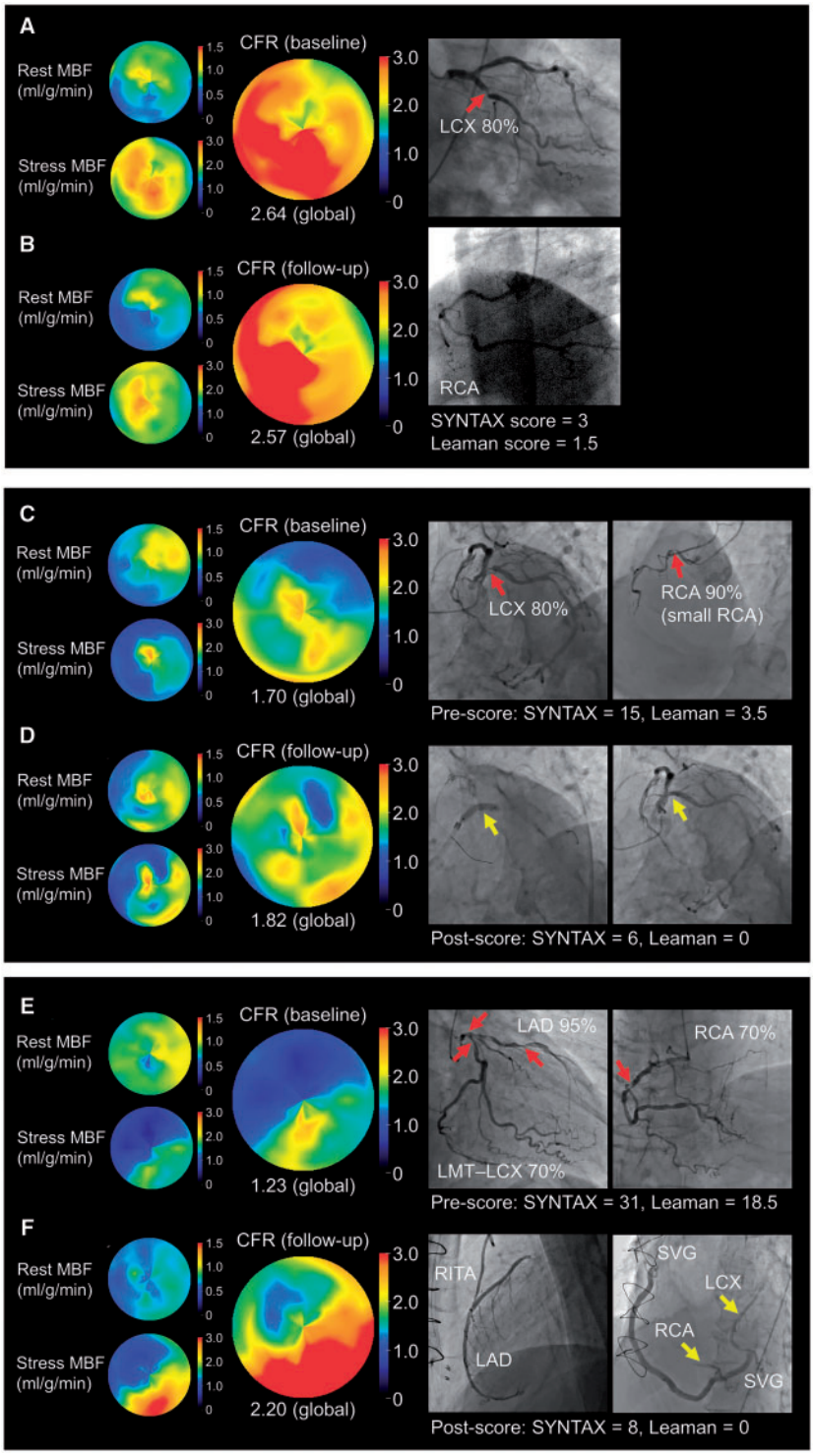

Figure 2 Eighty-two-year-old man treated with optimal medical therapy alone (*A*, *B*). A global CFR of 2.64 at baseline (*A*) was slightly decreased to 2.57 at follow-up (*B*). Sixty-six-year-old man receiving PCI (*C*, *D*). The polar map of CFR at baseline (*C*) shows a regional decrease in the anterior to lateral wall. Global CFR was modestly increased from 1.70 to 1.82 (*D*) after PCI to the LCX (*yellow arrows*). Seventy-eight-year-old man receiving CABG (*E*, *F*). A global CFR of 1.23 at baseline (*E*) was increased to 2.20 (*F*) after CABG using a RITA graft to the LAD, a left internal thoracic artery graft to the LCX, and a SVG graft from the aorta to the RCA and LCX. All grafts were patent 8 days after the CABG (*F*). CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; RCA, right coronary artery; RITA, right internal thoracic artery; SVG, saphenous vein graft.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

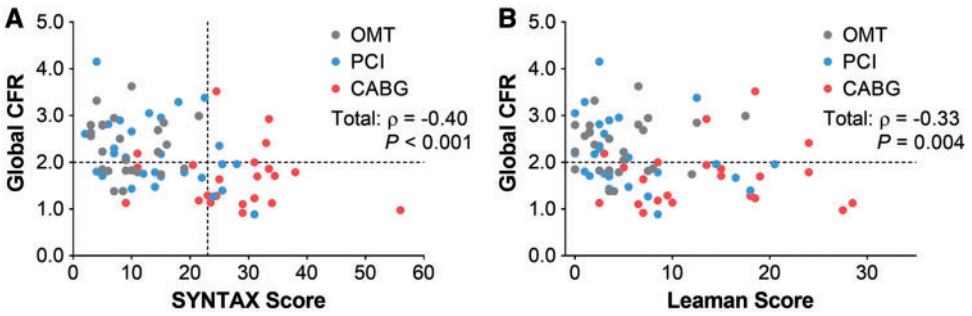

Figure 3 Relationship between CFR and the SYNTAX score (*A*) or the Leaman score (*B*). (*A*) The vertical dotted line indicates a SYNTAX score of 23.

Table 2 Proportion of patients achieving risk factor targets and angiographic completeness of revascularization during the study period

