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GRAND ROUNDS

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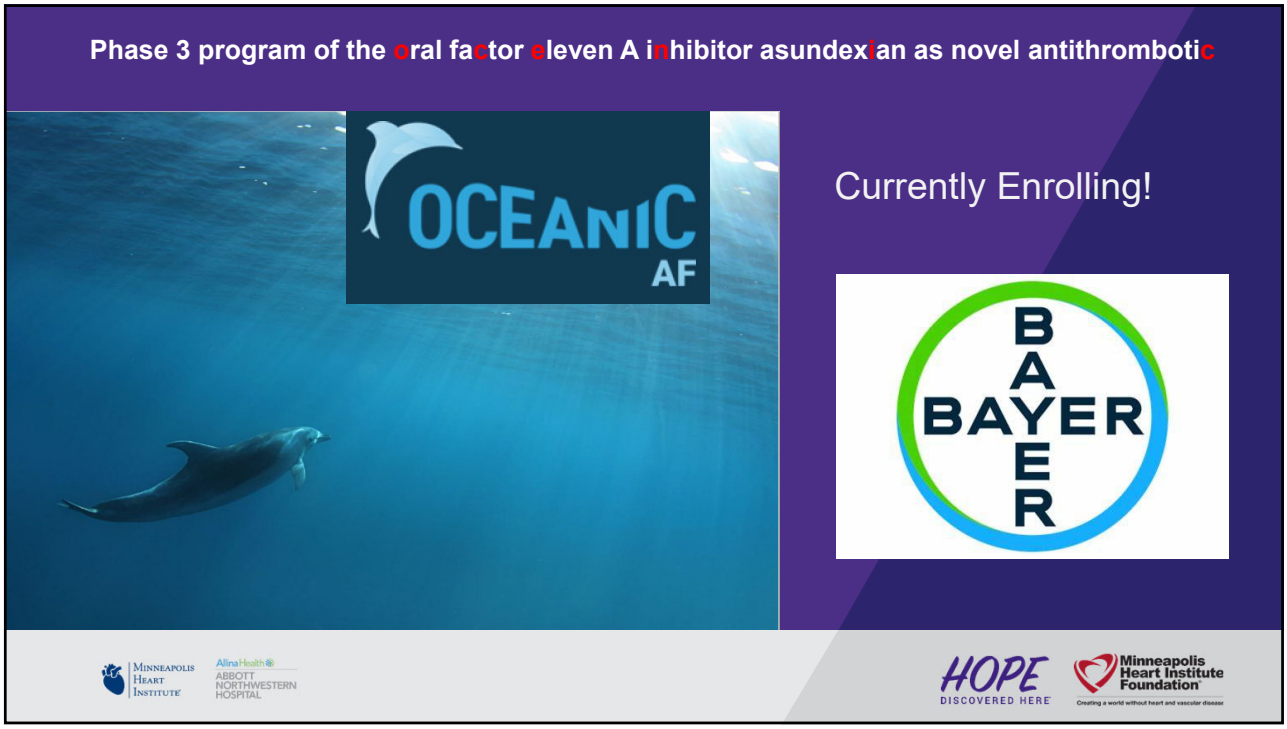
Phase 3 program of the oral factor eleven A inhibitor asundexian as novel antithrombotic
OCEANIC AF
Currently Enrolling!
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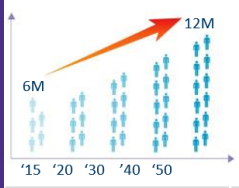
AF is a growing problem with greater morbidity and mortality

AF = most common cardiac arrhythmia, and growing

AF increases risk of stroke



~6 M
people with AF in U.S., expected to more than double by 2030[1]

5x
greater risk of stroke with AF[2]

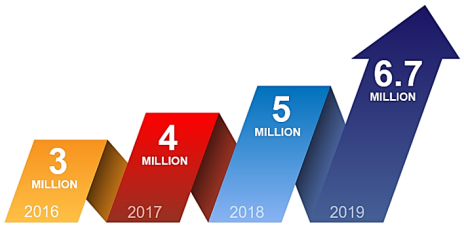
1. [1]Benjamin EJ. et al, Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. Circulation. 2018; 137: e67-e492.
2. Holmes DR, *Seminars in Neurology* 2010;30:528–536.

FXa Inhibitor Use is Rapidly Growing

Guidelines recommend FXa inhibitors for patients with venous thromboembolism and atrial fibrillation[1-3]

- **AHA/ACC/HRS** — American Heart Association, American College of Cardiology, The Heart Rhythm Society
- **CHEST** — American College of Chest Physicians
- **ESC** — European Society of Cardiology

Over 6 million patients are currently on FXa inhibitors in the US[4,a]



1. January CT, et al. J am Coll Cardiol. 2019;74(1):104-132. 2 Lip GYH, et al. Chest. 2018; 154(5): 1121-1201. 3. Steffel J, et al. Europace. 2021;23(10):1612-1676. 4. Data on File, REF-140412. AstraZeneca Pharmaceuticals LP.

