Multi-Modality Imaging in Myocardial Infarction with Non-Obstructive CAD (MINOCA)

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Standardized AHA Diagnostic Criteria for MINOCA

The diagnosis of MINOCA is made in patients with acute myocardial infarction that fulfill the following criteria:

(1) Acute Myocardial Infarction (Modified from the 4th Universal Definition of Myocardial Infarction Criteria)
(a) Detection of a rise and/or fall of cTn with at least one value above the 99th percentile upper reference limit.
and
(b) Corroborative clinical evidence of infarction evidenced by at least one of the following:
   (i) Symptoms of myocardial ischemia
   (ii) New ischemic ECG changes
   (iii) Development of pathological Q waves
   (iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
   (v) Identification of a coronary thrombus by angiography or autopsy.

(2) Non-obstructive coronary arteries on angiography:
• Defined as the absence of obstructive disease on angiography (i.e. no coronary artery stenosis ≥50%), in any major epicardial vessel**.
• This includes patients with:
  o Normal coronary arteries (no angiographic stenosis)
  o Mild luminal irregularities (angiographic stenosis <30% stenoses)
  o Moderate coronary atherosclerotic lesions (stenoses >30% but <50%).

(3) No Specific Alternate Diagnosis for the Clinical Presentation:
• Alternate diagnoses include, but are not limited to, non-ischemic causes such as sepsis, pulmonary embolism, myocarditis, etc.

Tamis-Holland, Jneid, Reynolds et al Circ 2019
Which types of patients get MINOCA?

MINOCA disproportionately affects women

**STEMI**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Non-obstructive CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION Registry</td>
<td>142,417</td>
<td>4% 2%</td>
</tr>
<tr>
<td>GUSTO IIb</td>
<td>2,251</td>
<td>7% 10%</td>
</tr>
<tr>
<td>Meta Analysis</td>
<td>20,352</td>
<td>8% 9%</td>
</tr>
</tbody>
</table>

**NSTEMI**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Non-obstructive CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION Registry</td>
<td>180,106</td>
<td>5% 15%</td>
</tr>
<tr>
<td>GUSTO IIb</td>
<td>1,749</td>
<td>4% 9%</td>
</tr>
<tr>
<td>Meta Analysis</td>
<td>6,743</td>
<td>5% 10%</td>
</tr>
</tbody>
</table>

% with non-obstructive CAD

Also 23% of female, 16% of male decedents aged <55 at autopsy with pathologic evidence of MI

Smilowitz NR...Reynolds HR Circ Cardiovasc Qual Outcomes 2017; Hochman JS et al. NEJM 1999; Berger JS...Hochman JS et al. JAMA 2009; Smilowitz NR.....Hochman JS, Reynolds HR AHJ 2011
MINOCA is more common among certain racial and ethnic minorities

<table>
<thead>
<tr>
<th>Race</th>
<th>ACTION-GWTG registry</th>
<th>18,918 MINOCA 2009-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>White (n=276,661)</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>Black/African American (n=33,566)</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Asian (n=5,281)</td>
<td>3.8%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>American Indian/Alaskan Native (n=1,934)</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander (n=380)</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (n=16724)</td>
<td>6.8%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

% with non-obstructive CAD

MINOCA patients are often young

Age Structure of MINOCA population in ACTION-GWTG registry

... but 27% were aged over 70
Conventional risk factors are common among patients with MINOCA

ACTION-GWTG registry N=18,918 MINOCA

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence in MINOCA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>20%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>45%</td>
</tr>
<tr>
<td>Smoking (Current or Recent)</td>
<td>27%</td>
</tr>
<tr>
<td>Any of the above</td>
<td>75%</td>
</tr>
</tbody>
</table>

Smilowitz NR et al Circ CV Qual Outcomes 2017

Clinicians and patients ask:

*Was this really MI?*

*What is the treatment?*

*What is the prognosis?*
Are outcomes of MINOCA patients worse than with no prior CVD? Are normal and non-obstructive CAD prognosis the same?

