MR-INFORM: STRESS PERFUSION IMAGING TO GUIDE THE MANAGEMENT OF PATIENTS WITH STABLE CORONARY ARTERY DISEASE

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BACKGROUND

• Management of patients with stable coronary artery disease is based on reduction of risk factors, optimal medical therapy (OMT) and revascularization in those with resistant symptoms and proven ischemia.

• Invasive angiography with PCI remains the main management strategy in patients with stable angina despite medication.
Optimal invasive strategy

• The FAME and DEFER studies demonstrated convincingly, that adding intracoronary pressure measurements (FFR) to invasive angiography and limiting revascularization to patients with hemodynamically significant stenoses results in a prognostic benefit.

• A combination of OMT with invasive angiography supported by FFR seems the current best invasive management strategy for patients with stable angina.
Optimal non-invasive strategy

- Non-invasive ischemia testing with perfusion imaging has been shown to accurately predict the presence of a flow limiting stenosis as well as predict outcome.
- Cardiovascular magnetic resonance (MR) perfusion imaging has demonstrated the highest accuracy of non-invasive testing without requiring radiation as well as gaining significant information on anatomy, function and myocardial structure in a single session.
- A combination of OMT with MR-perfusion imaging seems the current best non-invasive management strategy for patients with stable angina.
Hypothesis

Guiding the initial management of patients with stable angina and intermediate to high risk of coronary artery disease receiving OMT by MR-perfusion imaging is non-inferior to invasive angiography supported by FFR.
Trial Structure

Sponsor: Guy’s and St. Thomas’ Hospital and King’s College London, UK
Funding: Biomedical Research Centre (National Institute of Health Research, UK), German Centre for Cardiovascular Research (DZHK) and Bayer Healthcare, Germany (unrestricted grant)
CRO: pharmtrace, Berlin, Germany

• 9 UK Sites
  – King’s College London and Guy’s and St. Thomas’ Hospital, London
  – King’s College Hospital, London
  – Heart Hospital, London
  – Leeds General Infirmary, Leeds
  – Glenfield General Hospital, Leicester
  – Golden Jubilee National Hospital Glasgow
  – Bristol Heart Institute, Bristol
  – Freeman Hospital, Newcastle
  – Royal Brompton & Harefield Hospitals

• Portugal
  – Gaia Hospital, Porto

• 5 Germany
  – Elisabeth Hospital, Essen
  – Heart Centre Leipzig, Leipzig
  – University Hospital Heidelberg
  – Robert-Bosch-Hospital, Stuttgart
  – Helios Clinics Berlin-Buch, Berlin

• Australia
  – Flinders Medical Centre, Adelaide
Inclusion criteria

• Stable angina (CCS II-III)
  and

• either $\geq 2$ risk factors (smoking, diabetes, hypertension, hyperlipidemia, pos family hx)
  or

• positive exercise treadmill test

Exclusion criteria

• Contraindication to MR or adenosine
• Atrial fibrillation or frequent ectopic beats
• EF < 30%
• CCS class IV
• NYHA class III or IV
• Previous CABG
• PCI within the previous 6 months
• eGFR < 30 mL/min/1.73m$^2$
• Disability to lie supine for 60 minutes
• Medically unstable
• Pregnant, breast feeding, unable/unwilling to consent
### Randomization (1:1)

**FFR INFORMED**
- Invasive angiography in all patients
- FFR in all arteries >2.5 mm with a stenosis of 40-95%
- If FFR <0.8 revascularization (PCI or CABG) recommended
- CTO regarded as positive

**MR INFORMED**
- 1.5T multivendor
- Cine imaging
- Adenosine stress/rest first pass perfusion imaging using 0.075 mmol Gadovist / kg body weight for first pass
- Late gadolinium enhancement after top-up to 0.2 mmol/kg body weight
- If transmural defect or subendocardial defect >2 segments or in 2 adjacent slices was found, angiography with aim of revascularization recommended
Example, 67 y, male, CCS II, 2 RF
Optimal Medical Therapy (OMT)

All patients received OMT:
• Advice to all patients and their primary physicians
• Aspirin or clopidogrel
• Statin
• ACE inhibitor or ARB

Targets:
• Total cholesterol < 4 mmol/l
• LDL < 2 mmol/l
• BP ≤ 130/80 mmHg
• Random glucose < 6 mmol/l
• BMI < 25
• No smoking
Primary Endpoint

Composite endpoint of
• All cause mortality
• Nonfatal myocardial infarction (clinical presentation of ACS AND Q-waves OR troponin ≥99th percentile)
• Re-revascularization of a vessel targeted at the index revascularization procedure
Power Calculation

• An incidence of 10% and an equivalence margin of 10% were assumed

• 826 patients required to determine non-inferiority of an MR guided strategy compared to an FFR guided strategy with a power of 80% and a p<0.025.