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Current Therapies

- Current Antithrombotic Options
  - Aspirin
    - Meta-analysis (8 trials, 4876 participants), reduced stroke by 22% (6-35%)
    - Major bleeding risk 0.23%/year
  - Warfarin
    - Meta-analysis (6 trials, 2900 participants), reduced stroke by 64% (95% CI, 49-74%)
    - Major bleeding risk ~6%
  - Aspirin and Plavix
    - Pooled analysis (5 studies involving 24,084 participants) reduced stroke vs. aspirin alone ($p<0.05$)
    - Increased risk of major bleeding ($p<0.05$)

- Direct Oral Anticoagulants
  - Compared to warfarin
    - Dabigatran – lower ischemic stroke
    - Apixaban/edoxaban – lower hemorrhagic stroke and major bleeding
    - All DOACs – lower ICH

Bleeding complications!
Antidote cost!

Ann Intern Med. 2007 Jun 19;146(12):857-67 Zheng SL JAMA. Published online January 22 2019
J Manag Care Spec Pharm. 2017 Sep;23(9):968-978 Ruff CT, et al. Lancet 2013

Skeik N. *Vasc Med*. 2014 May 30;19(3):205-214

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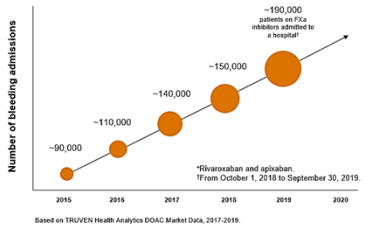
Patients on a FXa Inhibitor Hospitalized With a Major Bleed[1,2]

Bleeding admissions continue to rise as FXa inhibitor* use grows[3-5]*



~520 patients each day were hospitalized with a FXa inhibitor–related bleed in 2019[5]

~90 patients died each day following hospitalization as a result of FXa inhibitor–related bleeds[5-7]

On average, a hospital may see **3 to 4 FXa inhibitor–related life-threatening or uncontrolled bleeds per month**[8]

1. Milling TJ Jr, et al. *Am J Emerg Med*. 2018;36(3):396-402. 2. Kaatz S, et al. *J Blood Med*. 2017;8:141-149. 3. Data on File. REF-138702. AstraZeneca Pharmaceuticals LP. 4. Data on File. REF-138706. AstraZeneca Pharmaceuticals LP. 5. Data on File. US-63403. AstraZeneca Pharmaceuticals LP. 6. Piccini JP, et al. *Eur Heart J*. 2014;35(28):1873-1880. 7. Held C, et al. *Eur Heart J*. 2015;36(20):1264-1272. 8. Coleman CI, et al. *Future Cardiol*. 2021;17(1):127-135.

Annual Hospitalizations for Major Bleeds[1]
117,000

Annual Deaths Related to Major Bleeds[2]
20,000

1. Truven Health Analytics, 12 months ending December 31, 2016 for Commercial , Medicare and Medicaid pts.
2. Skaistis J, et al. *Plos One*. 2015;10(9);e0137444.

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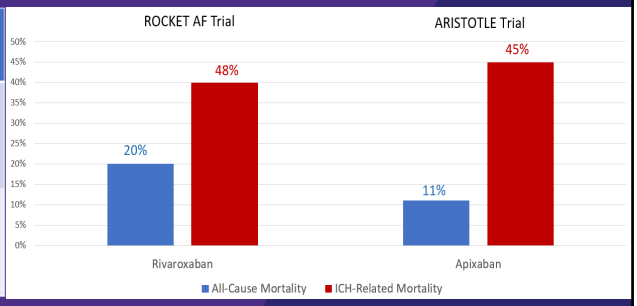
Rocket AF and Aristotle Trials

	Major Bleed (%/Year)	ICH (%/Year)	GI Bleed (%/Year)
Rivaroxaban (ROCKET-AF)	3.6%	0.5%	3.2%
Apixaban (ARISTOTLE)	2.13%	0.33%	0.76%



Patel MR et al. *N Engl J Med*.2011;365(10):883-991.
Granger CB et al. *N Engl J Med*. 2011;365(11):981-992.

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FXIa Inhibitor History

- Preclinical
  - FXI-deficient mice studies → benefit in reduced thrombus formation with no increase in bleeding time (even when given with dual antiplatelet agents), as seen in DOAC models[1]
  - Inherited FXI deficiency → lower clinical aPTT and categorized as mild bleeding phenotype with no direct association between activity levels and bleeding risk[2].
    - A lower stroke risk was particularly evident in patients with AF[4]
- Phase 1 studies
  - no relevant bleeding events were reported, shown to be safe and well tolerated[3]
- Phase 2 studies
  - Less bleeding compared to apixaban in AF patients, with some also receiving antiplatelet therapy
  - PACIFIC studies → n=4164, support for Asundexian 50mg dose selection, lower incidence of bleeding than apixaban, and potential benefit in prevention of ischemic strokes and TIAs

1. Wang X et al. Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. J Thromb Haemost. 2005 Apr;3(4):695-702 2.Visser M et al. Role of Factor Xia and Plasma Kallikrein in Arterial and Venous Thrombosis. Thromb Haemost. 2020 Jun;120(6):883-993. 3. Kubitza D. et al. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther. 2005 Oct;78(4)412-21 4. Georgi B. et al. Leveraging Human Genetics to Estimate Clnical Risk Reductions Achievable by Inhibiting Factor XI. Stroke. 2019 Nov;50(11):3004-12.

