Fractional flow reserve versus angiography in guiding management to optimize outcomes in non–ST-elevation myocardial infarction (FAMOUS-NSTEMI): Rationale and design of a randomized controlled clinical trial ☆

Colin Berry, MD, PhD, [a,b] Jamie Layland, MD, [a,b] Arvind Sood, MD, [c] Nick P. Curzen, BM (Hons), PhD, [d] Kanarath P. Balachandran, MD, [e] Raj Das, MD, [f] Shahid Junejo, MD, [g] Robert A. Henderson, DM, [h] Andrew H. Briggs, PhD, [i] Ian Ford, PhD, [j] and Keith G. Oldroyd, MD (Hons) [a] *Glasgow, East Kilbride, Southampton, Blackburn, Newcastle, Sunderland, and Nottingham, United Kingdom*

Background In patients with acute non–ST-elevation myocardial infarction (NSTEMI), coronary arteriography is usually recommended; but visual interpretation of the angiogram is subjective. We hypothesized that functional assessment of coronary stenosis severity with a pressure-sensitive guide wire (fractional flow reserve [FFR]) would have additive diagnostic, clinical, and health economic utility as compared with angiography-guided standard care.

Methods and design A prospective multicenter parallel-group 1:1 randomized controlled superiority trial in 350 NSTEMI patients with ≥1 coronary stenosis ≥30% severity (threshold for FFR measurement) will be conducted. Patients will be randomized immediately after coronary angiography to the FFR-guided group or angiography-guided group. All patients will then undergo FFR measurement in all vessels with a coronary stenosis ≥30% severity including culprit and nonculprit lesions. Fractional flow reserve will be disclosed to guide treatment in the FFR-guided group but not disclosed in the "angiography-guided" group. In the FFR-guided group, an FFR ≤0.80 will be an indication for revascularization by percutaneous coronary intervention or coronary artery bypass surgery, as appropriate. The primary outcome is the between-group difference in the proportion of patients allocated to medical management only compared with revascularization. Secondary outcomes include the occurrence of cardiac death or hospitalization for myocardial infarction or heart failure, quality of life, and health care costs. The minimum and average follow-up periods for the primary analysis are 6 and 18 months, respectively.

Conclusions Our developmental clinical trial will address the feasibility of FFR measurement in NSTEMI and the influence of FFR disclosure on treatment decisions and health and economic outcomes. (Am Heart J 2013;166:662-668.e3.)

Background

Acute non–ST-elevation myocardial infarction (NSTEMI) is the commonest form of acute coronary syndrome (ACS) and a leading global cause of premature morbidity and mortality.[1] A coronary angiogram is recommended in intermediate- to high-risk NSTEMI patients to detect obstructive coronary artery disease (CAD) and so identify patients who may benefit from coronary revascularization.[1-3] In ACS patients, stress testing before invasive management is not recommended[1,3]; and so functional information on ischemia is usually not available. Usual care is based on visual interpretation of coronary disease severity revealed by the angiogram; and treatment decisions include medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG). Because visual assessment of the angiogram may be inaccurate, judgments made by cardiologists in everyday practice are subjective,

potentially leading to misdiagnosis and incorrect treatment decisions.[4-6]

Recent studies (DEFER,[7] FAME,[8] FAME II[9]) in patients with stable CAD have presented a new approach to the management of CAD. *Fractional flow reserve* (FFR) is an index of the physiological significance of a coronary stenosis and is defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow.[7-12] An FFR ≤0.80 is an evidence-based physiological threshold that correlates with the presence of inducible ischemia on noninvasive testing.[11,12] Alternatively, an FFR >0.80 indicates that patients can be managed safely with medical therapy. DEFER[7] and FAME[8] highlighted the benefits of FFR measurement in stable CAD to more accurately identify flow-limiting stenoses and guide PCI, leading to improved outcomes and reduced costs[10] compared with angiography alone. Overall, FFR measurement can identify and exclude obstructive CAD with high diagnostic accuracy,[11-13] including in patients with prior MI.[12]

