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## Journal Pre-proof

### The Impact of Virtual Fractional Flow Reserve and Virtual Coronary Intervention Upon Treatment Decisions in the Cardiac Catheter Laboratory

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**The Impact of Virtual Fractional Flow Reserve and Virtual Coronary Intervention Upon Treatment**

**Decisions in the Cardiac Catheter Laboratory**

**Short title: Impact of vFFR and VCI on treatment decisions**

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**Brief Summary**

Fifty coronary angiograms were reviewed by two interventional cardiologists independently. Knowledge of vFFR led to a change in management in 27%. VCI and a stent sizing tool led to a change in recommended stent size in 48%. Disclosure of vFFR and VCI increased operator confidence ( $p < 0.001$ ). Twelve cases were reviewed by six additional operators. There was significant variation in the management plans based upon both angiographic assessment ( $\kappa = 0.30$ ) and vFFR ( $\kappa = 0.39$ ).

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**Abstract**

**Background:** Using fractional flow reserve (FFR) to guide percutaneous coronary intervention for patients with coronary artery disease (CAD) improves clinical decision making but remains under-

used. Virtual FFR (vFFR, computed from angiographic images) permits physiological assessment without a pressure wire and can be extended to virtual coronary intervention (VCI) facilitating treatment planning. This study investigated the effect of adding vFFR and VCI to angiography in patient assessment and management.

**Methods:** Two cardiologists independently reviewed clinical data and angiograms of 50 patients undergoing invasive management of coronary syndromes, and their management plans were recorded. The vFFRs were computed and disclosed, and the cardiologists submitted revised plans. Then, using VCI, the physiological results of various interventional strategies were shown, and further revision was invited.

**Results:** Disclosure of vFFR led to a change in strategy in 27%. VCI led to a change in stent size in 48%. Disclosure of vFFR and VCI resulted in an increase in operator confidence in their decision. Twelve cases were reviewed by six additional cardiologists. There was limited agreement in the management plans between cardiologists based upon either angiography ( $\kappa=0.31$ ) or vFFR ( $\kappa=0.39$ ).

**Conclusions:** vFFR has the potential to alter decision making, and VCI can guide stent sizing. However, variability in management strategy remains considerable between operators, even when presented with the same anatomical and physiological data.

## Abbreviations

|          |   |
|----------|---|
| CABG     | Coronary artery bypass graft                      |
| CMR      | Cardiac magnetic resonance                        |
| CMVR     | Coronary Microvascular Resistance                 |
| CTCA     | Computed tomography coronary angiography          |
| ECG      | Electrocardiogram                                 |
| FFR      | Fractional Flow Reserve                           |
| NSTE-ACS | Non ST-segment Elevation Acute Coronary Syndromes |
| OMT      | Optimal medical therapy                           |
| PCI      | Percutaneous Coronary Intervention                |
| VCI      | Virtual Coronary Intervention                     |
| vFFR     | Virtual Fractional Flow Reserve                   |

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## ***Introduction***

Using fractional flow reserve (FFR) to guide percutaneous coronary intervention (PCI) improves clinical outcomes and reduces costs compared with angiographic guidance<sup>1</sup>. FFR also impacts decisions regarding interventional strategy. In the RIPCORD study, knowledge of FFR altered the recommended treatment plan in 26% of patients<sup>2</sup>. However, FFR measurement is invasive, expensive, time-consuming and not available at all centres. It therefore remains under-used<sup>3</sup>. Computational fluid dynamics models of FFR (vFFR) based upon the angiogram can predict FFR without the need for invasive instrumentation<sup>4-6</sup>. Related modelling techniques also permit virtual coronary intervention (VCI) or 'virtual stenting' which enables the physiological response to alternative stenting strategies to be predicted *a priori*<sup>7</sup>. However, it remains unknown whether such virtual clinical methods have a similar impact upon clinical decision making as invasive FFR.

In this study, we investigated the effect of the VIRTUheart™ model of vFFR and VCI upon decision making for patients with acute or chronic coronary syndromes.

## ***Methods***

### ***Study design and patients***

This was an observational study involving retrospective analysis of prospectively collected data from patients attending the cardiac catheter laboratory at the Northern General Hospital, Sheffield, UK; a large tertiary cardiac centre in the North of England. We interrogated the research database to identify patients who had undergone PCI for chronic or non-ST-segment elevation acute coronary syndromes (ACS). The research database has been compiled over a number of years and consists of

nearly 500 coronary angiograms. These cases have already been pre-screened for their suitability for coronary modelling<sup>7</sup>. Seventy consecutive cases from the database, meeting the inclusion criteria were selected for analysis. Patients were excluded if they had presented with ST-segment elevation myocardial infarction, previous coronary artery bypass graft (CABG) surgery, chronic total coronary artery occlusions or if the angiographic images were unsuitable for modelling. From the initial seventy, fifty patient cases were identified for inclusion in the study (in keeping with sample size calculation below). A patient flow diagram is shown in Supplementary figure S1. The research was approved by the NHS Research Ethics Committee and the institutional review board. As this was an observational study utilising routinely collected clinical data no formal consent was required.