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Asundexian: Mechanism of Action

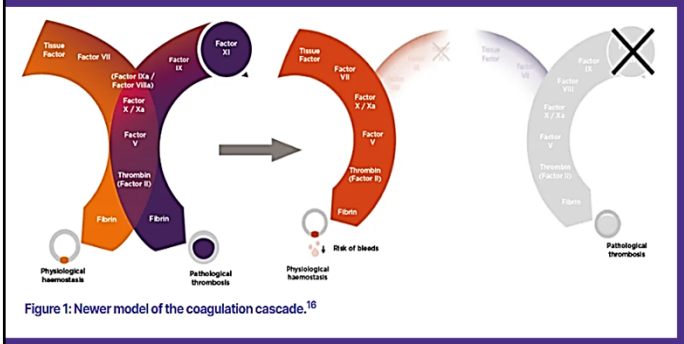
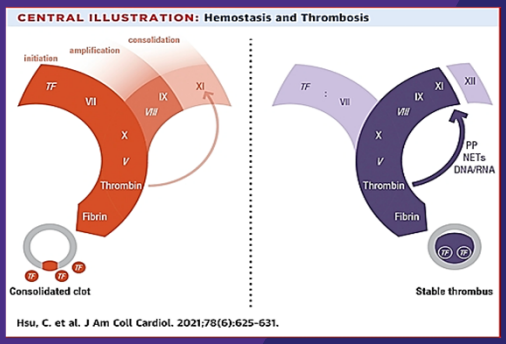
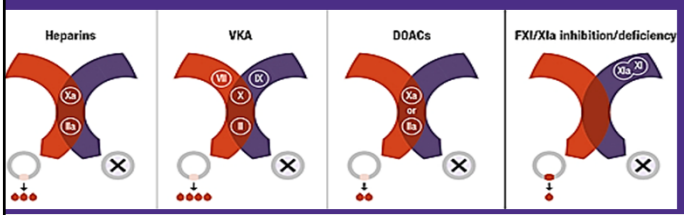


Figure 1: Newer model of the coagulation cascade.[16]





Through selective inhibition of the intrinsic pathway, asundexian may prevent pathological clot formation (thrombosis) without hindering hemostasis (physiologic response to injury)

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OCEANIC-AF

Phase 3 program of the **O**ral fa**C**tor **E**leven **A** i**N**hibitor asundexi**a**n as novel antithrobot**i**C – **A**trial **F**ibrillation study

Coming February 2023!

EPIC message: *MCHH EP OCEANIC-AF*

CONDITION:
Atrial Fibrillation

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SPONSOR:
Bayar AG

DESCRIPTION:

OCEANIC-AF is a multicenter, international, randomized, active comparator-controlled, double-blind, double-dummy, parallel-group, phase 3 study.

The purpose of the study is to investigate the efficacy of the oral FXIa inhibitor asundexian in prevention of stroke and systemic embolism and its safety (bleeding risk) compared with apixaban in adult participants with AF at risk for stroke. Asundexian is expected to have superior or at least similar efficacy while leading to less bleeding when compared with the NOAC apixaban.

Expected to be conducted at 1100 sites, with 18,000 participants randomized over 2 years (already underway). Patients are expected to be on study drug 9-33 months.

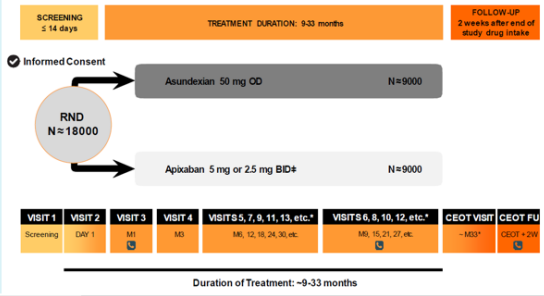
CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- Documented AF with indication for indefinite treatment with oral AC
- CHA_2DS_2-VASc score ≥3 (male) or ≥4 (female) **OR** 2 (male) or 3 (female) with 1 of the following:
  - Age ≥70, previous stroke, TIA or SE, renal dysfunction with eGFR <50, prior non-traumatic major bleeding, current single agent antiplatelet therapy for 6+ months, ≤6 consecutive weeks of treatment with oral AC

Exclusion:

- Mechanical heart valve prosthesis (TAVR ok)
- Moderate-to-severe mitral stenosis
- AF only due to reversible cause
- Successful ablation, LAA occlusion, or plans for 1 in next 6 months
- Recent ischemic stroke
- Active non-trivial bleeding, chronic bleeding disorder, hx non-traumatic intracranial hemorrhage
- Significant liver disease or hepatic insufficiency
- eGFR < 25 at randomization
- Major surgery in last 30 days
- Chronic AC for non-AF reason, dual AP therapy
- VKA in past 10 days prior to randomization
- NSAIDs for +4 weeks during study period
- Combined P-gp and strong/mod CYP3A4 inducers



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OCEANIC-AF Endpoints

	Objectives		Endpoints
Primary	Efficacy	**Asundexian is superior to apixaban for prevention of stroke or SE**	• Composite of stroke or systemic embolism
	Safety	**Asundexian is superior to apixaban as assessed by ISTH major bleeding**	• ISTH major bleeding
	Net clinical benefit	**Compare the effects of asundexian and apixaban with respect to benefit and risk**	• Composite of stroke, systemic embolism or ISTH major bleeding

