

eTable 1. Anti-anginal therapy at 3 months follow-up according to randomized strategy.

| Medication | OMT n=48 | PCI n=52 | P Value |
|-------------------------|------------|------------|---------|
| Nitrate | 16 (33.3%) | 7 (13.5%) | 0.018 |
| Ivabradine | 0 (0%) | 1 (1.9%) | 0.334 |
| Beta Blocker | 41 (85.4%) | 40 (76.9%) | 0.279 |
| Calcium channel blocker | 14 (29.2%) | 16 (30.8%) | 0.861 |
| Nicorandil | 3 (6.3%) | 4 (7.7%) | 0.778 |

OMT= Optimal medical therapy, PCI= Percutaneous coronary intervention and optimal medical therapy group. A p value of <0.05 was considered statistically significant.

eTable 2: Breakdown of cases by ^{GZ}FFR vessel.

| Grey Zone Vessel | Frequency | % (n=104) |
|------------------|-----------|--------------|
| Intermediate | 1 | 1.0 |
| LAD | 79 | 76.0 |
| LCX | 8 | 7.7 |
| LPDA | 1 | 1.0 |
| OM1 | 1 | 1.0 |
| RCA | 14 | 13.5 |
| Total | 104 | 100.0 |

OM1=Obtuse Marginal 1, LCX=Left Circumflex, LPDA= Left Posterior Descending Artery.

eTable 3: *Baseline SAQ scores pre randomisation*

| SAQ parameter | Group | N | Mean | SD | P value |
|------------------------|-------|----|------|----|---------|
| Physical limitation | OMT | 48 | 67 | 21 | 0.40 |
| | PCI | 52 | 63 | 28 | |
| Anginal stability | OMT | 48 | 56 | 27 | 0.71 |
| | PCI | 52 | 58 | 26 | |
| Anginal frequency | OMT | 48 | 70 | 24 | 0.67 |
| | PCI | 52 | 68 | 30 | |
| Treatment satisfaction | OMT | 48 | 88 | 17 | 0.80 |
| | PCI | 52 | 89 | 14 | |
| Quality-of-life | OMT | 48 | 54 | 23 | 0.71 |
| | PCI | 52 | 52 | 29 | |

eTable 4 Baseline MRI Results: Mass and Function

| MRI Mass and Function by Treatment Group | | | | | |
|--|-------|----|-------|------|-------|
| | Group | N | Mean | SD | p |
| End Diastolic Volume | OMT | 50 | 153.6 | 36.4 | 0.637 |
| | PCI | 47 | 156.8 | 30.9 | |
| End Systolic Volume | OMT | 50 | 64.2 | 26.6 | 0.613 |
| | PCI | 47 | 66.6 | 19.5 | |
| Stroke Volume | OMT | 50 | 88.1 | 23.3 | 0.586 |
| | PCI | 47 | 90.4 | 17.2 | |
| Ejection Fraction | OMT | 50 | 58.9 | 9.7 | 0.608 |
| | PCI | 47 | 58.1 | 6.4 | |

| Entire Cohort | N | Mean | SD |
|----------------------|----|-------|------|
| End Diastolic Volume | 97 | 155.2 | 33.7 |
| End Systolic Volume | 97 | 65.4 | 23.3 |
| Stroke Volume | 97 | 89.2 | 20.5 |
| Ejection Fraction | 97 | 58.6 | 8.3 |

eTable 5: This table includes all patients with MRI data at enrollment and demonstrates the numbers of patients according to the numbers of segments with detectable ischemia in the ^{GZ}FFR territory.

| Total number Grey Zone FFR segments per patient with any detectable ischemia | 0 | 1 | 2 | 3 | 4 |
|--|-----------|---------|-----------|---------|-------|
| Total Patient number (n=98)(%) | 74(75.5%) | 8(8.2%) | 10(10.2%) | 5(5.1%) | 1(1%) |

Note transmuralty of ischemia not shown.

eTable 6: Major segmental ischemia on MRI according to treatment group.

