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

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ABSTRACT

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

Methods: We performed an open label, randomised, controlled trial in 17 UK centres, recruiting 1100 patients undergoing ICA for the investigation of stable angina or non-ST elevation MI. Patients were randomised to either angiography alone (***Angiography***) or angiography with systematic pressure wire assessment of all epicardial vessels greater than 2.25mm in diameter (***Angiography + FFR)***. The co-

primary outcomes, assessed at one year, were (a) NHS hospital costs & (b) quality of life (QoL). Pre-specified secondary outcomes included clinical events.

Results: In the ***Angiography + FFR***arm, the median(IQR) number of vessels examined was 4 (3-5). The median(IQR) hospital costs were similar: ***Angiography***£4136 (2613-7015), ***Angiography + FFR***£4510 (2721-7415); P=0.137. There was no difference in median(IQR) QoL using the visual analogue scale (VAS) of the EuroQol EQ-5D-5L: ***Angiography***75 (60-87), ***Angiography + FFR***75 (60-90); P=0.88. The number of clinical events were (death 5 v 8; stroke 3 v 4; myocardial infarction 23 v 22; unplanned revascularisation 26 v 33) with a composite, hierarchical event rate of ***Angiography***=8.7% (48/552) vs. ***Angiography + FFR***=9.5% (52/548); P=0.64.

Conclusions: A strategy of systematic FFR assessment, when compared with angiography alone, did not result in a significant reduction in cost or improvement in QoL.

Clinical Trials Registration: https://clinicaltrials.gov/ct2/show/NCT01070771

KEYWORDS

Coronary physiology; randomised control trial; coronary angiography; cost analysis; quality of life

Abbreviations

ACS	Acute Coronary Syndrome
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
CRF	Case Record Form
FFR	Fractional Flow Reserve
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group

ICA	Invasive Coronary Angiography
IQR	Inter-quartile Range
MI	Myocardial Infarction
NHS	National Health Service (UK)
OMT	Optimal Medical Therapy
PBPP	Public Benefit and Privacy Panel for Health and Social Care
PCI	Percutaneous Coronary Intervention
PW	Pressure Wire
QoL	Quality of Life
SD	Standard Deviation
TIMI	Thrombolysis in Myocardial Infarction
UK	United Kingdom
VAS	Visual Analogue Scale

Clinical Perspective

- This is the first completed randomised clinical trial to test, in patients undergoing diagnostic angiography, a strategy of systematic measurement of fractional flow reserve (FFR) in all vessels of sufficient calibre to be potential targets for revascularisation (a median of 4 vessels were examined in patients randomised to FFR).
- Use of FFR was associated with longer procedure duration, greater use of contrast and radiation and a pressure wire related complication rate of 1.8%.
- When compared to angiography alone, after one year of follow-up, use of FFR 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 would suggest that there is no benefit in a strategy of systematic evaluation of all vessels at the time of angiography.

Introduction

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 labelled as being suitable for percutaneous coronary intervention with stents (PCI) has been well described in a series of randomised trials.[1,2,3] Based upon these data, as well as clinical studies demonstrating significant changes in the way patients are treated when pressure wire assessment is employed during diagnostic angiography,[4,5,6] current guidelines recommend using fractional flow reserve (FFR) for the functional assessment of lesion severity in patients with intermediate-grade coronary artery disease (typically 40 – 90% stenosis) without evidence of myocardial ischaemia in non-invasive testing, or in those with multivessel disease.[7] The RIPCORD concept proposes routine pressure wire assessment of all epicardial vessels that are of a calibre amenable to revascularization at the stage of diagnostic angiography, and specifically, before the patients are triaged to optimal medical therapy alone (OMT), or additional revascularisation 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 randomised trial, to improve clinical outcomes when compared to conventional management.

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

RIPCORD2 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 utilisation, quality of life and clinical outcomes when compared to 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, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Ethical 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 Research Governance guidelines. The study protocol, patient information sheet, and consent form were approved by the National Research Ethics Service before commencing the trial (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 https://clinicaltrials.gov ;unique identifier NCT02892903.