### ***Original procedure***

Patients underwent standard, multiple single plane coronary angiography prior to PCI. PCI was performed using standard techniques according to the operator's normal practice. Treatment decisions made by the operator at the time were noted but not disclosed to the cardiologists in this study.

### ***Modelling protocol***

Angiograms were screened against the criteria for accurate modelling, namely: adequate image centering; at least two orthogonal views; inclusion of the whole arterial segment of interest; sufficient contrast between vessel and background; minimal vessel overlap; sufficiently long acquisitions to capture several cardiac cycles with at least one good diastolic frame; and minimal panning. Vessels with a minimum diameter of 2.5mm and at least 30% diameter stenosis by visual estimation were included. Cases which did not meet these criteria were excluded. Using the VIRTUheart<sup>TM</sup> system, diseased vessels were reconstructed and vFFR and up to four alternative,

plausible VCI strategies were constructed, based on advice from an independent interventionist (figure 3)<sup>8</sup>. vFFR was computed pre- and post-VCI.

### ***Impact of vFFR and VCI upon clinical decisions***

Cases were independently reviewed by two interventionists blinded to each other and to the original procedure. Each cardiologist was presented with the clinical history, ECG and baseline angiographic images. Based upon these conventional data sources, they were asked to give their recommendation for treatment (on a per-patient level); optimal medical therapy [OMT], PCI, CABG surgery or 'more information required', which could include measured FFR or any other investigation they felt was required in order for them to make a decision. If they selected PCI, they were asked to specify the vessel(s) for revascularisation and the number and size of stent(s) they would recommend based upon their clinical practice. At each stage, they were asked to rate their confidence in their decision on a scale 0-10 (10 being high). After making the initial recommendations, they were shown the results of baseline vFFR modelling (including the stent sizing tool, which displays the vessel width at any chosen point as well as the distance between any two pre-specified points along the vessel path (supplementary figure S2)) and asked to re-state their management plan and their confidence in the decision based upon those additional data. Finally, they were shown the VCI results and, again, were asked to state any changes in the management plan. At each stage, the interventional cardiologists were asked to utilise the vFFR and VCI data in combination with their own clinical judgment to reflect real world practice. The importance they ascribed to the modelling was left to their discretion. All of the participating cardiologists were presented with the most recently published accuracy data for both vFFR and VCI prior to commencing the study<sup>8</sup>. The study protocol is illustrated in Figure 1. To further explore inter-observer variability, a subset of 12 cases were randomly selected and shown to six additional interventional cardiologists, independent of each

other and of the original clinical team. They were presented in the same way as above. The primary outcome was the number/percentage of cases in which the patient-level treatment recommendation changed based upon virtual physiology.

### *Analysis and sample size*

Continuous data were presented as mean ( $\pm$ SD) and categorical data as number (percentage) unless stated otherwise. Patient-level treatment strategies based upon angiographic, vFFR and VCI assessment were compared. Agreeability between operators was assessed using Cohen's kappa coefficient. Confidence scores were compared using repeated measures ANOVA. Statistical analysis was carried out using SPSS version 21 (SPSS Inc, New York, US). Based upon the RIPCORD study, it was estimated that a change of management would be observed in about 25% of patients; a change <10% being deemed unimportant. The number of patients required in the study is directed by  $p$ , the proportion of cases in which the decision is different after the intervention than it was before. The 95% confidence intervals for  $p$  are derived from the formula:  $\hat{p} \pm 1.96 \sqrt{\hat{p}(1-\hat{p})/n}$ . A sample size of 50 provides 95% confidence intervals of 12% to 37% for this effect size.

### *Results*

#### **Patient and vessel characteristics**

Patient baseline characteristics are summarised in Table 1. Fifty potentially suitable patients were identified from hospital records, with a total of 86 diseased vessels. Eight (9%) vessels were unsuitable for vFFR modelling, so 78 lesions were included in the final analysis from 50 patients. Cases included 43 left anterior descending (LAD), 17 circumflex (LCX), 13 right (RCA), three diagonal (D1) and two obtuse marginal (OM) arteries. Mean baseline vFFR was 0.73 ( $\pm$ 0.17).

