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:
  - Normal coronary arteries (no angiographic stenosis)
  - Mild luminal irregularities (angiographic stenosis <30% stenoses)
  - 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

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Which types of patients get MINOCA?

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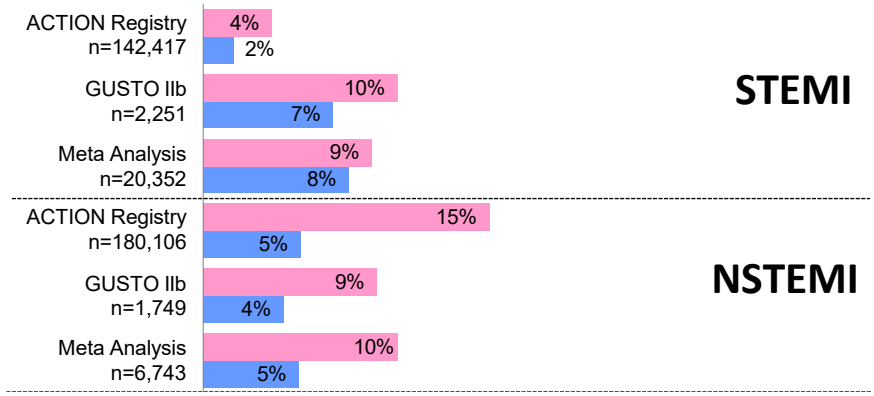
MINOCA disproportionately affects women



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

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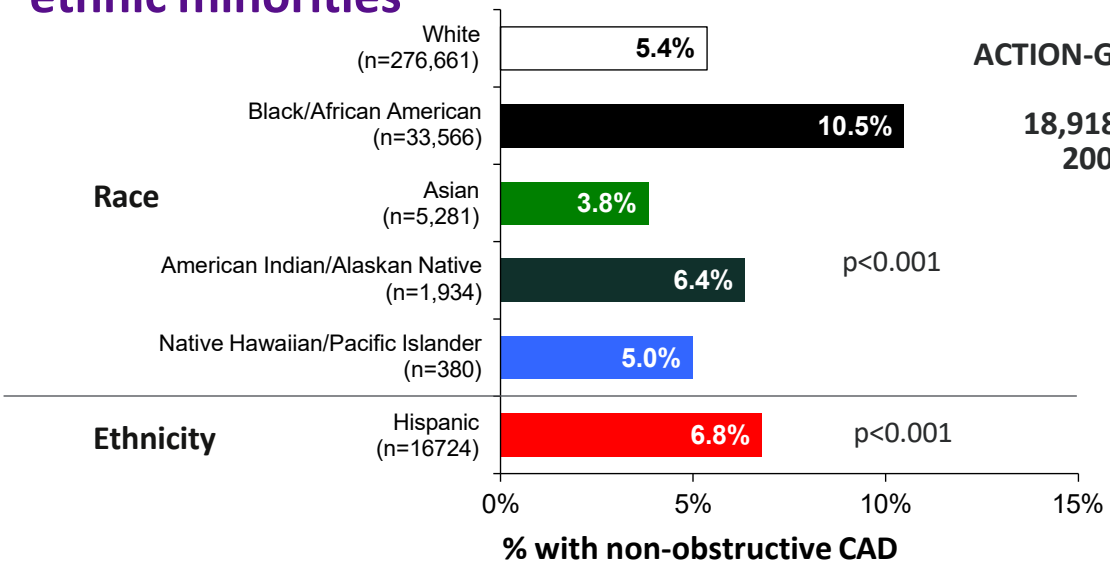
MINOCA is more common among certain racial and ethnic minorities



ACTION-GWTG registry

18,918 MINOCA
2009-2014

Smilowitz NR et al Circ Cardiovasc Qual Outcomes 2017

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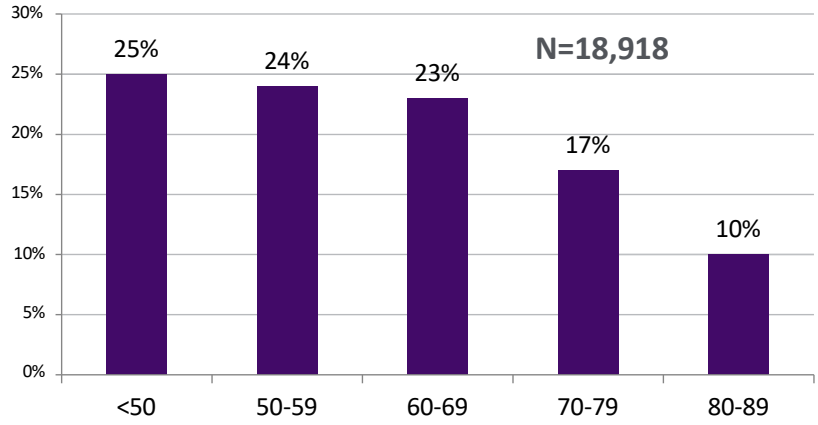
MINOCA patients are often young

Age Structure of MINOCA population in ACTION-GWTG registry



… but 27% were aged over 70

Smilowitz NR et al Circ CV Qual Outcomes 2017

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Conventional risk factors are common among patients with MINOCA

ACTION-GWTG registry N=18,918 MINOCA

Risk Factor	Prevalence in MINOCA patients
Diabetes	20%
Hypertension	65%
Dyslipidemia	45%
Smoking (Current or Recent)	27%
Any of the above	**75%**

Smilowitz NR et al Circ CV Qual Outcomes 2017

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Clinicians and patients ask:

Was this really MI?

What is the treatment?

What is the prognosis?

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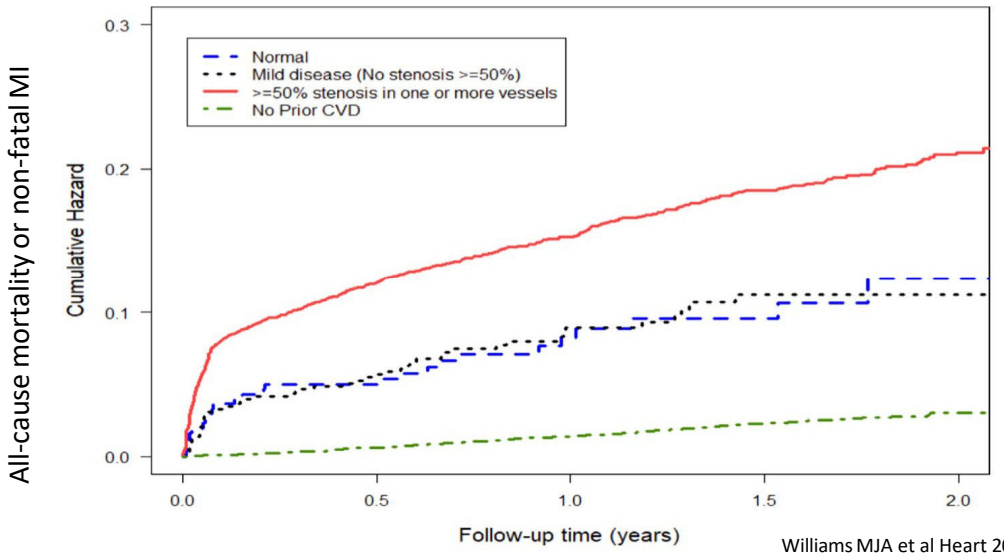
Are outcomes of MINOCA patients worse than with no prior CVD? Are normal and non-obstructive CAD prognosis the same?



MI-CAD n=7,408

897 MINOCA:
308 normal coronaries
589 mild CAD

No CVD n=8,305

Williams MJA et al Heart 2018

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Major adverse cardiovascular events after MINOCA

	>9,000 MINOCA patients SWEDEHEART Registry	>16,000 MINOCA pts Cath-PCI Registry age ≥65	~30,000 MINOCA pts meta-analysis
Outcome	**4-year Event Rate**	**1-year Event Rate**	**1-year Event Rate**
Death	**13.4%**	**12.3%**	**3.4%**
Recurrent MI hosp.	**7.1%**	**1.3%**	**2.6%**
Heart Failure hosp.	**6.4%**	**5.9%**	**3.9%**
Stroke, MACE	**4.3% stroke, 24% 4-year MACE**	**18% 1-year MACE**	**9.6% 1-year MACE**
	Lindahl et al Circ 2017	Dreyer et al EHJ 2019	Pasupathy et al Circ Outcomes 2021

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

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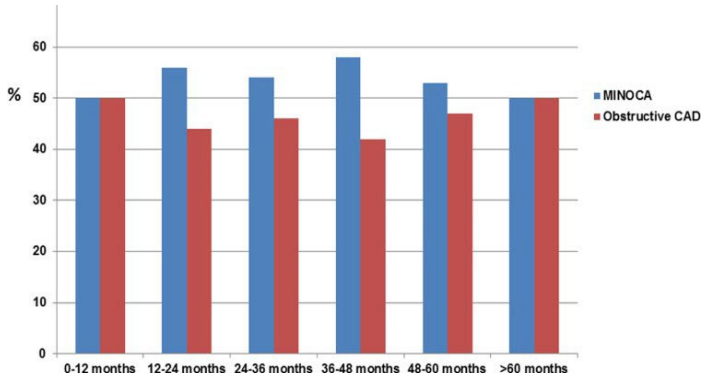
Reinfarction after MINOCA – MINOCA again?

- SWEDEHEART 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)



Nordenskjold et al., Am J Med 2018

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The best treatment of MINOCA is unknown

No treatment trials have been performed

For now, we use mechanistic and observational data to guide management

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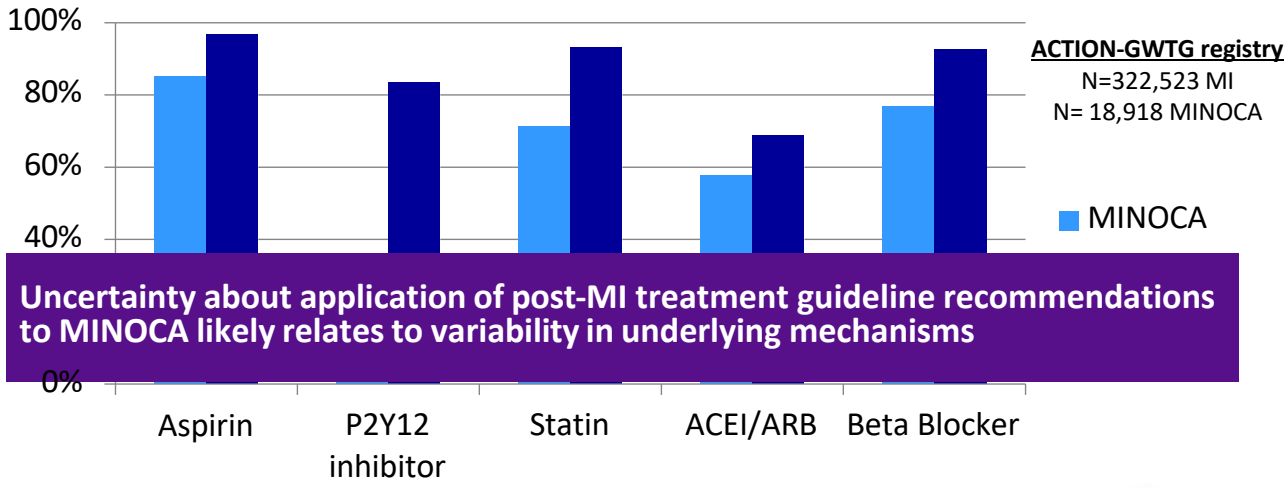
What is current practice?

