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ORIGINAL RESEARCH ARTICLE

Routine Pressure Wire Assessment Versus Conventional Angiography in the Management of Patients With Coronary Artery Disease: The RIPCORD 2 Trial

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BACKGROUND: Measurement of fractional flow reserve (FFR) has an established role in guiding percutaneous coronary intervention. We tested the hypothesis that, at the stage of diagnostic invasive coronary angiography, systematic FFR-guided assessment of coronary artery disease would be superior, in terms of resource use and quality of life, to assessment by angiography alone.

METHODS: We performed an open-label, randomized, controlled trial in 17 UK centers, recruiting 1100 patients undergoing invasive coronary angiography for the investigation of stable angina or non–ST-segment–elevation myocardial infarction. Patients were randomized to either angiography alone (angiography) or angiography with systematic pressure wire assessment of all epicardial vessels >2.25 mm in diameter (angiography+FFR). The coprimary outcomes assessed at 1 year were National Health Service hospital costs and quality of life. Prespecified secondary outcomes included clinical events.

RESULTS: In the angiography+FFR arm, the median number of vessels examined was 4 (interquartile range, 3–5). The median hospital costs were similar: angiography, £4136 (interquartile range, £2613–£7015); and angiography+FFR, £4510 (£2721–£7415; *P*=0.137). There was no difference in median quality of life using the visual analog scale of the EuroQol EQ-5D-5L: angiography, 75 (interquartile range, 60–87); and angiography+FFR, 75 (interquartile range, 60–90; *P*=0.88). The number of clinical events was as follows: deaths, 5 versus 8; strokes, 3 versus 4; myocardial infarctions, 23 versus 22; and unplanned revascularizations, 26 versus 33, with a composite hierarchical event rate of 8.7% (48 of 552) for angiography versus 9.5% (52 of 548) for angiography+FFR (*P*=0.64).

CONCLUSIONS: A strategy of systematic FFR assessment compared with angiography alone did not result in a significant reduction in cost or improvement in quality of life.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01070771.

Key Words: coronary angiography ■ costs and cost analysis ■ physiology ■ quality of life ■ randomized controlled trial

The additional value of having intracoronary physiological data in the form of fractional flow reserve (FFR), above and beyond angiographic assessment alone, in patients who have already been labeled as being suitable for percutaneous coronary intervention (PCI) with stents has been well described in a

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Clinical Perspective

What Is New?

- This is the first completed randomized clinical trial to test, in patients undergoing diagnostic angiography, a strategy of systematic measurement of fractional flow reserve in all vessels of sufficient caliber to be potential targets for revascularization (median of 4 vessels examined in patients randomized to fractional flow reserve).

What Are the Clinical Implications?

- Use of fractional flow reserve was associated with longer procedure duration, greater use of contrast and radiation, and a pressure wire–related complication rate of 1.8%.
- Compared with angiography alone, after 1 year of follow-up, use of fractional flow reserve was not associated with any difference in patent-reported quality of life or total hospital costs. The incidence of adverse cardiac events was also similar.
- This study suggests that there is no benefit in a strategy of systematic evaluation of all vessels at the time of angiography.

Nonstandard Abbreviations and Acronyms

CABG	coronary artery bypass graft
FAME	Fractional Flow Reserve Versus Angiography for Multivessel Evaluation
FFR	fractional flow reserve
FUTURE	Functional Testing Underlying Coronary Revascularization
IQR	interquartile range
MI	myocardial infarction
NHS	National Health Service
OMT	optimal medical therapy
PCI	percutaneous coronary intervention
PW	pressure wire
QoL	quality of life
RIPCORD	Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?
TIMI	Thrombolysis in Myocardial Infarction

series of randomized trials.[1–3] On the basis of these data and clinical studies demonstrating significant changes in the way that patients are treated when pressure wire (PW) assessment is used during diagnostic angiography,[4–6] current guidelines recommend using FFR for the functional assessment of lesion severity in patients with intermediate-grade coronary artery disease (typically 40%–90% stenosis) without evidence of myocardial ischemia in noninvasive testing or in those with multivessel disease.[7] The RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) concept proposes routine PW assessment of all epicardial vessels that are of a caliber amenable to revascularization at the stage of diagnostic angiography, specifically before the patients are triaged to optimal medical therapy alone (OMT), additional revascularization with PCI, or coronary artery bypass graft surgery (CABG). The original proof-of-concept RIPCORD study[8] demonstrated that the declaration of functional significance was altered in 32% of lesions when FFR data were available in addition to the angiograms alone and that this led to a consequent change in management plan in 26% of the population. However, these potential advantages have not been demonstrated in a randomized trial to improve clinical outcomes compared with conventional management.

Despite these data, the uptake of the use of FFR or equivalent intracoronary PW-derived indices has been low; in the 2019 to 2020 UK national data, for example, a PW is used in only ≈10.0% (10 047 of 100 112) of all PCI cases, with a further 13 303 PW tests being performed as a purely diagnostic test.[9] One explanation for this modest uptake is concern about the potential cost of using PWs on a more routine basis.

RIPCORD 2 was designed to test the hypothesis that systematic FFR assessment of all relevant coronary arteries at the stage of the diagnostic angiogram would provide superior resource use, quality of life (QoL), and clinical outcomes compared with the use of the angiogram alone.

METHODS

Data Sharing

On application to the corresponding author and with the approval of the Trial Steering Committee, the data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Ethics Approval

This trial was conducted according to the principles of the International Conference on Harmonisation–Good Clinical Practice standards, the Declaration of Helsinki, and National Health Service (NHS) Research Governance guidelines. The study protocol, patient information sheet, and consent form were approved by the National Research Ethics Service before the trial was started (Research Ethics Committee reference 16/LO/0570). All patients gave informed consent for participation. The study was registered before inclusion of the first patient at ClinicalTrials.gov (NCT02892903).

Trial Oversight

The trial was investigator initiated and funded by an unrestricted research grant from Boston Scientific Corp. The company had no role in the design or conduct of the trial or in the data collection, analysis, or reporting. The trial steering committee oversaw the conduct of the trial, which was run by a Trial Management Committee, ensuring that (1) it was conducted in a manner consistent with the protocol, (2) the data were complete, and (3) the analyses were performed according to a prespecified plan. The sponsor was University Hospital Southampton NHS Trust.