	Objectives		Endpoints
Secondary	Efficacy	Compare the effects of asundexian and apixaban with respect to composite and individual **efficacy endpoints**	• Composite of ischemic stroke or systemic embolism • All-cause mortality • Ischemic stroke • CV death • Composite of CV death, stroke, or MI
	Safety	Compare asundexian and apixaban with respect to composite and individual **bleeding endpoints**	• Composite of ISTH major or CRNMB • Clinically relevant non-major bleeding • Hemorrhagic stroke • Intracranial hemorrhage • Fatal bleeding • Minor bleeding
	Net clinical benefit	To compare the benefit and risk of asundexian and apixaban with respect to a **composite of efficacy and safety endpoints**	• Composite of stroke, systemic embolism, or ISTH major bleeding, or all-cause mortality • Composite of disabling stroke (mRS ≥ 3), critical bleeding , or all-cause mortality

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OCEANIC-AF Risks

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data / Rationale for Risk	Mitigation Strategy
Study Intervention asundexian		
A risk for bleeding cannot be excluded in participants with AF included in the Phase 3 study and randomized to asundexian or to the comparator apixaban.	Bleeding is the main safety concern related to antithrombotic therapies. For an inhibitor of FXIa a lower bleeding risk is expected than with the comparator drug.	Exclusion criteria are phrased to exclude patients with a higher risk for bleeding (e.g. recent major surgery / active bleeding at randomization). Bleeding will be closely monitored in the study and will be adjudicated by an independent Clinical Events Committee. Furthermore, an IDMC will be installed monitoring unblinded study data on an ongoing basis.
Liver-related adverse effects.	The findings regarding liver-related adverse events were reassuring during the PACIFIC Phase 2 studies. Liver-related adverse effects will continue to be monitored to further characterize the clinical profile of asundexian.	Patients with known significant liver disease or known hepatic insufficiency classified as Child-Pugh B or C will be excluded from Phase 3, liver parameters are part of the safety laboratory panel and follow-up will be required for certain liver events. Furthermore, an IDMC will be installed monitoring unblinded study data on an ongoing basis.

Study drug will be discontinued if:

- ALT/AST > 8 x ULN
- ALT/AST > 5 ULN for 2+ weeks
- ALT/AST > 3 ULN and (total bilirubin >2 x ULN or INR 1.5)
- ALT/AST > 3 ULN with appearance of fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, and/ or eosinophilia (>5%)

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OCEANIC-AF Screening and Enrollment

- Screening from EP clinic
  - Estimated to look at ~75 patient charts per week
  - Coordinator will send staff message if you have a patient that looks eligible for screening
- Accepting referrals
  - Send staff message, including patient chart, to **MCHH EP OCEANIC-AF** pool
  - Coordinator will complete pre-screen and get back to you prior to patient visit, if scheduled
- Able to meet at Centennial Lakes (pending) and ANW clinic for initial discussion, but screening/randomization will need to be at ANW
- Current goal is to enroll 2-3 patients per week.
- Already enrolled first patient!