	OMT (*n* = 25)			PCI (*n* = 28)			CABG (*n* = 22)			*P* (between groups at follow-up)
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*	
Systolic blood pressure <130 mmHg	17 (68)	16 (64)	0.71	17 (61)	17 (61)	1.00	13 (55)	16 (73)	0.26	0.72
Diastolic blood pressure <80 mmHg	22 (88)	21 (84)	0.65	26 (93)	25 (89)	0.65	21 (95)	21 (95)	1.00	0.52
Non-diabetes/haemoglobin A_{1c} <7.0%	22 (88)	22 (88)	1.00	19 (68)	20 (71)	0.56	13 (59)	16 (73)	0.18	0.27
Triglycerides <150 mg/dL	19 (76)	16 (67)	0.41	19 (68)	19 (68)	1.00	15 (75)	16 (80)	0.65	0.64
Non-HDL-C <130 mg/dL	19 (76)	17 (68)	0.56	20 (71)	23 (82)	0.26	16 (73)	19 (86)	0.26	0.51
No smoking	21 (84)	22 (88)	0.32	24 (86)	25 (89)	0.32	17 (77)	21 (95)	0.046	0.70
Achieving ≥5 risk factor targets	18 (72)	14 (64)	0.16	13 (46)	19 (68)	0.08	11 (50)	17 (77)	0.034	0.29
SYNTAX score 0–8	12 (48)	NA	NA	8 (29)	19 (68)	<0.001	0 (0)	10 (45)	<0.001	0.22[a]
Leaman score = 0	3 (12)	NA	NA	2 (7)	16 (57)	<0.001	0 (0)	16 (73)	<0.001	<0.001[a]
Anginal symptoms	20 (80)	2 (8)	<0.001	16 (57)	0 (0)	<0.001	13 (59)	1 (8)	<0.001	0.38

Values are represented as *n* (%).
CABG, coronary artery bypass grafting; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LV, left ventricular; NA, not applicable; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.
[a]Comparison between the OMT group at baseline and the PCI and CABG groups at follow-up.