Study Design and Population

RIPCORD 2 is an open label, prospective, randomized controlled trial. The rationale for and design of the study have previously been described.[10] In brief, patients with either stable angina or non–ST-segment–elevation myocardial infarction (MI) who were scheduled for invasive coronary angiography were screened in 2 phases for eligibility according to trial inclusion and exclusion criteria, as detailed in the study protocol (Supplemental Appendix A). Initial clinical screening determined broad suitability, after which patients were approached for consent. For consented patients, further screening was then performed after angiography to determine their suitability for randomization. A key inclusion criterion was the presence, by visual assessment, of at least 1 stenosis of ≥30% narrowing in a coronary vessel of a caliber suitable for either PCI or a bypass graft.

Randomization

Randomization was performed in the catheter laboratory after angiography. Investigators were required to report the reasons why consented patients did not proceed to randomization. Eligible patients were randomized with the use of a web interface secured by password access. Patient registration by initials, date of birth, and unique study number was required before the release of an allocation. Randomization tables were prepared by the trial coordinating center, with allocation stratified by center and using block sizes of 2, 4, and 6 with random variation of block size to avoid the possibility of investigators being able to predict the next allocation from the historic pattern. A backup randomization option using opaque, serial-numbered, sealed envelopes was provided but was used for only 11 patients in 5 different centers.

Study Methods

In patients randomized to FFR assessment after angiography (angiography+FFR), FFR measurement was then performed in all coronary arteries of sufficient caliber for PCI or placement of a bypass graft conduit, examining all major vessels and branches regardless of the presence or absence of atheroma. Occluded and subocclusded vessels with TIMI (Thrombolysis in Myocardial Infarction) grade flow of <3 were not examined. All FFR measurements were made after administration of intracoronary nitrate and during hyperemia induced by either intracoronary or intravenous adenosine, according to operator discretion. An FFR of ≤0.80 was considered to be positive. Any PW could be used, but use of the Boston Scientific COMET wire was encouraged, and the cost of this device was reimbursed as part of the trial. Before the start of RIPCORD 2, the COMET wire accuracy and drift were investigated in a randomized trial.[11]

Trial data were recorded in a bespoke case record form, presented through a secure online web interface. The case record form enforced detailed tracking of clinical and adverse events from randomization to hospital discharge or 24 hours (whichever occurred sooner) in the index admission. Adverse events in this phase were subject to formal adjudication by a Clinical Events Committee to independently determine any potential relationship to the study procedures.

In all patients, investigators were required to declare the final management plan for each patient in terms of OMT, PCI, or CABG. This decision could be deferred pending the performance of additional tests or to allow further discussion. The nature of additional tests performed was recorded in the case record form.

Patients were contacted at 1 year, and angina symptoms recorded with the Canadian Cardiovascular Society scale. They also completed the EuroQol EQ-5D-5L questionnaire.

We examined information on all hospital attendance (including the index admission) for all patients for 365 days after their randomization. This was received through a download of Hospital Episode Statistics data from NHS Digital in England. Equivalent data sets were obtained from NHS Wales informatics services and from the Public Benefit and Privacy Panel for Health and Social Care in Scotland to ensure UK-wide follow-up. Office for National Statistics mortality data were obtained from NHS Digital and the Public Benefit and Privacy Panel for Health and Social Care.

Outcome Measures

The trial had coprimary end points: total hospital cost and QoL. The primary economic outcome measure reports hospital costs from, and including, the index admission to any hospital episode starting within 365 days after randomization. All inpatient admissions, outpatient visits, and attendances at accident and emergency departments were included. Costs were calculated with the NHS tariff system. Codes from individual episodes were entered into a standardized grouper program (NHS Digital HRG4+ Payment Grouper 19/20) that returns Healthcare Resource Group designations, which can then be allocated costs from relevant NHS tariff reference values. Costs incurred for each patient over the period were summed. The results reflect the real cost of hospital-based health care to the payer and the sums received by the provider hospitals. Costs for primary care, routine medications, or societal costs were not included.

The primary QoL outcome was a comparison of the visual analog scale reported on completion of the EQ-5D-5L instrument at 1 year. This is a validated, international, generic measure of QoL. Use of a generic tool allows a more holistic assessment of the impact of medical care, including, for example, general recovery from interventions and the potential impact of noncardiac complications. Prespecified subgroup analysis for the primary outcomes was performed in relation to (1) the sex of the patient, (2) the initial presentation (stable versus acute coronary syndrome), and (3) the angiographic (pre-FFR) investigator-reported distribution of the obstructive coronary artery disease, classified as 1-, 2-, and 3-vessel disease based on a

reported stenosis reducing the luminal diameter by ≥50% in the left main stem or by ≥70% in the other vessels.

Adverse clinical events were reported as secondary outcomes, including all-cause mortality, stroke, MI, and unplanned revascularization. For patients admitted with an acute coronary syndrome, MI adjudication required evidence of reinfarction or a distinct new MI event after randomization. Unplanned revascularization was defined as any PCI or CABG procedure not declared as part of the original management plan. Events were determined by an examination of diagnostic codes from the Hospital Episode Statistics data. An explanation of the methodology used is presented in Supplemental Appendix B.

Resource use in the angiography phase, the management plan recommended for patients, and angina symptoms by Canadian Cardiovascular Society grade were also reported.

Statistical Methods and Power Calculations

All analyses were performed on an intention-to-treat basis on the randomized population with SPSS version 26 (IBM). All comparative testing was 2 sided. A value of $P \leq 0.05$ was assumed to indicate statistical significance. Data for the primary outcomes and other continuous data were not normally distributed and are reported as medians and interquartile ranges (IQRs). Comparisons were made with the Mann-Whitney *U* test for medians. Discrete variables were reported as numbers and proportions and compared by the Pearson χ^2 test or Fisher exact test if the number of observations in any group was ≤5. Clinical events are reported as the number and proportion of both all events observed and in terms of a patient-level hierarchical composite (ordered; death, stroke, MI, revascularization). The absolute risk difference in hierarchical event rates is presented with the 95% CI, calculated by the method of Newcombe. The time to the first adverse clinical event in each patient was compared by use of the log-rank test. Subgroup analyses were performed for the primary economic and QoL outcomes with a regression interaction test.