FFR measurement in unstable CAD

Fractional flow reserve measurement requires maximal coronary hyperemia that theoretically may be less readily achieved in patients with recent MI because of microvascular injury.[14,15] However, some recent studies support the notion that FFR measurements are valid in medically stabilized MI patients.[16-20] Ntalianis et al[16] measured FFR in 112 nonculprit coronary lesions repeatedly (average interval 35 ± 4 days) in 101 patients with recent acute MI and found similar FFR values at each time point. In one other study, FFR correctly identified inducible ischemia on single photon emission computed tomography in 57 patients >6 days after MI[15]; and in a follow-up study of 124 ACS patients, deferring revascularization in lesions with an FFR ≥0.75 was safe.[17] In hospitalized patients with recent MI, FFR-guided management is associated with lower in-hospital costs compared with deferred management guided by myocardial stress perfusion scintigraphy.[18] Based on invasive measurement of coronary vasodilator capacity, we have recently shown that vasodilator reserve is similar in patients with stable angina and NSTEMI, consistent with preserved coronary vasodilator capacity in medically stabilized NSTEMI patients.[19] Finally, nearly one-third of the patients randomized in FAME had a history of medically stabilized unstable angina or NSTEMI 5 or more days from randomization (or <5 days if the peak creatine kinase was <1,000 IU[20]; and the benefit of FFR-guided PCI was similar in patients with unstable versus stable coronary disease.[20] The FAME investigators concluded that their post hoc analysis could not prove equivalence of effects between subgroups because FAME[8] was neither designed nor powered to do so.

Therefore, the potential diagnostic, prognostic, and health economic impact of FFR measurement to inform the management of unselected patients with recent medically stabilized NSTEMI has not been established.

Specific uncertainties with angiography-guided treatment decisions in NSTEMI

First, treatment decisions for nonobstructive (FFR >0.80) culprit coronary lesions lack an evidence base to guide management.[1,2] On the one hand, a stent for coronary plaque rupture might reduce the risk of recurrent thrombosis. On the other hand, optimal medical therapy with dual antiplatelet drugs and high-dose statins might suffice; and unnecessary stenting can be harmful (eg, stent thrombosis, restenosis). Second, in NSTEMI patients with multivessel coronary disease, evidence is lacking as to whether nonculprit obstructive lesions should undergo revascularization or not.[1,2] A post hoc analyses of the contemporary large-scale ACUITY trial found that incomplete coronary revascularization was a multivariable predictor of major adverse cardiac events at 1 year and that the risk was related to the number of nonrevascularized lesions.[21] In a recent analysis of NSTEMI patients in whom FFR was measured during usual care in our hospital, we found that FFR disclosure influenced cardiologists' treatment decisions.[22]

Rationale for a trial of FFR-guided management versus angiography alone in NSTEMI

First, FFR measurement is not a current standard of care in NSTEMI patients.[1-3]

Second, the prognostic relationship between FFR values and clinical outcomes in NSTEMI patients is uncertain and may not be the same as in patients with stable coronary disease.[14] Therefore, to study the prognostic importance of FFR, it will be measured in all patients and disclosed in the FFR-guided group but not disclosed in the angiography-guided control group. Because all patients will be followed up for clinical events, the relationships between FFR and health outcomes (composite cardiovascular events) will be evaluated.

Third, because stress testing is not generally appropriate in patients with recent MI, FFR-guided management could obviate the need for "deferred" management.[18]

Fourth, FFR has the potential to guide revascularization of culprit and nonculprit lesions. Because there are no data to support stenting in nonobstructive culprit lesions, we propose that the treatment decisions are consistently guided by the FFR values in both culprit and nonculprit lesions using the established FFR threshold of 0.80 for revascularization. Non–flow-limiting lesions (FFR >0.80) would be treated with optimal medical therapy,[1] and flow-limiting lesions (FFR ≤0.80) should be revascularized by PCI or CABG.

