MHIF FEATURED STUDY: DAPA ACT HF

CONDITION: Acute Heart Failure

Pt: Mosi Bennett, MD

RESEARCH CONTACT: Sarah Schwager
Sarah.Schwager@allina.com | 612-863-6257

SPONSOR: TIMI Study Group, Brigham and Women’s Hospital

DESCRIPTION:

Dapagliflozin and Effects on Cardiovascular Events in Acute Heart Failure - evaluating in-hospital initiation of dapagliflozin in patients who have been stabilized during hospitalization for heart failure. All patients with heart failure, regardless of ejection fraction, are eligible to receive study medication for the two-month study follow-up.

CRITERIA LIST/QUALIFICATIONS:

Inclusion: Acute heart failure

Exclusion:
- GFR<25
- Recent CRT, valve repair or replacement, or revascularization
- Type 1 diabetes or history of DKA

Acute heart failure is the most common cardiovascular reason for hospital admission.
Stratified medicine in ischaemic heart disease

Colin Berry
Professor of Cardiology
December 2021

Disclosures

Institutional agreements between the University of Glasgow (employer) and Abbott Vascular, AstraZeneca, Coroventis, DalCor, GSK, HeartFlow, A. Menarini Farmaceutica Internazionale, Novartis and Siemens.

Research grants from the BHF, EU and MRC
Objectives

1. Create awareness on small vessel disease leading to angina.

2. Describe stratified medicine, including endotypes and linked therapy.

3. Future directions: new trials, systemic disease, sex disparities, guidelines

Chest Pain Clinics

~1 million visits pa, £1 billion costs

- Diagnostic test e.g. CTCA
- Blocked coronary arteries
- No obstructive coronary lesions

1 in 5 (200,000)

2 in 5 (400,000) may have Small Vessel Disease

- Stents
- Bypass surgery

NHS - no specific tests
Diagnosis & treatment sub-optimal
50% re-attend hospital
x2↑ risk CV death / MI
Intact perfused human heart

Human coronary circulation

3D stereo-arteriography

Which test first: Anatomical vs. Functional?

Anatomy

CTCA

Invasive

Microvessels invisible

Function

Ischaemia

WF Fulton, MD Thesis, 1963
University of Glasgow
INOCA
Ischaemia and no obstructive coronary artery disease

Microvascular Angina
Vasospastic Angina

INOCA and prognosis

Case control study
Copenhagen, 1998–2009
11,223 patients
5705 participants
Copenhagen City Heart Study
CFR and IMR and prognosis

Lee JM et al JACC 2016

<table>
<thead>
<tr>
<th>Group</th>
<th>CFR</th>
<th>IMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>D</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>CFR</th>
<th>IMR</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
<td>1.000 (Reference)</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Low</td>
<td>2.116 (0.386-11.589)</td>
<td>0.388</td>
</tr>
<tr>
<td>D</td>
<td>Low</td>
<td>High</td>
<td>5.623 (1.234-25.620)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Breast P for overall comparison = 0.002

No. at Risk
- Group A: 141
- Group B: 26
- Group C: 31
- Group D: 16

Days From Index Procedure

Lee JM et al JACC 2016

Standard care pathways
Outpatient clinic
Catheter Laboratory

Medical assessment
Exercise test
Anatomical imaging
Cardiac CT scan
NICE-95 Update
Nov. 2016

Obstructive disease
>70% narrowed artery, 2 in 3
Small vessel disease unknown or uncertain

Undifferentiated chest pain
Non cardiac, 2 in 5
No diagnosis, 2 in 5
Non-obstructive disease or normal, 2 in 3
Non-obstructive or normal, 1 in 3