31.3%), *P* = 0.002] (*Figure 6*). There was no significant difference in percent change in regional CFR between coronary territories receiving PCI [19.3% (-11.9–40.7%)] and OMT alone (*Figure 6*). In addition, the percent change in regional CFR after PCI did not differ between stenoses with fractional flow reserve ≤0.8 and those with ischaemia on stress perfusion imaging [-3.7% (-30.9–65.4%) vs. 19.4% (-11.6–40.0%), *P* = 0.86].

3.4 Predictors of changes in CFR in response to coronary revascularization

The characteristics of patients with increased CFR from baseline to follow-up compared with those without improvement are summarized in Supplementary material online, *Table S4*. Independent predictors of changes in CFR between baseline and follow-up PET are summarized in *Table 3*. The ΔSYNTAX score (Model 1) and ΔLeaman score (Model 2) were independently associated with changes in CFR. Importantly, the extent of improvement in angiographic disease burden, but not the pretest likelihood or left ventricular ejection fraction, was independently associated with changes in CFR. There was no significant interaction between ΔSYNTAX score and revascularization with CABG (Model 3), indicating that CABG did not amplify the effects of revascularization on CFR.

3.5 Propensity score-matched analysis

Supplementary material online, *Table S5* shows the clinical characteristics of the matched cohort. The two groups (*n* = 9 in each group) were well matched at baseline. The CABG group showed a significant increase in CFR [1.64 (1.13–2.07) vs. 1.87 (1.52–2.48), *P* = 0.004], while the PCI group did not [1.78 (1.47–2.46) vs. 2.34 (1.47–2.74), *P* = 0.50]. Although there was no significant interaction between time and the two revascularization groups (*P* = 0.69), probably due to small sample size, the tendency was consistent with the unmatched cohort.

4. Discussion

In this prospective multicentre study, we demonstrated that revascularization of obstructive CAD improved CFR and stress MBF and that the degree of improvement was correlated with the degree of reduction of epicardial CAD burden. Importantly, these changes were

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

observed in the context of aggressive risk factor control. Finally, the benefit of PCI for improving CFR was confined to patients with baseline CFR <2.0, whereas CABG was beneficial regardless of baseline CFR.

The findings of this study extend previous cross-sectional correlations between CFR and angiographic findings[3] and prognostic studies of CFR[1–3] to further understand how coronary revascularization impacts this marker. While the nuclear substudy of the COURAGE trial evaluated the impact of revascularization and OMT on single-photon emission CT findings of ischaemia,[23] this modality is relatively insensitive compared to CFR. Our study represents the first multicentre, prospective study to demonstrate that revascularization improves overall myocardial perfusion and coronary vasomotor function as measured by PET CFR and stress MBF.

The significant association between reduction in angiographic CAD burden and improvement in CFR has important clinical implications, especially for planning coronary revascularization when multiple stenotic lesions are present. Farooq *et al.*[18] reported that a greater reduction in the post-procedure residual SYNTAX score was associated with a better outcome. Our findings support this and offer potential mechanistic insights into the underlying pathophysiology of the observation that more complete revascularization is associated with better prognosis.