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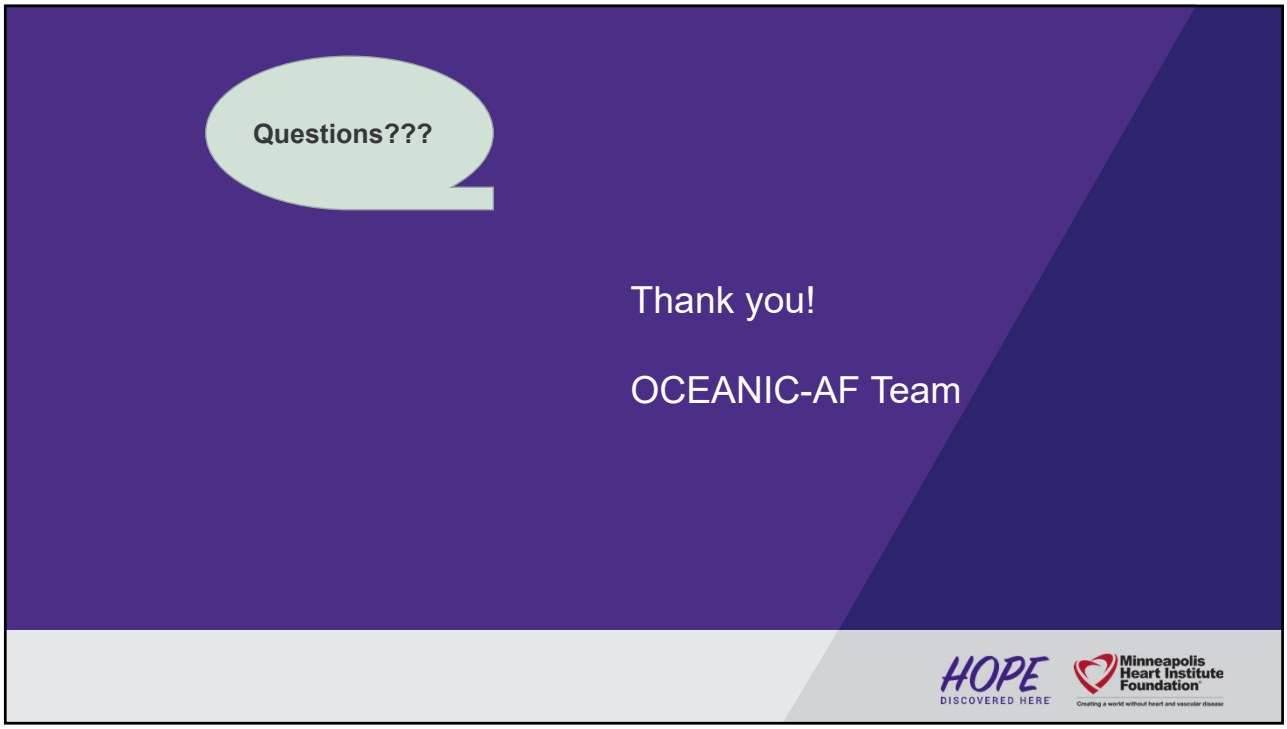
Questions???
Thank you!
OCEANIC-AF Team
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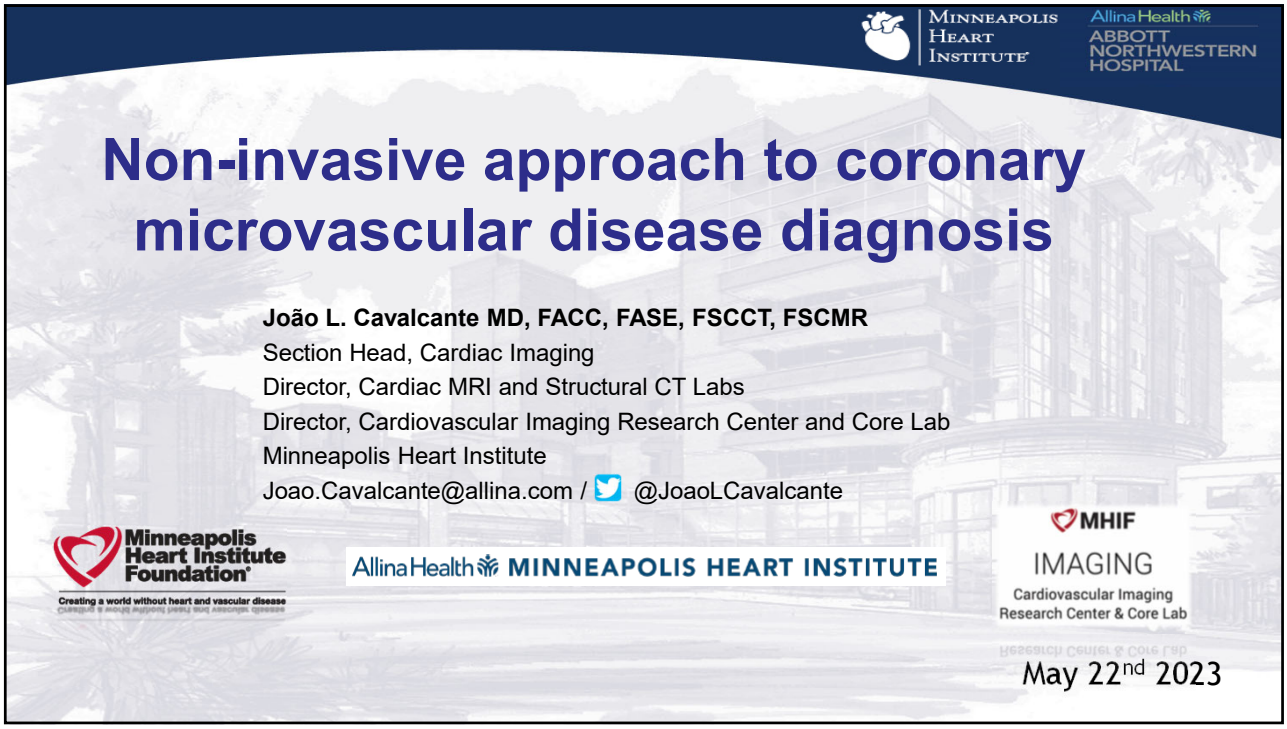
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Non-invasive approach to coronary microvascular disease diagnosis
João L. Cavalcante MD, FACC, FASE, FSCCT, FSCMR
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Director, Cardiac MRI and Structural CT Labs
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MHIF
IMAGING
Cardiovascular Imaging Research Center & Core Lab
May 22nd 2023

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Personal Disclosures:

- Consultant (4C Medical, Abbott Structural, Anteris, AriaCV, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic, VDyne, WL Gore, Xylocor)
- Research Collaborations (Siemens Healthineers, Dr. Peter Kellman, NIH/NHLBI)
- Research Grant: Abbott Structural, Boston Scientific, Edwards Lifesciences, Abbott Northwestern Hospital Foundation
- Co-Investigator for SUMMIT Trial, Triluminate (sponsor: Abbott)

Imaging Core Lab:

- Institutional Contracts: Abbott, Boston Scientific, Edwards Lifesciences, Medtronic
- Research Support: Circle CV Imaging, Medis, 3Mensio
- Research Grants: Siemens Healthineers, Ziosoft

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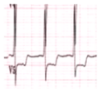
"All that wheezes is not asthma..."
"All that causes angina/ischemic chest pain is not epicardial CAD."