| Group | 1 Segment ischemia | 2 Segment ischemia | 3 Segment ischemia | 4 Segment ischemia | Total number of segments with significant ischemia |
|-------|--------------------|--------------------|--------------------|--------------------|--|
| OMT | 4 (7.8%) | 8 (15.7%) | 2 (3.9%) | 1 (2%) | 11 (21.6%) |
| PCI | 4 (8.5%) | 2 (4.3%) | 3 (6.4%) | 0 (0%) | 6 (12.8%) |

This table illustrates the numbers of patients with segmental ischaemia in their ^{Qz}FFR territory according to the total number of segments with ischaemia between 25%-100% transmural as well as those patients that met the study definition for significant ischemia with (≥2 segments with ≥25% ischemia or ≥1 segment with ≥50% ischemia). OMT= Optimal medical therapy, PCI= Percutaneous coronary intervention and optimal medical therapy group.

eTable 7: 12-month Seattle Angina Score Delta values according to treatment strategy

| Questionnaire Parameter | Group | N | Mean delta | Standard. Deviation | P value |
|------------------------------------|-------|----|------------|---------------------|---------|
| SAQ Summary Delta Score | OMT | 45 | 9.8 | 18 | 0.208 |
| | PCI | 44 | 15.1 | 21 | |
| Physical limitation Delta Score | OMT | 45 | 2.9 | 20 | 0.07 |
| | PCI | 44 | 11.6 | 24 | |
| Anginal stability Delta Score | OMT | 45 | .5 | 32 | 0.62 |
| | PCI | 44 | -2.8 | 32 | |
| Anginal frequency Delta Score | OMT | 45 | 13.5 | 25 | 0.77 |
| | PCI | 44 | 15.2 | 29 | |
| Treatment satisfaction Delta Score | OMT | 45 | -2.3 | 16 | 0.35 |
| | PCI | 44 | .9 | 17 | |
| Quality of Life Delta Score | OMT | 45 | 12.9 | 24 | 0.27 |
| | PCI | 44 | 18.5 | 24 | |

OMT= Optimal medical therapy, PCI= Percutaneous coronary intervention and optimal medical therapy group. A p value of <0.05 was considered statistically significant. SAQ Summary Score is the average of the sum of the Physical Limitation, Anginal Frequency and Quality of life scores.

eTable 8. This table illustrates the difference in Seattle Angina questionnaires in the ORBITA placebo group at 6 weeks versus the ^{GZ}FFR PCI group at 3 months.

| Study | SAQ Parameter | SAQ DELTA at Follow-up Mean (SD) | P |
|-----------------------|---------------------|----------------------------------|-------|
| ^{GZ} FFR PCI | PHYSICAL LIMITATION | 16.1 (26.1) | 0.008 |
| ORBITA PLACEBO | | 5 (21.2) | |
| ^{GZ} FFR PCI | ANGINAL FREQUENCY | 20.6 (27.6) | 0.03 |
| ORBITA PLACEBO | | 9.6 (28.4) | |
| ^{GZ} FFR PCI | ANGINAL STABILITY | -3.4 (32.9) | 0.77 |
| ORBITA PLACEBO | | -5.1 (31.6) | |