Fifth, when stenting is performed, the poststent FFR can be used to ensure that an optimal stent result is

achieved, that is, FFR >0.9 in both the culprit and nonculprit lesions treated by PCI.[23]

Study hypothesis

Our first hypothesis is that routine FFR measurement increases the proportion of NSTEMI patients that will be managed medically. Our second hypothesis is that routine FFR measurement in NSTEMI patients is feasible and has additive diagnostic, clinical, and health economic utility compared with standard care based on visual assessment of the angiogram.

Methodology

Primary aim

The primary aim is to determine if the treatment and outcomes of NSTEMI patients whose management is guided by FFR disclosure differ compared with those of patients whose treatment is guided by visual interpretation of the angiogram alone (FFR measured, not disclosed).

Secondary aims

The secondary aims are (1) to determine the feasibility and safety of routine FFR measurement in NSTEMI, (2) to determine the level of agreement between functional (FFR) and visual assessments of coronary disease severity in NSTEMI patients, (3) to determine the relationships between FFR values during the baseline procedure (and receiver operating characteristic) and cardiac events during follow-up in all patients, (4) to provide preliminary data on whether FFR-guided management is associated with improved health outcomes and quality of life in the longer term compared with angiography-guided treatment decisions, and (5) to perform a health-economic analysis.

Standard care of NSTEMI patients in the National Health Service. The participating hospitals adhere to current guidelines for optimal medical therapy[1,3] and optimal revascularization.[1-3] A left main stenosis of ≥50% and an epicardial coronary stenosis >70% are usually taken to be obstructive lesions for which revascularization should be considered.[1,2] In contemporary practice, FFR is only measured in a minority of patients (<10% of patients overall[22,24]) and is not standard care. Patients who may be candidates for CABG will be discussed at the Multidisciplinary Heart Team meeting in each center. If staged PCI is planned, then all procedures should take place during the index hospitalization.

Setting and design. A prospective multicenter parallel-group 1:1 randomized controlled superiority trial will be conducted in 6 UK centers including 3 academic cardiothoracic centers and 3 nonacademic regional hospitals (Figure 1). The first patient was randomized on October 25, 2011; and the trial is expected to complete follow-up in November 2013 (Figure 2).

Study population. We estimate that approximately 1,400 consecutive NSTEMI patients with a clinical diagno-

Figure 1
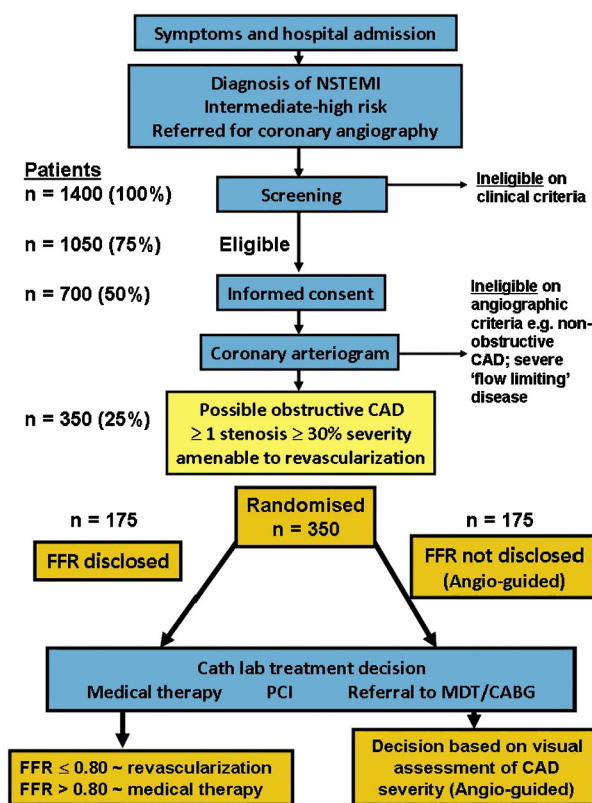
Flow diagram of the trial.

sis of confirmed or suspected type 1 MI[25] will be screened before coronary angiography. An *NSTEMI* is defined according to the occurrence of acute ischemic symptoms (eg, chest discomfort) and elevated cardiac biomarkers but without ST-segment elevation on the electrocardiogram.[25] Type 1 represents spontaneous MI due to a reduction in myocardial blood flow secondary to atherosclerotic plaque rupture and/or coronary thrombosis in one or more arteries.[25] Although underlying coronary disease is usually present, there may be mild or no coronary disease. The inclusion and exclusion criteria are described in Table. Patients who give informed consent but who are not randomized will be included in a registry. The reasons for exclusion from the trial after consent but before randomization (eg, coronary angiogram findings) and inclusion in the registry will be prospectively recorded. Similar information will be collected in the registry and randomized patients, including during follow-up. We aim to maximize participant retention and follow-up through telephone contact and use of national electronic databases for long-term follow-up.