### **Impact of disclosing vFFR result**

After revealing the vFFR results, the operators changed their initial management strategy on 22 occasions (22%, 95% CI: 15% to 31%). Each patient case is considered twice (as each case was reviewed independently by the two operators), therefore 'occasion' refers to a particular case assessed by an individual operator. Details of the nature of these changes are shown in Figure 2. PCI strategy (number and location of vessels for PCI) changed in a further five (5%), so the total number of occasions in which management changed was 27 (27%, 95% CI: 19-36%) (20% of patients for operator A and 34% of patients for operator B). In cases where PCI was selected, vFFR resulted in a change in stent size in 47%. The amendments comprised an increase in length in 48%, a reduction in length in 32%, a reduction in diameter in 32% and an increase in diameter in 10%.

### **Effect of disclosing VCI results**

For cases in which PCI was recommended, disclosure of the VCI results led to a change in stent size in 33% of occasions. The amendments comprised an increase in stent length in 44%, a reduction in stent length in 30%, a reduction in stent diameter in 22% and an increase in stent diameter in 4%. On one occasion, VCI led to a change in initial strategy. This was a case with a borderline vFFR, prompting the cardiologist to recommend an invasive pressure wire. However, VCI revealed an excellent result with minimal stenting, which provided sufficient reassurance to proceed with PCI without the need for a pressure wire.

### **Overall effect of vFFR and VCI**

Stent size was amended with either vFFR or VCI on 48% occasions. The amendments comprised an increase in length in 42%, a reduction in length in 28%, an increase in diameter in 4% and a reduction in diameter in 25%. Mean stent widths after angiographic, vFFR and VCI assessments were  $2.91\pm 0.34$ ,  $2.85\pm 0.31$  and  $2.83\pm 0.32$  respectively ( $P=0.04$ ). Mean stent lengths after angiographic, vFFR and VCI assessment were  $23.0\pm 8.5$ ,  $24.2\pm 8.7$  and  $23.9\pm 8.3$  mm, respectively ( $P=0.37$ ).

### **Confidence in the management plan**

Based upon angiographic assessment alone, mean confidence scores in patient-level management, vessel-level management and stent sizing were 8.11, 8.38 and 6.94 out of 10, respectively.

Disclosure of vFFR increased operator confidence in all three domains (patient-level management  $+0.47 \pm 1.27$ ,  $P<0.001$ ; vessel-level  $+0.48 \pm 1.23$ ,  $P<0.001$ ; stent sizing  $+1.0 \pm 1.14$ ,  $P<0.001$ ). After VCI results were revealed, the confidence level in patient-level management and stent sizing both increased significantly ( $+0.14 \pm 0.63$ ,  $P=0.03$ ;  $+0.72 \pm 0.62$ ,  $P<0.001$ ) but there was no significant change in confidence in vessel-level management ( $+0.07 \pm 0.63$ ,  $P=0.31$ ). Summarised data are shown in Table 2. Confidence in angiography-based management was not related to whether the operator went on to change their plan based upon physiology or not (8.18 versus 7.82,  $P=0.32$ ). However, initial confidence in stent size was significantly lower in those cases in which stent size recommendation subsequently changed (6.63 versus 7.15,  $P=0.02$ ).

### **Inter-observer variability**

The subset of 12 cases reviewed independently by a total of eight interventional cardiologists comprised nine LADs, six LCXs and five RCAs. Mean vFFR was 0.73 ( $\pm 0.15$ ). Baseline characteristics are summarised in Table 3. There was minimal agreement between the cardiologists' management plans ( $k=0.30$ , 95% CI: 0.21-0.39) either before (ie based upon the angiogram) or after ( $k=0.39$ , 95% CI 0.31-0.47) vFFR assessment. All of the management plans are illustrated in Table 4.

## ***Discussion***

In this study, we have analysed the potential for angiography-based computed coronary physiology, namely a virtual FFR (vFFR), with its derivative, virtual coronary intervention (VCI), to alter patient management. Knowledge of the baseline vFFR led to a change in management in 27%. VCI led to a change in recommended stent size in 48%. Of note, the proportion of cases in which management was changed based upon the physiology varied greatly, and when eight cardiologists were studied, the proportion of patients in whom changes were recommended varied between none and 50% (average 33%). There were also marked differences between their management plans, whether based both upon traditional angiography or physiology. However, both vFFR and VCI significantly improved the cardiologist's confidence in their management plans.