Symptoms and signs of myocardial ischemia with angiographically normal coronaries

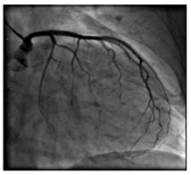
Clinical Progress Series

Pathophysiological Dilemma of Syndrome X

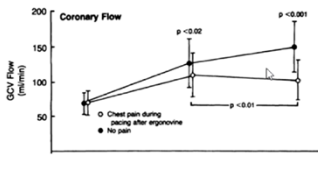
Richard O. Cannon III, MD; Paolo G. Camici, MD; and Stephen E. Epstein, MD



Typical angina
±ST depression



Normal coronary angiogram



Circulation Vol 85, No 3 March 1992

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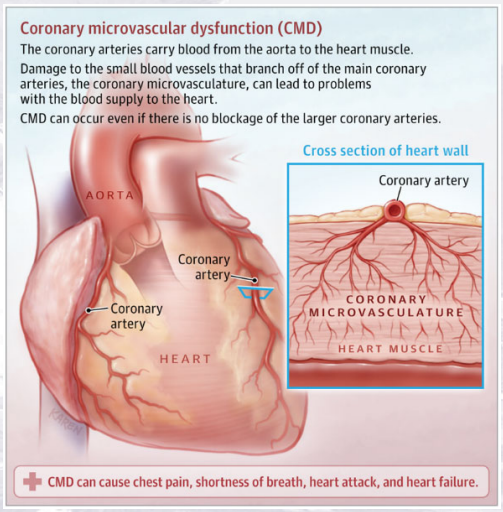
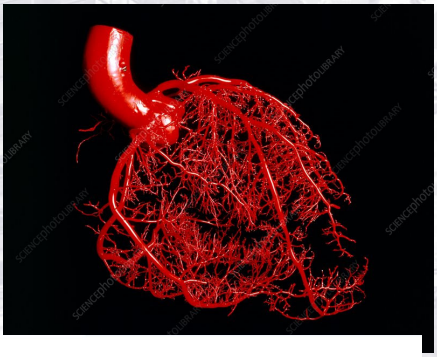
Why is this important!?

2/3 of women who present with symptoms of chest pain and ischemia (angina), have no evidence of obstructive disease





Health > Diseases & Conditions > Cardiovascular Disease > Heart

Microvascular Disease Is Hard to Detect and Very Dangerous

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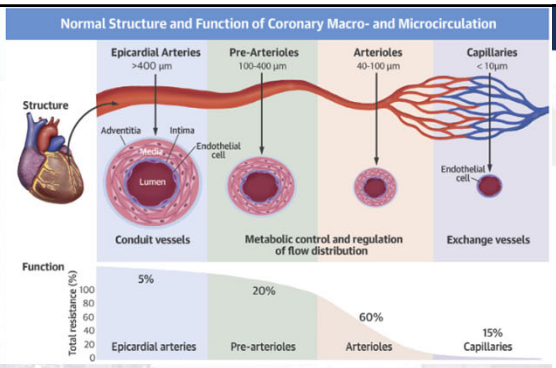

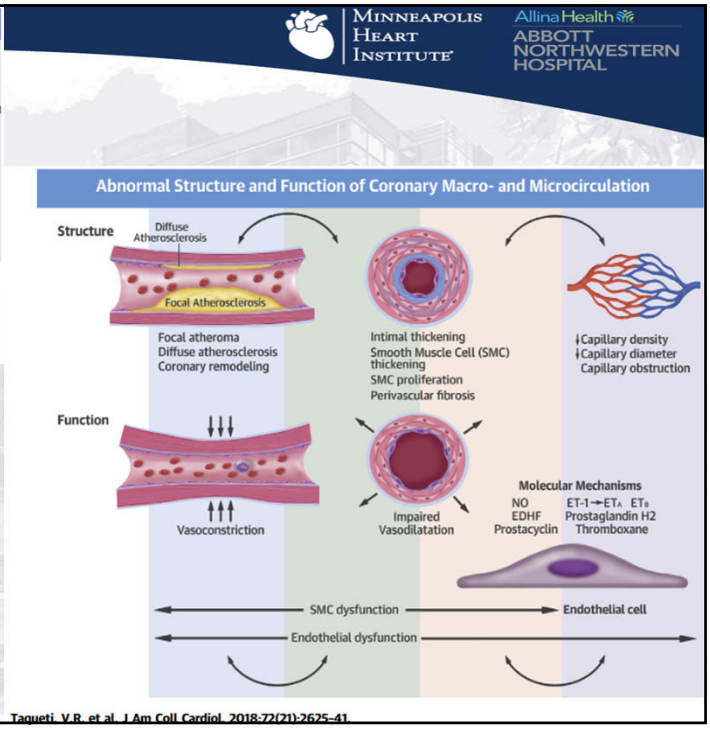

Taqueti, V.R. et al. J Am Coll Cardiol. 2018;72(21):2625-41.