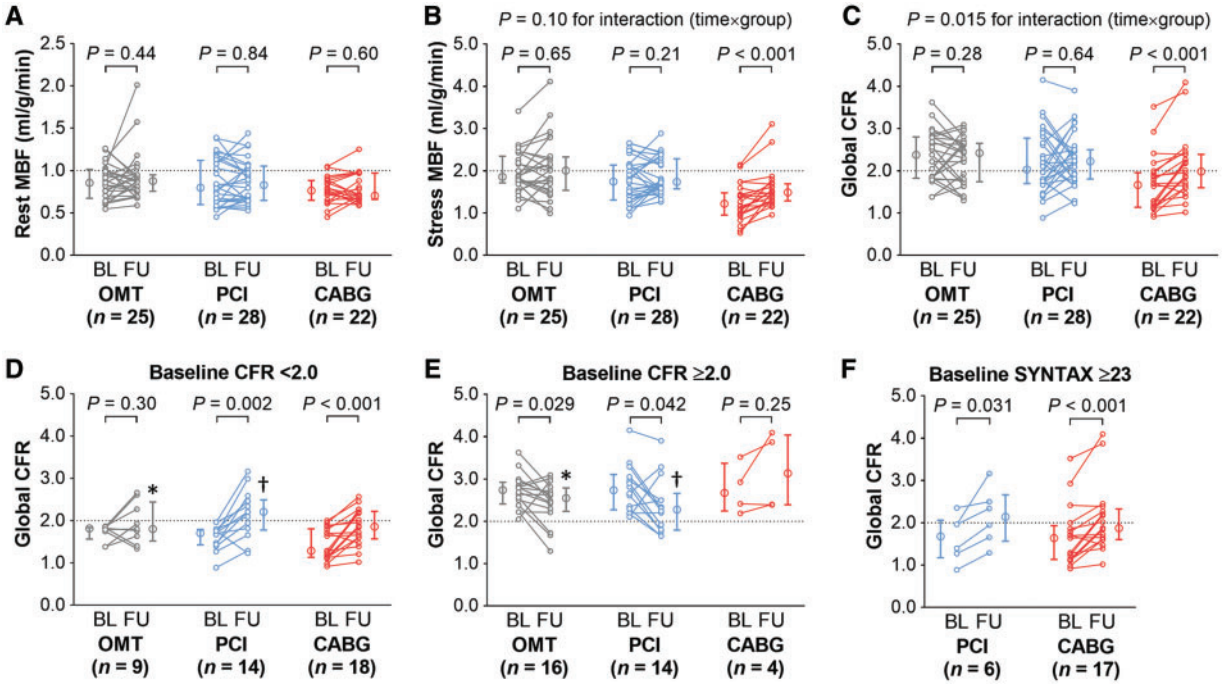

Figure 4 Comparisons of change in quantitative myocardial perfusion. Resting MBF (*A*), stress MBF (*B*), and global CFR (*C*). Individual changes in CFR from baseline (BL) to follow-up (FL) in patients with CFR <2.0 (*D*) or ≥2.0 (*E*) and in patients with baseline SYNTAX score ≥23 (*F*). Vertical bars represent medians with interquartile ranges. CABG, coronary artery bypass grafting; OMT, optimal medical therapy; PCI, percutaneous coronary intervention. *$P = 0.025$ for interaction between time and CFR. †$P < 0.001$ for interaction between time and CFR.

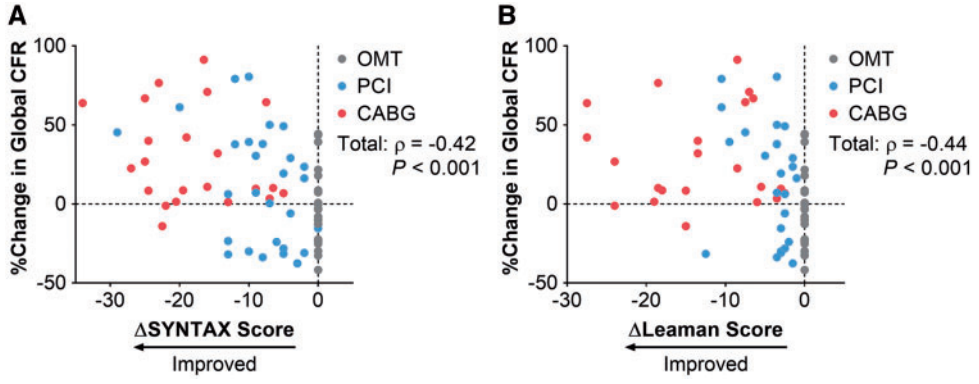

Figure 5 Relationship between changes in CFR and the SYNTAX score (*A*) or the Leaman score (*B*). CABG, coronary artery bypass grafting; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