Catheter laboratory study protocol. Once the coronary angiogram has been obtained, the cardiologist

Figure 2

Gantt chart.
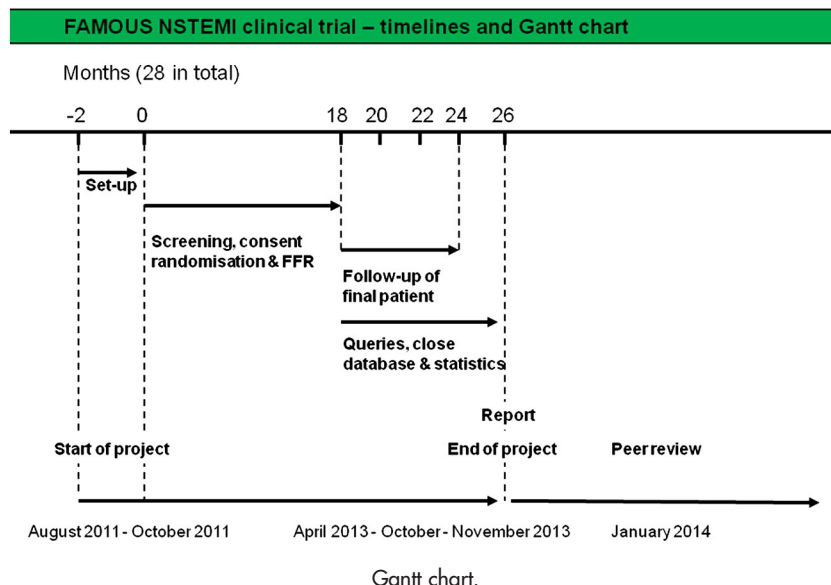
Table. FAMOUS NSTEMI study design
Inclusion criteria
Medically stabilized NSTEMI with an elevated troponin (>upper limit of normal for local reference range) with ≥1 risk factor for CAD (eg, diabetes, age >65 y, prior CAD, prior peripheral vascular disease, hypertension, hyperlipidemia, family history of CAD)
≥1 noncritical coronary stenosis ≥30% severity with normal coronary blood flow (Thrombolysis in Myocardial Infarction grade III) in which FFR measurement might have diagnostic value
Invasive management within 72 h of hospital admission or a history of recurrent ischemic symptoms within 5 d
Exclusion criteria
Ongoing ischemic symptoms not controlled by medical therapy
Cardiogenic shock or hemodynamic instability
Angiographic exclusion: highly tortuous or calcified arteries, left main stenosis >80% (ie, consistent with severe left main disease)
Life expectancy of <1 y
MI with persistent ST elevation
Intolerance to antiplatelet drugs
Unsuitable for either PCI or CABG on clinical or angiographic grounds
CAD <30% reference vessel diameter
Noncoronary cardiac surgery (eg, an indication for concomitant valve repair or replacement)
Inability to give informed consent
Age <18 y (no upper age limit)

will assess whether the patient is eligible to be randomized based on angiographic criteria (Table).

The main angiographic inclusion criterion is the presence of one or more noncritical coronary stenoses ≥30% severity that are associated with (1) normal coronary blood flow (ie, Thrombolysis in Myocardial Infarction grade III), (2) amenable to revascularization by PCI or CABG, and (3) FFR measurement is feasible and may have diagnostic value (Table). A minimum stenosis

severity of 30% is adopted for FFR measurement in our study because visual assessment of the angiogram may underestimate stenosis severity. Inclusion of a more severe stenosis (eg, >90% severity) is permissible provided the cardiologist believes FFR has the potential to influence the treatment decision based on coronary and patient characteristics. Left main stem disease is included. The pressure wire (Certus, St Jude Medical, Uppsala, Sweden) will be used in all patients to provide an FFR value across all coronary narrowings ≥30% severity as appropriate. Our aim is to maximize inclusion of eligible patients to minimize selection bias.