Trial Oversight

The trial was investigator-initiated and funded by an unrestricted research grant from Boston Scientific Corporation. 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: (a) it was conducted in a manner consistent with the protocol, (b) the data were complete, and (c) the analyses were performed according to a prespecified plan. The sponsor was University Hospital Southampton NHS Trust.

Study Design and Population: RIPCORD2 is an open label, prospective, randomised, controlled trial. The rationale for, and design of, the study have been previously described.[10] In brief, patients with either stable angina or non-ST elevation 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. [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 randomisation. A key inclusion criterion was the presence, by visual assessment, of at least one stenosis of 30% or greater narrowing in a coronary vessel of calibre suitable for either PCI or a bypass graft.

Randomisation: This was performed in the catheter laboratory, after angiography. Investigators were required to report the reasons why consented patients did not proceed to randomisation. Eligible patients were randomised using a web interface secured by password access. Patient registration by initials, date of birth and unique study number were required before the release of an allocation. Randomisation tables were prepared by the trial coordinating centre, with allocation stratified by centre 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 randomisation option, using opaque, serial-numbered, sealed envelopes was provided but was only used for 11 patients, in 5 different centres.

Study Methods: In patients randomised to FFR assessment after angiography (***Angiography + FFR***, FFR measurement was then performed in all coronary arteries of sufficient calibre for PCI or placement of a bypass graft conduit, examining all major vessels and branches irrespective of the presence or absence of atheroma. Occluded and sub-occluded vessels, with Thrombolysis in Myocardial Infarction (TIMI) grade flow of less than 3, were not examined. All FFR measurements were made after administration of intracoronary nitrate and during hyperaemia induced by either intracoronary or intravenous adenosine, according to operator discretion. An FFR of ≤0.80 was considered to be positive. Any pressure wire 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. Prior to the start of RIPCORD2, the COMET wire accuracy and drift were investigated in a randomised trial. [11]

Trial data were recorded in a bespoke case record form (CRF), presented via a secure online web interface. The CRF enforced detailed tracking of clinical and adverse events from randomisation to hospital discharge or 24 hours (whichever was the 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 for further discussion. The nature of additional tests performed was recorded in the CRF.

Patients were contacted at one year and angina symptoms recorded using the Canadian Cardiovascular Society (CCS 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 randomisation. This was received via a download of Hospital Episode Statistics (HES) data from NHS Digital in England. Equivalent datasets were obtained from NHS Wales informatics services and from the Public Benefit and Privacy Panel for Health and Social Care (PBPP) in Scotland, to ensure UK-wide follow up. Office for National Statistics mortality data was obtained from NHS digital and the PBPP.

Outcome Measures: The trial had co-primary endpoints: (a) total hospital cost, and (b) quality of life (QoL). The primary economic outcome measure reports hospital costs from, and including, the index admission to any hospital episode starting within 365 days after randomisation. All inpatient admissions, outpatient visits and attendances at accident and emergency departments were included. Costs were calculated using the NHS tariff system. Codes from individual episodes were entered into a standardised 'grouper program' (NHS Digital HRG4+ Payment Grouper 19/20) that returns Healthcare Resource Group (HRG) designations which can then be allocated costs from relevant NHS tariff reference values. Costs incurred in respect of 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 in primary care, routine medications or societal costs were not included.

The primary quality of life outcome was a comparison of the visual analogue scale (VAS) reported on completion of the EQ-5D-5L instrument at 1 year. This is a validated, international, generic measure of quality of life. Use of a generic tool allows for a more holistic assessment of the impact of medical care including, for example, general recovery from interventions and the potential impact of non-cardiac complications. Prespecified subgroup analysis for the primary outcomes was performed in relation to (i) the sex of the patient, (ii) the initial presentation (stable versus ACS) and (iii) the angiographic (pre-FFR) investigator-reported distribution of the obstructive coronary artery disease,

classified as one, two and three vessel, 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, myocardial infarction (MI) and unplanned revascularisation. For patients admitted with an acute coronary syndrome, MI adjudication required evidence of re-infarction or a distinct new MI event after randomisation. Unplanned revascularisation 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 HES data. An explanation of the methodology used is presented in Appendix B.