Secondary prevention medication use



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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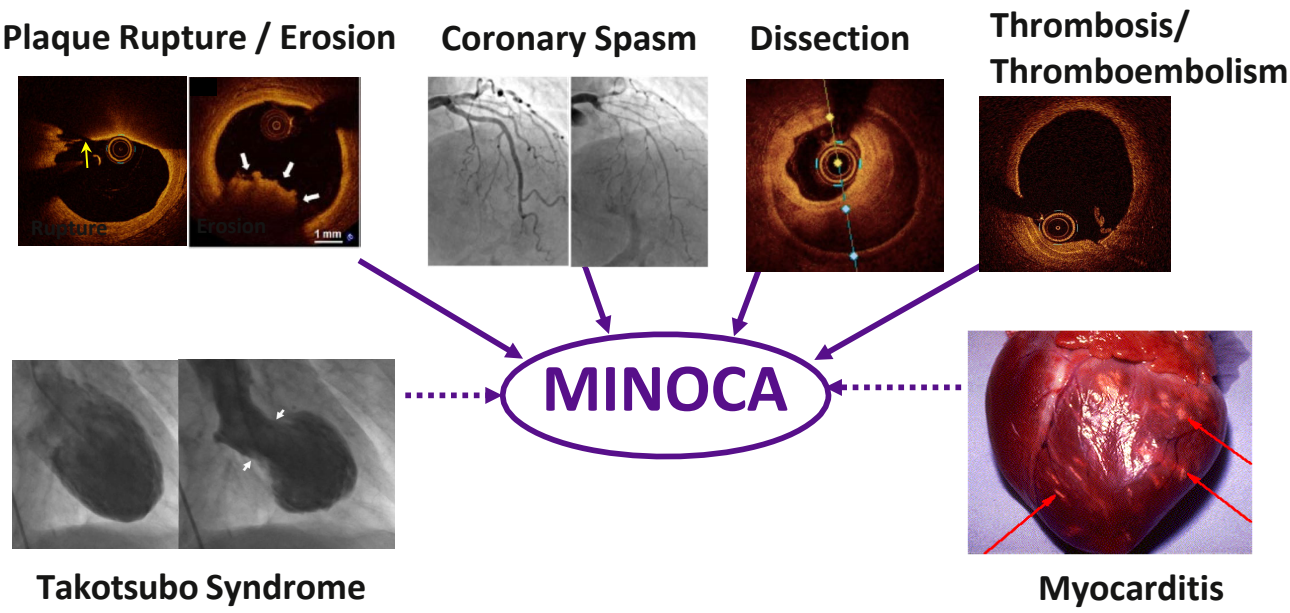

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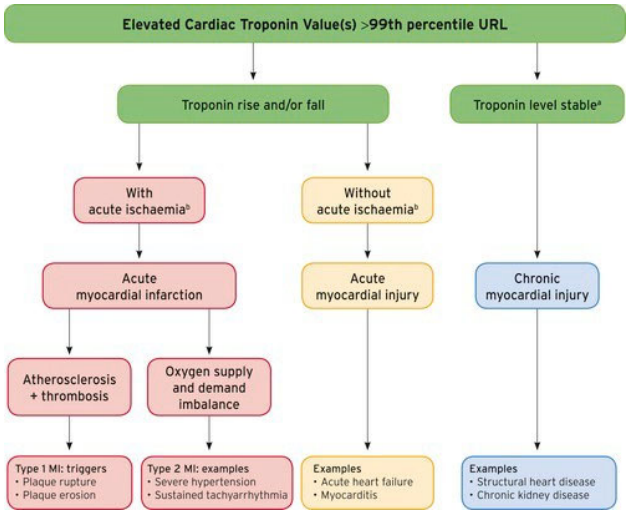
There is always a differential diagnosis



Fourth Universal Definition of Myocardial Infarction (2018)

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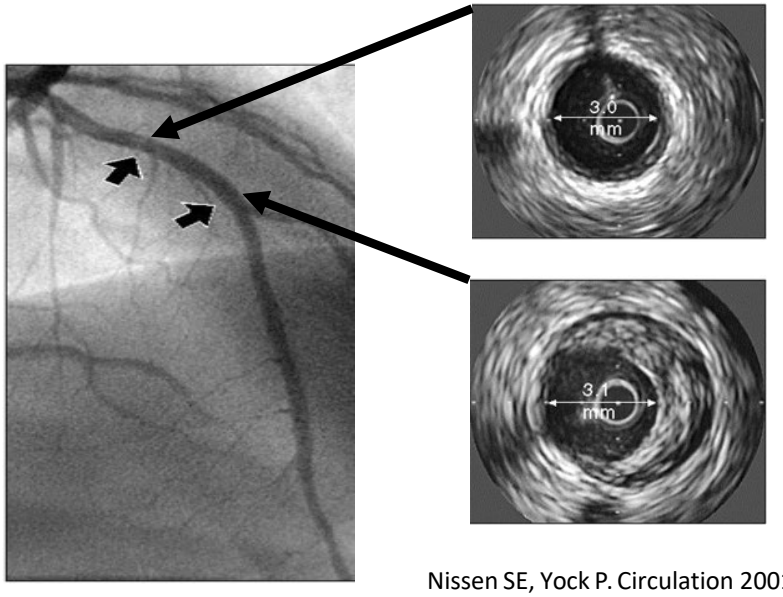
Limitations of Coronary Angiography



Nissen SE, Yock P. Circulation 2001

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Not All Plaque Rupture is Angiographically Evident

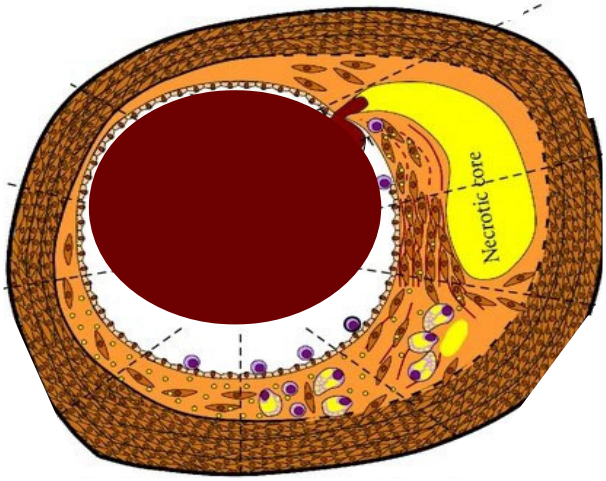

Image adapted from Funk SD et al Int J Vasc Med 2012

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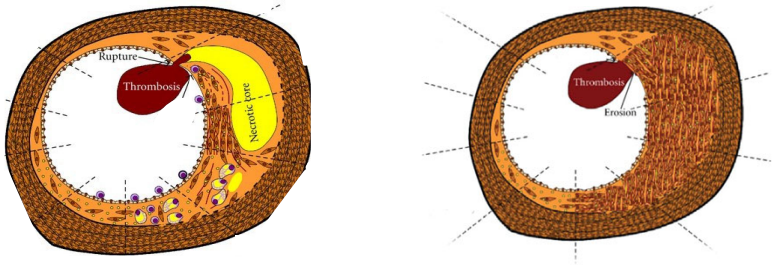
Not All Plaque Rupture/Erosion is Angiographically Evident



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

Zeng et al iJACC 2023; Reynolds et al Circulation. 2011 Sep 27;124(13):1414-25; Reynolds et al Circulation. 2021 Feb 16;143(7):624-640., Ouldzein et al Ann Cardiol Angeiol (Paris). 2012 Feb;61(1):20-6, Opolski et al JACC Cardiovasc Imaging. 2019 Nov;12(11 Pt 1):2210-2221. Gerbaud et al JACC Cardiovasc Imaging. 2020 Dec;13(12):2619-2631. Guagliumi et al JACC Cardiovasc Interv. 2014 Sep;7(9):958-68 Souza et al Coron Artery Dis. 2015 Sep;26(6):469-75; Khuddus et al J Interv Cardiol. 2010 Dec;23(6):511-9. Lee et al Circulation. 2015 Mar 24;131(12):1054-60. Iqbal S et al Am Heart J. 2014 May;167(5):715-22. Images adapted from Funk SD et al Int J Vasc Med 2012

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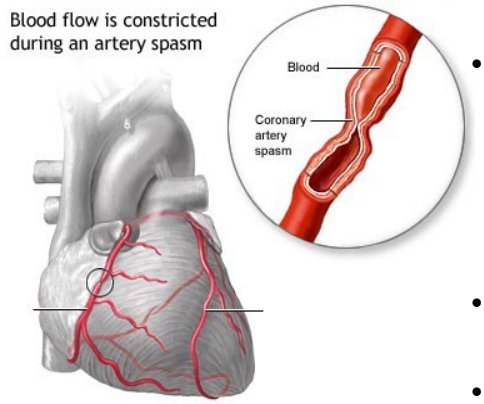
Coronary artery spasm: common cause of MINOCA



- 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

Montone RA et al EHJ 2018; Pirozzolo G et al Clin Res Cardiol 2019; Choo EH et al JAHA 2019; Gerbaud et al iJACC 2020, Montone RA et al JAHA 2021, Camilli M et al JACC 2022

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Predictors of Coronary Spasm in MINOCA

	Spasm (n=95)	No Spasm (n=301)	p
Age (y)	57.5±11.8	63.8±12.5	<0.001
Male	73%	53%	0.001
Typical Chest Pain	93%	75%	<0.001
Prior Angina	20%	10%	<0.001
ST Elevation	22%	13%	0.03
EF	62.5±9.5	57.8±11.6	0.001

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

Choo EH et al JAHA 2019

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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