### ***Impact of vFFR upon patient management***

When baseline vFFR results were revealed, a change in the proposed management plan occurred in 27-33% of patients. The effect of revealing coronary physiology upon cardiologists' decision making has previously been examined in the RIPCORD<sup>2</sup> and FFR<sub>CT</sub> RIPCORD<sup>9</sup> trials. In RIPCORD, there was a change in the patient-specific management plan in 26% of cases with FFR compared to angiography alone, and in FAMOUS it was 22%<sup>10</sup> remarkably similar proportions to our study. Our study differed from RIPCORD and FAMOUS in a number of ways. First, ours included both chronic and acute coronary syndromes, reflecting current practice<sup>11</sup>. Second, only patients who had initially been selected for PCI were included. This was to ensure there was a high proportion of lesions to assess. Third, and most importantly, RIPCORD and FAMOUS used invasive FFR whereas our study used vFFR which is not yet as well validated as invasive FFR<sup>12,13</sup>. Fourth, in our study, the interventional cardiologist was asked to incorporate the vFFR and VCI data into their management plan as they saw

fit, based upon the whole clinical, angiographic and physiological setting, without mandating treatment based solely upon the FFR, in order to explore the impact of virtual coronary physiology in real world practice. This probably explains the wide variation in treatment recommendations between individuals when presented with the same vFFR. In acute cases, we found that operators frequently chose to proceed to revascularisation irrespective of the vFFR. In the FFR<sub>CT</sub> RIPCORD study, FFR<sub>CT</sub> changed treatment decisions compared to those made based upon CTCA alone in 36% of cases<sup>9</sup>. The single largest group change was from 'more information required' (i.e. an invasive pressure wire) to either OMT or PCI, constituting 53% of the cases in which management changed. This accorded with our findings (70%). In our study, an invasive pressure wire was recommended in 30% of cases. Whilst this is higher than the observed usage of 5-10%<sup>3</sup>, because this was a virtual study, this might not translate into actual pressure wire usage; and in the FFR<sub>CT</sub> RIPCORD study, the equivalent figure was 19%. Moreover, this study was carried out in a tertiary cardiology centre with ready access to pressure wire usage.

### ***Inter-observer variability***

Our initial findings of a large variation in recommendations between our two experts mandated further study with a larger group of interventional cardiologists. When the same patient cases were reviewed by eight cardiologists, patient-level management changed, based upon vFFR, in 33%, but the range was 0-50%, so the impact of vFFR was considerable, but the difference between operators was even greater. There was also significant variation between management plans, with minimal increase in agreement following vFFR disclosure. Inter-observer variability in assessing coronary angiograms is well documented<sup>14-18</sup> but the impact upon treatment decisions is less well known. In our study, a major factor was trust in the vFFR, especially when the 3D reconstruction differed from their perception of the angiogram. Despite several studies demonstrating disagreement between visual and physiological assessment, many operators believe angiography to be superior. The ERIS study<sup>19</sup> analysed the use of physiological assessment in 76 centres. Invasive physiology was used in

fewer cases than recommended, the predominant reason being confidence in the history and the angiogram. We found that the operators' initial confidence in their management plan was unrelated to their decision according with physiology or whether they went on to change their plan based upon physiology. This suggests that being confident in angiographic assessment is not a good reason to refrain from physiological assessment. In our study, in an average of 38%, after vFFR was made available, the management plan still contradicted what would be recommended by vFFR alone. The most common reason for this (33%) was the presence of other clinical or technical factors that precluded PCI, such as diffuse disease, distal disease, or non-invasive imaging confirming non-viability. However, in 22% of cases, the operator stated that they were more convinced by their angiographic assessment than the vFFR.

### ***Impact of VCI upon treatment planning***

Although disclosure of the VCI results had little impact upon patient-level management beyond that achieved with vFFR, the procedural details (size of stent) changed in 33% of cases based upon VCI alone, and in 48% when combined with the stent sizing feature. VCI is intended to be a treatment planning tool, so its main use is in cases in which the operator has already decided that PCI is warranted, based upon either angiographic or physiological assessment. VCI then allows the operator to plan the procedure more precisely. We have demonstrated, for the first time, that this approach has the potential to significantly impact treatment decisions. This could maximise physiological benefit from PCI, potentially leading to improved outcomes, and possibly reduce the risks of over- or under- sizing and excessive stent length. This concept needs to be explored. In addition, vFFR allied to VCI may offer the non-interventional cardiologist appreciation of the possibilities for treatment. Previous work demonstrates that VCI based on invasive pressure wire data is not only more accurate but can also generate absolute flow and microvascular data<sup>20</sup>.