The details of the power calculation have previously been reported[10] and are available in full in Supplemental Appendix C. In brief, we assumed an average baseline cost of £4615 and expected a wide SD (£1850). Conventional calculations suggest that a sample size of 1030 subjects would provide 80% power at an α of 0.05 to detect an absolute change of 7% (£325). Because of expected nonparametric data, we increased the sample size to 1100. Given the nature of the tracked Hospital Episode Statistics data, we expected almost complete data. In terms of the EQ-5D-5L data, we assumed a baseline mean score of 74.3 (SD, 16.7). Evaluable data on 1040 patients would afford 80% power to detect an absolute difference of 3 points or 4% of the observed value. The study was not powered to detect differences in individual clinical events.

RESULTS

Patients were randomized at 17 UK centers between September 29, 2016, and June 15, 2018. Details of the centers and the recruitment numbers are available in Supplemental Appendix D. Figure 1 summarizes patient flow in the trial. After the initial screening, 1818 patients were consented. After angiography, 718 were excluded, half of these because of angiographically determined disease-free coronary arteries. Concern about the use of PW resulted in exclusion of a further 283 of 718 (39.5%); the reasons declared are presented in Figure 1. A total of 1100 patients were randomized, 552 to angiography and 548 to angiography+FFR. Adherence to the randomized investigation strategy, patient retention, and evaluable data at 1 year were good (Figure 1). Economic and clinical event data were obtained in 551 of 552 (99.8%) of the angiography arm and 546 of 548 (99.6%) of the angiography+FFR arm, and QoL data were complete in 537 of 552 (97.3%) in the angiography arm and 528 of 548 (96.4%) in the angiography+FFR arm.

Baseline characteristics of the patients were similar between the randomized groups (Table 1). Just over half the population were recruited in the context of non–ST-segment–elevation. The mean age was 64 years; ≈75% of the patients were male; and 19% had diabetes. The majority had preserved left ventricular systolic function, and more than two-thirds were reported to have either no or single-vessel disease as determined by angiographic assessment alone. About 8% had potentially flow-limiting disease in the left main stem. The median British Cardiovascular Intervention Society Jeopardy Score was 2 (IQR, 0–6).[12]

Information from the catheterization laboratory procedures is presented in Table 2. For patients randomized to angiography+FFR, the median number of vessels tested with FFR was 4 (IQR, 3–5). More than 85% of these cases involved the use of a single PW. In the angiography+FFR group, cases were longer in duration and involved more radiation exposure and greater use of radiographic contrast ($P<0.001$; Table 2). The rate of PW-related complications was 1.8%, and the nature of the complications is shown in Table 2. The relationship between the angiographic assessment of lesion severity and the FFR measurement demonstrated a typical pattern with discordance for lesions classified as both mild and severe (Figure 2). Information about the distribution of measured FFR values in presented in the Supplemental Material.

Table 3 summarizes information about the management plan declared for the trial patients. In the angiography+FFR group, investigators were able, immediately after the catheterization laboratory procedure, to declare the definitive management plan in >98% of cases. In contrast, in the angiography group, a further test was required in 14.7% of patients. This is reflected in the descriptive statistics for the interval from randomization to declaration of the final management plan, with 10% of the angiography group having a delay of >50 days. There were no significant differences in the broad management strategy adopted (in terms of medical therapy, PCI, or CABG) and, in patients to be treated with revascularization, no significant differences in the plan for the number of segments (PCI) or vessels (CABG) to be treated.

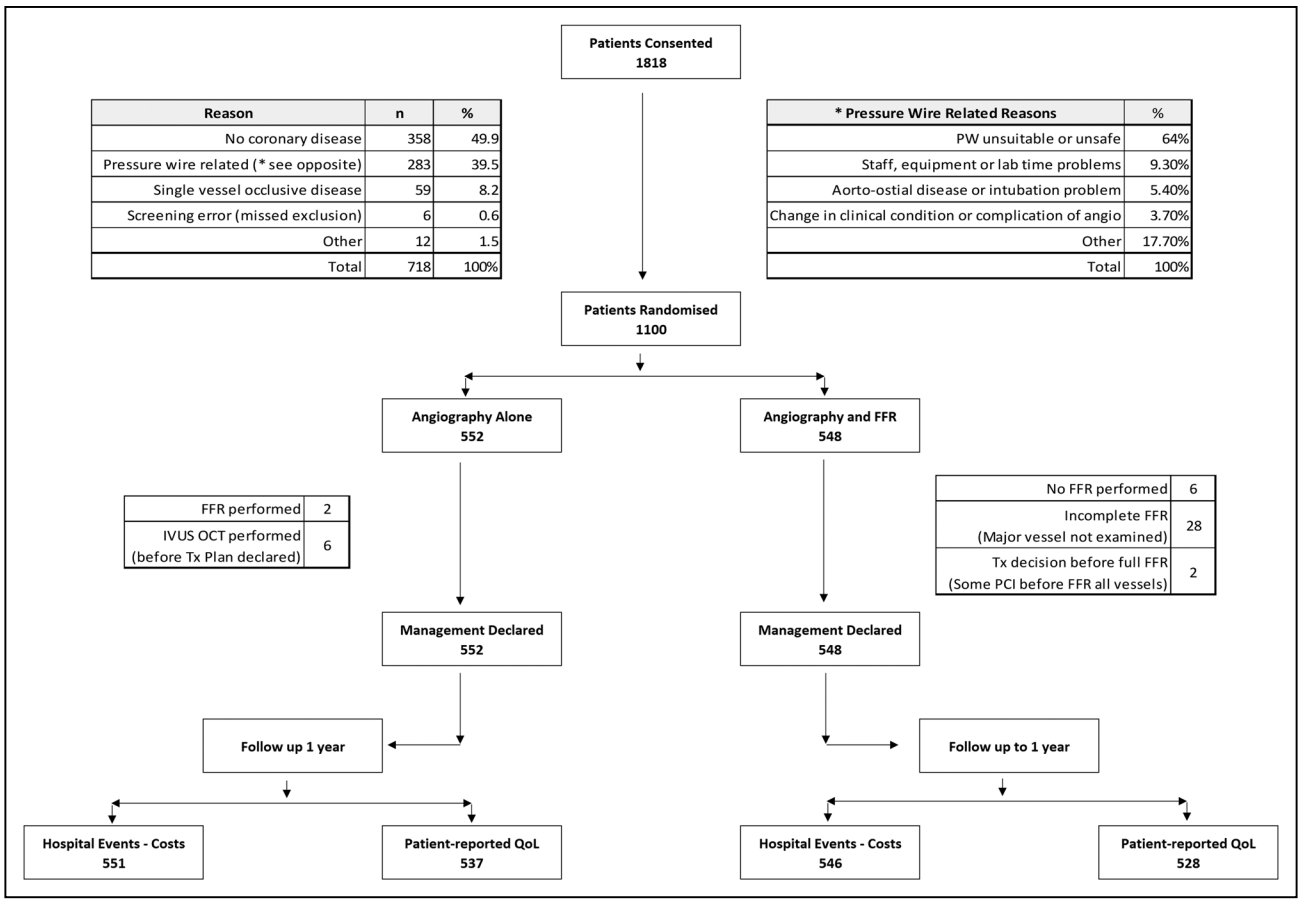

Figure 1. Patient flow in the trial.
FFR indicates fractional flow reserve; IVUS OCT, intravascular ultrasound optical coherence tomography; PCI, percutaneous coronary intervention; PW, pressure wire; QoL, quality of life; and Tx, treatment.