Our study suggests that baseline CFR could be helpful in selecting the management strategy in patients with obstructive CAD. The results from multivariate analyses highlight the importance of complete revascularization in ameliorating reduced CFR. This adds to data from Taqueti *et al.*[3] suggesting that CABG may be more beneficial than PCI in patients with severely reduced CFR. While the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA trial; ClinicalTrials.gov number, NCT01471522) is evaluating how relative measures of ischaemia should be used to select treatment strategy for CAD, it is unlikely to directly address the question of whether CFR has a role in this decision-making process. Our data provide the basis for further studies directly aimed at this question.

Our findings may help to explain the results of the ORBITA trial.[24] In the ORBITA trial, all patients were pretreated with OMT at randomization, and PCI for single-vessel stenosis did not significantly increase exercise time over a placebo procedure. One reason for this may be the lack of significant increase in global CFR by PCI for single-vessel stenosis.

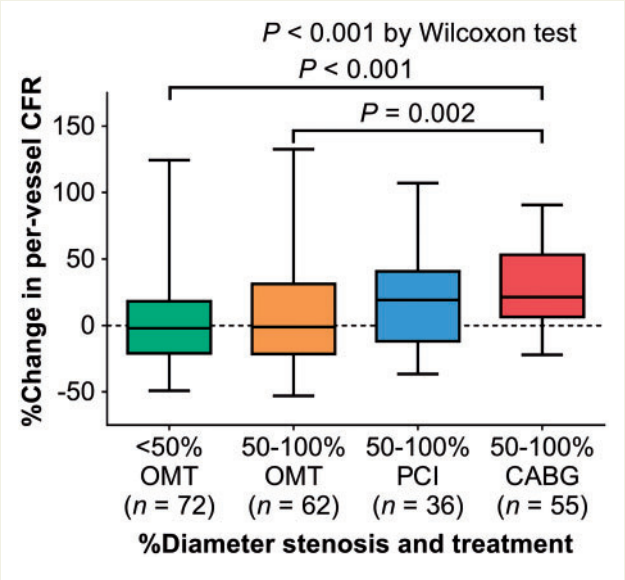

Figure 6 Per-vessel relationship between changes in regional CFR and coronary arteries categorized by diameter stenosis and treatment. CABG, coronary artery bypass grafting; OMT, optimal medical therapy; PCI, percutaneous coronary intervention.

The moderately strong correlation between CFR and angiographic CAD burden in the present study was in line with previous studies using the CAD prognostic index.[3] The Leaman score[19] and CAD prognostic index[3] only take into account the number of diseased vessels and the severity of stenosis, while the SYNTAX score[16] includes not only these factors, but also coronary lesion complexity (e.g. bifurcation lesions, long lesions, heavy calcification). The robustness of these results across angiographic scores supports the generality of the relationship between CFR and the anatomic extent of CAD. Importantly, the residual variability in CFR among patients with obstructive CAD may be explained by diffuse disease and microvascular dysfunction. Importantly, patients with reduced CFR and SYNTAX score <23, for whom microvascular dysfunction may have been a major contributor to CFR reduction, comprised 29% of the cohort (*Figure 3*).

4.1 Study limitations

In contrast to other PET studies highlighting the benefits of OMT (including statins, beta-blockers, and nitrates) and risk factor modification on CFR,[25] this study found no effects for OMT on myocardial perfusion. One reason for this is that a relatively high prevalence of patients already on OMT before inclusion in the study, which reflects evidence-based practice in the modern era. In addition, CFR values were not provided on PET reports to referring cardiologists; therefore, the impact of these metrics on cardiologists' decision making cannot be determined. We did not assess myocardial viability and changes in left ventricular ejection fraction in all the study patients, which may affect the change in CFR after treatment. However, the appropriateness of coronary revascularization was evaluated with conventional myocardial perfusion imaging or invasive fractional flow reserve. Most critically, our findings are subject to selection bias and confounding because of the observational nature of the study, which may introduce bias where the OMT group was reserved for either very mild or very severe CAD, whereas PCI would be performed for less advanced CAD compared with CABG. The results of the subgroup analysis of patients with baseline CFR <2.0, while interesting, may be not robust due to the relatively small sample size. Nonetheless, the change with treatment observed in this small cohort is consistent with the results of the COURAGE nuclear substudy.[23] Due to the multicentre observational nature of the study, there are some