1 in 3 - 5
Clinical conundrums in daily practice

Diagnostic wire to assess flow-limitation

Diagnosis of coronary endotypes

1. Diffuse epicardial and microvascular disease, including focal epicardial stenosis
   - FFR ↓
   - IMR ↑
   - CFR ↓

2. Focal epicardial stenosis (with preserved microvascular function)
   - FFR ↓
   - IMR ↓
   - CFR ↑

3. Isolated microvascular disease
   - FFR ↑
   - IMR ↑
   - CFR ↓

4. Diffuse epicardial and microvascular disease
   - FFR ↑
   - IMR ↑
   - CFR ↓

Ford, Corcoran, Berry. EHJ 2017
**Fractional Flow Reserve (FFR)**

- Coronary Flow Reserve (CFR)

**Acetylcholine (ACh) Bolus**

- IV Adenosine
  - Fractional Flow Reserve (FFR)

**Microvascular Angina**

1. Microvascular angina
2. Vasospastic angina
3. Mixed angina
4. Non-Cardiac (normal IDP)

**Coronary Flow Reserve (CFR)**

- Index of Microvascular Resistance (IMR)

**Microvascular Angina**

- 1 - Calcium channel blocker
- 2 - Long-acting Nitrate
- Avoid beta-blockers
- Event prevention: ACEI, Statin
- Lifestyle and cardiac rehabilitation

**Interventional Diagnostic Procedure (IDP)**

- IC Acetylcholine
  - ACh infusion (Microvascular spasm)

**Microvascular Angina**

- No Obstructive CAD

- Normal adenosine physiology (FFR 0.84, CFR 5.3, IMR 9)

- Occlusive vasospasm with ACh (resolves with nitrate)

- Epicardial vasospasm
- Microvascular vasospasm

- Endothelial dysfunction but no gross vasospasm to ACh
Stratified Medicine

The identification of subgroups of patients (endotypes) within an undifferentiated population, identified by disease mechanisms and/or therapy responses.

MRC Framework (2015)

2015, grant rejected “do not resubmit”
Primary Endpoint = Angina Severity (SAQ SS)

Baseline Characteristics, n = 151

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 76)</th>
<th>Intervention (n = 75)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>60 [53, 68]</td>
<td>62 [54, 69]</td>
</tr>
<tr>
<td>Female</td>
<td>58 (76%)</td>
<td>53 (71%)</td>
</tr>
<tr>
<td>BMI [Q1, Q3]</td>
<td>30 [26, 34]</td>
<td>30 [26, 35]</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>14 (18%)</td>
<td>13 (17%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>15 (20%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Predicted 10-year CHD risk*</td>
<td>18% [10, 28]</td>
<td>19% [12, 39]</td>
</tr>
</tbody>
</table>

* ASSIGN CV score
Primary Endpoint – Δ SAQ at 6 months

Between-Group Difference

<table>
<thead>
<tr>
<th>Units</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>11.7 Units</td>
<td>5.0 to 18.4</td>
<td>0.001</td>
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<tr>
<td>14.5 Units</td>
<td>7.3 to 21.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9.3 Units</td>
<td>0.5 to 18.1</td>
<td>0.040</td>
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</tbody>
</table>

SAQ Change from Day 0

- Summary Score
- Physical Limitation
- Angina Frequency

Secondary Endpoints
Post Randomization Diagnostic/Clinical Utility

- Changed Diagnosis
  - Intervention: 52%
  - Control: 0%
- Diagnostic Certainty (MVA/VSA)
  - Intervention: 83%
  - Control: 18%
- Missed Diagnosis
  - Intervention: 3%
  - Control: 36%
- Change angina therapy to treat MVA/VSA
  - Intervention: 87%
  - Control: 30%

All, P<0.001
Secondary Endpoints – Health Status

<table>
<thead>
<tr>
<th>Intervention</th>
<th>95% CI</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Quality of Life (EQ5D-5L):</td>
<td></td>
<td></td>
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<tr>
<td>Index Score</td>
<td>0.1</td>
<td>0.01 – 0.18</td>
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<tr>
<td>VAS score</td>
<td>14.54</td>
<td>7.77 – 21.31</td>
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</table>