Assessment of the coronary angiogram and recording of the initial treatment decision. Once the coronary angiogram has been obtained, the cardiologist will report the severity of all coronary lesions as > or <70% of the reference vessel diameter (50% for left main) based on visual interpretation of the angiogram and in line with usual care. The cardiologist will then establish an intended treatment plan based on all of the available clinical information and the angiogram findings. The cardiologist's interpretation of the diagnostic angiogram and the treatment plan will then be recorded at that time in the catheter laboratory. Therefore, the initial treatment decision will be established before randomization or treatment group assignment is known and before the pressure wire is passed into the coronary arteries. Therefore, no FFR measurements will be acquired before randomization.

Randomization. Once the coronary angiographic findings and treatment plan have been recorded and if, in the opinion of the treating cardiologist, the patient remains eligible to continue in the study, randomization will then be

performed. Randomization will take place immediately in the catheter laboratory using a Web-based computer randomization tool provided by the independent Clinical Trials Unit. The randomization sequence was created using the method of randomized permuted blocks.

Patients who had consented but were ineligible on angiographic criteria will be entered into a registry.

FFR measurement

Myocardial FFR measurement is described in the online Appendix Supplementary material.

FFR-guided group

Fractional flow reserve will be measured by the cardiologist immediately after randomization, and the FFR result will used to guide treatment decisions based on a threshold of 0.80. An FFR ≤.80 should result in a treatment decision for revascularization by PCI or CABG combined with optimal medical therapy; and an FFR >0.80 should result in treatment with optimal medical therapy alone, in line with contemporary guidelines for optimal secondary prevention drug therapies, cardiac rehabilitation, and risk factor modification.[1] Any changes in treatment following FFR disclosure compared with the initial treatment plan prior to FFR disclosure will be recorded.

Angiography-guided group and blinding

In patients randomized to the angiography-guided group, the RadiAnalyzer Xpress (St Jude Medical) will be turned out of view by the research team such that it is impossible for the clinical team to see the pressure wire recording. The pressure wire recording will not be displayed on any other monitor in the catheter laboratory, and the clinicians and patients will not know the results. When the coronary pressure display is out of view of the clinical team, the cardiologist will then measure FFR as described above, guided by the research staff who will monitor and record the pressure wire data. Therefore, the patient and the clinical team responsible for the patient, including the interventional cardiologists and nurses, will be blinded to the pressure wire recording. Quality control checks, including assessments of equalized pressure recordings and verification of symptoms and hemodynamic changes with intravenous adenosine, will be conducted in the usual way, with the guidance of the unblinded research team. These steps will be followed for all FFR measurements.

Quality assurance procedures are described in the online Appendix Supplementary material.

End points
Primary outcome

The between-group difference is the proportion of patients allocated to medical therapy only instead of

revascularization at baseline. The treatment decision will be made by the clinical team in the cardiac catheter laboratory during the index procedure or shortly afterward during the index hospitalization including when a multidisciplinary heart team review is indicated.

Secondary outcomes

1) The safety and feasibility of routine FFR measurement at baseline.
2) The percentage rate of discordance between an FFR ≤ or >0.80 and coronary stenosis severity (stenosis > or <70% of reference vessel diameter [50% for left main] assessed visually in all patients in the catheter laboratory before randomization);
3) *Major adverse cardiac events* are defined as cardiac death or hospitalization for MI or heart failure after randomization. Therefore, emphasis has been placed on "spontaneous" "hard" outcomes. Because the decision for revascularization may be susceptible to bias, this event is not included in the primary outcome. Information on hospitalizations for other adverse events (ie, unstable angina, renal failure, stroke, PCI, CABG) will be prospectively recorded.