Coprimary QoL Outcome

There were no differences in the primary QoL outcome of median EQ-5D visual analog scale score: 75 (IQR, 60–87) for the angiography arm versus 75 (IQR, 60–90) for the angiography+FFR arm (P=0.88). The EQ-5D index score, used in utility calculation, was also very similar for the groups, as was the pattern of angina symptoms reported by Canadian Cardiovascular Society classification (Table 4).

Coprimary Total Hospital Cost Outcome

The median total hospital cost over the period was similar for the 2 groups: £4136 for angiography (IQR, £2613–£7015) versus £4510 (IQR, £2721– £7415; P=0.137) for angiography+FFR. There were no differences in terms of inpatient and outpatient cost, nights in hospital, or number of outpatient visits (Table 4).

Clinical Events

Table 5 and Figure 3 show the clinical events experienced by patients in the year after randomization. Event rates were not significantly different between groups in terms of both individual events and a composite of major adverse cardiac events.

The results of the prespecified subgroup analyses are shown in Table 6. There were no differences between male and female patients or between stable and acute coronary syndrome presentations. There was a statistically significant interaction between the angiographic severity of coronary artery disease and QoL such that, for patients with more significant disease, QoL was better in the angiography+FFR group (P=0.03). There are no significant differences for the other subgroups.

A post hoc analysis for the subgroup of patients manifesting at least 1 obstructive lesion at initial angiographic assessment showed similar findings and is presented in the Supplemental Material.

DISCUSSION

The main findings of this randomized trial are that a strategy of systematic FFR in all major coronary arteries amenable to revascularization was cost neutral compared with angiography-guided management and overall was not associated with any difference in QoL or angina status at 1 year.

Table 1. Baseline Characteristics

	Angiography (n=552)	Angiography+ FFR (n=548)
Age, mean (SD), y	64.3 (10.2)	64.3 (10.0)
Male, n/d=p%	426/552=77.2	403/548=73.5
White race, n/d=p%	532/552=96.4	519/548=94.7
Body mass index, mean (SD), kg/m^2	29.1 (5.3)	29.1 (5.2)
Diabetes, any, n/d=p%	97/552=17.6	113/548=20.6
Type 1	4/552=0.7	8/548=1.5
Type 2 diet treated	20/552=3.6	19/548=3.5
Type 2 drug treated	54/552=9.8	68/548=12.4
Type 2 insulin treated	19/552=3.4	18/548=3.3
ACS presentation, n/d=p%	292/550=53.1*	276/548=50.4
eGFR, mean (SD), mL·min^{-1}·1.73 m^{-2}	77.2 (13.2)	76.9 (13.0)
LV function, n/d=p%†		
EF [scolor_start FADADD]≥[/scolor]55%	234/318=73.6	217/286=75.6
EF 45%–54%	54/318=17.0	52/286=18.2
EF 35%–44%	22/318=6.9	16/286=5.6
EF <35%	8/318=2.5	1/286=0.3
History of, n/d=p%		
MI	129/551=23.4‡	117/546=21.4§
PCI	140//552=25.4	147/547=26.9‖
Any smoking	356/548=65.0¶	316/542=58.5#
Hypertension	294/550=53.5**	315/547=57.6††
Hyperlipidemia	317/550=57.6‡‡	315/548=57.5
Angiographic disease, n/d=p%		
0-Vessel disease	143/552=25.9	156/548=28.5
1-vessel disease	265/552=48.0	218/548=39.8
2-Vessel disease	108/552=19.6	112/548=20.4
3-Vessel disease	36/552=6.5	62/548=11.3
Left main stem reported >50%, n/d=p%	48/552=8.7	43/548=7.8
Proximal LAD reported >70%, n/d=p%	97/552=17.6	95/548=17.3
BCIS Jeopardy Score, median (IQR)	2 (0–6)	2 (0–6)

ACS indicates acute coronary syndrome; BCIS, British Cardiovascular Interventional Society; d, denominator; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; IQR, interquartile range; LAD, left anterior descending coronary artery; LV, left ventricular; MI, myocardial infarction; n, numerator; p, resulting percentage; and PCI, percutaneous coronary intervention.

Missing data: *2 cases; †angiography, 234 cases; FFR, 262 cases; ‡1 case; §2 cases; ‖1 case; ¶4 cases; #6 cases; **2 cases; ††1 case; ‡‡2 cases.

Table 2. Procedural Details

	Angiography (n=552)	Angiography+ FFR (n=548)	*P* value*
Procedure time, mean (SD), min†	42.4 (27.0)	69.0 (27.0)	<0.001
Contrast used, mean (SD), mL†	146.3 (87.0)	206.0 (96.2)‡	<0.001
Radiation dose, mean (SD), cGy/cm^2	5029.7 (5540.6)	6608.7 (5292.3)‡	<0.001
Pressure wires used, n/d=p%			
0	500/552=99.6	6/548=1.1	
1	2/552=0.04	472/548=86.1	
2		59/548=10.8	
3		10/548=1.8	
4		1/548=0.2	
Any IVUS use, n/d=p%	18/552=3.3	18/548=3.3	
Any OCT use, n/d=p%	12/551=2.2‡§	8/547=1.5‡	
Vessels examined with FFR, n			
Median	0	4	
IQR	0–0	3–5	
5th–95th centile	0–0	2–7	
PW-related complications, n/d=p%			
Any complication	0/552=0	10/548=1.8	
Coronary dissection requiring CABG	0/552=0	2/548=0.4	
Coronary dissection requiring PCI	0/552=0	4/548=0.7	
Acute MI‖	0/552=0	1/548=0.2	
Retained wire elements	0/552=0	1/548=0.2	
Arrythmia requiring specific drug Tx	0/552=0	2/548=0.4	

CABG indicates coronary artery bypass graft surgery; d, denominator; FFR, fractional flow reserve; IQR, interquartile range; IVUS, intravascular ultrasound; MI, myocardial infarction; n, numerator; OCT, optical coherence tomography; p, resulting percentage; PCI, percutaneous coronary intervention; PW, pressure wire; and Tx, treatment.