***Clinical applicability in the future***

For the purpose of this study, vFFR and VCI were performed in all cases regardless of complexity. In reality, not all cases will require vFFR and/or VCI and determining when these should be used remains an important question. A severe lesion, or a completely normal vessel does not warrant vFFR. Its benefit, like invasive FFR, is in moderate lesions where the haemodynamic significance is unclear. However, correctly identifying these cases remains challenging. The purpose of VCI is for treatment planning, so it is most relevant in cases where the operator is unsure on the optimal stenting strategy regardless of the baseline vFFR (eg one versus multiple stents in the setting of diffuse or tandem lesions). Ultimately it will be up to the operator when they wish to utilise these technologies, therefore more work is required to provide outcome data and convince cardiologists that a virtual physiology based approach is superior to an angiography based approach. Significant variation in the confidence in the virtual technology, when it disagreed with the operators own angiographic assessment, was a key contributor to the inter-observer variability demonstrated in this study.

***Limitations***

First, only patients undergoing PCI were studied. We could not assess the potential impact upon a wider group of patients with coronary disease. Second, the sample was relatively small. Third, stent sizing decisions were made without the aid of balloon markers, intravascular imaging or other cues, which would normally be available to assist the operator with sizing during the invasive procedure. Fourth, vFFR was computed using generic boundary conditions, although previous work has demonstrated acceptable accuracy with this method. All operators were advised of the accuracy of the tools before they began their assessment. Fifth, in a virtual study with modest numbers we cannot report on complications or outcomes. Sixth, operators were encouraged to state their

treatment recommendations based upon the real-life practice; but as this was a virtual study, it was not possible to control for potential bias. Seventh, this was not an all-comers study; cases were selected from a pre-screened research database. We have previously reported that the proportion of 'real-world' cases that are suitable for coronary modelling is about 80%<sup>7</sup>. Eighth, our cases include a higher proportion of LAD arteries than LCX and RCA due to a slightly higher exclusion rate of these arteries due to difficulties with the 3D reconstruction. The LAD is generally well imaged in multiple views and its course tends to be less torturous which permits more accurate segmentation (3D reconstruction). The RCA is more challenging because it typically traverses multiple planes which makes the selection of truly orthogonal views more challenging. Moreover, often only two images of the RCA are routinely acquired so there are no alternative images available if one is unsuitable. However, the software is continually being updated to overcome these issues. A larger study would be required to determine the true magnitude of this effect.

### ***Conclusion***

Disclosure of vFFR can lead to a change in planned patient management in about a third of cases compared to angiography-based assessment. Combining our novel stent sizing tool with VCI resulted in change in recommended stent sizing in almost half. Virtual physiology and VCI increased operator confidence in their selected treatment strategy. However, the treatment plans, and how virtual physiology was incorporated into them, varied significantly between interventional cardiologists. Our findings suggest that virtual physiology has the potential to alter management; but, as with measured indices, it remains the interventional cardiologist who places this into the context of the clinical picture, and their own decision-making algorithms, with varying results.

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### Disclosures

The authors have no conflicts of interest to declare.

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## Tables

**Table 1: Patient and lesion characteristics**

| Patient characteristics (N=50) |          |
|--------------------------------|----------|
| Mean age (years)               | 66 ± 11  |
| Male                           | 36 (72%) |
| Hypertension                   | 33 (66%) |
| Hyperlipidaemia                | 20 (40%) |
| T2DM                           | 12 (24%) |
| Current smoker                 | 12 (24%) |
| Previous MI                    | 6 (12%)  |
| Indication for PCI:            |          |
| <i>Stable angina</i>           | 17 (34%) |

|                                      |             |
|--------------------------------------|-------------|
| <i>NSTEMI</i>                        | 33 (66%)    |
| <b>Vessel characteristics (N=64)</b> |             |
| Vessel                               |             |
| <i>LAD</i>                           | 37 (58%)    |
| <i>LCX</i>                           | 14 (22%)    |
| <i>RCA</i>                           | 10 (16%)    |
| <i>OM</i>                            | 2 (3%)      |
| <i>Dx</i>                            | 1 (2%)      |
| Baseline vFFR                        | 0.73 ± 0.16 |
| No. of stents                        | 1.1 ± 0.3   |
| Mean stent length (mm)               | 21.3 ± 7.4  |
| Mean stent width (mm)                | 3.1 ± 0.4   |

*Dx* – Diagonal artery, *LAD* = Left anterior descending artery, *LCX* = Left Circumflex artery, *MI* = Myocardial Infarction, *NSTEMI* = No n ST Elevation Myocardial Infarction, *OM* = Obtuse Maris artery, *RCA* = Right Coronary artery, *T2DM* = Type 2 Diabetes Mellitus, *vFFR* = Virtual Fractional Flow Reserve