The prognostic value of FFR in all patients for subsequent adverse events will be assessed. The outcomes will be assessed during the study until the final randomized patient has completed a minimum of 6 months of follow-up. The 3-year event rates will also be assessed.

4) Health care costs (including revascularization procedures, stents, bed days) will be prospectively recorded for the index and any subsequent hospitalizations.
5) Quality of life (EuroQoL, EQ-5D).

Statistical methods

The sample size calculation and pilot data[22] statistical and health economic[28,29] analyses plans are described in the online Appendix Supplementary material.

Follow-up and timetable

A quality-of-life assessment will be completed at 6-month intervals (EuroQoL, EQ-5D). Clinical follow-up will continue for an average of 1.5 years (range 6-30 months). Follow-up assessments for adverse events will be performed by the clinical research staff by telephone or in person (eg, outpatient clinic review), as appropriate. Medical records will also be checked. Follow-up contact will occur at 6 monthly intervals until the last patient has achieved a minimum of 6 months of follow-up. Follow-up in the longer term will be supported by electronic record linkage with central government health records. The active phase of the project is intended to last about 30 months.

Ethics

FAMOUS-NSTEMI has full UK National Research Ethics Service approval (Reference 11/S0703/6).

Registration

The trial registration numbers are: NCT01764334; ISRCTN97489534.

Trial management. The trial will be conducted in line with Guidelines for Good Clinical Practice in Clinical Trials.[30] Trial management will include a Trial Management Group, Trial Steering Committee, Clinical Event Committee, and Data and Safety Monitoring Board (online Appendix Supplementary material).[31]

Definition of adverse events

1) *Major adverse cardiovascular event* is the composite of "cardiovascular death, nonfatal MI, unplanned hospitalization for transient ischemic attack or stroke."
2) *Major adverse cardiac events* are defined as "cardiac death, or unplanned hospitalization for MI or heart failure."

Percutaneous coronary intervention and CABG are nonmajor adverse events.

3) *Myocardial infarction* is defined according to the criteria specified in the Third Universal Definition of Myocardial Infarction (including type 4 MI for PCI and type 5 for CABG).[25]
4) *Contrast agent–induced nephropathy* is defined as either a > 25% increase of serum creatinine or an absolute increase in serum creatinine of 0.5 mg/dL after a radiographic examination using a contrast agent.[32]
5) *Bleeding* is defined according to the ACUITY criteria[33]: major bleed = intracranial or intraocular bleeding, bleeding at the site of angiography requiring intervention, a hematoma of 5 cm in diameter, a reduction in hemoglobin level of at least 4 g/dL in the absence of overt bleeding or 3 g/dL with a source of bleeding, or transfusion.

Sources of funding

Discussion

Should our hypotheses prove correct, then favorable outcomes from our developmental clinical trial will inform the design and justification for undertaking a large multicenter outcome trial to further validate these initial findings.

Randomization is performed after coronary anatomy is known because coronary lesion severity defines the patients who are eligible to be randomized. However, this design renders the trial susceptible to selection bias, as may have occurred in other trials (eg, COURAGE, BARI2D, FAME, and FAME-2), potentially favoring inclusion of patients with less complex coronary disease. To facilitate inclusion of patients with complex disease (eg, chronic total occlusion, critically narrowed lesions), an FFR of 0.5 can be assigned without requirement to pass the pressure wire. This approach is intended to facilitate the inclusion of all eligible patients. Because FFR group assignment is "open," by design, we have attempted to minimize treatment bias at the time of the procedure and during follow-up by not disclosing the FFR values in the angiography-guided group. Nondisclosure of FFR in the control group differentiates our study from FAME-2 where FFR values were known in all of the randomized patients.[9]

Acknowledgements

Disclosures

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Appendix. Clinical setting

Standard care of NSTEMI patients in the National Health Service

The participating hospitals adhere to current guidelines for optimal medical therapy[1,3] and optimal revascularization.[1-3] A left main stenosis of ≥50% and an epicardial coronary stenosis >70% are usually taken to be obstructive lesions for which revascularization should be considered.[1,2] Patients who may be candidates for CABG will be discussed at the Multidisciplinary Heart Team meeting. If staged PCI is planned then all procedures should take place during the index hospitalization.

