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

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ABSTRACT

Aims: 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 and Results: 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. Pre-specified secondary outcomes included clinical events.

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.

KEYWORDS

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

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 patient 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 RIPCORDER 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 RIPCORDER study⁸ 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.

RIPCORDER2 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: RIPCORDER2 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 RIPCORDER2, 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 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 $\geq 50\%$ in the left main stem or by $\geq 70\%$ 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 reported¹⁰ and is available in full in Appendix C. In brief, we assumed an average baseline cost of £4615, and expected a wide standard deviation (£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).

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.

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 both FFR and iFR.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 RIPCORDER 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 RIPCORDER2, 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 RIPCORDER2, 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 RIPCORDER2. 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 RIPCORDER2 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 association 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 HEART¹⁹, 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 RIPCORDER2 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 or iFR 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 RIPCORDER2 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 RIPCORDER2 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. Nor did systematic FFR of all epicardial coronary vessels significantly alter the distribution of management, or the clinical event rate. This strategy therefore has no overall advantage compared to angiography alone.

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All other authors have presented no disclosures.

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

¹ Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*. 2001;103:2928–2934.

² Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engström T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56:177–184. doi: 10.1016/j.jacc.2010.04.012.

³ De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001. doi: 10.1056/NEJ-Moa1205361.

⁴ Nagaraja V, Mamas M, Mahmoudi M, Rogers C, Curzen N. Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: how consistent is the effect? *Cardiovasc Revasc Med*. 2017;18:320–327. doi: 10.1016/j.carrev.2017.01.014.

⁵ Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee MM, Shaikat A, O'Donnell A, Nam J, Briggs A, Henderson R, McConnachie A, Berry C; FAMOUS – NSTEMI investigators. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015;36:100–111.

⁶ Van Belle E, Gil R, Klauss V, Balgith M, Meuwissen M, Clerc J, Witzendichler B, Cercek M, Vlachojannis M, Lang I, Commeau P, Vincent F, Testa L, Wasek W, Debry N, Kische S, Gabrielli G, Sardella G. Impact of routine invasive physiology at time of angiography in patients with multivessel coronary artery disease in reclassification of revascularisation strategy. Results from the DEFINE REAL study. *JACC Cardiovascular Interventions* 2018;11:354-64.

⁷ Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J.* 2019 Jan 7;40(2):87-165. doi: 10.1093/eurheartj/ehy394. Erratum in: *Eur Heart J.* 2019 Oct 1;40(37):3096. PMID: 30165437.

⁸ Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, Hanratty C, Banning A, Wheatcroft S, Hobson A, Chitkara K, Hildick-Smith D, McKenzie D, Calver A, Dimitrov BD, Corbett S. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: the RIPCORDER study. *Circ Cardiovasc Interv.* 2014;7:248–255. doi: 10.1161/CIRCINTERVENTIONS.113.000978.

⁹ P. Ludman. National BCIS/NICOR PCI Audit 2019-20. *Personal Communication*, BCIS Website. <https://www.bcis.org.uk/audit-results/>

¹⁰ Elguindy M, Stables R, Nicholas Z, Kemp I, Curzen N. Design and Rationale of the RIPCORDER 2 Trial (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?). *Circ Cardiovasc Qual Outcomes.* 2018;11:e004191. DOI: 10.1161/CIRCOUTCOMES.117.004191

-
- ¹¹ Stables R, Elguindy M, Kemp I, Nicholas Z, Mars C, Mullen N L, Curzen N. A randomised controlled trial to compare two coronary pressure wires using simultaneous measurements in human coronary arteries: the COMET trial. *Eurointervention* 2019;14:e1-7.
- ¹² Layland J, Oldroyd K, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee M, Shuakat A, O'Donnell A, Nam J, Briggs A, Henderson R, McConnachie A, Berry C; FAMOUS–NSTEMI investigators. Fractional flow reserve vs. angiography in guiding management to optimise outcomes in non-ST segment elevation myocardial infraction: British Heart Foundation FAMOUS–NSTEMI randomised trial. *European Heart Journal* 2015;36:100-11.
- ¹³ Ciccarelli G, Barbato E, Toth G, Gahl B, Fournier S, Milkas A, Bartunek J, Vandreheyden M, Pijls N, Tonino P, Fearon W, Juni P, de Bruyne B. Angiography Versus Hemodynamics to Predict the Natural History of Coronary Stenoses Fractional Flow Reserve Versus Angiography in Multivessel Evaluation 2 Substudy. *Circulation*. 2018;137:1475–1485. DOI: 10.1161/CIRCULATIONAHA.117.028782
- ¹⁴ Barbato E, Toth GG, Johnson NP, Pijls NH, Fearon WF, Tonino PA, Curzen N, Piroth Z, Rioufol G, Jüni P, De Bruyne B. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol*. 2016;68:2247–2255. doi: 10.1016/j.jacc.2016.08.055.
- ¹⁵ Escaned J, Ryan N, Mejia-Renteria H, Cook CM, Dehbi HM, Alegria-Barrero E, Alghamdi A, Al-Lamee R, Altman J, Ambrosia A, Baptista SB, Bertilsson M, Bhindi R, Birgander M, Bojara W, Brugaletta S, Buller C, Calais F, Silva PC, Carlsson J, Christiansen EH, Danielewicz M, Di Mario C, Doh JH, Erglis A, Erlinge D, Gerber RT, Going O, Gudmundsdottir I, Härle T, Hauer D, Hellig F, Indolfi C, Jakobsen L, Janssens L, Jensen J, Jeremias A, Kåregren A, Karlsson AC, Kharbanda RK, Khashaba A, Kikuta Y, Krackhardt F, Koo BK, Koul S, Laine M, Lehman SJ, Lindroos P, Malik IS, Maeng M, Matsuo H, Meuwissen M, Nam CW, Niccoli G, Nijjer SS, Olsson H, Olsson SE, Omerovic E, Panayi G, Petraco R, Piek JJ, Ribichini F, Samady H, Samuels B, Sandhall L, Sapontis J, Sen S,