Table 3 Multivariate linear regression analysis for predicting the percent change in global coronary flow reserve in response to coronary revascularization

	Model 1			Model 2			Model 3		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
Intercept	-15.7	-51.6 to 20.3	0.39	-13.9	-49.5 to 21.8	0.44	-22.6	-60.1 to 14.9	0.23
Pretest likelihood of obstructive CAD (per 10%)	2.2	-2.0 to 6.3	0.30	2.4	-2.3 to 5.9	0.38	2.8	-1.5 to 7.0	0.20
History of PCI or CABG	-8.8	-24.8 to 7.2	0.28	-11.0	-26.9 to 4.8	0.17	-10.1	-26.1 to 6.0	0.22
Left ventricular ejection fraction <50%	-1.7	-17.8 to 14.5	0.84	-1.8	-17.9 to 14.4	0.83	-2.5	-18.7 to 13.7	0.76
CABG group	2.7	-19.2 to 24.7	0.80	1.1	-21.7 to 23.9	0.92	20.8	-15.2 to 56.8	0.25
ΔSYNTAX score	-1.4	-2.5 to -0.3	0.012	–	–	–	-2.0	-3.4 to -0.6	0.007
Interaction (ΔSYNTAX score × CABG group)	–	–	–	–	–	–	1.4	-0.8 to 3.7	0.21
Log (1 - ΔLeaman score) (per 1)	–	–	–	11.8	2.7 to 20.8	0.011	–	–	–

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; PCI, percutaneous coronary intervention.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

variations in baseline CFR between groups and in follow-up procedures after coronary revascularization between hospitals. The significance of the coronary haemodynamic findings after revascularization needs to be evaluated in patients with a similar atherosclerotic burden and a predefined procedure of follow-up angiography. Finally, we did not assess the association between changes in CFR after treatment and the patients' outcomes. Further long-term follow-up studies are needed to determine whether an increase in CFR leads to better outcomes in patients with CAD.

5. Conclusion

Coronary revascularization ameliorated reduced CFR in patients with obstructive CAD. Improvement in CFR was proportionate to reduction in angiographic CAD burden by coronary revascularization. These results suggest that patients with reduced CFR and high-risk CAD may have greater potential to benefit from coronary revascularization.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Acknowledgements

The authors thank Yuuki Tomiyama, PhD, and Keisuke Kawauchi for technical assistance. We acknowledge the contributions of the following cardiologists who participated in this study: Hisashi Matsuo (Keiwakai Ebetsu Hospital), Yoichi Yamada, Mitsunori Otsubo (ShinSapporo Hospital of Cardiology), and Tetsuro Kohya (Sapporo City General Hospital).

Conflict of interest: none declared.

Funding

This work was supported by the Japan Heart Foundation & Astellas Grant for Research on Atherosclerosis Update; the Uehara Memorial Foundation [to T.A.], a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science [grant number JP16K10264 to M.N.], and the Takeda Science Foundation [to M.N.].