![Graph showing cumulative hazard over follow-up time for MINOCA patients compared to those with no prior CVD.](image)

- MI-CAD n=7,408
- 897 MINOCA: 308 normal coronaries
- 589 mild CAD
- No CVD n=8,305

### Major adverse cardiovascular events after MINOCA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&gt;9,000 MINOCA patients SWEDHEART Registry</th>
<th>&gt;16,000 MINOCA pts Cath-PCI Registry age ≥65</th>
<th>~30,000 MINOCA pts meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>13.4%</td>
<td>12.3%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Recurrent MI hosp.</td>
<td>7.1%</td>
<td>1.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Heart Failure hosp.</td>
<td>6.4%</td>
<td>5.9%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Stroke, MACE</td>
<td>4.3% stroke, 24% 4-year MACE</td>
<td>18% 1-year MACE</td>
<td>9.6% 1-year MACE</td>
</tr>
</tbody>
</table>

Predictors of adverse outcomes across studies: ST elevation, lower EF, older age

- Smilowitz et al 2017
- Nordenskjold et al Am J Med 2019
- Pelliccia et al Am J Med 2019
- Lindahl et al Circ 2017
- Dreyer et al EHJ 2019
- Pasupathy et al Circ Outcomes 2021
Reinfarction after MINOCA – MINOCA again?

- SWEDHEART registry identified 570 MINOCA patients with recurrent MI
- Of 340 patients who underwent repeat angiography, 47% had MI-CAD with the second event
- No difference in mortality at 38 months between recurrent MINOCA or MI-CAD (13.9% vs 11.9%, p=0.54)

The best treatment of MINOCA is unknown

No treatment trials have been performed

For now, we use mechanistic and observational data to guide management
What is current practice?
Secondary prevention medication use

![Graph showing medication use percentages for Aspirin, P2Y12 inhibitor, Statin, ACEI/ARB, and Beta Blocker.]

Uncertainty about application of post-MI treatment guideline recommendations to MINOCA likely relates to variability in underlying mechanisms

Smilowitz NR et al Circ CV Qual Outcomes 2017

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Plaque Rupture / Erosion  Coronary Spasm  Dissection  Thrombosis/Thromboembolism

MINOCA

Takotsubo Syndrome  Myocarditis
There is always a differential diagnosis

Elevated Cardiac Troponin Value(s) >99th percentile URL

- Troponin rise and/or fall
- Troponin level stable

With acute ischemia
- Acute myocardial infarction
  - Atherosclerotic
    - Type 1 MI triggers
      - Platelet aggregation
      - Thrombosis
  - Supply-demand mismatch
    - Chronic heart failure
    - Renal failure
- Oxygen supply and demand imbalance
  - Type 2 MI examples
    - Severe hypertriglyceridemia
    - Sustained ischemia

Without acute ischemia
- Acute myocardial injury
- Chronic myocardial injury

Examples
- Structural heart disease
- Chronic kidney disease

Fourth Universal Definition of Myocardial Infarction (2018)

Atherosclerotic (Type 1)

- Not Atherosclerotic (Type 2)
  - Coronary Artery Spasm
  - Coronary Dissection
  - Supply-Demand Mismatch
- MI causing Sudden Death (Type 3)
- Stent Thrombosis (Type 4b)
- Peri-Procedural MI (Types 4a + 5)
- Not MI
Limitations of Coronary Angiography

Nissen SE, Yock P. Circulation 2001

Not All Plaque Rupture is Angiographically Evident

Image adapted from Funk SD et al Int J Vasc Med 2012
Not All Plaque Rupture/Erosion is Angiographically Evident

How common are rupture, erosion or thrombus in MINOCA? →
- Single-center studies using IVUS or OCT demonstrated plaque rupture, erosion or thrombus in 29-50% of patients with MINOCA – 43% in a recent multi-center study (HARP)
  - Lower rate than STEMI (~75%) and higher than asymptomatic patients with CAD (5-10%) or INOCA (0%)
  - If myocarditis and spasm ruled out first: 80%
- Angiogram may not be helpful: 30% of MINOCA with “normal” angiogram had an OCT culprit lesion, and culprit only located in the worst plaque on angio half the time when present