**Treatment satisfaction:**

<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
<th>95% CI</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>10.73</td>
<td>2.37 – 19.09</td>
<td>0.013</td>
</tr>
<tr>
<td>Convenience</td>
<td>14.34</td>
<td>7.30 – 21.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global satisfaction</td>
<td>16.47</td>
<td>7.28 – 25.66</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mechanisms of benefit

**12 month Treatment Effect: Weight**

- Weight: -1.3kg (-4.2 to 1.7)  P=0.403
- BMI (kg/m2): -0.5kg/m2 (-1.7 to 0.7)  P=0.407

**12 month Treatment Effect: Office BP & pulse**

- SBP: -11.9 mmHg (-19.3 to -4.5)  P=0.002
- DBP: -4.8 mmHg (-6.5 to -1.1)  P=0.011
- Pulse: -3.3 bpm (-7.3 to 0.7)  P=0.105

**Functional Capacity (DASI score)**

- DASI: 4.5 units (-0.9 to 9.8)  P=0.102

**Physical Activity**

- Cardiac Rehab: 40%  RR 1.73 (1.28 to 2.32)  P=0.001
- Mod or Hi Activity: 61%  RR 1.23 (0.85 to 1.79)  P=0.276
### Invasive Coronary Function Testing in Angina (CorMicA): One Year RCT Outcomes

**Randomized 151 Patients**
- **Intervention:** Invasive Coronary Function Guided Care (n=75)
- **Control:** Angiography guided Care (n=76)

**Linked Diagnosis:**
- Microvascular angina
- Vasospastic angina
- Non-cardiac

**Therapy:**
- Stratify Antianginals
- Non-pharmacological

**Main Results:**
- Improved Angina: 122% \( \uparrow \) 27%
  - Improved Angina: 11 (5 to 18) \( \uparrow \) 14 (7 to 20)
  - \( P < 0.001 \) \( \uparrow P < 0.001 \)

**Sustained Benefits:**
- Improved Angina and Quality of Life

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**European Heart Journal**

**Guidelines**

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Juhani Knuuti, William Wijns, Antti Saraste, Davide Capodanno, Emanuele Barbato, Christian Funck-Brentano, Eva Prescott, Robert F Storey, Christi Deaton, Thomas Cuisset ...

Show more


Published: 31 August 2019
ESC guidelines, Chronic Coronary Syndromes
Angina without obstructive disease in the epicardial coronary arteries - INOCA

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td><strong>Guidewire-based CFR and/or microcirculatory resistance</strong> measurements should be considered in patients with persistent symptoms, but coronary arteries that are either angiographically normal or have moderate stenoses with preserved iwFR/FFR.</td>
<td>IIa</td>
<td>B</td>
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<td><strong>Transthoracic Doppler of the LAD, CMR, and PET</strong> may be considered for non-invasive assessment of CFR.</td>
<td>IIb</td>
<td>B</td>
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</table>
Non-invasive imaging of CMD
Pathological validation of perfusion MRI

LV – left ventricle, RV – right ventricle, LCA – left coronary artery, RCA – right coronary artery, GCV – great cardiac vein, RA – right atrium

Arai & Hsu, US NIH
Corcoran, Orchard, Berry, University of Glasgow

Kotecha et al iJACC 2021
Directions
Guidelines, sex disparities, MINOCA, systemic disease.
False negative - anatomical imaging

Stereo-arteriogram
40 µm

Coronary angiogram
0.5 mm

Left main

Left anterior descending

Circumflex

William Fulton MD, 1963
© University of Glasgow

Sex differences, IHD

CorMica all-comers registry

<table>
<thead>
<tr>
<th></th>
<th>Obstructive CAD</th>
<th>INOCA</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>206</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>63 (9.6)</td>
<td>61.3 (10.0)</td>
<td>0.081</td>
</tr>
<tr>
<td>Female</td>
<td>38%</td>
<td>68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prev MI</td>
<td>29%</td>
<td>16%</td>
<td>0.008</td>
</tr>
<tr>
<td>10-year CVD risk</td>
<td>24% [10, 28]</td>
<td>20% [12, 39]</td>
<td>0.003</td>
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</table>
### In context