References

1. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 2011;**124**:2215–2224.
2. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, Renaud JM, Ruddy TD, Sarveswaran N, Tee RE, Beanlands RS. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol* 2011;**58**:740–748.
3. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015;**131**:19–27.
4. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med* 2007;**356**:830–840.
5. Wilson RF, White CW. Does coronary artery bypass surgery restore normal maximal coronary flow reserve? The effect of diffuse atherosclerosis and focal obstructive lesions. *Circulation* 1987;**76**:563–571.
6. Pizzuto F, Voci P, Mariano E, Puddu PE, Sardella G, Nigri A. Assessment of flow velocity reserve by transthoracic Doppler echocardiography and venous adenosine infusion before and after left anterior descending coronary artery stenting. *J Am Coll Cardiol* 2001;**38**:155–162.
7. Nijjer SS, Petraco R, van de Hoef TP, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Al-Lamee R, Foin N, Sethi A, Malik IS, Mikhail GW, Hughes AD, Mayet J, Francis DP, Di Mario C, Escaned J, Piek JJ, Davies JE. Change in coronary blood flow after percutaneous coronary intervention in relation to baseline lesion physiology: results of the JUSTIFY-PCI study. *Circ Cardiovasc Interv* 2015;**8**:e001715.
8. Driessen RS, Danad I, Stuijfzand WJ, Schumacher SP, Knuuti J, Maki M, Lammertsma AA, van Rossum AC, van Royen N, Raijmakers PG, Knaapen P. Impact of revascularization on absolute myocardial blood flow as assessed by serial [^{15}O]H_2O positron emission tomography imaging: a comparison with fractional flow reserve. *Circ Cardiovasc Imaging* 2018;**11**:e007417.
9. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der WEE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
10. Kamiya K, Sakakibara M, Asakawa N, Yamada S, Yoshitani T, Iwano H, Komatsu H, Naya M, Chiba S, Yamada S, Manabe O, Kikuchi Y, Oyama-Manabe N, Oba K, Tsutsui H. Cardiac magnetic resonance performs better in the detection of functionally significant coronary artery stenosis compared to single-photon emission computed tomography and dobutamine stress echocardiography. *Circ J* 2014;**78**:2468–2476.
11. Manabe O, Naya M, Aikawa T, Obara M, Magota K, Kroenke M, Oyama-Manabe N, Hirata K, Shinyama D, Katoh C, Tamaki N. PET/CT scanning with 3D acquisition is feasible for quantifying myocardial blood flow when diagnosing coronary artery disease. *EJNMMI Res* 2017;**7**:52.
12. Naya M, Tsukamoto T, Morita K, Katoh C, Furumoto T, Fujii S, Tamaki N, Tsutsui H. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. *J Am Coll Cardiol* 2007;**50**:1144–1149.
13. Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA, Heymans MW, Kajander SA, Pietila M, James S, Sorensen J, Knaapen P, Knuuti J. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [^{15}O]H_2O PET imaging. *J Am Coll Cardiol* 2014;**64**:1464–1475.
14. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, Paulus WJ, Heyndrickx GR, Wijns W. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation* 1994;**89**:1013–1022.
15. Stuijfzand WJ, Uusitalo V, Kero T, Danad I, Rijnierse MT, Saraste A, Raijmakers PG, Lammertsma AA, Harms HJ, Heymans MW, Huisman MC, Marques KM, Kajander SA, Pietila M, Sorensen J, Royen N. V, Knuuti J, Knaapen P. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. *Circ Cardiovasc Imaging* 2015;**8**:e002400.
16. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50–56.
17. Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia-Garcia H, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Stahle E, James S, Carrie D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW. The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. *EuroIntervention* 2013;**8**:1277–1285.
18. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, Holmes DR, Mack M, Morice MC, Stahle E, Colombo A, de Vries T, Morel MA, Dawkins KD, Kappetein AP, Mohr FW. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013;**128**:141–151.
19. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 1981;**63**:285–299.
20. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, Redmon JB, Sperling L, Rutter MK; BARI 2D Group. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D trial. *J Am Coll Cardiol* 2015;**66**:765–773.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019

21. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr, Muhlbaier LH, Califf RM. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;**118**:81–90.
22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;**46**:399–424.
23. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE, COURAGE Investigators. 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**:1283–1291.
24. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;**391**:31–40.
25. Zoghbi GJ, Dorfman TA, Iskandrian AE. The effects of medications on myocardial perfusion. *J Am Coll Cardiol* 2008;**52**:401–416.

Downloaded from https://academic.oup.com/cardiovascres/article-abstract/115/1/119/5051230 by Hokkaido University Library user on 08 January 2019