**Table 2. Confidence scores in patient-level management, vessel-level management and stent sizing following angiographic assessment, vFFR assessment and VCI (scale 1-10).**

|                | Angio     | vFFR      | VCI       | P value |
|----------------|-----------|-----------|-----------|---------|
| Cardiologist A |           |           |           |         |
| Patient level  | 8.64±1.38 | 8.76±1.35 | 8.86±1.31 | 0.04    |
| Vessel level   | 9.21±0.95 | 9.21±1.01 | 9.25±0.87 | 0.52    |
| Stent size     | 7.34±1.03 | 7.92±0.91 | 8.62±0.91 | <0.001  |
| Cardiologist B |           |           |           |         |
| Patient level  | 7.58±1.43 | 8.22±1.17 | 8.39±0.92 | <0.001  |
| Vessel level   | 7.59±1.48 | 8.29±1.24 | 8.38±1.04 | <0.001  |
| Stent size     | 6.56±0.73 | 7.72±0.95 | 8.42±0.84 | <0.001  |
| Combined       |           |           |           |         |
| Patient level  | 8.11±1.50 | 8.49±1.29 | 8.63±1.15 | <0.001  |
| Vessel level   | 8.38±1.48 | 8.71±1.23 | 8.79±1.06 | <0.001  |
| Stent size     | 6.94±0.97 | 7.81±0.94 | 8.51±0.88 | <0.001  |

Values = Mean ± SD. vFFR = Virtual Fractional Flow Reserve; VCI = Virtual Coronary Intervention. P value shown for significance of change in confidence level after vFFR and VCI assessment (repeated measures ANOVA).

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**Table 3: Baseline patient and vessel characteristics for the subset of 12 patients**

| <b>Patient characteristics (N=12)</b> |             |
|---------------------------------------|-------------|
| Mean age (years)                      | 64±10       |
| Male                                  | 8(67%)      |
| Hypertension                          | 7 (58%)     |
| Hyperlipidaemia                       | 5 (42%)     |
| T2DM                                  | 1 (8%)      |
| Current smoker                        | 4 (33%)     |
| Previous MI                           | 2 (17%)     |
| Indication for PCI:                   |             |
| <i>Stable angina</i>                  | 4 (33%)     |
| <i>NSTEMI</i>                         | 8 (67%)     |
| <b>Vessel characteristics (N=20)</b>  |             |
| Vessel                                |             |
| <i>LAD</i>                            | 9 (45%)     |
| <i>LCX</i>                            | 6 (30%)     |
| <i>RCA</i>                            | 5 (25%)     |
| Baseline vFFR                         | 0.73 ± 0.15 |

Values are mean ± SD or number (%). LAD = Left Anterior Descending; LCX = Left Circumflex; MI = Myocardial Infarction; NSTEMI = Non-ST-Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; RCA = Right Coronary Artery; T2DM = Type 2 Diabetes Mellitus; vFFR = Virtual Fractional Flow Reserve.

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**Table 4: Recommended management plans provided by cardiologists for a subset of 12 patients after angiographic assessment and vFFR assessment.**

|    | A     |       | B     |       | C     |       | D     |       | E     |       | F     |       | G     |       | H     |       |
|----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|    | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   | Ang   | FFR   |
| 1  | Dark  | Light | Dark  | Light | Dark  | Light | Light | Light | Light | Light | White | White | Light | Light | White | White |
| 2  | Dark  | White | Dark  | White | Dark  | White | Dark  | White | Dark  | Dark  | White | White | Dark  | Dark  | White | White |
| 3  | Dark  | Light | Dark  | Dark  | Dark  | Light | Dark  | Dark  | Dark  | Light | Dark  | Dark  | Dark  | Dark  | Dark  | Dark  |
| 4  | Dark  | Light | Dark  | Light | Dark  | Light | Light | Light | Light | Light | White | White | Dark  | Light | Light | Light |
| 5  | Dark  | White | Dark  | Dark  | Light | Dark  | Dark  | White | Light | Dark  | Dark  | Dark  | Dark  | Dark  | Dark  | Dark  |
| 6  | Light | Light | Light | Light | Dark  | Light | Light | Light | Light | Light | Light | Light | Light | Light | Light | Light |
| 7  | White | White | Dark  | White | Light | White | White | White | Dark  | Dark  | White | White | Dark  | White | Dark  | White |
| 8  | Dark  | Dark  | Light | Light | Dark  | Dark  | Light | Dark  | Light | Light | Light | Light | Light | Dark  | Light | Light |
| 9  | Light | Light | Light | Light | Dark  | Light | Light | Light | Light | Light | Dark  | Light | Light | Light | Light | Light |
| 10 | Light | Light | Light | Light | Dark  | Dark  | Light | Light | Light | Light | Light | Light | Light | Light | Light | Light |
| 11 | Light | Light | Light | Light | Light | Light | Light | Light | Dark  | Light | Light | Dark  | Dark  | Dark  | Dark  | Dark  |
| 12 | Dark  | Light | Dark  | Dark  | Light | Dark  | Light | Light | Light | Light | Dark  | White | Dark  | Dark  | Light | Dark  |