Multidisciplinary heart team meeting

Patients with coronary disease amenable to CABG may be referred to the multidisciplinary heart team meeting. In the angiography-guided group, the FFR data will not be disclosed at this meeting. For staged PCI, the recommendation is for the second procedure to be performed during the index admission. For CABG, the recommendation is for surgery within 30 days of referral.

Myocardial FFR measurement

FFR is the ratio of distal coronary pressure to aortic pressure measured during coronary hyperemia.[7-12] According to eligibility criteria in the protocol (Table I), FFR should be measured in all coronary arteries with one or more stenoses ≥30% of the reference vessel diameter based on visual assessment of the angiogram, with normal coronary blood flow (TIMI grade III) and in the opinion of the attending cardiologist FFR measurement will be feasible and may have diagnostic value. Left main stem disease is included and the upper limit for left main stenosis severity is 80%. In order to facilitate the inclusion of patients with complex disease, an FFR of 0.5 can be assigned without requirement to pass the pressure wire in occluded arteries, left main lesions >80% and critical severe epicardial coronary lesions (e.g. >90% severity) in which the cardiologist believes FFR has no diagnostic value. This approach is intended to facilitate and maximize the inclusion of all eligible patients.

FFR will be measured according to best practice as described in the investigator guideline. The cardiologist should pass the pressure wire across the target coronary stenosis. The pressure wire (Certus, St Jude Medical, Uppsala) is similar to the guidewires that are normally used in PCI except that the wire has a pressure-sensitive sensor 3 cm from its distal tip. The pressure wire will be calibrated initially to ensure standardized measurements and when positioned at the distal end of the guide catheter the pressure wire recording will be equalized with the aortic pressure. The wire is then passed into the coronary artery of interest and advanced at least 6 cm distal to the coronary stenosis using standard

techniques. Once the marker is appropriately positioned and after an initial 2 minute rest period, an intravenous infusion of adenosine (140 mcg/kg/min–210 mcg/kg/min) via a central vein or large antecubital vein is started to establish coronary hyperemia. Typical changes in blood pressure (i.e. fall in systolic pressure >10%), heart rate (i.e. rise in heart rate >20%) and symptoms will be recorded prospectively to confirm a hemodynamic response to adenosine during a period of at least 2 minutes. When there is an inadequate response with the standard dose of adenosine (140 mcg/kg/min) then the dose can be increased up to 210 mcg/kg/min in order to best ensure maximal hyperemia. If intravenous adenosine is not tolerated then intracoronary adenosine could be administered or FFR will be not be recorded and this will be noted in the Case Report Form. Our protocol has been developed according to previous studies on the hemodynamic response to intravenous adenosine when used for stress testing (online Appendix Supplementary references).

Microvascular function

Coronary microvascular function is clinically-relevant in NSTEMI[19] and has prognostic importance.[26,27] Pressure wire-derived parameters of microcirculatory function can be easily obtained using thermodilution techniques around the same time as the FFR measurements. Therefore, wherever feasible, the index of microcirculatory resistance (IMR) and the resistive reserve ratio (RRR), a measure of microcirculatory vasodilator capacity) will also be measured.[19,26,27] Measurement of microvascular parameters will not affect FFR measurements or blinding. In the angiography-guided group, these data will be acquired by the cardiologist who will be blind to the results which will be recorded by the research team and not disclosed.

Trial management

Quality assurance of FFR and blinding during the index procedure

The initial treatment decision will be prospectively recorded before randomisation and any change to this decision after randomization, such as after FFR disclosure in the FFR-guided group will also be recorded prospectively in the catheter laboratory during the procedure. At this time, the protocol also requires prospective confirmation that in the 'angiography-guided control group', the clinical team were blinded to the pressure wire recordings and FFR values throughout. The investigator is also required to confirm that the protocol was preserved. Adherence to the blinding protocol will be monitored with site visits.