DaCosta et al. Heart 1998; Mansourati et al. Thromb Haemost 2000; Van de Water et al. JACC 2000; DaCosta et al. Eur Heart J. 2001; DaCosta et al. Thromb Haemost 2004; Stepien K et al Int J Cardiol 2019; Gandhi et al Int J Cardiol Heart Vasc 2019

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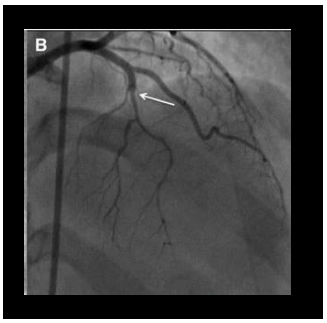
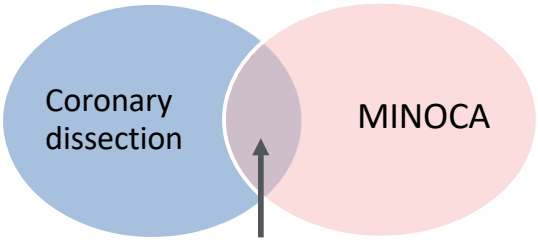
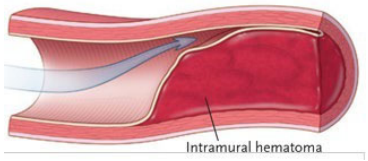
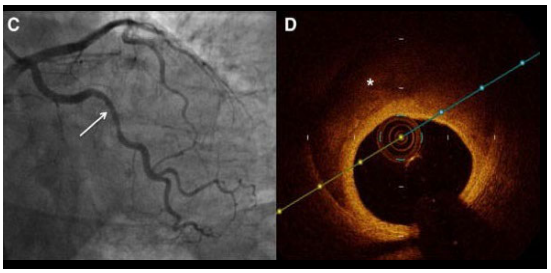
Coronary dissection is a cause of MINOCA, but most dissection is not MINOCA (>50% stenosis)





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





Zeng M et al iJACC 2023, Raparelli et al Can J Cardiol 2018, Gerbaud et al iJACC 2020, Reynolds et al Circ 2021; Images from Hayes SN ...Wood MJ Circ 2018

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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.

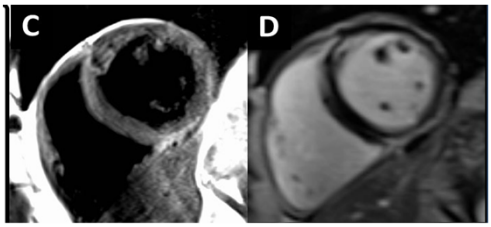

TABLE 1 Characteristics Independently Associated With CMR-Confirmed Myocarditis in Patients With a Provisional Diagnosis of MINOCA in a Meta-Analysis of Individual Patient Data

	OR (95% CI)	p Value
Angiographically normal coronaries	2.30 (1.12-4.71)	0.023
Female	0.32 (0.16-0.63)	<0.001
Older age (per yr)	0.96 (0.95-0.97)	<0.001

CI = confidence interval; CMR = cardiac magnetic resonance; MINOCA = myocardial infarction with nonobstructive coronary arteries; OR = odds ratio

Hausvater A et al iJACC 2020, Sorensson P et al iJACC 2021; Agewall S et al EHJ 2016; Tornvall P et al Atherosclerosis 2015

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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

Hausvater A et al JAHA 2019, Dastidar AG et al iJACC 2019, Sherrid MV et al AJC 2020, Reynolds HR et al Circ 2011

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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?*

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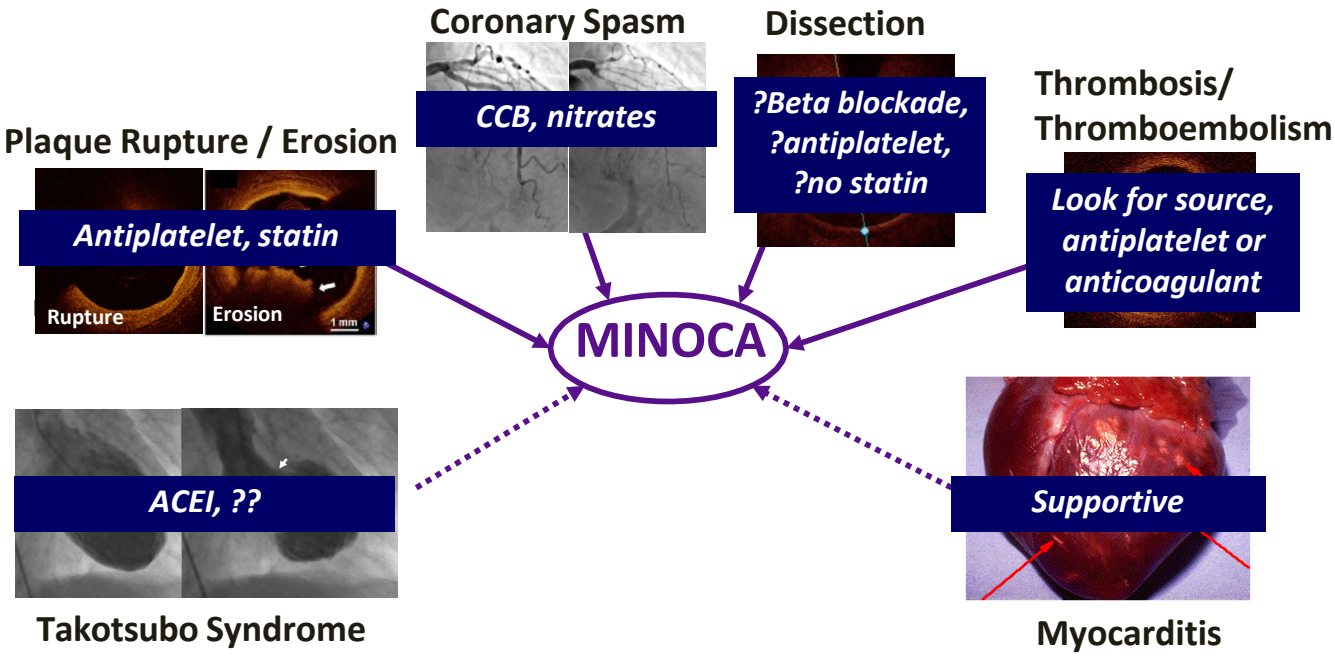
Treating MINOCA based on underlying cause



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How Can We Make the Etiologic Diagnosis?

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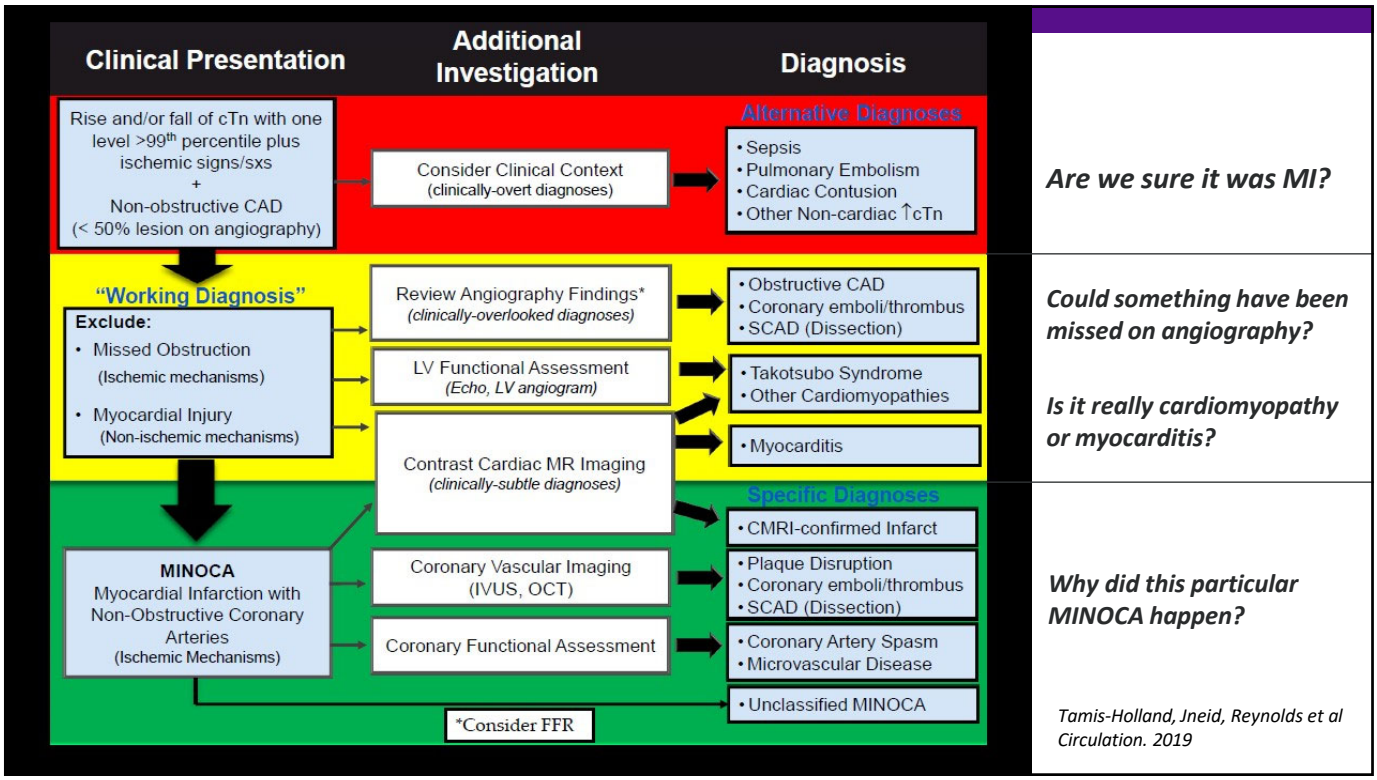

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AHA Go Red for Women Strategically Focused Research Network
Sarah Ross Soter Center for Women's Cardiovascular Research

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

Woman with MI referred for cath with intent to perform PCI → Study Consent → Clinical Cath → **MINOCA** → **OCT (3 Vessel)** → **Cardiac MRI (within 1 week)**

Clinical Cath → MI-CAD (≥50% stenosis) or angiographic SCAD → Not eligible for OCT + CMR

Patients with an alternate explanation for troponin elevation were not enrolled

Cardiac MRI (within 1 week):
- LGE
- Imaging for edema
  - T2-weighted imaging
  - T1 mapping
- LV function

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

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HARP: Demographics and Presentation

301 women with clinical diagnosis of MI, 16 sites ⇨ 170 MINOCA ⇨ 23 OCT contraindications, 2 not interpretable ⇨ 145 OCT ⇨ 116 CMR