Twelve patient cases (1-12) were reviewed by eight cardiologists (A-H). For each case, the cardiologist provided a management plan (OMT, PCI, CABG or more information required) based upon conventional angiography (column Ang). A second plan was then made after vFFR results were made available (column FFR).

CABG = Coronary Artery Bypass Graft surgery, OMT = Optimal Medical Therapy, PCI = Percutaneous Coronary Intervention, vFFR = Virtual Fractional Flow Reserve

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Table 5: Case example: Breakdown of management plans made by each cardiologist after angiographic, vFFR and VCI assessment.

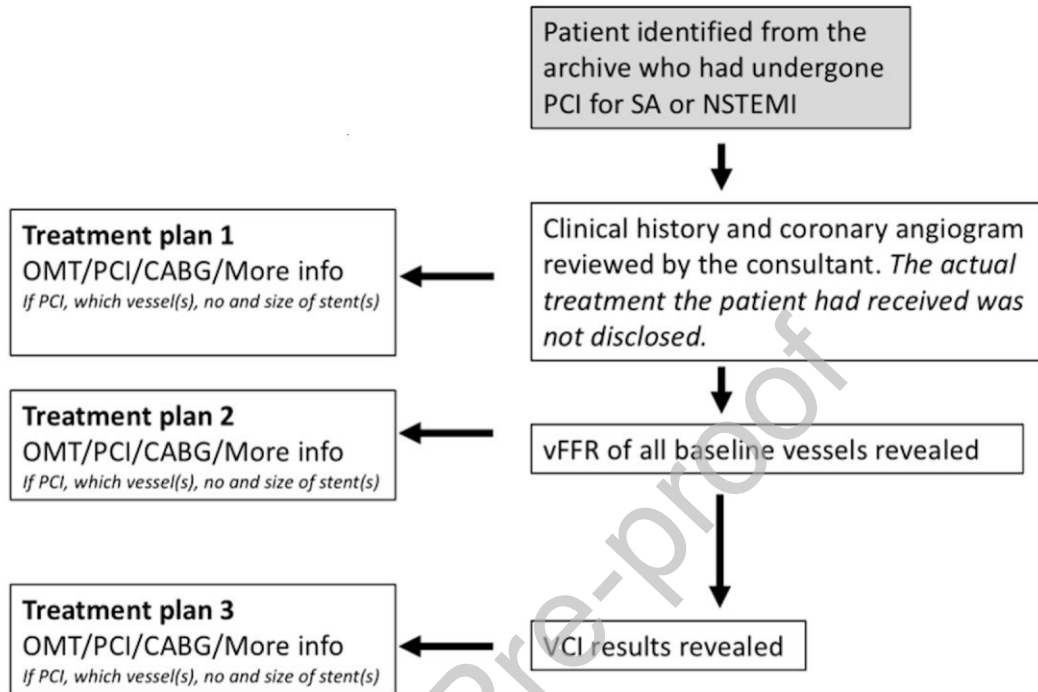
| Cardiologist | Angiographic                     |                   |              | vFFR |                   |  | VCI  |                   |  |
|--------------|----------------------------------|-------------------|--------------|------|-------------------|--|------|-------------------|--|
|              | Plan                             | Vessel(s) for PCI | Stent size   | Plan | Vessel(s) for PCI | Stent size                                 | Plan | Vessel(s) for PCI | Stent size                                 |
| A            | OMT                              |                   | -            | OMT  |                   | -  | OMT  |                   | -  |
| B            | PCI                              | RCA               | 2.25 x 28 mm | PCI  | RCA<br>LCX        | 2.25 x 32mm,<br>2.75 x 32 mm<br>2.5 x 28mm | PCI  | RCA<br>LCX        | 2.25 x 32mm,<br>2.75 x 32 mm<br>2.5 x 28mm |
| C            | PCI                              | RCA               | 3.0 x 48mm   | PCI  | RCA               | 3.0 x 48mm                                 | PCI  | RCA               | 3.0 x 48mm                                 |
| D            | PCI and PW LCX                   | RCA               | 2.5mm x 30mm | PCI  | RCA               | 2.5 x 38mm                                 | PCI  | RCA               | 2.5 x 38mm                                 |
| E            | PW LAD, if +ve surgical referral | -                 | -            | PCI  | RCA               | 2.75 x 30mm                                | PCI  | RCA               | 2.75 x 30mm                                |
| F            | OMT                              |                   | -            | OMT  |                   | -  | OMT  |                   | -  |
| G            | PW LAD, if +ve surgical referral | -                 | -            | PCI  | LCX               | 2.5 x 23mm                                 | PCI  | LCX               | 2.5 x 26mm                                 |