*Mann-Whitney *U* test.

†Figures relate to total use in the index procedure.

‡Missing data: 1 case.

§Intracoronary imaging was used in 5 cases before declaration of the Tx plan (a protocol violation).

‖MI event with typical pain, acute electrocardiographic change, and subsequent rise in troponin, managed conservatively.

Given the previous evidence supporting FFR-guided management used selectively, a randomized trial to assess the comprehensive and systematic use of this approach during diagnostic angiography was indicated. The existing literature can be considered in 3 categories: (1) observations on the association between FFR level and subsequent ischemic clinical event rates, (2) randomized trials assessing the value of FFR guidance compared with angiographic guidance alone in patients with established coronary artery disease who had already been committed to PCI, and (3) observational studies describing the effect of using FFR assessment at the time of angiography on decision making and management of the patients. All 3 categories suggest the potential for profound benefit from routine FFR in clinical practice. Specifically, in the first category, a large body of

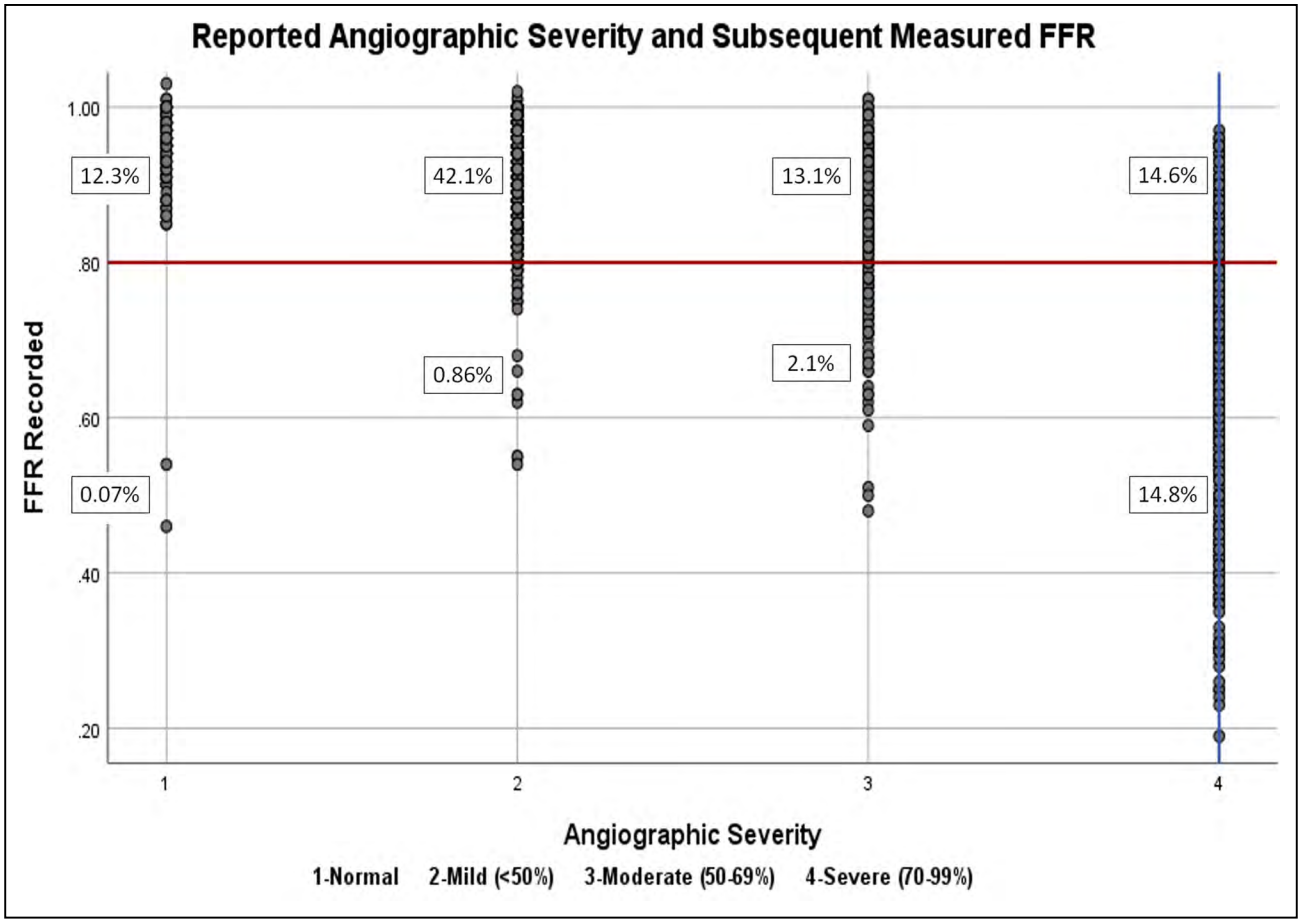

Figure 2. Relationship between individual vessel assessment by visual angiographic appearance (estimated diameter stenosis percent) and FFR for each lesion.
FFR indicates fractional flow reserve.

observational data demonstrate a consistent inverse association between vessel-specific FFR and subsequent risk of major adverse cardiac events.[13,14] In the second category of evidence, 3 randomized trials have shaped our understanding of the potential value of FFR in patients who had already been committed to PCI on the basis of angiographic appearances. Thus, in DEFER (Deferral Versus Performance of Percutaneous Coronary Intervention of Functionally Nonsignificant Coronary Stenosis), there was no clinical outcome disadvantage to deferral of PCI, however severe the angiographic appearance, if the FFR was >0.75.[1] This observation has since been reproduced in larger randomized trials using PW indices.[15] In FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation),[2] which included patients already identified as having multivessel disease suitable for PCI, the arm randomized to FFR guidance had a better clinical outcomes despite receiving fewer stents in fewer lesions with less radiation and contrast compared with the angiogram-guided arm. In FAME2,[3] patients with FFR-positive lesions that were suitable for PCI had a worse clinical outcome if stenting was deferred compared with the group who received intervention, but this trial has an important limitation in that it was not blinded. We should note that the RIPCORD concept addresses the potential impact of FFR assessment at the stage of the diagnostic angiogram rather than in patients already triaged to PCI. In the third category of FFR literature, studies report the substantial impact of obtaining FFR data in cohorts of patients undergoing diagnostic angiography. These data are consistent and the effect is large, with a change in management between 21% and 48% of cases.[4,6] All these data build a plausible case that routine, systematic measurement of FFR should lead to substantial change in angiogram-guided decision making and patient management and improved clinical outcome, possibly at lower cost (as suggested by FAME in particular). Until now, no randomized trial has been available to test this hypothesis.