Resource utilisation in the angiography phase, the management plan recommended for patients and angina symptoms by CCS grade were also reported.

Statistical Methods and Power Calculations: All analyses were performed on an intention to treat basis on the randomised population, using SPSS version 26 (IBM). All comparative testing was two-sided. A P value of ≤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 inter-quartile range (IQR). Comparisons were made with the Mann-Whitney U Test for medians. Discrete variables were reported as numbers and proportion, and compared by the Pearson Chi Square test or Fisher's exact test if the number of observations in any group was 5 or fewer. 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, revascularisation). The absolute risk difference in hierarchical event rates is presented with the 95% confidence interval (CI), calculated by the method of Newcombe. The time to the first adverse clinical event in each patient was compared using the log rank test. Subgroup analyses were performed for the primary economic and QoL outcomes using a regression interaction test.

The detail of the power calculation has been previously reported[10] and is available in full in Appendix C. In brief, we assumed an average baseline cost of £4615, and expected a wide standard deviation (SD) (£1850). Conventional calculations suggest a sample size of 1030 subjects would provide 80%

power at an alpha of 0.05, to detect an absolute change of 7% (£325). Because of expected non-parametric data, we increased the sample size to 1100. Given the nature of the tracked HES data, we expected almost complete data. In terms of the EQ-5D-5L data, we assumed a baseline mean (SD) score of 74.3 (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 randomised at 17 UK centres between 29/09/2016 and 15/06/2018. Details of the centres and the recruitment numbers are available in Appendix D. Figure 1 summarises patient flow in the trial. After 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 283/718 (39.5%) and the reasons declared are presented in Figure 1. A total of 1100 patients were randomised, 552 to ***Angiography***and 548 to ***Angiography + FFR***. Adherence to the randomised investigation strategy, patient retention and evaluable data at one year was good (Fig 1). Economic and clinical event data were obtained in 551/552 (99.8%) of the ***Angiography***arm and 546/548 (99.6%) of the ***Angiography + FFR***arm, and QoL data were complete in ***Angiography***537/552 (97.3%) and ***Angiography + FFR***528/548 (96.4%).

The baseline characteristics of the patients were similar between the randomised groups (Table 1). Just over half the population were recruited in the context of non-ST elevation MI. The mean age was 64 years, about 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 (IQR) BCIS Jeopardy Score was 2 (0-6).[12]

Information from the cath lab procedures is presented in Table 2. For patients randomised to ***Angiography + FFR***the median ((IQR) number of vessels tested using FFR was 4 (3-5). Over 85% of these cases involved the use of a single pressure wire. In the ***Angiography + FFR***group, cases were longer in duration, involved more radiation exposure and greater use of radiographic contrast

(P<0.001); (Table 2). The rate of pressure wire-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 supplementary material.

Table 3 summarises information about the management plan declared for the trial patients. In the ***Angiography + FFR***group investigators were able, immediately after the catheter laboratory procedure, to declare the definitive management plan in more than 98% of cases. By 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 randomisation to declaration of the final management plan, with 10% of the ***Angiography*** group having a delay of more than 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 revascularisation, no significant differences in the plan for the number of segments (PCI) or vessels (CABG) to be treated.

Co-Primary Quality of Life Outcome. There were no differences in the primary QoL outcome of median (IQR) EQ5D VAS score: ***Angiography*** 75 (60, 87) versus ***Angiography + FFR*** 75 (60, 90); P=0.88. The EQ5D index score, used in utility calculation, was also very similar for the groups, as was the pattern of angina symptoms reported by CCS classification. (Table 4)

Co-Primary Total Hospital Cost Outcome. The median (IQR) total hospital cost over the period was similar for the two groups: ***Angiography*** £4136 (2613, 7015) v ***Angiography + FFR*** £4510 (2721, 7415); P=0.137. There were no differences in terms of inpatient and outpatient cost, nights in hospital or the number of outpatient visits. (Table 4)

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

The results of the pre-specified sub-group 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 CAD and QoL, such that QoL was better, for patients with more significant disease, 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 one obstructive lesion at initial angiographic assessment, showed similar findings and is presented in the supplementary information.