|   |     |     |            |     |     |            |     |     |            |
|---|-----|-----|------------|-----|-----|------------|-----|-----|------------|
| H | PCI | RCA | 3.0 x 38mm | PCI | RCA | 3.0 x 38mm | PCI | RCA | 3.0 x 38mm |
|---|-----|-----|------------|-----|-----|------------|-----|-----|------------|

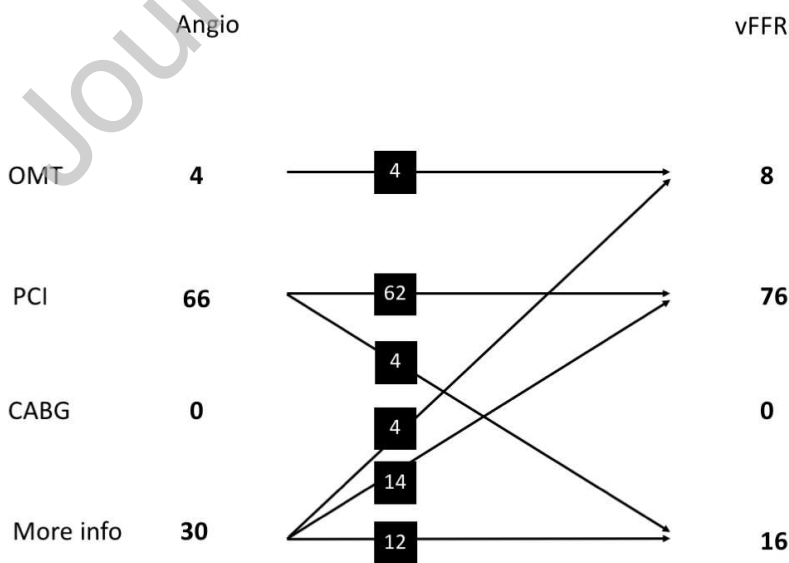
LAD = Left Anterior Descending Artery, LCX = Left Circumflex Artery, OMT = Optimal Medical Therapy, PCI= Percutaneous Coronary Intervention, PW = Pressure wire, RCA = Right coronary artery,

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**Figure legends**

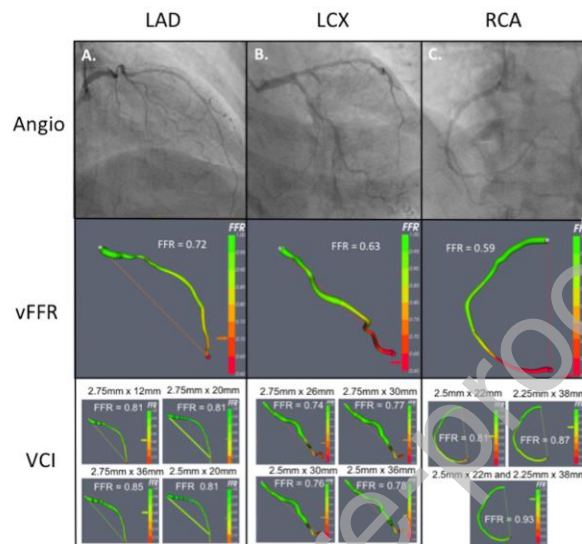


**Figure 1: Diagrammatic representation of study protocol**



## Figure 2: Summary of management plans made after angiographic and vFFR assessment

Detailed breakdown of management plan allocation by angiography alone and after vFFR assessment.



**Figure 3: Illustrative case example**

A 78-year-old female with a background of T2DM and hypertension attended A&E with severe chest tightness. The troponin was  $>10\times$  ULN. There were no localising features on ECG. Baseline angiographic images of the LAD, LCX and RCA are shown in the top left, centre and right panels respectively above the corresponding vFFR and VCI results. Up to four VCI strategies are shown for each vessel (selected after consultation with an independent interventional cardiologist). For each, the reconstructed artery is displayed as well as the predicted post treatment vFFR. The stent details are displayed above the image. The operators' management plans based upon angiographic, vFFR and VCI assessment are shown in Table 5.

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