This is the first completed randomized trial to have used a strategy of systematic FFR for all vessels with a diameter suitable for revascularization. In FAMOUS NSTEMI (Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non-ST-Elevation Myocardial Infarction),[12] which had a much smaller population (n=350), patients were randomized to have assessment with angiography guidance alone or additional FFR of vessels that the operator considered to

Table 3. Management Plan for Trial Patients

	Angiography (n=552)	Angiography+ FFR (n=548)	*P* value
Additional tests performed before declaration of management			
Any test, n/d=p%	81/552=14.7	10/548=1.8	<0.00001*
Magnetic resonance imaging	51/552=9.1	8/548=1.5	
Stress echocardiography	17/552=3.1	1/548=0.2	
Nuclear perfusion scan	5/552=0.9	0/548=0	
Repeat invasive angiography with FFR or OCT	4/552=0.7	0/548=0	
CT coronary angiography	3/552=0.4	0/548=0	
Exercise tolerance test	1/552=0.2	1/548=0.2	
Final management plan, n/d=p%			
Medical therapy	165/552=29.9	175/548=31.9	
PCI	336/552=60.9	308/548=56.2	0.20*
CABG	51/552=9.2	65/548=11.9	
Delay to management plan, d†			
75th Centile	0	0	
90th Centile	51	0	
95th Centile	92	3	
For PCI cases, n	336	308	
Coronary segments targeted for PCI, n/d=p%			
1	255/336=75.9	217/308=70.5	
2	63/336=18.8	67/308=21.8	0.08‡
3	16/336=4.8	21/308 - 6.8	
≥4	2/336=0.6	3/308=1.0	
For CABG cases, n	51	65	
Graft targets			
Missing data, n/d=p%	3/51=5.9	2/65=3.1	
1	3/51=5.9	2/65=3.1	
2	9/51=17.6	13/65=20.0	0.97‡
3	18/51=35.3	23/65=35.4	
4	12/51=23.5	18/65=27.7	
≥5	6/51=11.7	7/65=10.8	

CABG indicates coronary artery bypass graft surgery; CT, computed tomography; d, denominator; FFR, fractional flow reserve; n, numerator; OCT, optical coherence tomography; p, resulting percentage; and PCI, percutaneous coronary intervention.

*Pearson χ^2 test.

†Delay from randomization to declaration of the management plan.

‡Fisher exact test.

Table 4. Patient-Reported Symptoms, QoL, and Costs at 1 Year

Patient reporting at 1 y	Angiography (n=552)	Angiography+ FFR (n=548)	*P* value
EQ-5D VAS data available, n/d=p%	537/552=97.3	528/548=96.4	
Primary QoL outcome			
EQ5D VAS score, median (IQR)	75 (60–87)	75 (60–90)	0.88*
EQ-5D index data available, n/d=p%	538/552=97.5	528/548=96.4	
EQ-5D index score, median (IQR)	0.821 (0.664–1.0)	0.837 (0.668–1.0)	0.68*
CCS angina data available, n/d=p%	536/552=97.1	528/548=96.4	
CCS grade 0	377/536=69.0	372/528=70.5	0.744†
CCS grade 1	72/536=13.4	66/528=12.5	
CCS grade 2	60/536=11.2	56/528=10.6	
CCS grade 3	15/536=2.8	15/528=2.8	
CCS grade 4	12/536=2.2	19/528=3.6	
Hospital costs at 1 y			
Cost data available, n/d=p%	551/552=99.8	546/548=99.6	
Primary economic outcome			
Total hospital costs, median (IQR), UK£	4136 (2613–7015)	4510 (2721–7415)	0.137‡
Admitted patient care	3306 (1782–5219)	3702 (2162–5984)	
Accident and emergency	0 (0–155)	0 (0–163)	
Outpatient care	628 (308–1172)	600 (253–1240)	
Hospital costs, mean (SEM), UK£	5385 (222)	6515 (261)	
Total hospital costs, maximum, UK£	46 742	43 449	
Nights in hospital, median (IQR), n	2 (0–4)	2 (0–4)	
Outpatient visits, median (IQR), n	5 (2–10)	5 (2–11)	

CCS indicates Canadian Cardiovascular Score for Angina; d, denominator; FFR, fractional flow reserve; IQR, interquartile range; n, numerator; p, resulting percentage; QoL, quality of life; and VAS, visual analog scale.

*Mann-Whitney *U* test.

†Pearson χ^2 test.

‡Mann-Whitney U test.

have significant stenosis(es). The availability of FFR data did indeed have a profound effect on the decision making and management of the study population. Specifically, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the angiography-guided group (40 [22.7%] versus 23 [13.2%]; difference, 9.5% [95% CI, 1.4%–17.7%]; *P*=0.022). At 12 months, revascularization rates remained significantly lower in the FFR-guided group. These results contrast starkly with those we describe in RIPCORD 2, which had a sample size almost 3 times larger but with population that was made up of a mixture of stable patients and those with non–ST-segment–elevation MI and who had more variable patterns of coronary disease.

Another randomized trial, FUTURE (Functional Testing Underlying Coronary Revascularization), attempted to

Table 5. Clinical Events

Clinical events at 1 y	Angiography (n=552)		Angiography+FFR (n=548)		Hierarchical risk difference (95% CI), %	*P* value
	All events, n	Hierarchical, n/d=p%	All events, n	Hierarchical, n/d=p%		
Death	5	5/552=0.91	8	8/548=1.46	0.55 (−0.84, 2.04)	
Stroke	3	8/552=1.45	4	12/548=2.19	0.74 (−0.93, 2.49)	
MI	23	30/552=5.43	22*	31/548=5.66	0.22 (−2.54, 2.99)	
Unplanned revascularization	26†	48/552=8.7	33†	52/548=9.49	0.79 (−2.63, 4.23)	
Hierarchical MACEs		48/552=8.7		52/548=9.5	0.79 (−2.63, 4.23)	0.64‡

The table shows the total number of events (of each type) experienced by patients in the 2 randomized groups. In the hierarchical analysis, we present the number of patients experiencing at least 1 event ordered by event severity (death; stroke; MI; unplanned revascularization). The MACE *P* value is from the log-rank test for time to the first event. Event curves are presented in Figure 3. d indicates denominator; FFR, fractional flow reserve; MACE, major adverse cardiovascular event; MI, myocardial infarction n, numerator; and p, resulting percentage.