Coronary artery spasm: common cause of MINOCA

- Spontaneous spasm at cath is helpful
- Provocative testing not routinely done at the time of acute angiography
- Recent studies using provocative testing
  - 24%-66% induced spasm
  - Spasm type:
    - 45-65% epicardial, 35-55% microvascular
    - Most with spasm also had some nonobs. CAD
- Myocardial bridge may be a clue to spasm – ACh testing abnormal in 30/34 with MB, 88%
- Exposure to air pollution independently associated with positive testing for spasm in MINOCA/INOCA

Predictors of Coronary Spasm in MINOCA

<table>
<thead>
<tr>
<th></th>
<th>Spasm (n=95)</th>
<th>No Spasm (n=301)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.5±11.8</td>
<td>63.8±12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>73%</td>
<td>53%</td>
<td>0.001</td>
</tr>
<tr>
<td>Typical Chest Pain</td>
<td>93%</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior Angina</td>
<td>20%</td>
<td>10%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST Elevation</td>
<td>22%</td>
<td>13%</td>
<td>0.03</td>
</tr>
<tr>
<td>EF</td>
<td>62.5±9.5</td>
<td>57.8±11.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

…but not HTN, DM, dyslipidemia, FH CAD, smoking, vital signs, peak troponin, lipid values

Choo EH et al JAHA 2019

Thrombosis, thromboembolism, thrombophilia in MINOCA patients

- Exogenous hormone use
- Factor V Leiden/activated protein C resistance in 9-15% of younger MINOCA patients (3-5% of age- and sex-matched MI-CAD patients)
- Up to 24% of MINOCA patients may have an inherited thrombophilia (Factor V Leiden, protein C or S deficiency, antiphospholipid antibodies), similar to cryptogenic stroke
- When antiphospholipid antibodies present in an MI patient, ~20% had MINOCA

Coronary dissection is a cause of MINOCA, but most dissection is not MINOCA (>50% stenosis)

SCAD with <50% stenosis, diagnosed by OCT or IVUS (~1-5% of MINOCA)

Myocarditis – an alternate diagnosis found on CMR

- Clinical presentation mimicking MI is common
- CMR is diagnostic – non-ischemic LGE pattern with matching edema
- This CMR pattern is present in ~15-33% of cases clinically diagnosed as MINOCA
  - More common with angiographically normal coronaries, among men, in younger patients
  - The sooner the scan, the more likely myocarditis will be identified
- Treatment is supportive
  - No antiplatelets, no statin, etc.
Takotsubo Syndrome – MI or Not?

• Reversible LV dysfunction syndrome with elevated troponin, presents as MINOCA
• Diagnosis may be suspected based on wall motion pattern, triggering by stress but cath is still needed because AMI can cause a similar wall motion pattern
• CMR may be useful to differentiate from infarct
• There is a differential diagnosis:
  – Coronary spasm, LAD or left main SCAD, LAD or left main plaque rupture, hypertrophic cardiomyopathy
• Microvascular/multivessel spasm may mediate takotsubo, in which case it should be considered vascular → MI


How many MINOCA patients have each underlying cause?

• The answer is important for
  – Clinical trials
    • Should we select for a specific cause or finding to test a strategy?
  – Interim treatment
    • Can we tailor therapy when we don’t have all the imaging available?
  – Patient counseling
    • Doc, do I really need all these medications?
How Can We Make the Etiologic Diagnosis?
AHA Go Red for Women Strategically Focused Research Network
Sarah Ross Soter Center for Women’s Cardiovascular Research

Women’s Heart Attack Research Program (HARP)

Objectives - to determine frequency of:
- Vascular causes of MINOCA on optical coherence tomography (OCT)
- Myocardial abnormalities on cardiac MRI (CMR) - ischemic or non-ischemic
- Various underlying etiologies identified based on OCT + CMR

Core laboratories blinded to detailed clinical information, results of other imaging tests

OCT Core Lab
Dr. Akiko Maehara,
Cardiovascular Research Foundation

CMR Core Lab
Dr. Raymond Kwong,
Brigham and Women’s Hospital

Angiography Core Lab
Dr. Ziad Ali,
Cardiovascular Research Foundation
# HARP: Demographics and Presentation

