Defining a gold standard for ischaemia: Effects of interventional revascularization vs. optimal medical therapy on exercise capacity in patients with stable coronary artery disease

STUDY PROTOCOL V3.0

Steering committee

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Background

Previous studies have suggested that there is no added benefit to performing percutaneous coronary intervention (PCI) above treatment with medical therapy alone in patients with stable angina.[1, 2] However these data were based on subjective measures of angina symptoms and there was no attempt to blind investigators or patients to the treatment they had received which may have biased the results.[1, 2] As yet no study has investigated the effect of PCI on symptoms as measured by objective measures of exercise capacity and non-invasive and invasive measures of coronary ischaemia under blinded conditions.

Fractional flow reserve (FFR) has been used to measure the physiological significance of coronary stenosis[3] for many years. PCI was shown to be superior to medical therapy in patients with functionally significant FFR values; however, while the study was halted prematurely due to a significantly higher rate of urgent revascularization in the medical therapy arm,[4] a significant limitation was the lack of blinding between the 2 study arms. A novel invasive approach for assessing coronary stenosis severity, the instantaneous wave free ratio (iFR), has been developed[5] and has been shown to correlate well with FFR.[6] It is likely that a positive physiological assessment using these techniques will be associated with a larger improvement in exercise capacity following PCI. Exercise capacity in patients on optimal medical therapy (OMT) will be most limited in those with positive functional tests.

Hypotheses

Hypothesis 1:
Under bias-resistant blinded conditions, PCI increases objective exercise capacity more than OMT alone, with OMT given to both groups.

a. Principal endpoint: Exercise time on treadmill
b. Secondary endpoints:
    i. Peak VO_2
    ii. Exercise time to development of angina
    iii. Exercise time to ST depression of 1 mm

Hypothesis 2:
The stenting induced increment in exercise capacity is related to the severity at baseline. We define the stenting induced increment in the physiological variable as the increment seen in the PCI+OMT group minus the increment seen in the Placebo+OMT group.

a. Physiological severity defined as baseline FFR
b. Physiological severity defined as baseline iFR
c. Anatomic severity assessed by quantitative coronary angiography

Hypothesis 3:
Under bias-resistant blinded conditions, these techniques can identify the changes pre- and post-PCI:

a. Duke treadmill score
b. Dobutamine stress echocardiography (DSE) analysed, blinded to order and patient, by 2 independent observers
c. iFR (measured twice 10min apart)
d. FFR (measured twice 10min apart)

e. Exercise increment in high sensitivity-Troponin I (hsTNI)

Value of results

1. If these are confirmed, this would confirm that PCI+OMT leads to an improvement in exercise capacity over blinded Placebo+OMT alone.
2. The improvement is greatest in patients with physiologically significant lesions.

Sample size calculation

Hypothesis 1 will be tested by comparing the endpoint variables between the groups. This will be done by an unpaired t-test (Mann-Whitney if skewed distribution). The expected difference in exercise duration would be 30s or greater. The expected standard deviation is based on observational studies using the treadmill Bruce protocol in patients with coronary artery disease.[7]