The trial will be conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials.[32] Trial management will include a Trial Management Group

(TMG), Trial Steering Committee (TSC), Clinical Event Committee (CEC), and Data and Safety Monitoring Board (DSMB) (online Appendix). Day to day study activity will be coordinated by the TMG, which will be responsible to the TSC. The TSC will be responsible for overall trial supervision. In order to adjudicate and validate adverse clinical events, source clinical data will be reviewed by an independent CEC comprised of at least 3 cardiologists. The DSMB will follow an agreed charter prepared according to the DAMOCLES guidelines.[33] The DSMB will have access to unblinded data including the FFR results. The DSMB will include one interventional and one non-interventional cardiologist and a biostatistician (Chair), not affiliated to any of the institutions involved in the study and therefore independent of the study team. Progression during the study will require approval from the DSMB after the 35th randomized patient.

Statistical methods

The sample size calculation, pilot data[22] statistical and health economic[28,29] analyses plans are described in the online Appendix Supplementary material.

Sample size calculation

With 322 randomized subjects (161 subjects in the FFR disclosed and non-disclosed groups), the study will have 90% power at a 5% level of significance to detect a 50% relative increase in the proportion of patients assigned to medical treatment in the disclosure group from about 15% to 30%. This difference is based on observations made in a pilot study[22] performed to inform the design of the current trial. We have assumed zero loss to follow up since the primary outcome is measured during the initial procedure. Allowing for any technical difficulties or loss of data at the time of the procedure the total sample size will be 350 patients (Figure 1).

Approximately 1400 patients will be screened and 350 patients will be randomized in <2 years (Figure 1). Potentially 25% of screened patients may be ineligible (e.g. unsuitable for PCI or CABG). Some patients may not wish to take part (~25%) and following initial angiography a further 25% may be ineligible based on coronary anatomy and disease resulting in 350 randomized patients. We anticipate the rate of major adverse cardiac events in the control group will be ~20% during ~1.5 years mean follow-up (or at least 35 events in 175 patients) such that the relationship between FFR and cardiac outcome in NSTEMI can be evaluated. The Glasgow Clinical Trials Unit (Robertson Centre for Biostatistics) will act as an independent coordinating center for data management and will conduct the statistical analyses.

Statistical analysis

The primary outcome of the between group difference in the proportions of patients allocated to medical therapy will be assessed using Fisher's Exact test and the differences in proportions estimated with a 95% confidence interval. The rate of discordance between FFR and coronary stenosis severity assessments will be estimated over all patients and segments and a 95% confidence intervals calculated taking into account the within subject clustering. Additional modelling will be carried out to investigate evidence of heterogeneity in the rates of discordance across segments. Rates of major coronary events at 6 months, 12 months and 3 years will be analyzed using logistic regression analysis. In addition Kaplan-Meier time to event curves will be calculated to describe the time course of events in each group. Rates of the feasibility of FFR assessment and adverse events rates will be summarized.

Health economics

A decision model will be constructed to reflect the treatment of NSTEMI patients and the effects of the two diagnostic options (FFR or the visual interpretation of the angiogram alone).[28,29] The model will be made probabilistic so as to characterise the uncertainty surrounding parameter estimates and ultimately reflect uncertainty in the cost-effectiveness estimate. The decision model can then be run to estimate the cost-effectiveness of using FFR measurements to guide clinical treatment decisions compared to the use of angiography results alone in the current trial. The health economic model in this developmental study will also inform the design of a future multicenter clinical trial.

Magnetic resonance imaging (MRI) sub-study

Since FFR is not validated in patients with unstable coronary disease, we set up an MRI sub-study at the lead site to determine the level of agreement between inducible ischemia as revealed by stress MRI (a non-invasive gold standard) and FFR. Study participants will be invited to have an adenosine stress perfusion MRI at 3.0 Tesla before invasive angiography and/or within 10 days afterwards, and again at 6 months to assess left ventricular remodeling and function. Clinicians will be blinded to the MRI results which will not influence catheter laboratory treatment decisions. The sub-study has ethics approval and all patients will give written informed consent.

Supplementary References

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