<table>
<thead>
<tr>
<th>Demographics and History</th>
<th>Women with MINOCA (n=145)</th>
<th>MI Presentation</th>
<th>Women with MINOCA (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, IQR)</td>
<td>60 [52, 69]</td>
<td>Peak troponin, median (IQR)</td>
<td>0.94 ng/mL [0.34, 4.38]</td>
</tr>
<tr>
<td>Race/ethnicity other than white, non-Hispanic</td>
<td>50%</td>
<td>Peak troponin as multiple of local upper limit of normal, median (IQR)</td>
<td>17 x ULN [7 x, 61 x]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46%</td>
<td>STEMI presentation</td>
<td>3.5%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16%</td>
<td>Segmental wall motion abnormality on echocardiogram (N=111)</td>
<td>44%</td>
</tr>
</tbody>
</table>

| Race/ethnicity other than white, non-Hispanic | 3.5% |
| Coronary angiogram reported as normal by site | 53% |
| Maximal % stenosis by core laboratory, median (IQR) | 30% [26%, 37%] |

Reynolds, Maehara, Kwong et al Circ 2021

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### OCT Findings

- **Culprit Lesion n=67 (46%)**
  - Plaque Rupture n=8 (6%)
  - Intra-Plaque Hemorrhage n=31 (21%)
  - Layered Plaque n=19 (13%)
  - Thrombus without plaque rupture n=5 (3%)
  - Intimal Bump (Spasm) n=3 (2%)
  - SCAD n=1 (1%)

- **Plaque Rupture**

- **Layered Plaque**

3-vessel OCT in 59%, 2-vessel in 32%, 1-vessel in 8%

No major complications of OCT; transient spasm in 46

Reynolds et al Circ 2021
Will you know it when you see it?

MINOCA

Plaque Rupture

MI-CAD (Japanese Comparator Cohort)

Intra-Plaque Cavity

Layered plaque

Reynolds, Maehara, Kwong et al Circ 2021

Autopsy findings in sudden death include intraplaque hemorrhage

49 pts with fatal IHD
76% men, age 42-87

63 of 103 rupture plaques had IPH without luminal thrombus

Fark E. Br Heart J 1983; 50:127-134; OCT from Reynolds HR, Maehara A et al Circ 2021. Slide courtesy of Akiko Maehara MD
Clinical Correlates of OCT Culprit Lesion

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes vs. No Diabetes</td>
<td>5.41 (1.77, 19.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Abnormal vs. Normal Angiography</td>
<td>5.43 (2.50, 12.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.05 (1.02, 1.09)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

but not peak troponin or vessel-level angiographic stenosis severity per core laboratory

<table>
<thead>
<tr>
<th>Stenosis Level</th>
<th>Percent of OCT Culprit Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10% stenosis</td>
<td>12/82 (14.6%)</td>
</tr>
<tr>
<td>11-30% stenosis</td>
<td>44/227 (19.4%)</td>
</tr>
<tr>
<td>31-49% stenosis</td>
<td>14/55 (25.9%)</td>
</tr>
<tr>
<td>P value</td>
<td>0.263</td>
</tr>
</tbody>
</table>

• Women with more vessels imaged were more likely to have a culprit lesion

Reynolds, Maehara, Kwong et al Circ 2021

Intracoronary Imaging Across Studies of MINOCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent with OCT Culprit Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARP (n=145, all female, multi-center)</td>
<td>46%</td>
</tr>
<tr>
<td>Zeng et al (n=190, retrospective, some lytic)</td>
<td>52%</td>
</tr>
<tr>
<td>Tanaka et al (n=82, retrospective)</td>
<td>51%</td>
</tr>
<tr>
<td>Gerbaud et al (n=40, some CMR before OCT)</td>
<td>80%</td>
</tr>
<tr>
<td>Opolski et al (n=38)</td>
<td>29%</td>
</tr>
<tr>
<td>Reynolds (n=50, all female, IVUS)</td>
<td>38%</td>
</tr>
</tbody>
</table>

Lessons from intracoronary imaging studies:
• OCT culprit lesion in 30% of “normal” angiograms (HARP)
• More vessels imaged = more culprit lesions found
• HARP and other studies show culprit vessels are harder to identify that we often think