<table>
<thead>
<tr>
<th></th>
<th>CoreMCA</th>
<th>ORBITA</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>61</td>
<td>66</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>74</td>
<td>27</td>
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<tr>
<td>Angina</td>
<td></td>
<td></td>
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<tr>
<td>Summary Score</td>
<td>51</td>
<td>?</td>
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<tr>
<td>Limitation</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>Frequency</td>
<td>59</td>
<td>71</td>
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<tr>
<td>Stability</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>EQ5D - QoL</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Enrolment, years</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>Centres, n</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

**IHD differs in women vs. men**

Angina by cause

- **Men**
  - CHD: 60%

- **Women**
  - Blocked arteries

**SCOT-HEART, 2015**
IHD differs in women vs. men

Angina by cause

- **Men**
- **Women**

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocked arteries</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>20%</td>
<td>80%</td>
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</tbody>
</table>

SCOT-HEART, 2015

CorMicA study, 2018

Ischaemic heart disease

- **CHD**
  - Coronary Heart Disease

- **INOCA**
  - Ischemia with no obstructive coronary arteries

Sex Bias: Terminology in Clinical Trials

SCOTHEART – Angina due to CHD …. If No, angina excluded Option to stop therapy
Angina frequency, limitation, QoL **Worse in CTCA group**

Sex bias in UK guidelines?

‘Syndrome X’ (therapeutic nihilism)

…. no mention of microvascular angina, MINOCA, or SCAD
ESC – new guidelines
Angina without obstructive disease in the epicardial coronary arteries - Microvascular angina

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<td>B</td>
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Microvascular angina – a multisystem disorder?

- Vascular Dementia
- Lacunar Stroke
- White matter disease
- Chronic Kidney Disease
- Ischemic nephropathy
- Retinopathy
- Nerve fiber disease
- Endothelial Dysfunction
- Coronary Microvascular Disease

References:
Berry, et al JAHA 2018
MINOCA
Vasospasm & prognosis

n = 80

n = 37 +

5 years

Montone, Crea
EHJ 2018

Future directions: clinical trials
Stratified Medicine trials

**CorCTCA**
Diagnostic study & nested RCT
BHF Clinical Fellowship
n = 250 trial; 2017 - 2021

**CorMed**
Imaging Registry
Angiogram ± coronary function tests
Stress MRI, 1.5T or 3.0T
n = 2460; 2016 - 2026

**CorPEF**
Diagnostic study
Heart failure (J. McMurray)
Coronary function tests, stress MRI
n = 150; 2017 - 2020

**CorMicA pilot trial**
Diagnostic strategy trial, MRI
BHF Centre of Excellence
n = 150; 2016 - 2017

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**CorCTCA**
Diagnostic study & nested RCT
BHF Clinical Fellowship
n = 250 trial; 2017 - 2022

**CorMed**
Stress MRI, 1.5T or 3.0T
n = 2460; 2016 - 2026

**CorPEF**
Diagnostic study
Heart failure (J. McMurray)
Coronary function tests, stress MRI
n = 110; 2017 - 2020

**CorMicA trial**
Diagnostic strategy trial, MRI
BHF Centre of Excellence
n = 391; 2016 - 2017

**CorCMR**
Clinical trial
Stress MRI (heart and brain)
n = 250; 2021 - 2024
~ >3 in 4 patients

Sidik, Berry et al. Am Heart J 2020
CorCTCA trial

CorCTCA population at baseline  
- N = 250
- Age, years: 60 ± 9
- Female: 156 (62%)
- BMI, kg/m²: 30.9 ± 6.0
- Current smoker: 53 (21%)
- History of MI: 8 (3%)
- Prior coronary stent: 3 (1%)
- History of stroke: 15 (6%)
- Type 2 diabetes mellitus: 30 (12%)
- Hypertension: 120 (48%)
- Dyslipidaemia: 147 (59%)
- Family history CHD: 145 (58%)
- Predicted 10-year likelihood of coronary heart disease event, JBS3: 12.3 ± 8.9
- Aspirin: 156 (62%)
- Beta-blocker: 154 (62%)
- Calcium-channel blocker: 65 (26%)
- Nitrate: 41 (16%)
- Statin: 160 (64%)
- ACE inhibitor / ARB: 74 (30%)
- Total cholesterol, mmol/l: 5.1 ± 1.2
Angina, coronary angiography