Demographics and History	Women with MINOCA (n=145)
Age, years (median, IQR)	60 [52, 69]
Race/ethnicity other than white, non-Hispanic	50%
Hypertension	46%
Diabetes mellitus	16%

MI Presentation	Women with MINOCA (n=145)
Peak troponin, median (IQR)	0.94 ng/mL [0.34, 4.38]
Peak troponin as multiple of local upper limit of normal, median (IQR)	17 x ULN [7 x, 61 x]
STEMI presentation	3.5%
Segmental wall motion abnormality on echocardiogram (N=111)	44%
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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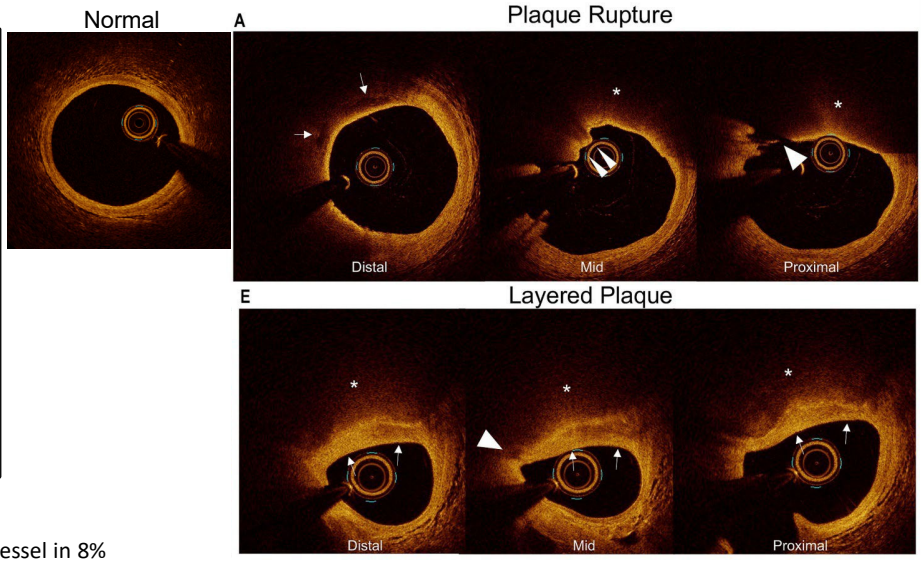
American Heart Association. Scientific Sessions

OCT Findings

OCT N=145

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%)



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

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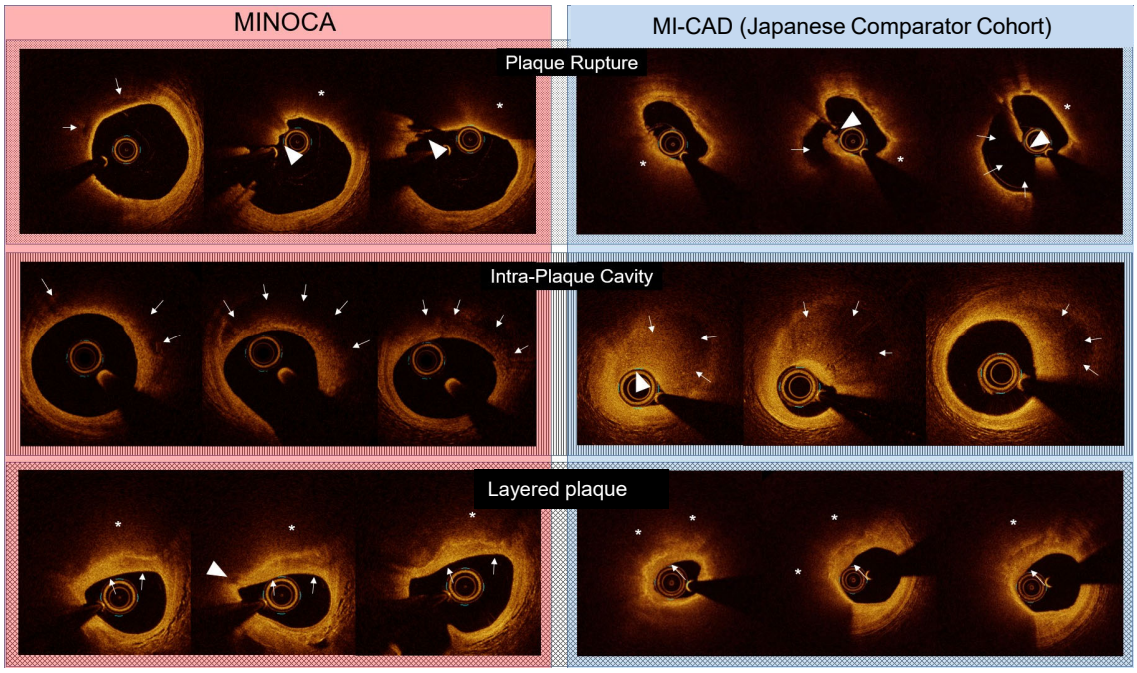
Will you know it when you see it?



Reynolds, Maehara, Kwong et al Circ 2021

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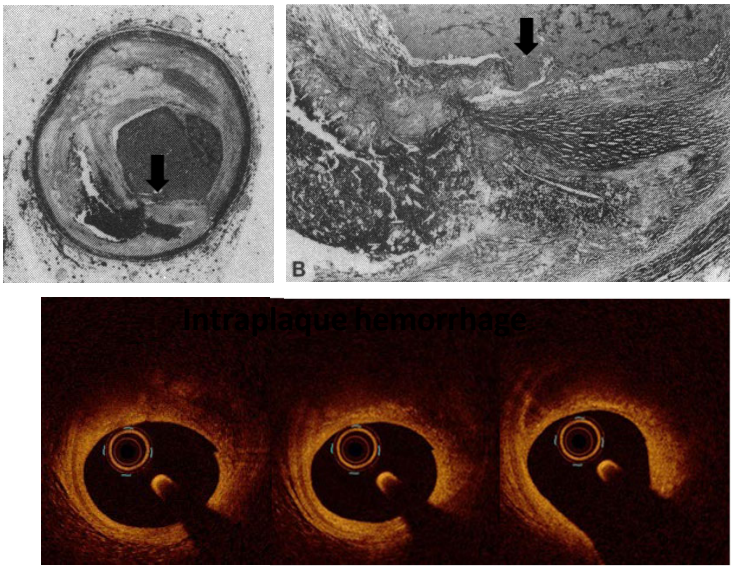
Autopsy findings in sudden death include intraplaque hemorrhage



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

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Clinical Correlates of OCT Culprit Lesion

	Odds Ratio (95% CI)	P value
Diabetes vs. No Diabetes	5.41 (1.77, 19.2)	0.005
Abnormal vs. Normal Angiography	5.43 (2.50, 12.4)	<0.001
Age, per year	1.05 (1.02, 1.09)	0.004

but <u>not</u> peak troponin or vessel-level angiographic stenosis severity per core laboratory

0-10% stenosis	11-30% stenosis	31-49% stenosis	P value
12/82 (14.6%)	44/227 (19.4%)	14/55 (25.9%)	0.263

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

Reynolds, Maehara, Kwong et al Circ 2021

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Intracoronary Imaging Across Studies of MINOCA

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

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

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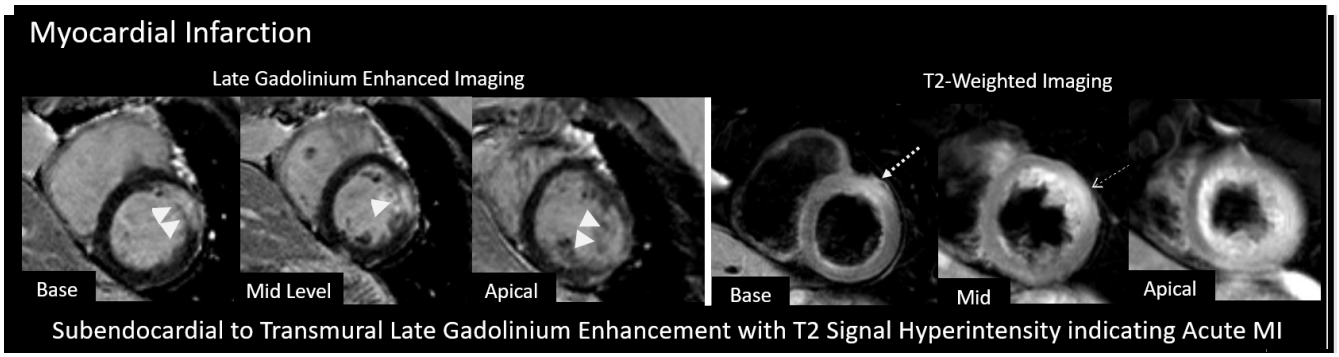
CMR Findings (N=116)

- Infarction n=38 (33%)
- Regional Injury n=24 (21%)
- Non-Ischemic n=24 (21%)
  - Myocarditis n=17 (15%)
  - Takotsubo Syndrome n=4 (3%)
  - Other Cardiomyopathy n=3 (3%)
- Normal n=30 (26%)



Median time from MI to CMR was 6 days (IQR 3.5, 9.0)
T2 weighted imaging in 98%, T1 mapping in 66%

Reynolds, Maehara, Kwong et al Circ 2021

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Correlates of Any CMR Abnormality

	Odds Ratio (95% CI)	P value
Peak troponin (log)	1.61 (1.20, 2.27)	0.003
Creatinine (log)	0.52 (0.31, 0.86)	0.012
Diastolic BP, per mmHg	1.05 (1.00, 1.10)	0.047

but <u>not</u> 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%)

Reynolds, Maehara, Kwong et al Circ 2021

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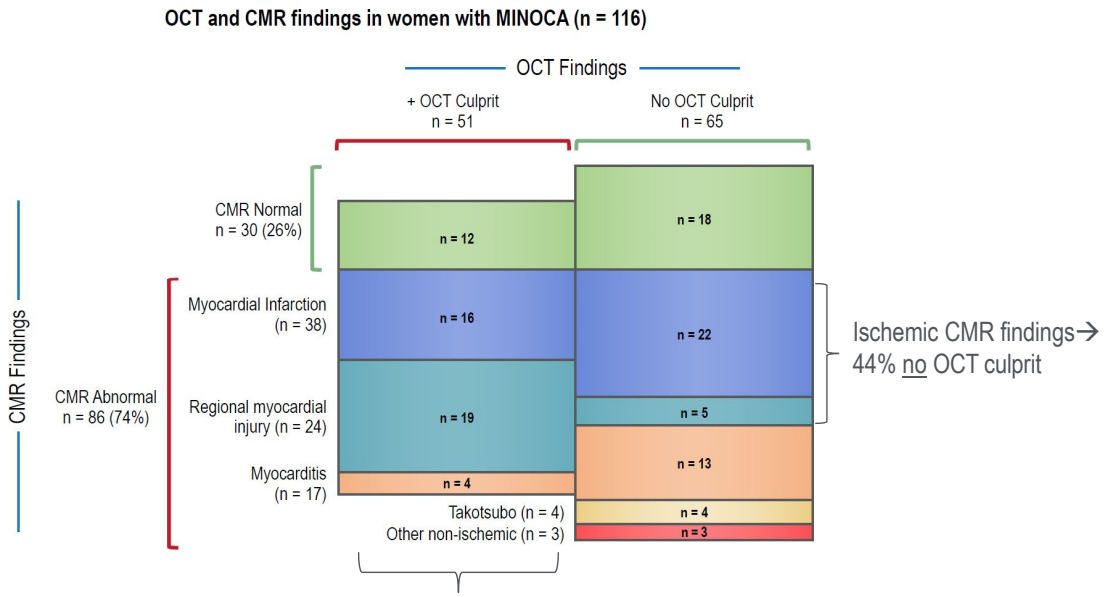