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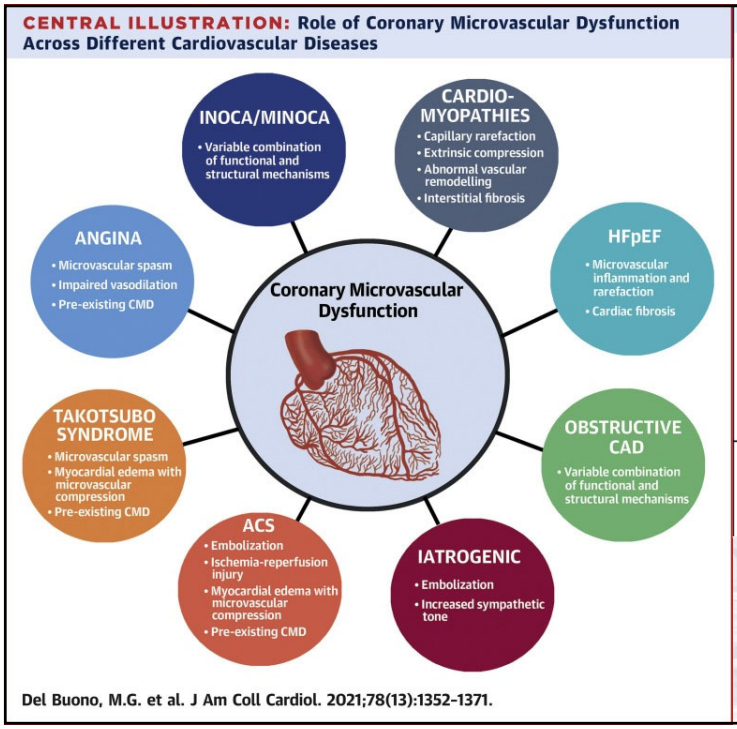

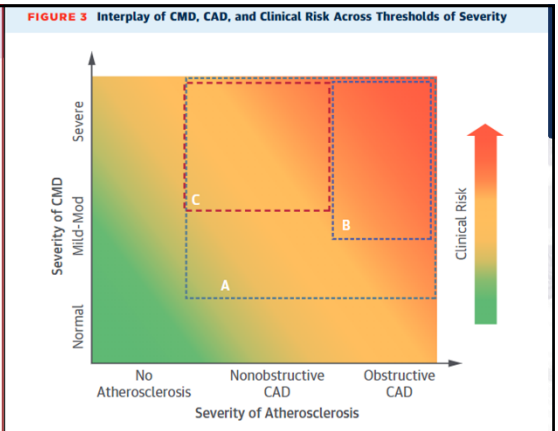

- Impaired vasodilation (vasomotor abnormality) is important determinant → ROS + oxidative stress
- Structural alterations → reduction in flow due to the "environment" → compression of the microvasculature (myocardial fibrosis, edema,

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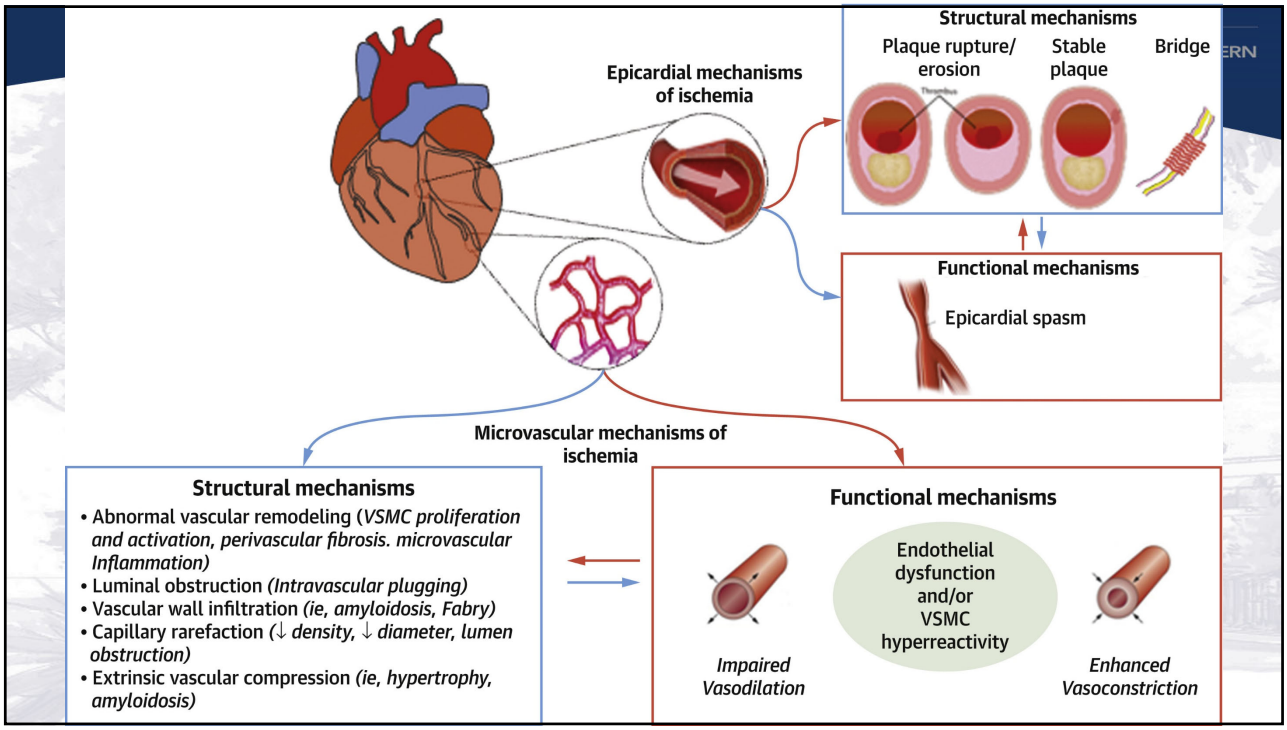

