Statistical Analysis Plan

Study Title: Systematic Evaluation by Randomisation of Intracoronary physiological techniques for Assessing tandem Lesions

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1. Background

Physiology-guided revascularisation improves clinical outcomes in patients with epicardial coronary artery disease when guided by either hyperaemic or resting pressure-derived physiological indices.[1–4] However, it remains unclear whether these pressure-derived indices, such as fractional flow reserve (FFR), can reliably assess individual lesions in serial coronary artery disease (CAD) due to the interplay between stenoses. Both resting and hyperaemic pressure-derived physiological indices have been shown to be susceptible to hemodynamic interplay between serial stenoses.[5,6] Furthermore, it has been demonstrated that 1 in 4 patients have residual ischaemia on physiological evaluation following percutaneous coronary intervention, despite an operator-determined angiographically successful result.[7] The presence of residual ischaemia is correlated to poor clinical outcomes.[8] Up to one-third of patients have serial disease on coronary angiography (two or more focal lesions, a focal lesion and a diffusely diseased segment or combinations of these disease patterns) and in these cases, each diseased segment has been shown to affect the measured physiology relating to the other. We have previously developed and validated a mathematical solution based solely on hyperaemic pressure inputs, FFR_{pred}, that accounts for the haemodynamic interplay between diseased segment. These pilot data demonstrated a significant reduction in error when estimating the true FFR contribution of a stenosis compared to resting and conventional hyperaemic physiological methods.[5,9]

The main aim of the current study is to compare FFR_{pred} (derived from the Abbott Pressure wire, with correction for haemodynamic interaction) with a non-hyperaemic physiology technique that assumes no interaction between diseased segments, namely one based on the trans-lesional iFR gradient (derived from the Phillips pressure wire, console and iFR Scout software).

Secondary and exploratory aims include comparing FFR_{pred} with other techniques that use the FFR pullback gradient to predict post-treatment FFR, but in contrast to FFR_{pred} assume that there is no interaction between diseased segments. These include prediction based on the trans-lesional FFR gradient (FFR_{Δ}) and the whole-vessel pressure pullback gradient (PPG). We also aim to evaluate whether less-invasive techniques (based on angiography alone) can be used as surrogates for invasive physiology in patients with serially diseased coronary arteries.

2. Definitions

Physiological Indices	
Pa	Mean aortic pressure (mmHg)
Pd	Mean distal coronary pressure (mmHg)
FFR	Pd/Pa at stable hyperaemia (range 0 to 1.0)
iFR	Pd/Pa during the wave free period (range 0 to 1.0)
PPG	Pressure Pullback Gradient (via Coroventis) (range 0 to 1.0)
Key Measures	
FFR_{Δ}	FFR gradient across the treated segment
FFR_{pred}	Predicted final FFR corrected for haemodynamic interaction
iFR_{Δ}	iFR gradient across the treated segment by iFR Scout
Study Outcomes	
FFR_{pred} error	[Post PCI FFR] – [FFR_{pred}] / [post PCI FFR]
FFR_{Δ} -based prediction error	[Post PCI FFR] – ([Pre PCI distal FFR] + [FFR_{Δ}]) / [post PCI FFR]
iFR_{Δ} -based error	[Post PCI iFR] – ([Pre PCI distal iFR] + [iFR_{Δ}]) / [post PCI iFR]
MACE	Target vessel revascularisation, myocardial infarction, stroke, all-cause death

3. Study Objectives

Primary objective:

- To compare the error of FFR_{pred} versus that based on iFR_{Δ} at predicting the physiological residual disease significance, following treatment of a target lesion, in a serially diseased coronary artery.

Secondary objectives:

- To compare the error of FFR_{pred} versus that based on FFR_{Δ} at predicting the physiological residual disease significance, following treatment of a target lesion, in a serially diseased coronary artery.
- To assess how invasive physiological evaluation influences management strategy.
- To explore the difference in clinical outcomes between treatment groups at 30-days and 1-year.

Exploratory objectives:

- To explore the correlation between the pressure pullback gradient (PPG) and the change in FFR and iFR following PCI.
- To explore the factors associated with a) the discordance between predicted and actual invasive pressure indices, and b) the discordance between FFR and iFR.
- To explore the accuracy of the quantitative flow ratio (QFR) against invasive indices of stenosis severity in serial lesions, and in predicting residual stenosis significance (by FFR or iFR) following treatment of a selected target lesion.

4. Outcomes

Primary Outcome:

- Difference in error of core lab assessed FFR_{pred} at predicting final FFR versus iFR_{Δ} based prediction of final iFR.

Secondary Outcomes:

- Difference in error of core lab assessed FFR_{pred} versus prediction based on FFR_{Δ} at predicting final FFR.