Seto AH, Sezer M, Sharp ASP, Shin ES, Singh J, Takashima H, Talwar S, Tanaka N, Tang K, Van Belle E, van Royen N, Varenhorst C, Vinhas H, Vrints CJ, Walters D, Yokoi H, Fröbert O, Patel MR, Serruys P, Davies JE, Götzberg M. Safety of deferral of coronary revascularisation on the basis of iFR and FFR measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovascular Interventions* 2018;11:1437-49.

¹⁶ Rioufol G, Dérimay F, Roubille F, Perret T, Motreff P, Angoulvant D, Cottin Y, Meunier L, Cetran L, Cayla G, Harbaoui B, Wiedemann JY, Van Belle É, Pouillot C, Noirclerc N, Morelle JF, Soto FX, Caussin C, Bertrand B, Lefèvre T, Dupouy P, Lesault PF, Albert F, Barthelemy O, Koning R, Leborgne L, Barnay P, Chapon P, Armero S, Lafont A, Piot C, Amaz C, Vaz B, Benyahya L, Varillon Y, Ovize M, Mewton N, Finet G; FUTURE Trial Investigators. Fractional Flow Reserve to Guide Treatment of Patients With Multivessel Coronary Artery Disease.

J Am Coll Cardiol. 2021 Nov 9;78(19):1875-1885. doi: 10.1016/j.jacc.2021.08.061.PMID: 34736563

¹⁷ Puymirat E, Cayla G, Simon T, Steg P, Montalescot G, Durand-Zaleski J, le Bras A, Gallet R, Khalife Khalife, Morelle J-F, Motreff P, Lemesle G, Dillinger J-G, Lhermusier T, Silvain T, Roule V, Labeque J-N, Range G, Ducrocq G, Cottin Y, Blanchard D, Nelson AC, Bernard De Bruyne B, Chatellier G, Danchin N for the FLOWER-MI Study Investigators. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med.* 2021 May 16. doi: 10.1056/NEJMoa2104650. Online ahead of print.

¹⁸ Curzen N, Nicholas Z, B Stuart, S Wilding, K Hill, J Shambrook, Z Emlinton, D Ball, C Barrett, L Johnson, J Nuttall, K Fox, D Connolly, P O’Kane, A Hobson, A Chauhan, N Uren, GP McCann, C Berry, J Carter C Roobottom, M Mamas, R Rajani, I Ford, P Douglas, MA Hlatky. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment & Management of Stable Chest Pain: The FORECAST Randomised Trial. *Eur Heart J* 2021 (*in press*).

¹⁹ The SCOT HEART Investigators. Coronary CT angiography and 5 year risk of myocardial infarction. *N Engl J Med* 2018;379:924-33

²⁰ Maron DJ, Hochman JS, Reynolds HR, Harmony R. Reynolds, M.D., Sripal Bangalore, M.D., M.H.A., Sean M. O'Brien, Ph.D., William E. Boden, M.D., Bernard R. Chaitman, M.D., Roxy Senior, M.D., D.M., Jose López-Sendón, M.D., Karen P. Alexander, M.D., Renato D. Lopes, M.D., Ph.D., Leslee J. Shaw, Ph.D., Jeffrey S. Berger, M.D., Jonathan D. Newman, M.D., M.P.H., Mandeep S. Sidhu, M.D., M.B.A., Shaun G. Goodman, M.D., Witold Ruzyllo, M.D., Ph.D., Gilbert Gosselin, M.D., Aldo P. Maggioni, M.D., Harvey D. White, D.Sc., Balram Bhargava, M.D., D.M., James K. Min, M.D., G.B. John Mancini, M.D., Daniel S. Berman, M.D., Michael H. Picard, M.D., Raymond Y. Kwong, M.D., M.P.H., Ziad A. Ali, M.D., D.Phil., Daniel B. Mark, M.D., M.P.H., John A. Spertus, M.D., M.P.H., Mangalath N. Krishnan, D.M., Ahmed Elghamaz, M.D., Nagaraja Moorthy, M.D., D.M., Whady A. Hueb, M.D., Marcin Demkow, M.D., Kreton Mavromatis, M.D., Olga Bockeria, M.D., Ph.D., Jesus Peteiro, M.D., Ph.D., Todd D. Miller, M.D., Hanna Szwed, M.D., Ph.D., Rolf Doerr, M.D., Matyas Keltai, M.D., Ph.D., D.Sc., Joseph B. Selvanayagam, M.B., B.S., D.Phil., P. Gabriel Steg, M.D., Claes Held, M.D., Ph.D., Shun Kohsaka, M.D., Stavroula Mavromichalis, M.S., Ruth Kirby, R.N., Neal O. Jeffries, Ph.D., Frank E. Harrell, Jr., Ph.D., Frank W. Rockhold, Ph.D., Samuel Broderick, M.S., T. Bruce Ferguson, Jr., M.D., David O. Williams, M.D., Robert A. Harrington, M.D., Gregg W. Stone, M.D., Yves Rosenberg, M.D., M.P.H. for the ISCHEMIA Research Group. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N. Engl. J. Med.* 2020; 382(15), 1395–1407.