Reynolds et al Circ 2021; Zeng et al iJACC 2022; Gerbaud et al iJACC 2020; Taruya et al EHJ Cardiovasc Img 2020; Opolski et al iJACC 2019; Reynolds et al Circ 2011
**CMR Findings (N=116)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction</td>
<td>38</td>
<td>33%</td>
</tr>
<tr>
<td>Regional Injury</td>
<td>24</td>
<td>21%</td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>24</td>
<td>21%</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>17</td>
<td>15%</td>
</tr>
<tr>
<td>Takotsubo Syndrome</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Other Cardiomyopathy</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Normal</td>
<td>30</td>
<td>26%</td>
</tr>
</tbody>
</table>

**Median time from MI to CMR was 6 days (IQR 3.5, 9.0)**

T2 weighted imaging in 98%, T1 mapping in 66%

**Correlates of Any CMR Abnormality**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak troponin (log)</td>
<td>1.61 (1.20, 2.27)</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine (log)</td>
<td>0.52 (0.31, 0.86)</td>
<td>0.012</td>
</tr>
<tr>
<td>Diastolic BP, per mmHg</td>
<td>1.05 (1.00, 1.10)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

**but not the presence of an OCT culprit, or angiographic stenosis severity**

- Shorter time from MI to CMR was also associated with CMR abnormalities
- The median infarct size was 3.8 g
- We were unable to identify a troponin threshold below which the likelihood of abnormal CMR was low (<15%)
**OCT and CMR findings in women with MINOCA (n = 116)**

- **OCT Findings**
  - OCT Culprit: n = 51
  - No OCT Culprit: n = 65

- **CMR Findings**
  - CMR Normal: n = 30 (26%)
  - CMR Abnormal: n = 86 (74%)

- Ischemic CMR findings → 44% no OCT culprit

- OCT culprit → ischemic findings on CMR in 69%

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**CMR and rate of MI across studies of MINOCA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent with MI on CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARP (n=145, all female, multi-center)</td>
<td>54%*</td>
</tr>
<tr>
<td>Bergamaschi et al (n=437)</td>
<td>43%*</td>
</tr>
<tr>
<td>Liang et al (n=888, retrospective)</td>
<td>27%</td>
</tr>
<tr>
<td>Mileva et al (n=3624, meta-analysis)</td>
<td>22%</td>
</tr>
<tr>
<td>Sörensson et al (n=148, SMINC-2, prospective)</td>
<td>22%</td>
</tr>
</tbody>
</table>

* Included regional edema in the definition of MI
Non-ischemic CMR diagnoses in 20-50%

Reynolds et al Circ 2021; Liang et al EHJ CV Imaging 2023; Bergamaschi et al iJACC 2023; Mileva N et al iJACC 2023; Sörensson et al iJACC 2021
Key Findings from Women’s HARP
Multi-modality imaging in women with MINOCA

- 64% of MINOCA with imaging evidence of MI
- 21% with non-ischemic, alternate cause
- OCT and CMR provided useful diagnostic information, independently and in combination – 85% with cause identified overall
- CMR findings correlated well with OCT culprit lesions, demonstrating that non-obstructive culprit lesions frequently cause MINOCA
- Coronary artery spasm or thromboembolism likely caused MI/regional ischemic injury in cases without OCT culprit
- Mechanisms of MINOCA in women were often similar to mechanisms of MI-CAD: atherothrombosis with possible contribution of coronary spasm

If thrombus is not occlusive, what causes myonecrosis in the setting of plaque rupture or erosion?

Superimposed spasm?
Transient thrombosis with spontaneous thrombolysis?

Embolization of atherothrombotic debris?

Images from Reynolds et al Circ 2011
If MINOCA is truly MI, why is there no LGE in some cases on CMR?

- Even though CMR has the potential to identify very small amounts of myocardial necrosis, studies in MI with obstructive CAD and in MINOCA show that many patients with MI do not have ischemic late gadolinium enhancement on CMR
- May relate to spatial distribution of infarcted myocytes, duration of vascular occlusion
- Regional edema is an earlier sign of injury


Why do female MI patients have MINOCA more often than males?