Reynolds, Maehara, Kwong et al Circ 2021

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CMR and rate of MI across studies of MINOCA

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

* 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

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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 overalls
- 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

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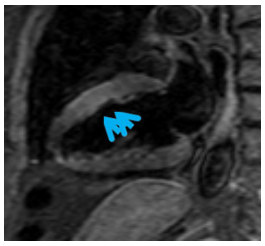
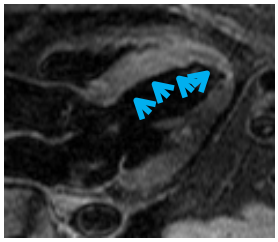
If thrombus is not occlusive, what causes myonecrosis in the setting of plaque rupture or erosion?

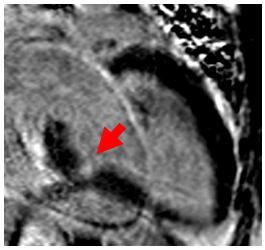
Superimposed spasm?

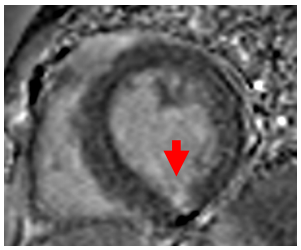
Transient thrombosis with spontaneous thrombolysis?





Embolization of atherothrombotic debris?





Images from Reynolds et al Circ 2011

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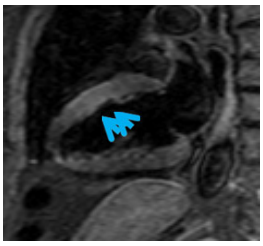
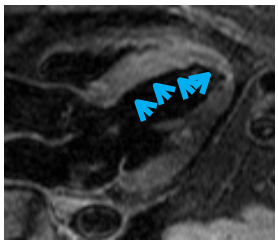
If MINOCA is truly MI, why is there no LGE in some cases on CMR?

- 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





Raman SD et al JACC 2010, Loutfi et al Clin Med Insights 2016; Abdelhafez et al Egyptian Heart J 2016; Reynolds et al Circulation 2011

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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

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Current HARP Study Sites

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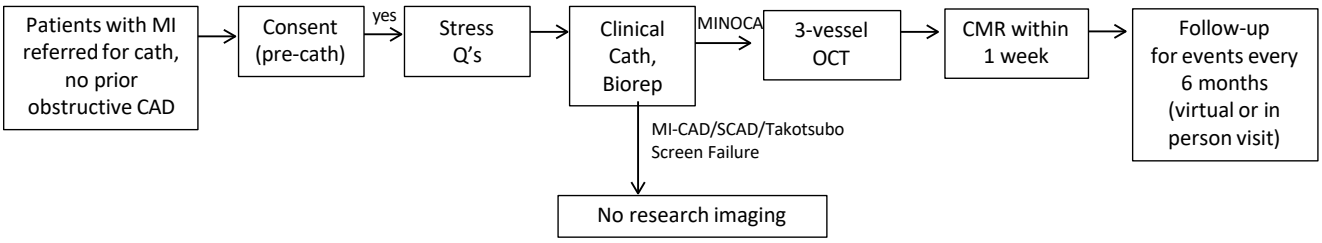
MINOCA Imaging Study Design



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Eligibility Criteria – Heart Attack Research Program

Inclusion Criteria

- Patient with MI
- Elevated troponin AND symptoms
- ECG changes and/or
- new wall motion abnormalities

Exclusion criteria

- Prior history of obstructive CAD
- Alternate explanation for troponin elevation (e.g., HF, CKD, hypertensive urgency) ***PI*
- Cocaine/other vasospastic agents in the recent past
- eGFR < 45
- Thrombolytic therapy for STEMI

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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 additonal testing?

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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

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OCT: Plaque Rupture with Thrombosis

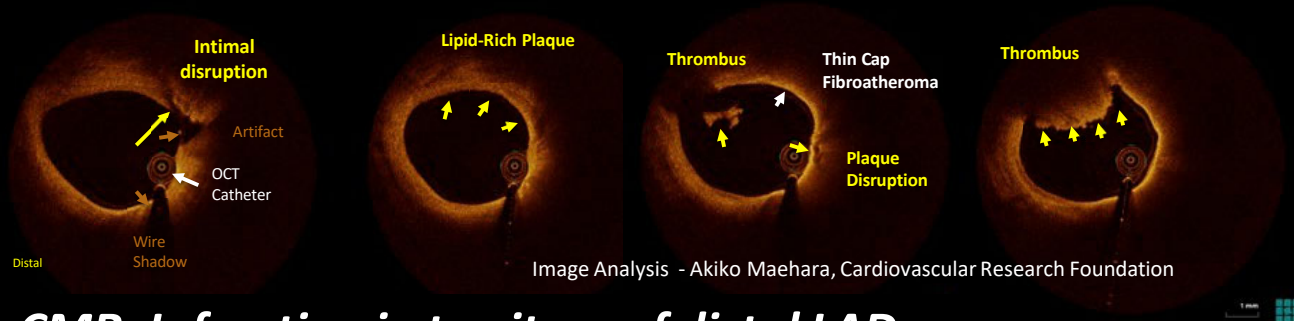

Image Analysis - Akiko Maehara, Cardiovascular Research Foundation

CMR: Infarction in territory of distal LAD

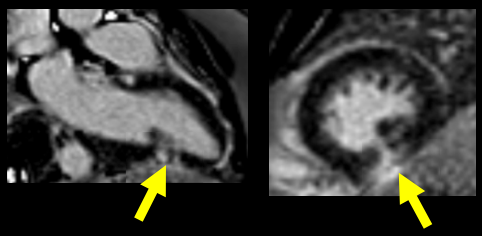

Image Analysis - Raymond Kwong, Brigham and Women's Hospital

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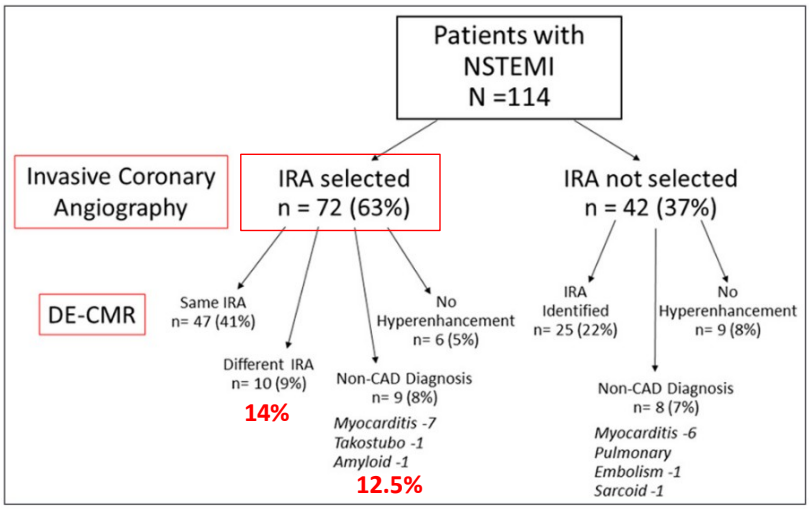
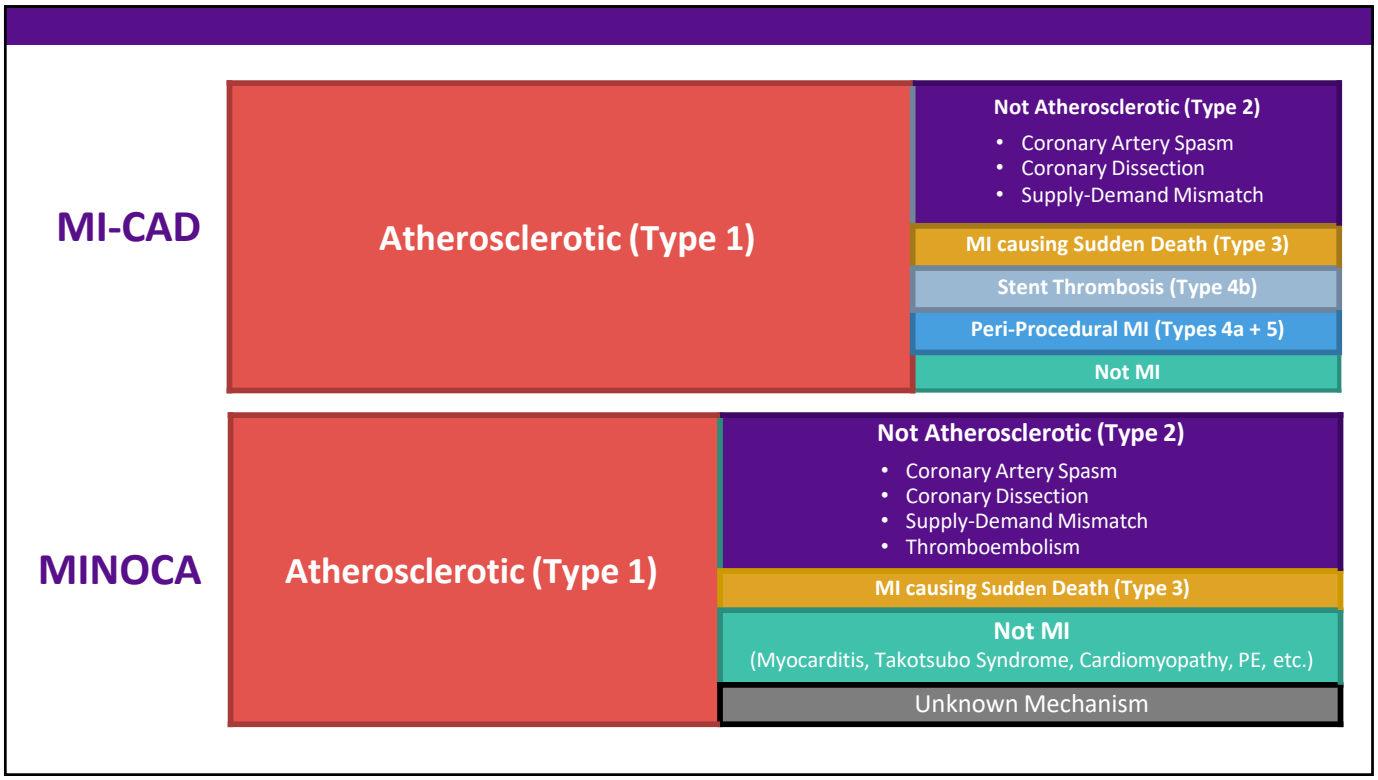
MI-CAD – Alternate Diagnosis on CMR in 12.5%



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

Heitner JF et al Circ Interventions 2019

52



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How Does Prognosis Relate to MINOCA Underlying Cause?