Discussion

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

Given the prior evidence supporting FFR-guided management used selectively, a randomised 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: (a) observation regarding the association between FFR level and subsequent ischaemic clinical event rates; (b) randomised trials assessing the value of FFR guidance, as compared with angiographic guidance alone, in patients with established coronary artery disease who had already been committed to PCI and (c) 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 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 randomised trials have shaped our understanding of the potential value of FFR in patients who had already been committed to PCI based upon angiographic appearances. Thus, in DEFER, there was no clinical outcome disadvantage to deferral of PCI, however severe their angiographic appearance, if the FFR was >0.75.[1] This observation has since been reproduced in larger randomised trials using PW indices.[15] In FAME,[2] which included patients already identified as having multivessel disease suitable for PCI, the arm randomised to FFR guidance had a better clinical outcomes despite receiving fewer stents in

fewer lesions, with less radiation and contrast, when compared to 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 to the group who received intervention, but this trial has an important limitation in that it was not blinded. Notably, 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 in between 21-48% 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, patient management and improved clinical outcome, possibly at lower cost (as suggested by FAME, in particular). Until now there has been no randomised trial available to test this hypothesis.

This is the first completed randomised trial to have employed a strategy of systematic FFR for all vessels of diameter suitable for revascularisation. In FAMOUS NSTEMI, [12] which had a much smaller population (n=350), patients were randomised to have assessment using angiography guidance alone or additional FFR of vessels that the operator considered to 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%) vs. 23 (13.2%), difference (95% CI): 9.5% (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 RIPCORD2, which had a sample size almost 3 times larger, but whose population was made up of a mixture of stable patients and those with non-ST elevation MI and who had more variable patterns of coronary disease.

Another randomised trial, FUTURE, attempted to address a similar question to RIPCORD2, but was terminated early because of initial concern that there was excess mortality in one arm, although this

was not subsequently confirmed.[16] The aim of FUTURE was to randomise patients with stable angina who had at least 2 coronary stenoses of 50% or greater to angiographic guidance alone or FFR plus angiogram guidance. The trial was stopped after recruiting 864 (out of a planned 1728 population) and reported that the performance of FFR resulted in a lower rate of PCI (71% vs 79%) and a higher rate of optimal medical therapy alone (17% vs 9%) whilst 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 RIPCORD2. However, in contrast to FUTURE, we did not find a significant difference in the overall distribution of medically treated or revascularised patients.

Given the previous body of evidence demonstrating clinical value of FFR measurement, the results of RIPCORD2 may be considered surprising and perhaps, even, counterintuitive. In fact, the clinical outcome is consistent with several other randomised trials that also examined the value of routine assessment of surrogates for myocardial ischaemia. For example, FLOWER MI, which assessed FFR-guided revascularisation of non-culprit disease in patients undergoing primary PCI for ST-elevation MI versus angiographic guidance alone, showed no difference in outcome between the groups.[17] Secondly, the recently presented FORECAST trial,[18] which randomised 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. Finally, our result is consistent with the overall outcome in the truncated FUTURE trial, as described above. We did observe an between the extent of coronary artery disease and quality of life, 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 revascularisation 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 using FFR can be beneficial for directing PCI, and that the FFR status is associated with risk of ischaemic events, how is it possible that systematic assessment of all coronary vessels using 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 ischaemia. 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[19], for example. Further, in stable patients, there is no additional prognostic benefit to revascularisation once OMT has been applied.[20] In contrast, in NSTEMI patients there is clear cut benefit from angiographically guided revascularisation at the index admission, regardless of an assessment of ischaemic burden. Given these data, it is possible that RIPCORD2 may be revealing the relative importance of these well- established management principles, within which vessel-specific ischaemia 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. But, at the diagnostic angiogram stage, unselected application of a technology that determines lesion-level ischaemia apparently carries less importance. It would be reasonable to assume, based upon all previous data, that some patients in RIPCORD2 angio alone arm had inexact revascularisation 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. Firstly, there was no blinding. This raises the possibility of investigator bias: the knowledge that patients were being assessed by FFR in one 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 have also had some influence on management decision-making. Second, we recruited a heterogeneous population of stable patients and those with non-ST elevation MI. This was done for pragmatic reasons relating to realistic speed of recruitment. Third, the trial was powered for hospital-related costs and quality of life, but not for clinical events. Our power calculation for hospital costs proved accurate in terms of the resulting