- Multi-modality imaging study including men and women

Do mechanisms differ between men and women?

- Imaging plus blood biorepository
- In-depth understanding of specific imaging findings and how they relate to clinical features, biomarkers, genetics

Can we target imaging to specific patients?

- Larger sample size will strengthen analyses

HARP 2.0 – Enrolling 200 additional men and women with MINOCA
MHIF is an enrolling center – site PI Dr. Yader Sandoval collaborators Drs. Cavalcante and Brilakis
Current HARP Study Sites

MINOCA Imaging Study Design

Patients with MI referred for cath, no prior obstructive CAD → Consent (pre-cath) → Stress Q's → Clinical Cath, Biorep → MINOCA → 3-vessel OCT → CMR within 1 week → Follow-up for events every 6 months (virtual or in person visit)

No research imaging
### Eligibility Criteria – Heart Attack Research Program

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient with MI</td>
<td>• Prior history of obstructive CAD</td>
</tr>
<tr>
<td>• Elevated troponin AND symptoms</td>
<td>• Alternate explanation for troponin elevation (e.g., HF, CKD, hypertensive urgency) <strong>PI</strong></td>
</tr>
<tr>
<td>• ECG changes and/or</td>
<td>• Cocaine/other vasospastic agents in the recent past</td>
</tr>
<tr>
<td>• new wall motion abnormalities</td>
<td>• eGFR &lt; 45</td>
</tr>
<tr>
<td></td>
<td>• Thrombolytic therapy for STEMI</td>
</tr>
</tbody>
</table>

### What is meant by “alternate explanation for troponin elevation” in the eligibility criteria and the MI definition?

- Some clinical scenarios result in cardiac symptoms and abnormal troponin
  - Heart failure
  - Aortic stenosis
  - Arrhythmia*
- Judgment may be required
- Ask yourself – if there is non-obstructive CAD, will I be sure I know why troponin was elevated in this patient without additional testing?
Putting it all together: case example
44 year old woman with anemia, menorrhagia

- Hemoglobin 7 g/dL two weeks prior to presentation
  - Chest pain for 2 hours, looks well
- Subtle inferior ST elevation (< 1 mm) with troponin 0.09
- Next troponin 3.25 with recurrent chest pain after transfusion → cardiac cath
  - 30-40% proximal LAD narrowing with ectasia
  - LAD wraps well around apex

**OCT: Plaque Rupture with Thrombosis**

**CMR: Infarction in territory of distal LAD**
MI-CAD – Alternate Diagnosis on CMR in 12.5%

Invasive Coronary Angiography

IRA selected
n = 72 (63%)

IRA not selected
n = 42 (37%)

DE-CMR

Same IRA
n = 47 (41%)

Different IRA
n = 10 (9%)

No Hyperenhancement
n = 6 (5%)

Non-CAD Diagnosis
n = 9 (8%)

Non-CAD Diagnosis
n = 8 (7%)

Myocarditis -7

Amyloid -1

Pulmonary Embolism -1

Sarcoid -1

Patients with NSTEMI
N =114

Plus infarct artery incorrectly identified in 14% (sometimes it was really MINOCA)

Heitner JF et al Circ Interventions 2019
How Does Prognosis Relate to MINOCA Underlying Cause?
Atherosclerotic Culprit Lesions May Be Associated with Poorer Prognosis than No Culprit on OCT

Keep in mind:
- Normal CMR can occur with plaque rupture
- Patients with normal CMR are still considered to have MINOCA
- Timing of CMR matters – more likely to be normal when done later

Meta-analysis of CMR findings in MINOCA

Keep in mind:
- Normal CMR can occur with plaque rupture
- Patients with normal CMR are still considered to have MINOCA
- Timing of CMR matters – more likely to be normal when done later
Does it matter which CMR diagnosis we find?