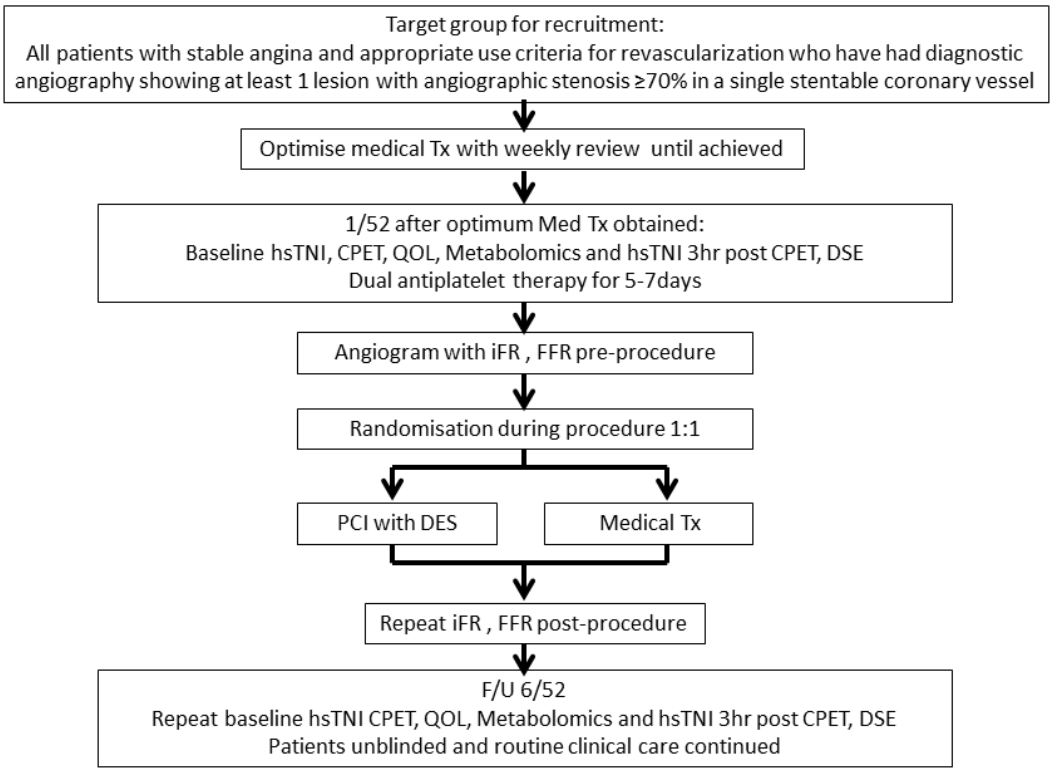
Table 1: Numbers of power to detect significant changes

Effect size	Standard Deviation	1-Beta	Alpha	n
30s	90s	0.8	0.05	143
45s	90s	0.98	0.05	143

To test hypothesis 2 we will plot the regression relationship between the increment in treadmill time pre/post and the baseline measure of severity. Separate regression relationships will be plotted for the PCI+OMT and Placebo+OMT groups. The difference between the 2 regression relationships will indicate the stenting induced increment. With a sample size of 143, the power to detect a significant relationship between the pre/post PCI increment and the baseline physiological variable, of the order of r=0.3, is 95% at the 5% significance level.

Hypothesis 3 is a simple test of the efficacy of each of the markers in detecting the change that occurs with stenting. For the continuous variables, iFR and FFR, our pilot experience is that these are extremely highly powered (>99.9%) because they undergo a relatively large positive change compared to their own reproducibility.[8] For Duke treadmill score, based on a conservatively assumed increment of 30s, i.e. 0.5 points, and a standard deviation of difference of 1.5 points, then 143 patients would give us 80% power at the 5% significance level.

Study protocol



Recruitment group:
Patients with stable angina and appropriate use criteria for revascularization; who have had diagnostic angiography showing at least 1 lesion with angiographic stenosis ≥70% in a single vessel.

Exclusion criteria:

a. Acute coronary syndrome
b. Previous coronary artery bypass graft surgery
c. Left main stem disease
d. Contraindications to PCI or drug-eluting stent (DES) implantation
e. Heavily calcified or tortuous vessels
f. Chronic total occlusion in target vessel
g. Life expectancy <2yr
h. Pregnancy
i. Age <18yr or >85yr
j. Angiographic stenosis ≥ 50% in non-target vessel
k. Inability to consent

Protocol:
Once enrolled in the study the patients will have the following:

1. **Aggressive optimization of medical therapy**
   Weekly clinic visits to introduce and uptitrate medications with the aim for treatment regimen to be as follows by 6 weeks with heart rate ≤60bpm and systolic blood pressure >100mmHg:
   i. Aspirin 75mg OD
   ii. Bisoprolol ≥5mg OD (or alternative β blocker)
   iii. Atorvastatin ≥40mg OD (or alternative statin)
   iv. Isosorbide Mononitrate S/R
   v. Amlodipine ≥5mg OD
   vi. Perindopril ≥4mg OD (or alternative ACEI)
   vii. Alternative anti-anginals at physician's discretion: verapamil, diltiazem, nicorandil, ivabradine, ranolazine
   viii. Dual antiplatelet therapy loading for 5-7 days prior to angiography