point estimate but under-estimated the spread of the data and this impacted power for this outcome. Further, the cost model did not include resource utilisation in non-hospital settings such as cardiac medications, GP visits and investigations. Fourth, the primary outcomes in RIPCORD2 were assessed after only one 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 pre-randomisation and functional tests. Sixth, we did not document pre-randomisation tests for ischaemia which may have guided the management strategy. Finally, our observation that 20% (283 of 1383) 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.

In conclusion, 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 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 to angiography alone.

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Conflict of Interest Disclosures

CB is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, Genentech, GSK, HeartFlow, Menarini, Neovasc, Siemens Healthcare, and Valo Health.

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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 Centres

Table 1: Baseline Characteristics

	Angiography	**Angiography plus FFR**
	n = 552	**n = 548**
Age - mean (SD)	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)	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% [a]	276/548 = 50.4%
eGFR - mean (SD)	77.2 (13.2)	76.9 (13.0)
LV Function (n/d = p%) [b]		
EF ≥ 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%)		
Previous Myocardial Infarction	129/551 = 23.4% [c]	117/546 = 21.4% [d]
Previous PCI	140//552 = 25.4%	147/547 = 26.9% [e]
Any Smoking	356/548 = 65.0% [f]	316/542 = 58.5% [g]
Hypertension	294/550 = 53.5% [h]	315/547 = 57.6% [i]
Hyperlipidaemia	317/550 = 57.6% [j]	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%	48/552 = 8.7%	43/548 - 7.8%
Proximal LAD Reported >70%	97/552 = 17.6%	95/548 = 17.3%
BCIS Jeopardy Score - median (IQR)	2 (0 - 6)	2 (0 - 6)

Missing Data:
a - 2 cases: b - Angio 234 cases, FFR 262 cases: c - 1 case: d -- 2 cases: e - 1 case
f -4 cases: g = 6 cases: h - 2 cases: I - 1 case: j - 2 cases

FFR - fractional flow reserve: SD - standard deviation: IQR - inter-quartile range: Tx - treatment: ACS - acute coronary syndrome: eGFR - estimated glomerular filtration rate: LV - left ventricular: PCI - percutaneous coronary intervention: LAD - left anterior descending coronary artery: BCIS - British Cardiovascular Interventional Society:

Table 2: Procedural Details

	Angiography	**Angiography plus FFR**	**P value[d]**
	n = 552	**n = 548**	
Procedure Time (mins) - mean (SD) [a]	42.4 (27.0)	69.0 (27.0)	<0.001
Contrast Used (mls) - mean (SD) [a]	146.3 (87.0)	206.0 (96.2) [b]	<0.001
Radiation Dose (cGy/cm^2) - mean (SD)	5029.7 (5540.6)	6608.7 (5292.3) [b]	<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% [b c]	8/547 = 1.5% [b]	
Number of Vessels Examined With FFR			
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%	

a Figures relate to total use in the index procedure b Missing Data: - 1 case
c Intracoronary imaging was used in 5 cases before declaration of the Tx plan (a protocol violation)
d Mann Whitney U Test
* MI event with typical pain, acute ECG change and subsequent rise in Troponin - managed conservatively