- The proportion of cases where there was a change in target lesion strategy (proximal, distal, or both) in patients proceeding to PCI, following the availability of pressure wire pullback information.
- The proportion of cases where there was a change in revascularisation modality (PCI, CABG, optimal medical therapy) following the availability of pressure wire pullback information.
- Difference in major adverse cardiovascular events (MACE) at 30 days and 1 year between iFR and FFR guided treatment.

Exploratory Outcomes:

- Predictive capacity of core lab assessed invasive PPG and QFR-PPG index for the change in FFR after PCI, and the final FFR after PCI.
- The predictors of discordance between predicted and actual invasive pressure indices, and the discordance between FFR and iFR (to include patient level characteristics such as baseline demographics, and anatomical and physiological characteristics such as target vessel, PPG, diameter stenosis and lesion length).
- Correlation between measures of core lab assessed baseline QFR and invasive FFR; and predicted QFR and FFR following PCI.

5. Key Measures

Fractional Flow Reserve (FFR)

FFR is defined as distal pressure (Pd) divided by aortic pressure (Pa) at maximal hyperaemia.

FFR_{Δ}

From the hyperaemic manual pressure wire pullback, the segment treated by PCI is identified. FFR_{Δ} is defined as the FFR gradient across the target segment.

FFR_{pred}

From the hyperaemic manual pressure wire pullback, the following calculation is applied to the segment treated by PCI to calculate FFR_{pred}.[9]

$$FFRpred = 1 - \frac{\Delta P}{P_d + \Delta P}$$

Equation 1

ΔP refers to the pressure drop across a lesion and Pd refers to distal coronary pressure.

An automated calculation (Virtustent) based upon this equation is available using Coroflow 3.5.1 (Abbott, IL, USA). A sensitivity analysis will be performed for the primary outcome based upon this automated calculation.

Post PCI FFR

Following treatment of one lesion by PCI, hyperaemia is induced and post PCI FFR is measured with the pressure transducer in the distal vessel.

Instantaneous Wave Free Ratio (iFR)

From the resting manual pressure wire pullback, iFR is calculated as a ratio of distal coronary artery pressure (Pd) to proximal pressure (Pa) over a specific period in diastole, referred to as the wave-free period. iFR is averaged across multiple cardiac beats.[6]

$$iFR = \frac{distal\ coronary\ pressure_{wave\text{-}free\ period}}{proximal\ coronary\ pressure_{wave\text{-}free\ period}}$$

Equation 2

iFR$_\Delta$

iFR$_\Delta$ is defined as the iFR gradient across the treated segment and is measured using the iFR Scout software (Philips, Amsterdam, NL).

Post PCI iFR

Following treatment of one lesion by PCI, post PCI iFR is measured with the pressure transducer in the distal vessel.

Secondary and Exploratory Outcomes

Management strategy

Strategy is assessed using two questions at two timepoints. These are: 1) Patient-level treatment modality (CABG; PCI; medical therapy), and 2) Vessel-level treatment strategy (proximal lesion only; distal lesion only; both lesions). They are assessed at A) after index invasive coronary angiography, B) after initial coronary physiology, including pullback trace of FFR or iFR (as randomised) (before PCI).

This endpoint will be assessed by the proportion of cases in which the management strategy changes after the availability of coronary physiology data. A change in treatment modality or target lesion is defined as a change in response from timepoint A to timepoint B.

Major adverse cardiovascular events (MACE)

MACE is defined as target vessel revascularisation, myocardial infarction, stroke, all-cause death. It is assessed at 30 days and 1 year.

Pressure pullback gradient (PPG)

The PPG provides a quantitative assessment of the hyperaemic manual pullback curve. Values closer to 0 indicate diffuse coronary disease, whilst values closer to 1 indicate more focal disease.[11] It is calculated automatically using Coroflow 3.5.1 (Abbott, IL, USA).

$$\text{PPG} = \frac{\frac{\text{Maximal pressure gradient over 20\% of the pullback duration}}{\text{Vessel FFR gradient}} + (1 - \text{proportion of pullback time with FFR deterioration})}{2}$$

Equation 3

6. Data Available

Angiography and invasive physiology data will be transferred to King's College London for core laboratory analysis. All core laboratory data will be analysed by trained readers working in pairs. Data will be analysed blinded to patient demographics and clinical outcomes. Readers will be blinded to final physiology measurements when assessing baseline physiology traces. In case of disagreement between readers, adjudication will be by a second pair of blinded readers. Demographics, treatment decisions and procedural information will be collected electronically via an eCRF (King's College London Clinical Trials Unit).