2. **Baseline functional assessment**
   To be performed on one visit 1 week after optimal medical treatment regimen is achieved. At this stage they will have the following:
   a. Clinical assessment:
      Quality of life questionnaire (European EQ-5D), Rose angina questionnaire, Seattle Angina Questionnaire, Short IPAQ
      CCS angina class
      Need for medical consultations or admissions
      Resting ECG, heart rate variability
   b. Blood and urine investigations: Fasting lipid profile, baseline hsTNI
   c. Cardiopulmonary exercise test (CPET):
      Using exercise tolerance test to measure:
      i. Exercise time on treadmill
      ii. Peak VO_2
      iii. Exercise time to development of angina
      iv. Exercise time to ST depression of 1 mm
   d. Blood investigations 3hr after completion of CPET: Metabolomics and hsTNI
   e. DSE with contrast enhancement:
      β blocker will be stopped for 3 days, prior to DSE. β blocker will be restarted immediately afterwards. Quantitative analysis with segment scoring reported in corelab each on 2 separate occasions by 2 operators.

3. **Invasive functional assessment**
   Coronary angiogram with iFR and FFR assessment (using IV adenosine 140mcg/kg/min) to each ≥70% coronary stenosis with pressure wire placed in distal vessel at least 3 vessel diameters beyond the last stenosis. Each measurement will be repeated twice with 10min interval between measurements. Normalisation will be documented prior to making each measurement. Operators will be blinded to the results of these functional tests. After each measurement the wire will be checked for drift and, if evident, measurements repeated.

4. **Sedation, randomization and blinding**

Patient will be sedated and randomized 1:1 to PCI+OMT or Placebo+OMT alone using computerized randomization. Patients will be given headphones during the course of the procedure. The nursing staff and physicians performing the PCI will have no further contact with the patient until after they are unblinded at the final follow-up point. Any other nursing staff or physicians involved in patient care and the research team will be blinded to the treatment strategy.

5. PCI

PCI group will have angioplasty and stent implantation with second generation DES as per operator's discretion to all lesions within the vessel that are deemed to be angiographically significant. Stent optimization with post-dilatation will be standard and intravascular ultrasound will be used as necessary.

6. Repeat invasive assessment

iFR and FFR assessment will be repeated in all coronary lesions post PCI in those who have had PCI.

7. Study protocol cross-over

Patients will not be eligible for randomization if:

a. They have complication necessitating PCI during invasive functional assessment procedure.

Patients will cross-over from Placebo+OMT to PCI+OMT arm in the following circumstances:

a. They have intractable angina necessitating PCI.
b. Positive ETT or DSE at follow-up functional assessment.
c. They develop acute coronary syndrome.

If patients cross-over, they will have repeat iFR/FFR measurement at angiography.

8. Follow-up functional assessment

To be performed 4-6wk after coronary angiogram +/- angioplasty.
At this stage they will have the following:

a. Clinical assessment:
   Quality of life questionnaire (European EQ-5D), Rose angina questionnaire, Seattle Angina Questionnaire, Short IPAQ
   CCS angina class
   Need for medical consultations or admissions
   Resting ECG, heart rate variability
b. Blood and urine investigations: Fasting lipid profile, baseline hsTNI
c. CPET:
   Using ETT to measure:
   i. Exercise time on treadmill
   ii. Peak VO_2
   iii. Exercise time to development of angina
   iv. Exercise time to ST depression of 1 mm
d. Blood investigations 3hr after completion of CPET: Metabolomics, hsTNI
e. DSE with contrast enhancement:

β blocker will be stopped for 3 days, prior to DSE. β blocker will be restarted immediately afterwards. Quantitative analysis with segment scoring reported in corelab each on 2 separate occasions by 2 operators.

f. Wear a physical activity tracker

9. Un-blinding and study end

Following the 4-6wk follow-up investigations, patients will be un-blinded to treatment group and routine medical care will be continued. Dual antiplatelet therapy will be stopped in blinded OMT group. At this stage, patients in the blinded OMT will be given the opportunity to undergo PCI at the discretion of the physician.