*One patient experienced 2 MI events.

†Three patients in each group experienced 2 unplanned revascularizations.

‡Log-rank test for time to first event.

address a question similar to that addressed in RIPCORD 2 but was terminated early because of initial concern that there was excess mortality in 1 arm, although this was not subsequently confirmed.[16] The aim of FUTURE was to randomize patients with stable angina who had at least 2 coronary stenoses of ≥50% to angiographic guidance alone or FFR plus angiogram guidance. The trial was stopped after 864 patients were recruited (of a planned 1728 population) and reported that the performance of FFR resulted in a lower rate of PCI (71% versus 79%) and a higher rate of OMT alone (17% versus 9%), whereas there was no difference in the rate of CABG. However, other than the original concern about all-cause mortality, clinical outcomes were not significantly different between the groups. The latter result is consistent with that of RIPCORD 2. However, in contrast to FUTURE, we did not find a significant difference in the overall distribution of medically treated or revascularized patients.

Given the previous body of evidence demonstrating clinical value of FFR measurement, the results of RIPCORD 2 may be considered surprising and perhaps even counterintuitive. In fact, the clinical outcome is consistent

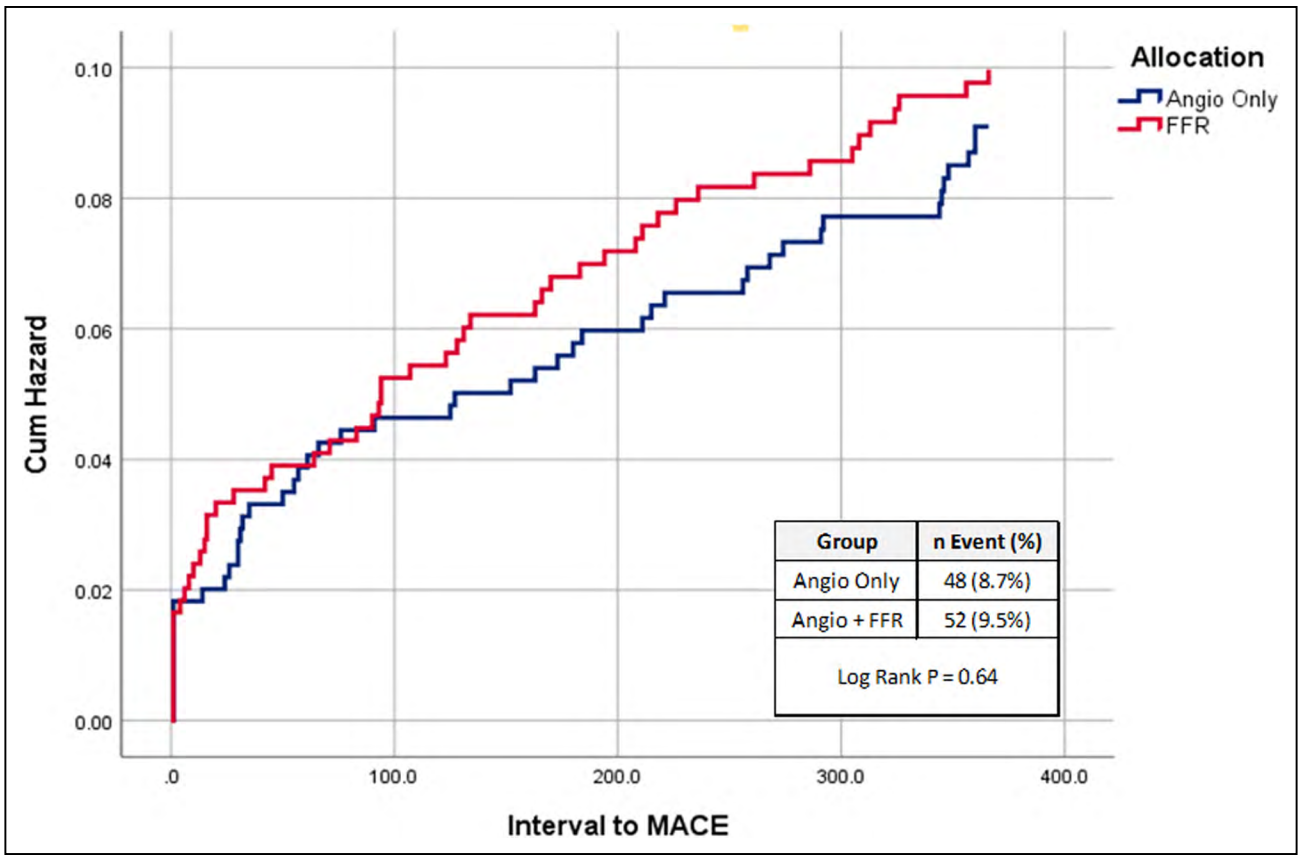

Figure 3. Event curves showing the time to the first MACE from randomization.
Angio indicates angiography; Cum Hazard, cumulative hazard; FFR, fractional flow reserve; and MACE, major adverse cardiovascular event.