**KEY QUESTION**
What is the prognostic value of CMR in patients with a working diagnosis of MINOCA?

**STUDY POPULATION**
252 patients with the working diagnosis of MINOCA that completed CMR imaging

- AMI 25%
- Myocarditis 15%
- NICM 44%
- Normal CMR 15%
- Other 3%
- MINOCA ruled out 57%
- MINOCA ruled in 25%

**KEY OUTCOME**
1595 patient years of follow-up

- CMR allows ruling-out true MINOCA in 57% of patients.
- CMR-diagnoses of AMI, myocarditis, and NICM were associated with worse MACE-free survival than patients with a normal CMR.

Normal CMR with excellent 10-year prognosis
Konst R et al Circ Imaging 2023

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Outcomes based on CMR:
Infarct worse than regional edema

- N=437 MINOCA total, 198 ischemic with interpretable CMR (n=116 infarct, 25% STE; n=45 regional edema, 37 normal)
- HR for 3-year MACE 1.2 for edema, 1.1 for LGE per %LV

Bergamaschi L et al iJACC in press 2023
How else does getting a diagnosis matter?

- Among 198 MINOCA patients, median follow up 2 yrs
  - Recurrent ED visits in 37% of those with indeterminate cause vs. 23% with a diagnosis made, p=0.048
  - MACE in 8.8% vs. 8.1%, p=0.86
  - More testing in those with a diagnosis made, particularly CMR

How should MINOCA be managed?

Pustjens TSF et al BMC Cardiovascular Dis 2021
ESC guidelines on ACS - MINOCA

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a working diagnosis of MINOCA, CMR imaging is recommended after invasive angiography if the final diagnosis is not clear.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

- CMR is also a class 2a recommendation in the 2021 chest pain guidelines, in cases of MINOCA (Gulati M et al. J Am Coll Cardiol. 2021 Nov. 78 (22) e187–e285.)

- “Secondary prevention therapies should be considered for those with evidence of CAD and to control risk factors”

Should Every Patient With MINOCA Have CMR?

- Highest yield subset comprised 26% of 719-patient cohort
- Older age, male sex independently associated with a CMR diagnosis
- Lowest peak troponin T with diagnostic CMR – 15 mg/L (similar to HARP)
- Lowest decile troponin still had 62% diagnostic CMR
Observational Study of Secondary Prevention after MINOCA

- Observational study of patients with MINOCA in the SWEDEHEART registry (n=9,466 MINOCA pts)
- Propensity-score matched cohorts by medical treatment
- Mean follow-up: 4.1 years
- Statins and ACE inhibitors (ACEi) / angiotensin receptor blockers (ARB) in MINOCA patients were associated with reduced major adverse cardiac events (MACE)
  - MACE = all-cause mortality, MI, ischemic stroke and heart failure
- DAPT and BB trended toward lower all-cause death; also suggested in meta-analysis

DeFilippo O et al. Int J Cardiol 2022

Statin HR 0.77 (0.68-0.87)
ACEi/ARB HR 0.82 (0.73-0.93)
Beta-Blocker HR 0.86 (0.74-1.01)
DAPT HR 0.90 (0.74-1.08)

StratMed-MINOCA (ongoing in Scotland, Berry PI)

Coronary angiogram ± PCI
Informed consent, n = 350
(All Included in the registry)

Microvascular function
Diagnostic guidewire – FFR, IMR, CFR;
1) LV end-diastolic pressure

Randomise
IMR ≥ 25
MRA  Control
IMR < 25
Registry

NTproBNP (primary outcome)
Biomarkers, MRI, questionnaires, walk test
Follow-up (30 days, 6 months)
< 20% loss-to-follow-up

Longer term health outcomes by e-record linkage
Precision medicine versus standard of care for patients with MINOCA) RCT (Italy, Crea, PI)

- Personalised diagnostic approach
  - OCT (to detect MB/PE or SCAI)
  - FIBH test (to detect coronary epicardial or microvascular spasm)
  - T3-echo and/or GE echo (if microembolisation is suspected)
  - CMR (suggested in all cases)

- Tailored pharmacologic approach
  - DAPT + PCI, statins, beta blockers, ACE/ARB (if evidence of plaque instability)
  - CCB and/or nitrates (if coronary spasm is detected)

Primary endpoint:
- Angina status assessment evaluated using the SAQSS at 1-year follow-up

Secondary endpoints:
- Composite of all-cause mortality, rehospitalisation for myocardial infarction, stroke or heart failure, repeated coronary angiography at 1 year
- Healthcare cost analysis
- Difference in morphological and functional characteristics at CMR

*Patients with Takotsubo syndrome and myocarditis (based on clinical history and CMR) will be excluded.