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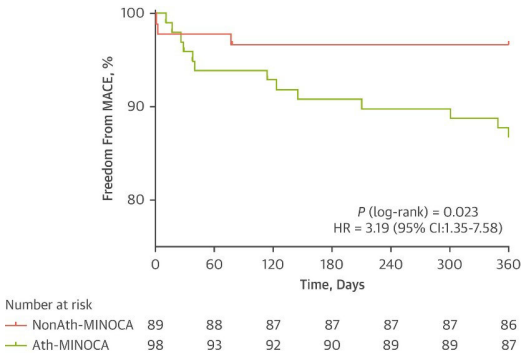
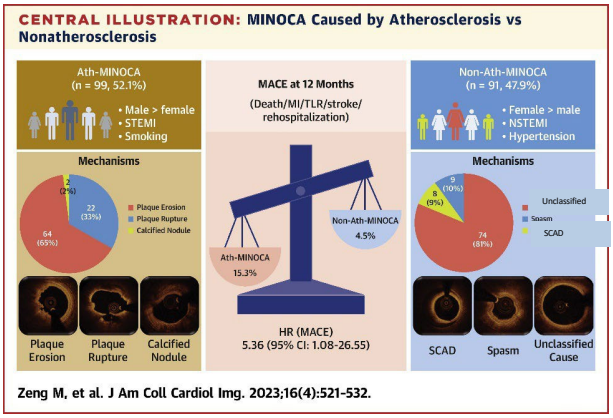
Atherosclerotic Culprit Lesions May Be Associated with Poorer Prognosis than No Culprit on OCT





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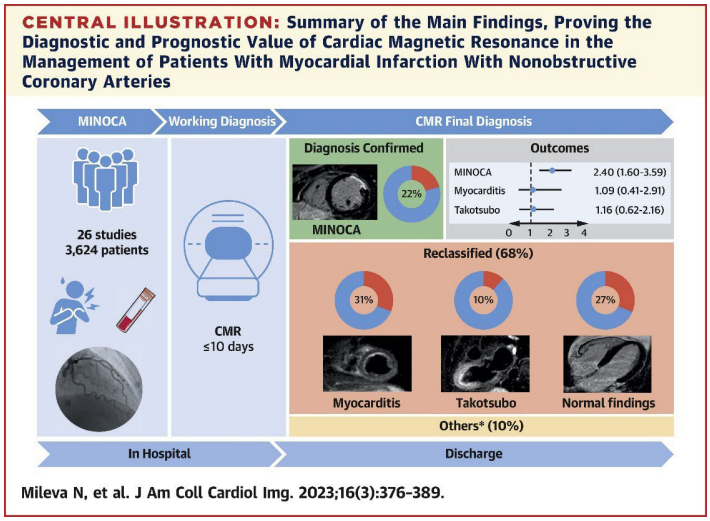
Meta-analysis of CMR findings in MINOCA



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

Mileva N et al iJACC 2023, Reynolds HR et al Circ 2021, Tornvall P et al Atherosclerosis 2015; Sorensson P et al iJACC 2021, Williams MGL et al iJACC 2022, Tamis-Holland J et al Circ 2019

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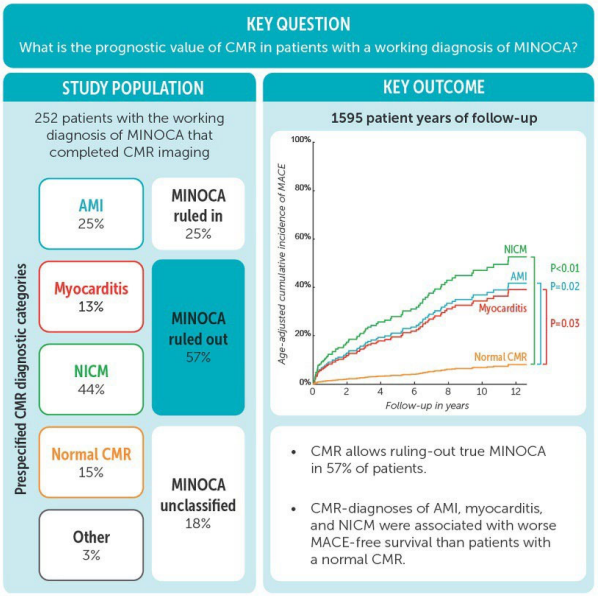
Does it matter which CMR diagnosis we find?



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

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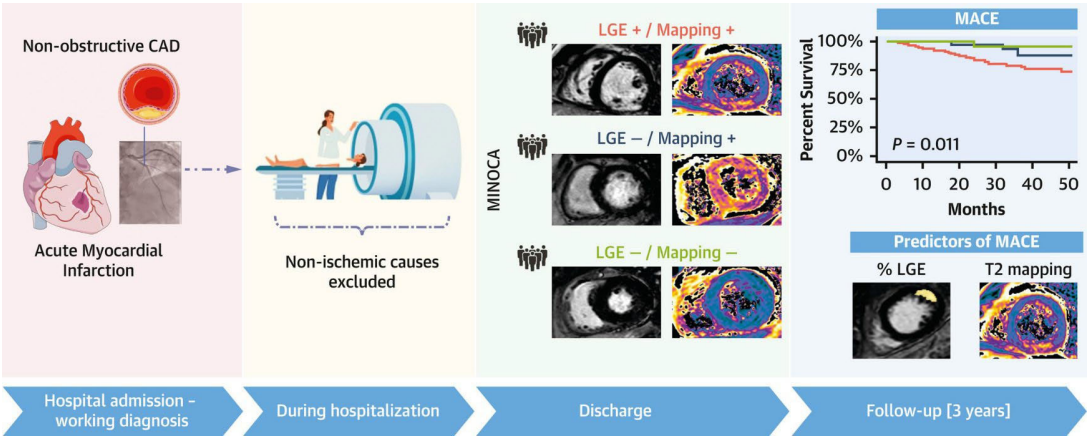
Outcomes based on CMR: Infarct worse than regional edema



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

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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

Pustjens TSF et al BMC Cardiovascular Dis 2021

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How should MINOCA be managed?

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ESC guidelines on ACS - MINOCA

Recommendations	Class[a]	Level[b]
In patients with a working diagnosis of MINOCA, CMR imaging is recommended after invasive angiography if the final diagnosis is not clear.[544,545]	I	B
Management of MINOCA according to the final established underlying diagnosis is recommended, consistent with the appropriate disease-specific guidelines.[546,550,552]	I	B
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to determine the underlying final diagnosis.	I	C

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doi: 10.1093/eurheartj/ehad191

- 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"

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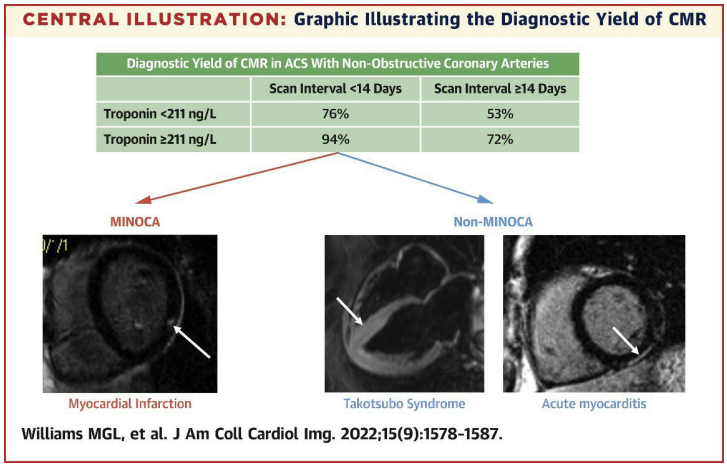
Should Every Patient With MINOCA Have CMR?



N=719
Median time to CMR 30d

- 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

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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

Lindahl B et al. Circulation. 2017 Apr 18;135(16):1481-1489
DeFilippo O et al. Int J Cardiol 2022

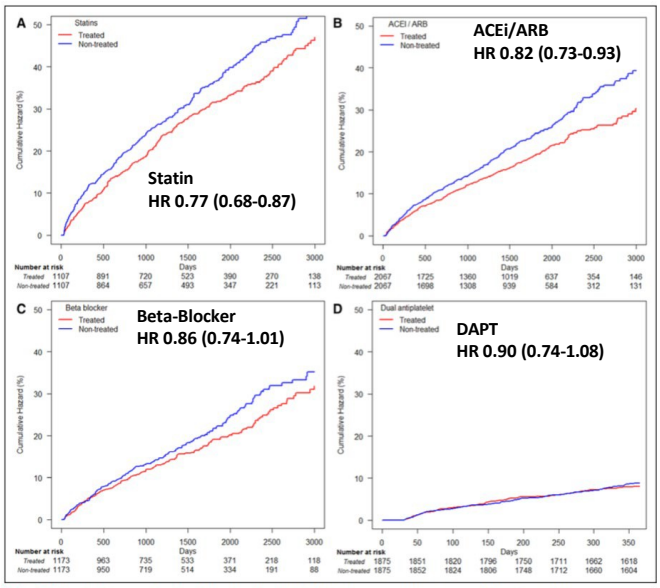

Figure 2. Survival curves for treated and untreated in the 1:1 propensity score–matched populations.
A, Statins. **B,** angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). **C,** β-blockers. **D,** Dual antiplatelet treatment.