Table 6. Subgroup Analyses for the Primary QoL and Economic Outcomes

	Angiography (n=552)	Angiography+FFR (n=548)	*P* value
Subgroups: patient reporting at 1 y			
EQ-5D VAS data available, n/d=p%	537/552=97.3	528/548=96.4	
EQ-5D VAS score, median (IQR)			
Male (n=829)	75 (60–90)	80 (60–90)	0.81*
Female (n=271)	75 (60–80)	75 (50–85)	
ACS presentation (n=568)	80 (60–90)	80 (60–90)	0.79*
Elective presentation (n=532)	75 (60–80)	75 (51–85)	
Angiographic 0-vessel disease (n=299)	75 (60–85)	75 (50–85)	0.03*
Angiographic 1-vessel disease (n=483)	80 (65–88)	79 (60–90)	
Angiographic 2-vessel disease (n=220)	75 (55–85)	80 (65–90)	
Angiographic 3-vessel disease (n=98)	78 (60–90)	80 (70–90)	
Angiographic 2-vessel disease, mean	*70*	*75*	
Angiographic 3-vessel disease, mean	*73*	*78*	
Subgroups: hospital costs at 1 y			
Hospital cost available, n/d=p%	551/552=99.8	546/548=99.6	
Total hospital costs, median (IQR), UK£			
Male (n=829)	4179 (2578–7093)	4537 (2810–7375)	0.48*
Female (n=271	4099 (2617–6657)	4424 (2418–7510)	
ACS presentation (n=568)	5216 (3635–7779)	5673 (4198–8850)	0.92*
Elective presentation (n=532)	2798 (1832–5420)	2847 (1848–5421)	
Angiographic 0-vessel disease (n=299)	3934 (1757–5868)	3370 (1509–6028)	0.18*
Angiographic 1-vessel disease (n=483)	4095 (2765–5999)	4401 (2998–6453)	
Angiographic 2-vessel disease (n=220)	5039 (3052–8645)	5104 (3424–11 082)	
Angiographic 3-vessel disease (n=98)	10 892 (5114–13 322)	10 770 (4527–16 169)	

ACS indicates acute coronary syndrome; d, denominator; IQR, interquartile range; n, numerator; p, resulting percentage; QoL, quality of life; and VAS, visual analog scale.

*Interaction test.

with several other randomized trials that also examined the value of routine assessment of surrogates for myocardial ischemia. First, FLOWER MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction), which assessed FFR-guided revascularization of nonculprit disease in patients undergoing primary PCI for ST-segment–elevation MI versus angiographic guidance alone, showed no difference in outcome between the groups.[17] Second, the recently presented FORECAST trial (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain),[18] which randomized 1400 patients with stable chest pain to usual care assessment or routine CT coronary angiography plus FFR_{CT}, reported no clinical outcome advantage for the test strategy apart from a reduction in the need for invasive angiography. Last, our result is consistent with the overall outcome in the truncated FUTURE trial, as described previously. We did observe an association between the extent of coronary artery disease and QoL such that the FFR strategy was associated with better QoL in patients with more widespread disease. However, there was no difference in the rate of revascularization or in clinical events at 1 year, although the trial was not powered to detect a difference in these secondary outcomes.

Given that information derived with FFR can be beneficial for directing PCI and that the FFR status is associated with risk of ischemic events, how is it possible that systematic assessment of all coronary vessels with FFR at the diagnostic angiogram stage has no overall benefit? One explanation may be that this is a reflection of the relative importance of the total burden of atheroma versus the burden of ischemia. An algorithm that follows the detection of a significant burden of coronary atheroma by the application of optimal disease-modifying medical therapy yields prognostic benefit, as shown in SCOT HEART (Scottish Computed Tomography of the Heart),[19] for example. Furthermore, in stable patients, there is no additional prognostic benefit to revascularization once OMT has been applied.[20] In contrast, in patients with non–ST-segment–elevation MI, there is clearcut benefit from angiographically guided revascularization at the index admission, regardless of an assessment of ischemic burden. Given these data, it is possible that RIPCORD 2

may be revealing the relative importance of these well-established management principles within which vessel-specific ischemia detection is of much lower value at the population level. This does not downgrade the evidence for benefit of FFR at directing PCI strategy in particular. However, at the diagnostic angiogram stage, unselected application of a technology that determines lesion-level ischemia apparently carries less importance. It would be reasonable to assume from all previous data that some patients in RIPCORD 2 angiography alone arm had inexact revascularization because the angiographic assessment would have been misleading with regard to vessel-specific targeting of stents or bypass grafts. Yet this has not apparently outweighed the overall value of the OMT plus tailored, angiographically guided treatment in the group as whole. The FFR strategy has, however, been associated with longer procedure times, greater use of contrast and radiation, and a small but typical rate of PW related complications. There is certainly no evidence of cost saving with a strategy of systematic FFR assessment.

This trial has a number of limitations. First, there was no blinding. This raises the possibility of investigator bias: The knowledge that patients were being assessed by FFR in 1 arm may have had an influence on the degree of scrutiny afforded to the angiographic assessment of patients in the other group. Quantitative coronary angiography was not used. This could also have had some influence on management decision making. Second, we recruited a heterogeneous population of stable patients and those with non–ST-segment–elevation MI. This was done for pragmatic reasons relating to realistic speed of recruitment. Third, the trial was powered for hospital-related costs and QoL but not for clinical events. Our power calculation for hospital costs proved accurate in terms of the resulting point estimate but underestimated the spread of the data, and this affected power for this outcome. Furthermore, the cost model did not include resource use in nonhospital settings such as cardiac medications, general practitioner visits, and investigations. Fourth, the primary outcomes in RIPCORD 2 were assessed after only 1 year. It is possible that a difference in clinical outcome will emerge between the groups as follow-up time is extended. Fifth, QoL and symptom status were not measured at baseline, so we cannot comment on any potential within-patient changes during the trial period. We have no systematic information about prerandomization and functional tests. Sixth, we did not document prerandomization tests for ischemia, which may have guided the management strategy. Last, our observation that 20% (283 of 1383) of patients who were otherwise eligible after the angiogram were considered not to be suitable for the FFR assessment by the investigator represents an important limitation with regard to practical application of the test strategy. This may have considerable relevance in real-life clinical practice.

Conclusions

Routine FFR assessment of all epicardial vessels of graftable or stentable diameter at the time of diagnostic angiography in patients with stable chest pain or after admission with non–ST-segment–elevation acute coronary syndromes is cost neutral compared with angiographic guidance alone and is not associated with significant differences in QoL or angina status at 1 year. This strategy therefore has no overall advantage compared with angiography alone.

ARTICLE INFORMATION

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Supplemental Material

Appendix A: Patient Inclusion and Exclusion Criteria

Appendix B: Determination of Clinical Events Using UK Hospital Episode Statistics

Appendix C: Additional Information on the Power Calculation

Appendix D: Post Hoc Subgroup Analysis Excluding Patients With no Angiographic Evidence of Flow-Limiting Disease at Initial Angiographic Assessment

Appendix E: Information on 2222 Individual FFR Measurements Made in Patients Randomized to FFR Assessment

Appendix F: Patient Recruitment and Trial Centers

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