Angiography

3D quantitative coronary angiography (QCA) and quantitative flow ratio will be analysed using Medis QFR Research Edition 2.2 (Medis Medical Imaging, Netherlands).

Baseline angiography will be first assessed for technical quality (2 angiographic projections separated by ≥25° without excessive overlap or foreshortening, and acquired at ≥12.5 frames per second). Aorto-ostial stenoses will be excluded from QFR analysis.

The distal boundary QFR analyses will be defined by reference to the coronary angiogram as the location of the pressure wire sensor during baseline measurements. Predicted change in QFR after PCI will be calculated but adjusting lesion markers to match the treated segment, with reference to the coronary angiogram.

Physiology

Patients will have undergone baseline pressure wire measurements with manual pullback using both the Abbott and Phillips pressure wires. After assessment for technical quality, core lab readers will use the coronary angiogram to judge the segments of the pullback that were treated by PCI.

7. Statistical Analysis

Timepoints for Analysis

The main analysis (which includes the primary outcome) will be performed after the study closes to recruitment, and after locking of the core laboratory database. The secondary outcome of 30-day and 1-year MACE will be analysed following completion of follow up for all participants. The SAP will be finalised before all analyses and unblinding of data.

Primary Outcome Power Calculation

60 paired comparisons will have 90% power to detect a difference in error of 6% between FFR_{pred} and prediction based on iFR_{Δ}. This is based upon a 2 tailed paired *t* test with a mean error of 14% (FFR_{pred}) and 20% (iFR_{Δ}-based prediction), a standard deviation of 14% for both measures, and correlation between measurements of 0.5, tested at the 5% significance level.[5]

However, as patients are enrolled based on angiographic criteria, it is anticipated that paired pre-and post-treatment physiology (which is essential for evaluation of the primary outcome measure) may not be obtained in a significant proportion of cases for one or more of the following reasons:

- The haemodynamic significance of angiographically diseased vessels may not reach the treatment thresholds (FFR 0.80 and/or iFR 0.89) and hence no PCI undertaken
- The vessel may be found to be diffusely diseased and hence unsuitable for PCI (these vessels will then be managed with medical therapy or bypass surgery). This will inform the secondary outcome (changes in management strategy based on physiology) but will not yield paired pre and post treatment physiology measurements).
- Post PCI physiology measurement may not be possible due to the patient's clinical status, inability to pass the pressure wire through the stented segment, or if the operator judges it necessary to treat both lesions with one contiguous stented segment, rather than treating one diseased segment, re-measuring physiology and proceeding to treat the second segment.

Assuming a 50% loss after enrolment due to the reasons above, the study has been designed to recruit 120 patients. However, trial progress will be monitored throughout, including the rate of accrual of paired physiology datasets. Recruitment will be stopped when 120 patients have been enrolled or 60 paired analysable physiology datasets are accrued, whichever occurs sooner.

Statistical Methods

In the case of secondary and exploratory endpoints that involve a continuous outcome, transformation may be necessary to allow for analysis with the most appropriate statistical method.

Primary outcome

Difference in error between FFR_{pred} FFR_{Δ} and iFR Scout

FFR_{pred} error is defined as ([post PCI FFR] – FFR_{pred}) / [post PCI FFR].

FFR_{Δ} -based error is defined as [Post PCI FFR] – ([Pre PCI distal FFR] + [FFR_{Δ}]) / [post PCI FFR]

iFR_{Δ} -based error is defined as [Post PCI iFR] – ([Pre PCI distal iFR] + [iFR_{Δ}]) / [post PCI iFR]

The error of each method will be compared using the paired *t* test. Continuous agreement between predicted and observed pressure-wire indices will be analysed using the Bland-Altman method and correlation analysis.

The primary analysis will be performed using manual calculation of with FFR_{pred} using equation 1 (section 5). A sensitivity analysis will be performed that uses Virtustent to calculate FFR_{pred}.

Secondary outcomes

- ***Impact of post angiography pressure wire pullback on treatment decisions***

  The relationship between treatment allocation and change in treatment decision will be assessed using the McNemar-Bowker Test.

- ***Difference in MACE at 30 days and 1 year between iFR and FFR guided treatment***

  An unadjusted time-to-event analysis will be performed with a Cox survival model will be used to derive hazard ratios. Due to paired comparisons within the same vessel, no adjustment for covariates is planned. Time to the first event (or censoring) will be measured from randomisation on an intention to treat basis. Cumulative event rates will be calculated and presented using Kaplan-Meier curves. As a measure of absolute treatment difference, cumulative event rates based on Kaplan-Meier estimates will be compared at 1-year and a 95% confidence interval for the difference calculated. Losses to follow-up are expected to be minimal and patients will be included up until the time they experience an event or are censored.

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