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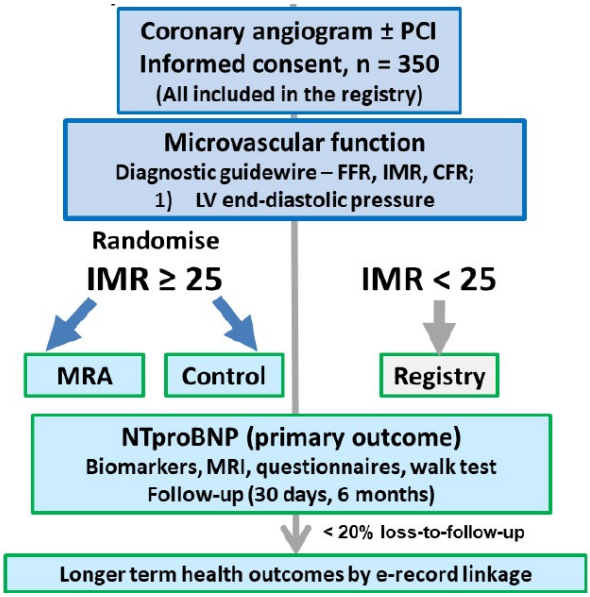
StratMed-MINOCA (ongoing in Scotland, Berry PI)



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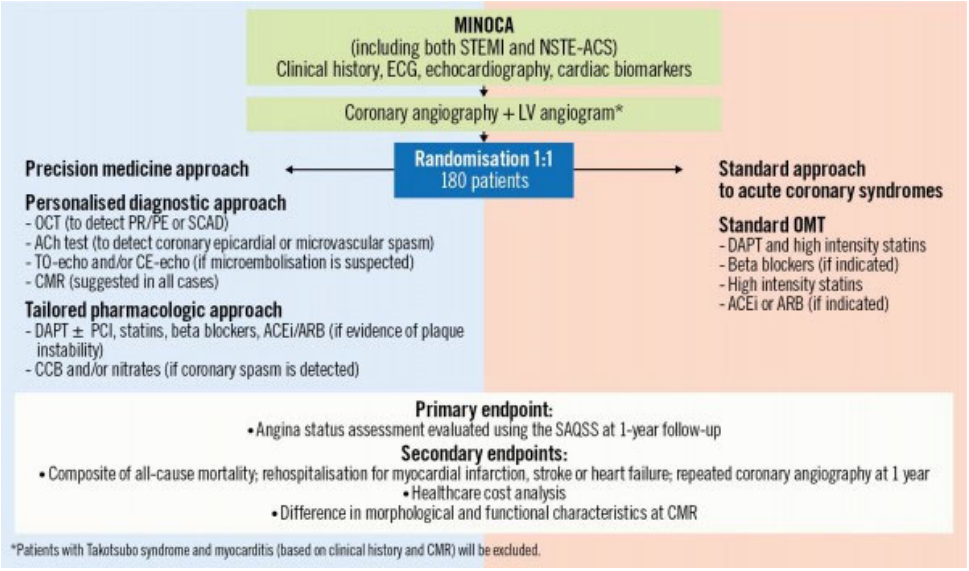
Precision medicine versus standard of care for patients with MINOCA) RCT (Italy, Crea, PI)



Montone RA et al
Eurointervention 2022

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What role do platelets play in MINOCA?

Jeffrey Berger, Soter Center Basic Project PI

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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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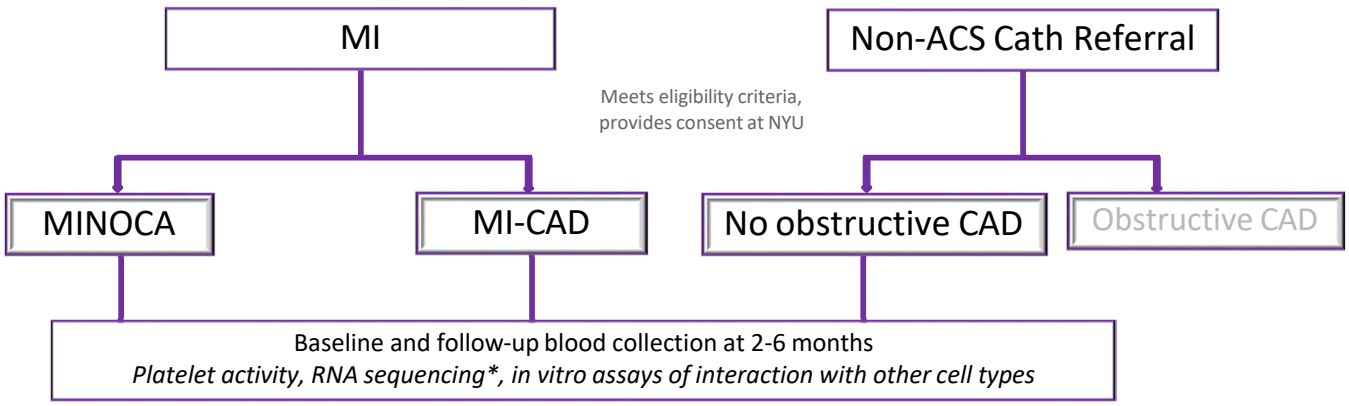
Basic Project Summary: Jeffrey Berger PI



Platelets do not have nuclei, do not actively transcribe DNA → platelet RNAseq represents pre-MI state

HARP

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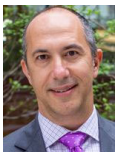
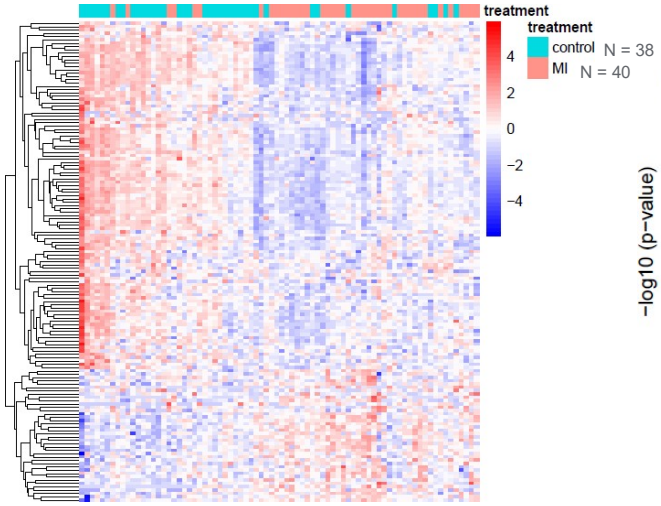
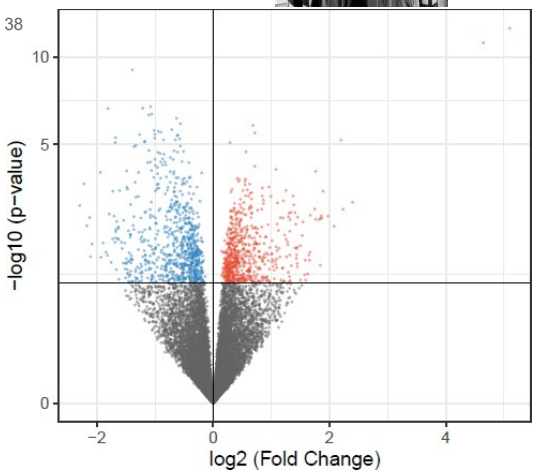
Platelet RNAseq: MI Patients vs. Controls







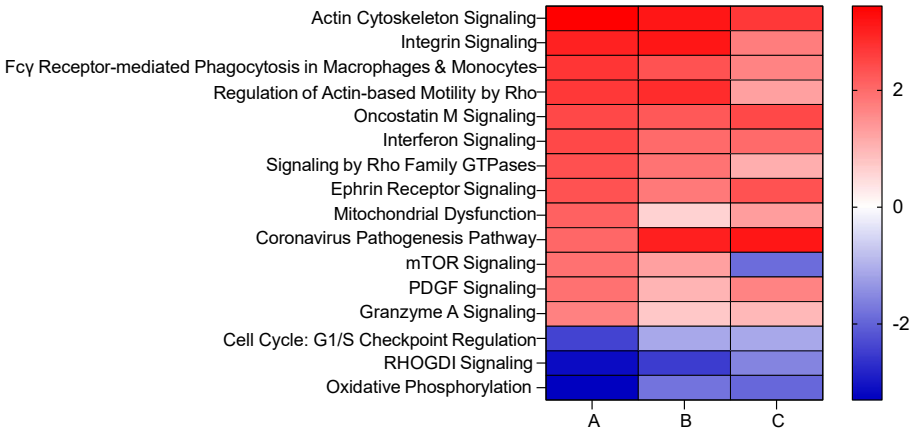
1419 transcripts differentially expressed between MI patients and controls, 762 transcripts downregulated, 657 upregulated.

69

IPA pathway analysis, genes p<0.05

Platelet RNAseq: MI Patients vs. Controls

Tessa Barrett, PhD



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)

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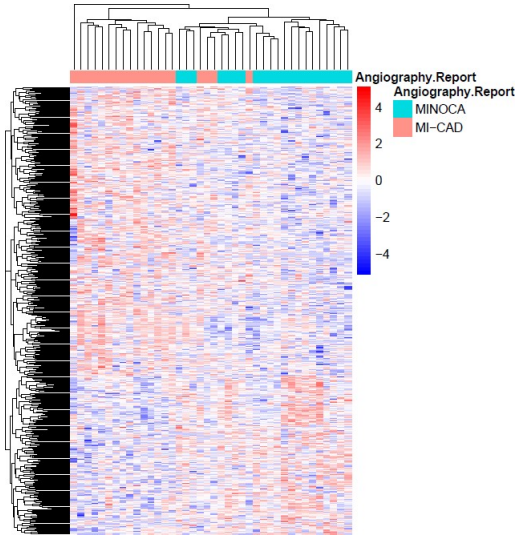
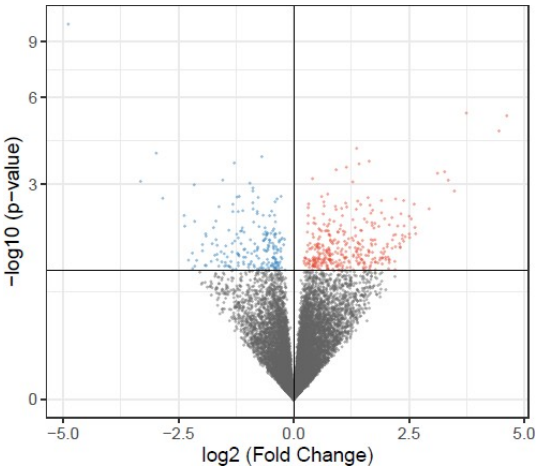
Platelet RNAseq: MI-CAD vs. MINOCA