• Allowing for a drop-out rate of 10% a total sample size of 918 was required.
Enrolment

Assessed for eligibility (n=16620)

Randomized (n = 918)

Excluded (n=15705)
- Not meeting inclusion criteria (n=13928)
- Refused to participate (n=1584)
- Other reasons (n=193)

Allocation

Allocated to FFR-INFORM (n=464)
- Received invasive angiography (n=448)
- Did not have angiography (n=17)

Allocated to MR-INFORM (n=454)
- Received MR perfusion imaging (n=446)
- Did not have MR-Perfusion study (n=8)

Follow-up

Lost to follow-up (n=14)

Lost to follow-up (n=16)

Recruitment period: 12/2010 – 08/2015
## Patient characteristics

<table>
<thead>
<tr>
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<th>FFR-INFORMED (n=464)</th>
<th>MR-INFORMED (n=454)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>61.6 ± 9.37</td>
<td>62.4 ± 9.61</td>
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<tr>
<td><strong>Gender (Male)</strong></td>
<td>329 (72.47%)</td>
<td>335 (72.20%)</td>
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<tr>
<td><strong>Ejection Fraction</strong></td>
<td>58.9 ± 7.88</td>
<td>61.2 ± 7.12</td>
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<tr>
<td><strong>Ethnicity (Caucasian)</strong></td>
<td>419 (90.69%)</td>
<td>409 (89.89%)</td>
</tr>
<tr>
<td><strong>CCS class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>415 (89.63%)</td>
<td>407 (90.04%)</td>
</tr>
<tr>
<td>III</td>
<td>48 (10.37%)</td>
<td>45 (9.96%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>138 (29.74%)</td>
<td>112 (24.72%)</td>
</tr>
<tr>
<td><strong>Previous Myocardial Infarction</strong></td>
<td>33 (7.11%)</td>
<td>39 (8.61%)</td>
</tr>
<tr>
<td><strong>Known CAD</strong></td>
<td>52 (11.21%)</td>
<td>72 (15.89%)</td>
</tr>
<tr>
<td><strong>Current Smoking</strong></td>
<td>76 (16.38%)</td>
<td>82 (18.06%)</td>
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Results of the index test

**FFR INFORMED**
- 3.5% not done
- 35.6% FFR +ve
- 13.4% FFR -ve
- 47.5% Angio -ve

**MR-INFORMED**
- 1.5% not done
- 48.8% MR+/Angio+
- 8.1% MR+/Angio-
- 41.5% MR-

Significant CAD by positive anatomical AND functional test
\[ p = 0.0047 \]
Revascularization rate

Revascularization rate
\[ p = 0.0053 \]
# MACE

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<tr>
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<th>FFR (n = 462)</th>
<th>MR (n = 450)</th>
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<tbody>
<tr>
<td>Events (n)</td>
<td>18 (3.9%)</td>
<td>15 (3.33%)</td>
</tr>
<tr>
<td>• Death</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(Angio +, CAGB planned, death before CAGB)</td>
<td>(2 non-cardiac, 1 MR+, Angio+, CAGB planned, death before CAGB, 1 death after CAGB)</td>
</tr>
<tr>
<td>• Myocardial Infarction</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>• Re-revascularization</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Absolute Risk Difference [95% CI]</td>
<td>-0.56 [-2.98; 1.86]</td>
<td></td>
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<tr>
<td>Hazard ratio [95% CI]</td>
<td>-0.852 [-0.43; 1.69]; p = 0.62</td>
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Discussion / Summary

- Guiding the initial management of patients with stable angina and an intermediate to high risk for coronary artery disease with non-invasive MR-perfusion imaging is non-inferior to a strategy with invasive angiography supported by FFR during a follow-up of one year.
- Both strategies are safe and result in a low total event rate.
- The number of revascularization procedures is significantly lower when guided by MR perfusion imaging in comparison to invasive angiography supported by FFR.
Investigators

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