What role do platelets play in MINOCA?

Jeffrey Berger, Soter Center Basic Project PI
**Why might platelets be important in MINOCA?**

- Many people have non-obstructive coronary plaques
- Atherosclerosis progresses over time through cycles of rupture and healing
- Most of these events are asymptomatic or mildly symptomatic
- With larger plaques, it becomes more likely that one of these events will rise to clinical attention
- Why do some people with small plaque ruptures have MINOCA, when others make larger thrombi that present as MI with occluded arteries, and still others are clinically silent?

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**Basic Project Summary: Jeffrey Berger PI**

- MI
  - Meets eligibility criteria, provides consent at NYU
- Non-ACS Cath Referral
- MINOCA
- MI-CAD
- No obstructive CAD
- Obstructive CAD

Baseline and follow-up blood collection at 2-6 months
*Platelet activity, RNA sequencing*, *in vitro assays of interaction with other cell types*

Platelets do not have nuclei, do not actively transcribe DNA → platelet RNAseq represents pre-MI state
Platelet RNAseq: MI Patients vs. Controls

1419 transcripts differentially expressed between MI patients and controls, 762 transcripts downregulated, 657 upregulated.

IPA pathway analysis, genes p<0.05

A: MI vs. Ctrls
B: MI vs. Ctrls (adjusting for age, race, ethnicity)
C: MI vs. Ctrls (adjusting for age, race, ethnicity, DM, HTN, HLD, CKD, smoking, BMI)
Platelet RNAseq: MI-CAD vs. MINOCA

542 transcripts differentially expressed between MI-CAD and MINOCA patients

MI-CAD vs. MINOCA

IPA pathway analysis, genes p<0.05

A: MI-CAD vs. MINOCA
B: MI-CAD vs. MINOCA (adjusting for age, race, ethnicity)
C: MI-CAD vs. MINOCA (adjusting for age, race, ethnicity, DM, HTN, HLD, CKD, smoking, BMI)
Which genes are differentially expressed in MINOCA vs. other women with MI, and control women without MI?

Whole blood RNASeq at acute timepoint

What can unsupervised whole blood RNA sequencing teach us about key pathways implicated in MINOCA?

Cluster 2 enriched for atherosclerotic culprit lesions (whether MINOCA or MI-CAD)
Take Home Points

MINOCA – is it MI?
YES: about 2/3 of the time

You had a heart attack with open arteries, or “MINOCA”. More testing may help us figure out why this happened to you and might help me understand which medicines you need.
Invasive testing is important in MINOCA

- Coronary CTA will detect plaque but not plaque rupture, erosion or thrombus; CMR-defined infarct can be from spasm and/or plaque
- Identification of underlying diagnosis facilitates tailoring of therapy
- Intracoronary imaging (OCT or IVUS) usually performed during the diagnostic angiogram but can be done afterwards, especially when there is an ischemic CMR finding that warrants further investigation
- Coronary spasm testing is usually reserved for patients with persistent chest pain, but could be considered acutely if suspicion is high and the patient is stable
CMR for everyone

- Key role is to rule out myocarditis and other non-ischemic causes of the suspected MINOCA presentation
  - Tell the patient from the outset CMR will be needed to guide treatment
  - CMR ideally performed in the first few days, but still adds value >2 weeks later
  - Normal CMR is still considered MINOCA (unless you find another cause), but may be associated with better prognosis than abnormal CMR
How to treat when the underlying diagnosis is uncertain, as it stands today?

- Antiplatelet therapy
- Statin (unless you are completely sure there is no atherosclerosis – CT can be helpful here)
- Calcium channel blockade, in case there was spasm
- ACEI/ARB (based on SWEDEHEART)
- Beta blockade if there is an infarct on MRI, low EF, or if dissection was suspected

THANK YOU

Please refer your patients for the HARP study!

PI: Yader Sandoval