542 transcripts differentially expressed between MI-CAD and MINOCA patients

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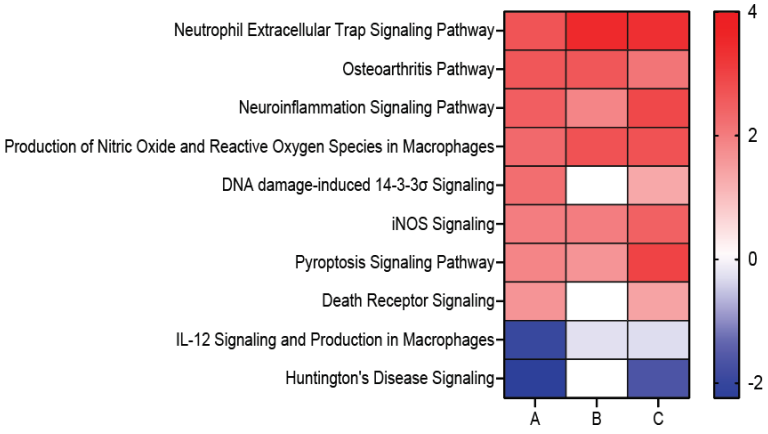
MI-CAD vs. MINOCA

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)

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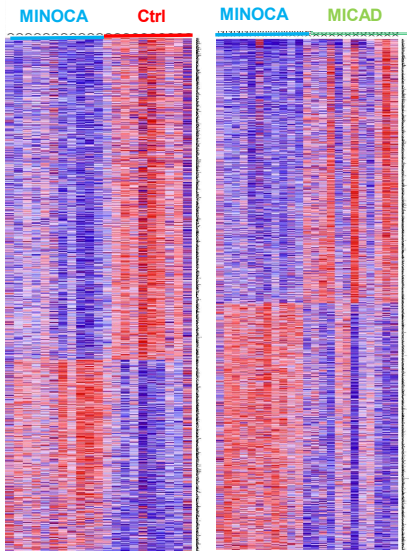
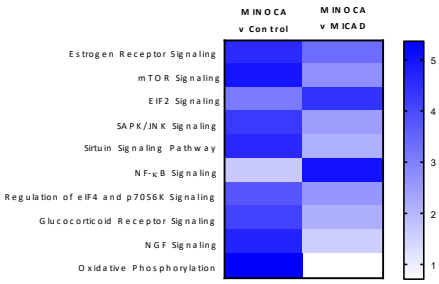
Which genes are differentially expressed in MINOCA vs. other women with MI, and control women without MI?





Whole blood RNASeq at acute timepoint
Barrett T et al. Circulation: Genomics and Prec Med 2018

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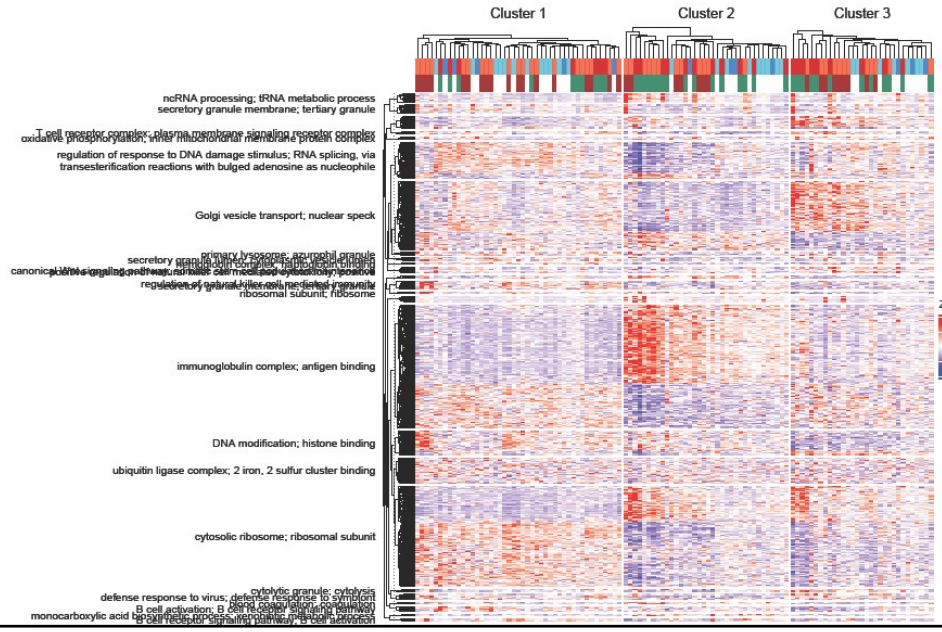
What can unsupervised whole blood RNA sequencing teach us about key pathways implicated in MINOCA?



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

Matthew Muller MS under mentorship of Kelly Ruggles

Health

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Take Home Points

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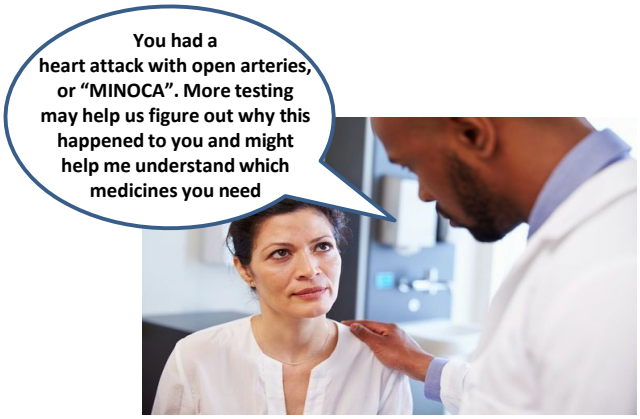
MINOCA – is it MI?

YES: about 2/3 of the time



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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

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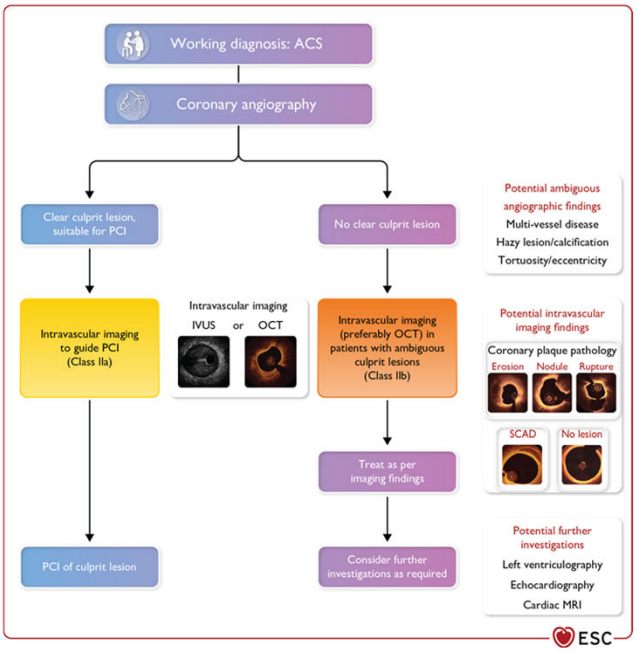
Figure 13

A practical algorithm to guide intravascular imaging in acute coronary syndrome patients



ESC

©ESC

www.escardio.org/guidelines

2023 ESC Guidelines for the management of acute coronary syndromes
(European Heart Journal: 2023 – doi:10.1093/eurheartj/ehad191)

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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

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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

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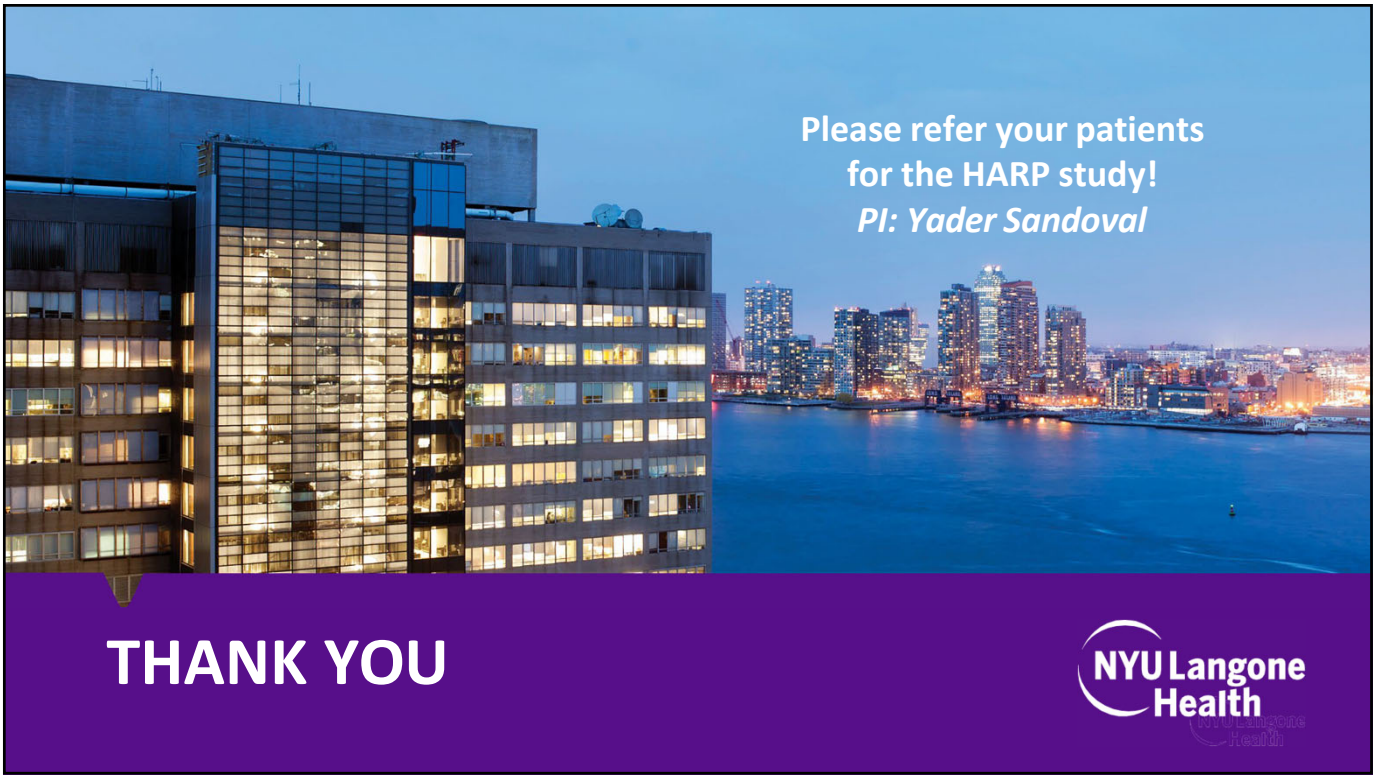

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