An Evaluation of a Physiology-guided PCI Optimisation Strategy (Target-FFR)

Clinical Investigation Plan / Study Protocol

Study Title:	**How often can optimal post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) results be achieved? - A randomised controlled trial of a coronary physiology-guided optimisation strategy (The Target FFR Study)**
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How often can optimal post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) results be achieved? – a randomised controlled trial of FFR targeted PCI (The Target FFR Study)

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Abstract

There has recently been renewed interest in the measurement of post percutaneous coronary intervention (PCI) Fractional Flow Reserve (FFR). Previous studies have suggested that post PCI FFR values $\geqslant$ 0.90 are associated with better clinical outcomes for patients but the available data suggest that despite angiographically satisfactory results, this is actually achieved in less than 40% of cases.
The main mechanisms for sub-optimal post PCI FFR measurements have been proposed to be stent underexpansion, unmasking of a second lesion in the target vessel post PCI, residual diffuse disease in the untreated segments and pressure drift (a technical artifact of pressure wire technology).
Using post PCI FFR to guide stent optimisation and/or further intervention in the target vessel has been shown to increase the frequency of achieving optimal post PCI FFR results (and therefore presumably better clinical outcomes). However, there are additional costs involved in the routine use of post PCI FFR and it is not clear just how often it is even possible to increase the initial post PCI FFR to $\geqslant$ 0.90. This uncertainty means that it is currently difficult to either recommend the routine use of post PCI FFR or justify its cost.
We propose a prospective study to assess the feasibility of achieving post PCI FFR $\geqslant$ 0.90 during standard PCI procedures in consecutive patients. We would also attempt to elucidate the mechanisms for sub-optimal FFR results when they occur. We would anticipate using the data from this developmental study to support a subsequent funding application to BHF/MRC/NIHR for a definitive phase 3 study of the impact of FFR targeted PCI on clinical outcomes.

Background

The utility of FFR for assessing the physiological significance of coronary stenoses and the benefits of FFR-guided decision making prior to PCI have been well established in several landmark trials.[1,2] There is also a growing body of evidence that post PCI FFR can predict clinical outcomes. Much of this data is from the era of bare-metal stents, when a post-stent FFR $\geqslant$ 0.95 was recommended as the cut-off value for optimum (physiologically guided) stent implantation. This value was validated in a series of intravascular ultrasound (IVUS) studies although it should be noted that most studies of IVUS guided stenting have shown little or no benefit in terms of longer term clinical outcomes.[3-6]
More recent studies on the prognostic value of FFR post drug-eluting stent (DES) implantation have suggested that a post PCI FFR of $\leqslant$ 0.90 correlated with greater adverse cardiac event rates.[7-12] However, these series have generally recruited small numbers of patients and have yielded conflicting results. For example, Leesar et al investigated a group of 66 patients undergoing PCI with primarily DES. They found that an FFR $\geqslant$ 0.96 was achieved in only 35 patients (53%) after PCI but adverse event rates were significantly lower in this group.[7] Conversely, Matsuo et al reported that a post-stent FFR of $\geqslant$ 0.90 was achieved in only 39% of their cohort of 69 patients and were unable to demonstrate that post-stent FFR predicted target lesion revascularisation (TLR) in patients who received DES.[8]
A larger, retrospective study of 664 lesions (in 574 patients) by Agarwal et al found that approximately 1 in 5 lesions (21%) demonstrated persistent ischaemia (post PCI FFR $\leqslant$ 0.81) after intervention despite angiographically satisfactory PCI results.[13] The authors report that a post PCI FFR of > 0.91 was achieved in 34% of their patients which increased to 43%

following subsequent interventions to achieve "functional optimization". After excluding patients with diabetes, CKD and/or diffuse coronary disease, achieving a final FFR > 0.91 was associated with lower adverse event rates compared to the final FFR $\leqslant$ 0.91 group (7.1% vs. 18.9%; p = 0.04).