SD - standard deviation: IQR - inter-quartile range: PW = pressure wire: FFR - fractional flow reserve: CABG - coronary artery bypass graft surgery: PCI = percutaneous *coronary intervention: MI - myocardial infarction: Tx - treatment:*

Table 3: Management Plan for Trial Patients

Additional Tests Performed Before Declaration of Management (n/d = p%)	**Angiography**	**Angiography plus FFR**	**P Value**
	n = 552	**n = 548**	
Any Test	81/552 = 14.7%	10/548 = 1.8%	<0.00001 [a]
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 Angio 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%	

FFR - fractional flow reserve: OCT - optical coherence tomography: CT - computer tomography:

Final Management Plan	**Angiography**	**Angiography plus FFR**	**P Value**
	n = 552	**n = 548**	
Medical Therapy (n/d = p%)	165/552 = 29.9%	175/548 = 31.9%	
PCI (n/d = p%)	336/552 = 60.9%	308/548 = 56.2%	0.20 [a]
CABG (n/d = p%)	51/552 = 9.2%	65/548 = 11.9%	
Delay to Management Plan (days)[c]			
75th Centile	0	0	
90th Centile	51	0	
95th Centile	92	3	
For PCI Cases (n/d = p%)	n = 336	n = 308	

Coronary Segments Targeted for PCI			
1	255/336 = 75.9%	217/308 = 70.5%	
2	63/336 - 18.8%	67/308 = 21.8%	0.08 [b]
3	16/336 = 4.8%	21/308 - 6.8%	
4 or more	2/336 = 0.6%	3/308 = 1.0%	
For CABG Cases (n/d = p%)	n = 51	n = 65	
Number of Graft Targets			
Missing data	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 [b]
3	18/51 = 35.3%	23/65 = 35.4%	
4	12/51 = 23.5%	18/65 = 27.7$	
5 or more	6/51 = 11.7%	7/65 = 10.8%	
a Pearson Chi Square Test b Fisher's Exact Test			
c Delay from randomisation to declaration of the management plan			

Table 4 Patient Reported Symptoms, Quality of Life and Costs at One Year

Patient Reporting at One Year	Angiography	Angiography plus FFR	P Value
	n = 552	n = 548	
EQ5D 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 [a]**
EQ5D Index Data Available (n/d = p%)	538/552 = 97.5%	528/548 = 96.4%	
EQ5D Index Score - median (IQR)	0.821 (0.664 - 1.0)	0.837 (0.668 - 1.0)	0.68 [a]
CCS Angina Data Available (n/d = p%)	536/552 = 97.1%	528/548 = 96.4%	
CCS 0	377/536 = 69.0%	372/528 = 70.5%	0.744 [b]
CCS 1	72/536 = 13.4%	66/528 = 12.5%	
CCS 2	60/536 = 11.2%	56/528 = 10.6%	
CCS 3	15/536 = 2.8%	15/528 = 2.8%	
CCS 4	12/536 = 2.2%	19/528 = 3.6%	

a Mann-Whitney U Test b Pearson Chi Square Test			
FFR - fractional flow reserve: EQ5D - EuroQual Patient-reported Outcome Measure: VAS - visual analogue scale: IQR - inter-quartile range: CCS - Canadian Cardiovascular Score for Angina			
Hospital Costs at One Year	**Angiography**	**Angiography plus FFR**	**P Value**
	n = 552	**n = 548**	
Cost Data Available (n/d = p%)	551/552 = 99.8%	546/548 = 99.6%	
Primary Economic Outcome			
Total Hospital Costs UK£ - median (IQR)	**4136 (2613 - 7015)**	**4510 (2721 - 7415)**	**0.137 [a]**
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)	
Total Hospital Costs UK£ - mean (SEM)	5385 (222)	6515 (261)	
Total Hospital Costs UK£ - max	46742	43449	
Nights in Hospital - median (IQR)	2 (0 - 4)	2 (0 - 4)	
Outpatient visits - median (IQR)	5 (2 - 10)	5 (2 - 11)	
a Mann-Whitney U Test			
FFR - fractional flow reserve: IQR - inter-quartile range: UK - United Kingdom			