Statistical analysis

Data will be summarised as mean (SD) or median (interquartile range) for skewed data. Statistical comparisons will be undertaken using a paired Student's t-test (after log transformation if necessary) or nonparametric alternative if data are not normalised by log transformation.

Study reporting

We anticipate that it will take 6 months to complete patient recruitment with study end 6 months later therefore total study time of 12 months. We will aim to begin recruitment after Ethics approval in October 2013 with first results available for presentation in autumn 2014.

Study sites and enrolment

We anticipate the study enrolling with 3-4 large high volume PCI centres with experience in all of the physiological techniques proposed in this study. We envisage enrolment would take place within 6 months.

Documentation

All documentation will be collected electronically using the Imperial College Clinical Trials Unit (ICTU). The ICTU has a track record for running large multi-centre international (eg. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.

Regulatory Issues

1. Ethics

Ethical approval has been obtained from our Local Research Ethics Committee. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

2. Consent

Signed participant consent to be involved in the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and a minimum of 48 hours allowed for consideration. The right of the participant to refuse to participate without giving reasons will be respected.

All participants are free to withdraw at any time without giving reasons and without prejudicing further treatment. On withdrawal from the study, identifiable data will be destroyed securely. Non-identifiable data will be deleted from the database.

3. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and registered under the Data Protection Act.

4. Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

5. Sponsor

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

6. Funding

The study will be funded internally through a charitable fund.

7. Audits

The study may be subject to inspection and audit by Imperial College London (under their remit as sponsor) and other regulatory bodies, to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8. Documentation

All documentation will be collected electronically using the Imperial College Clinical Trials Unit (ICTU). The ICTU has a track record for running large multi-centre international (eg. ASCOT study). Clinical, and physiological records will be saved to DVD and then to a central server within ICTU in accordance with GCP guidelines.

References

1. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, Zhang W, Hartigan PM, Lewis C, Veledar E, Bowen J, Dunbar SB, Deaton C, Kaufman S, O'Rourke RA, Goeree R, Barnett PG, Teo KK, Boden WE, Group CTR, Mancini GB. Effect of pci on quality of life in patients with stable coronary disease. *The New England journal of medicine*. 2008;359:677-687
2. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the defer study. *Journal of the American College of Cardiology*. 2007;49:2105-2111
3. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183-3193
4. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF, Investigators FT. Fractional flow reserve-guided pci versus medical therapy in stable coronary disease. *The New England journal of medicine*. 2012;367:991-1001
5. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: Results of the advise (adenosine vasodilator independent stenosis evaluation) study. *Journal of the American College of Cardiology*. 2012;59:1392-1402
6. Petraco R, Escaned J, Sen S, Nijjer S, Asrress KN, Echavarria-Pinto M, Lockie T, Khawaja MZ, Cuevas C, Foin N, Broyd C, Foale RA, Hadjiloizou N, Malik IS, Mikhail GW, Sethi A, Kaprielian R, Baker CS, Lefroy D, Bellamy M, Al-Bustami M, Khan MA, Hughes AD, Francis DP, Mayet J, Di Mario C, Redwood S, Davies JE. Classification performance of instantaneous wave-free ratio (ifr) and fractional flow reserve in a clinical population of intermediate coronary stenoses: Results of the advise registry. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2012
7. Senuzun F, Fadiloglu C, Burke LE, Payzin S. Effects of home-based cardiac exercise program on the exercise tolerance, serum lipid values and self-efficacy of coronary patients. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2006;13:640-645
8. de Bruyne B, Bartunek J, Sys SU, Pijls NH, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. 1996;94:1842-1849