Data from a small series of patients at our own institute would also appear to corroborate the previous findings that an initial post PCI FFR $\geqslant$ 0.90 is only achieved in less than 40% of patients. Of the 21 patients in this group, only 8 (38%) had an initial post PCI FFR $\geqslant$ 0.90. Following further stent optimisation and/or additional stenting, this increased to 12 patients (57%) with a final FFR $\geqslant$ 0.90.

Pijls et al measured post PCI FFR in 750 patients and reported a final FFR result > 0.90 in 68% of their cohort. They found that FFR after stenting is a strong independent predictor of outcome at 6 months and that the event rate was over three times higher in patients with post PCI FFR < 0.90 compared to those with an FFR between 0.90 and 0.95 (20.3% vs. 6.2%).[14]

In a meta-analysis from Johnson et al, almost 2/3 of 966 patients who had post PCI FFR measured had values below 0.90. The rate of MACE (death, MI, repeat revascularisation) was 40% at 3 years in patients within the lowest tertile of post PCI FFR [median IQR 0.83 (0.79-0.86)], almost twice as high as that in patients in the highest tertile of post PCI FFR [0.98 (0.96-1.00)]; p< 0.001].[15] This may of course reflect the effects of diffuse atherosclerosis but it may also indicate physiologically suboptimal revascularisation and thereby represents a target for improved treatment.

Rimac et al recently published one of the largest meta-analyses to date on the clinical value of post PCI FFR. They included a total of 105 studies from 1995 - 2015 (7470 patients) and found that higher post PCI FFR values ($\geqslant$ 0.90) were associated with reduced rates of repeat intervention and MACE. They concluded that FFR measurement after PCI was associated with prognostic significance and recommended further investigation to assess the role of post PCI FFR and validate cut off values in contemporary clinical practice.[16]

Original hypothesis

A simple Physiologically-guided Incremental Optimisation Strategy (PIOS) can increase the proportion of patients undergoing PCI in whom a post PCI FFR $\geqslant$ 0.90 can be achieved from 40% to 60%.

Experimental details and design of proposed investigation

Overall aim:

A randomised control trial of a physiologically-guided optimisation strategy to determine the feasibility of increasing the proportion of post PCI FFR measurements $\geqslant$ 0.90 in a consecutive series of patients undergoing standard PCI procedures.

Study Population:

260 consecutive patients with stable angina referred for invasive management to the cardiac catheterisation lab who have been selected to undergo PCI based on either angiographic appearances or prior FFR assessment. Patients will be caffeine free for >12 hours pre-procedure.

Inclusion criteria:

Patients >18 years of age with coronary artery disease including stable angina and stabilised non-ST-elevation myocardial infarction (NSTEMI) able to provide informed consent.

Exclusion Criteria:

- PCI in a coronary artery bypass graft
- Inability to receive adenosine (for example, severe reactive airway disease, marked hypotension, or advanced atrioventricular block without pacemaker).
- Recent (within 1 week prior to cardiac catheterization) ST-segment elevation myocardial infarction (STEMI) in any arterial distribution (not specifically target lesion).
- Severe cardiomyopathy (ejection fraction <30%).
- Renal insufficiency such that an additional 20 to 30 mL of contrast would, in the opinion of the operator, pose unwarranted risk to the patient.

Methods/Design:

Informed consent will be obtained prior to cardiac catheterisation in all potential subjects conforming to the inclusion and exclusion criteria.
Patients will then be randomised to one of two groups (described below) and PCI will be performed, using a pressure guidewire, according to standard practice at the Golden Jubilee National Hospital (including lesion pre-dilation and post-dilation of the stented segment).

<u>Group 1 (PIOS Group):</u>

Operator-blinded FFR will be measured post PCI.
If FFR is $\geqslant$ 0.90, no further intervention will be performed and the procedure is considered complete.
If FFR is < 0.90, the result will be disclosed to the operator and a hyperaemic pressure wire pullback during either a standard peripheral intravenous adenosine infusion (140mcg/kg/min) or an intracoronary adenosine infusion (360mcg/min) via a microcatheter will be performed. Depending on the result the operator would then have the following options:

A. If there is a step-up of $\geqslant$ 0.05 across the stented segment(s) further post-dilatation with a 0.25 - 0.50mm larger non-compliant balloon to at least 18 atmospheres should be performed followed by repeat FFR. Alternatively, the operator may choose to employ intracoronary imaging (IVUS or OCT) to guide post-dilation/optimisation of the stented segment.