Table 5: Clinical Events

Clinical Events at One Year	Angiography n=552		Angiography plus FFR n=548		Hierarchical Risk Difference % (95%CI)	P Value
	All Events	Hierarchical	All Events	Hierarchical		
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)	
Myocardial Infarction	23	30/552 = 5.43%	22[a]	31/548 = 5.66%	0.22% (-2.54, 2.99)	
Unplanned Revascularisation	26[b]	48/552 = 8.7%	33[b]	52/548 = 9.49%	0.79% (-2.63, 4.23)	
Hierarchical MACE[d]		48/552 = 8.7%		52/548 = 9.5%	0.79% (-2.63, 4.23)	0.64[c]

a One patient experienced 2 x MI events b Three patients in each group experienced 2 x unplanned revascularisations

c Log Rank Test for time to first event d Major Adverse Cardiovascular Event

FFR - fractional flow reserve:

The table shows the total number of events (of each type) experienced by patients in the two randomised groups.
In the hierarchical analysis, we present the number of patients experiencing at least one event, ordered by event severity (death; stroke; myocardial infarction; unplanned revascularisation).
The MACE P value is from the log rank test for time to the first event. Event curves are presented at Fig 3

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

Subgroups: Patient Reporting at One Year	**Angiography**	**Angiography plus FFR**	**P Value**
	n = 552	**n = 548**	
EQ5D VAS Data Available (n/d = p%)	537/552 = 97.3%	528/548 = 96.4%	
EQ5D VAS Score - median (IQR)			
Male (n = 829)	75 (60 - 90)	80 (60 - 90)	0.81 [a]
Female (n = 271)	75 (60 - 80)	75 (50 - 85)	
ACS Presentation (n = 568)	80 (60 - 90)	80 (60 - 90)	0.79 [a]
Elective Presentation (n = 532)	75 (60 - 80)	75 (51 - 85)	
Angiographic 0 Vessel Disease (n = 299)	75 (60 - 85)	75 (50 - 85)	0.03 [a]
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 One Year	**Angiography**	**Angiography plus FFR**	**P Value**
	n = 552	**n = 548**	
Hospital Cost Available (n/d = p%)	551/552 = 99.8%	546/548 = 99.6%	
Total Hospital Costs UK£ - median (IQR)			
Male (n = 829)	4179 (2578 - 7093)	4537 (2810 - 7375)	0.48 [a]
Female (n = 271	4099 (2617 - 6657)	4424 (2418 - 7510)	
ACS Presentation (n = 568)	5216 (3635 - 7779)	5673 (4198 - 8850)	0.92 [a]
Elective Presentation (n = 532)	2798 (1832 - 5420)	2847 (1848 - 5421)	
Angiographic 0 Vessel Disease (n = 299)	3934 (1757 - 5868)	3370 (1509 - 6028)	0.18 [a]
Angiographic 1 Vessel Disease (n = 483)	4095 (2765 - 5999)	4401 (2998 - 6453)	

Angiographic 2 Vessel Disease (n = 220)	5039 (3052 - 8645)	5104 (3424 - 11082)
Angiographic 3 Vessel Disease (n = 98)	10892 (5114 - 13322)	10770 (4527 - 16169)
ACS - Acute Coronary Syndrome		
a Interaction Test		
FFR - fractional flow reserve: EQ5D - EuroQual Patient-reported Outcome Measure: VAS - visual analogue scale: IQR - inter-quartile range: CCS - Canadian Cardiovascular Score for Angina: UK - United Kingdom		

Figure Legends

Figure 1

Patient flow in the trial

Figure 2

Relationship between individual vessel assessment by visual angiographic appearance (estimated diameter stenosis %) and fractional flow reserve (FFR) for each lesion

Figure 3

Event curves showing the time to the first MACE event from randomisation

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