Angina, No Obstructive CAD

Randomise, double-blind

n = 750, IDP
n = 750, IDP sham

Stratified medicine
Standard care

Seattle Angina Score
Primary outcome, 1 year

53

Schedule of Assessments

These activities can take place on the same day

Screening
- Informed Consent
- Medical History
- Vital signs
- Health Questionnaires

Visit 1
- 12 lead ECG
- Blood Samples
- Coronary Angiogram
- Randomisation
- Small vessel function tests
- Clinical diagnosis with linked treatment plan

Follow-up 1 at 1 month
- iCorMicA Symptom Log

Follow-up 2 at 3 months
- iCorMicA Symptom Log

Follow-up 3 at 6 months
- Health Questionnaires
- Medication list
- Follow-up for health events

Follow-up 4 at 9 months
- iCorMicA Symptom Log

Follow-up 5 at 12 months
- Vital signs
- Physical examination
- Medical History
- Health Questionnaires
- Blood samples
- Medication list

Follow-up 6 & 7 at 5 & 10 years
- Follow-Up review
- Health Questionnaires

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Outcomes

**Primary**
Seattle Angina Questionnaire (SAQ) Summary Score @ 1 year.

**Secondary**
Health status questionnaires, safety, healthcare resource use.

**Exploratory**
CV risk factor control, potential biomarkers.
**PRISE Study: Precision Medicine**

- rs9349379 (G allele)
- \( \uparrow \) PHACTRI expression
- \( \uparrow \) Circulating ET-1
- \( \uparrow \) ET-A receptor activation
  - Enhanced Ca²⁺ signalling
  - \( \uparrow \) Contraction
  - \( \uparrow \) Proliferation
- \( \uparrow \) Microvascular resistance
- \( \downarrow \) Myocardial perfusion

**ZIBOTENTAN**

- Microvascular angina

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**Precision medicine with zibotentan in microvascular angina**

- **Exclusion**: n=312
  - Screening
  - Informed consent
  - Genotyping
- **Drop out**: n=44
  - Medical optimisation
  - Single blind placebo

**TREATMENT**

- **Zibotentan 10mg OD**
- **Placebo**

**TIME**

<table>
<thead>
<tr>
<th>VISIT</th>
<th>Week 0-6</th>
<th>Week 7-9</th>
<th>Week 10-22</th>
<th>Week 23-34</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>C, Q, GB, B</td>
<td>C, Q, B</td>
<td>C, Q, B</td>
<td>C, Q, B</td>
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<tr>
<td>2</td>
<td>ETT, PD</td>
<td>ETT, PD, PK</td>
<td>ETT, PD, PK</td>
<td>ETT, PD, PK</td>
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<tr>
<td>3</td>
<td>+ spCMR</td>
<td>+ spCMR</td>
<td>+ spCMR</td>
<td>+ spCMR</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
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</table>

**Final visit**

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**Blood**: Clinical examination (C), Exercise tolerance test (ETT: Bruce protocol), GI – genomic blood test, Quality of life questionnaire (Q)

**Stress perfusion-cardiac magnetic resonance imaging** (spMRI; optional sub-study), Pharmacokinetic and Pharmacodynamic sampling (PK/PD)
Conclusions

1. **INOCA**: common (>obstructive CAD), under-recognition diagnosis & treatment.

2. **CorMicA trial**: *stratified medicine changes diagnosis, treatment, improves symptoms*

3. **Future directions**: educate on sex disparities, MINOCA, therapy development, and trials.
British Medical Association (BMA)
Women’s Health Report, August 2018

No mention of heart disease in women.