B. If there is a step-up of $\geqslant$ 0.05 across a relatively focal (<20mm) unstented segment which is technically suitable for further stenting then a further stent should be implanted followed by repeat FFR.
C. If the FFR remains < 0.90 after steps A +/- B, a further FFR pullback will be performed. If the criteria for Step B are again met, one additional stent may be deployed and a final FFR pullback performed. Following this, the FFR result will be accepted.
D. If the residual pressure gradient is interpreted to reflect diffuse atherosclerosis with no focal step-ups, the result is accepted.
E. At the end of the procedure the pressure wire sensor will be withdrawn to the tip of the guiding catheter and compared with the aortic pressure. A pressure drift of ≤ 0.03 will be accepted and the final FFR result adjusted accordingly.
F. If there is a drift of ≥ 0.04, the wire should be re-equalised and the final FFR measurement be repeated.
G. The patients will have their demographics and procedure details recorded. All patients will receive 3-month telephone follow-up.

Group 2 (Control Group):

Post PCI FFR will be recorded but not disclosed to the operator. The angiographically defined result will be accepted. The patients will have their demographics and procedure details recorded. All patients will receive 3-month telephone follow-up.

Primary Outcome

The primary end-point in this study will be the proportion of patients with a physiologically optimal result post PCI (FFR $\geqslant$ 0.90). We hypothesise that our PIOS intervention can increase the proportion of patients achieving this target from 40% to 60% and believe that an increment of at least this magnitude would be necessary to make a future larger study with both patient-oriented clinical (target vessel failure) and health care system (resource utilisation) outcomes acceptable to the interventional cardiology community and potential funders.

Secondary Outcomes

The main secondary outcome measure will centre on assessing change from baseline in self-reported health outcomes at 3 months using both generic and disease-specific quality of life measurement tools.
The EQ5D is a generic quality of life measurement tool which expresses preference for health status using a single index score and is the recommended tool by the National Institute for Health and Clinical Excellence (NICE) for calculation of Quality-Adjusted Life Years. It covers 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
The SAQ is a self-administered, disease-specific measure for patients with coronary artery disease that has previously been demonstrated to be valid, reproducible, and sensitive to

clinical change. The SAQ quantifies patients' physical limitations caused by angina, the frequency of and recent changes in their symptoms, their satisfaction with treatment, and the degree to which they perceive their disease to affect their quality of life.

The rate of target vessel failure and its component features (cardiac death, myocardial infarction, stent thrombosis, unplanned rehospitalisation with target vessel revascularisation) will be analysed at 3 months.

Additional secondary outcomes including procedural/patient safety factors will also be measured. These would include: procedure time, fluoroscopy dose, contrast dose, complications and cost of additional equipment employed (balloons/stents/intra-coronary imaging).

Power calculations

Assuming (as per data from previous studies) that 40% of patients in the control arm have a post PCI FFR $\geqslant$ 0.90 and that it is considered clinically relevant if the equivalent percentage in the PIOS treatment arm is at least 60%, we will require a sample size of 130 per group to have 90% power to be able to detect a difference in the population in these proportions at the 5% significance level.

Expected value of results

1. Confirmation that the proposed PIOS protocol significantly increases the proportion of patients obtaining a physiologically optimal post PCI result will demonstrate the feasibility of this strategy and should lead to an increase in post PCI pressure wire usage to achieve physiologically optimal results for patients.

2. The secondary outcome measures, albeit underpowered for clinical outcomes in this study, will hopefully still give a signal that achieving a target post PCI FFR $\geqslant$ 0.90 does yield objective benefits for patients. This could then form the basis for a larger phase 3 trial to confirm improved clinical outcomes and cost-effectiveness of FFR targeted PCI

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