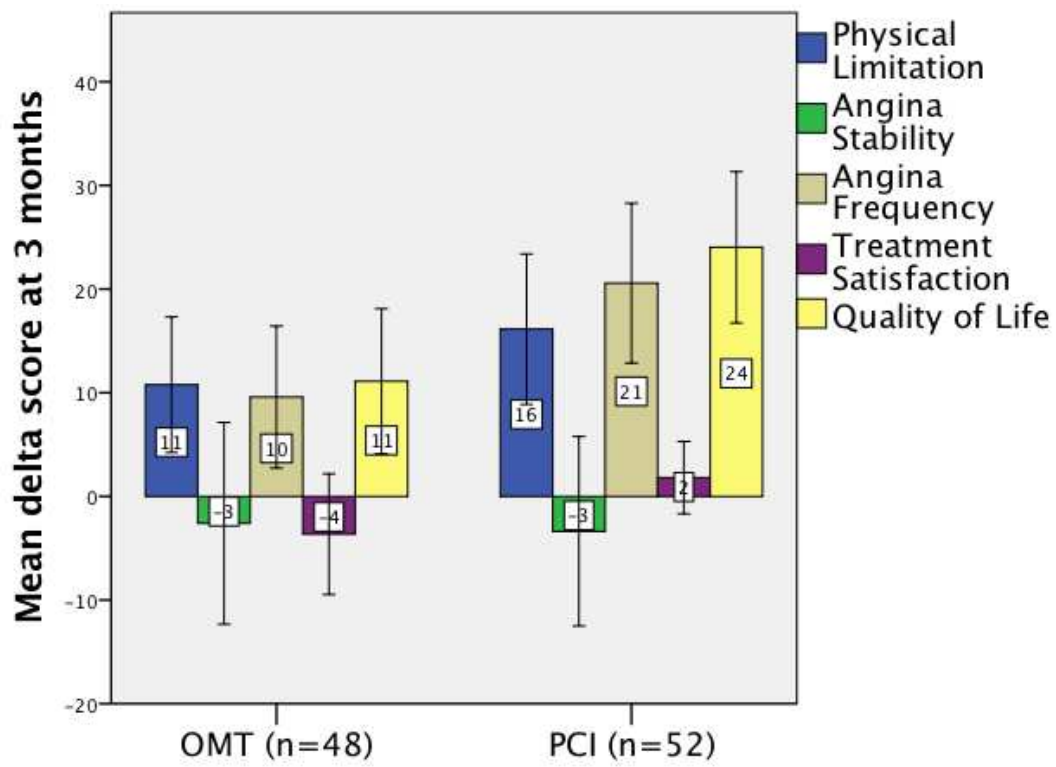
Higher delta scores indicate greater clinical improvement. Note only 3 SAQ parameters for ORBITA were published previously (25), $p < 0.05$ is considered significant.

eFigure 1: This figure illustrates a typical G^2 FFR patient.



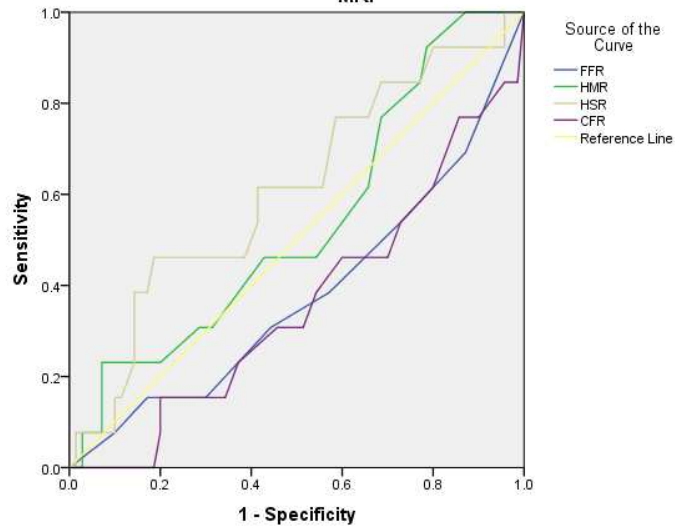
This patient was randomised to medical therapy following baseline angiography (which an intermediate lesion in the proximal LAD with preserved coronary flow reserve and low HSR).

eFigure 2. The Primary outcome: Mean delta in Seattle angina scores according to treatment group for each of the 5 sub- scores of the Seattle angina questionnaire.



eFigure 3: Receiver Operator Characteristics curve illustrating the diagnostic accuracy of all 4 coronary physiological measurements in reference to major ischaemia on cardiac MRI

ROC Curve: Invasive Physiology to Predict Major Perfusion Defect on Cardiac MRI



| Test | Area Under the Curve | 95% Confidence Interval | |
|------|----------------------|-------------------------|-------|
| | | Lower | Upper |
| FFR | 0.379 | 0.208 | 0.550 |
| HMR | 0.536 | 0.368 | 0.703 |
| HSR | 0.613 | 0.442 | 0.783 |
| CFR | 0.362 | 0.198 | 0.526 |