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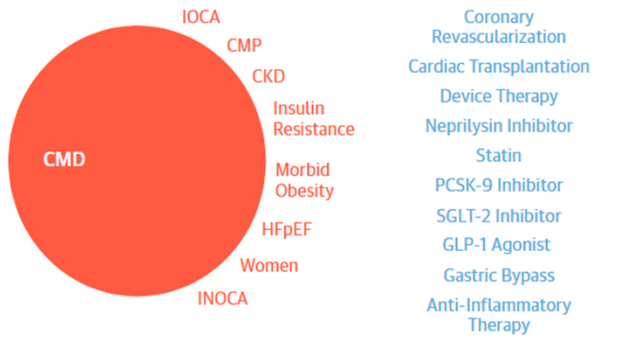
FIGURE 6 Conceptual Illustration of Overlapping Phenotypes in CMD and Potential Therapeutic Strategies



(A) CMD phenotypes. **(B)** Potential therapeutic strategies. CKD = chronic kidney disease; CMP = cardiomyopathy; GLP = glucagon-like peptide; HFpEF = heart failure with preserved ejection fraction; INOCA = ischemia and no obstructive coronary artery disease; IOCA = ischemia and obstructive coronary artery disease; PCSK-9 = pro-protein convertase subtilisin/kexin type 9; SGLT = sodium-glucose cotransporter.

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Diagnostic Criteria for Microvascular Angina and Vasospastic Angina in INOCA Patients

Criteria	Microvascular Angina	Vasospastic Angina
1. Symptoms of myocardial ischemia	Effort or rest angina	Nitrate-responsive angina – during spontaneous episode, with at least one of these: a. Rest angina, especially between night and early morning b. Marked diurnal variation in exercise tolerance, reduced in morning c. Hyperventilation can precipitate an episode d. Calcium channel blockers suppress episodes
2. Absence of obstructive CAD (<50% diameter reduction or FFR >0.80)	Coronary CTA Invasive coronary angiography	Coronary CTA Invasive coronary angiography
3. Objective evidence of myocardial ischemia	Presence of reversible defect, abnormality or flow reserve on a functional imaging test	Transient ischemic ECG changes – during spontaneous episode, including any of the following in at least two contiguous leads: a. ST elevation ≥0.1 mV b. ST depression ≥0.1 mV c. New negative U waves
4. Evidence of coronary dysfunction	Impaired coronary flow reserve (cut-off ≤2.0 or ≤2.5 depending on methodology used), invasive or noninvasively determined Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing Abnormal coronary microvascular resistance indice (e.g.,IMR ≥25) Coronary slow flow phenomenon, defined as TIMI frame count >25	Coronary artery spasm – defined as transient total or subtotal coronary artery occlusion (>90% constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (acetylcholine, ergot, or hyperventilation)

"Definitive" if all four criteria are met; "suspected" if criteria 1+2 are met but only criteria 3 or 4 are present or equivocal.[17,18] CAD, coronary artery disease; CTA, computed tomographic angiography; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; TIMI, thrombolysis in myocardial infarction.

Coronary Vasomotor Disorders International Study (COVADIS
Tacon PR, Wei J. ACC.org/Cardiology. Sept 202

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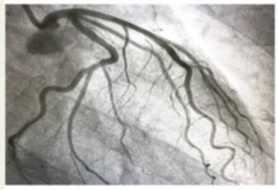
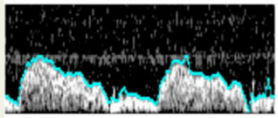
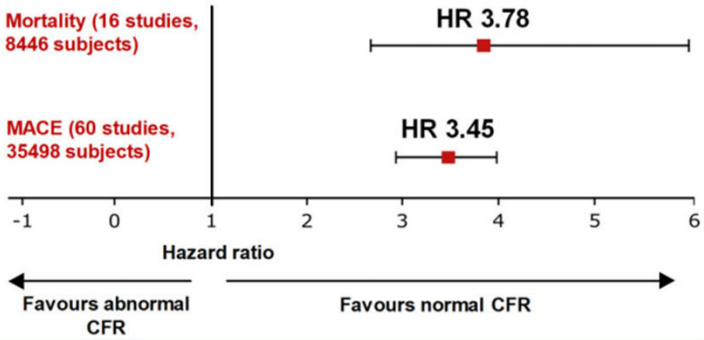
Normal coronary flow reserve (CFR) is strongly associated with a reduced risk of death and major cardiovascular events (MACE)







A systematic review and meta-analysis of 79 studies and 59740 individuals across multiple modalities of CFR measurement.

The association of coronary flow reserve with risk of death and major adverse cardiovascular events. HR, hazard ratio.

Kelshiker et al. Eur Heart J 2022 Apr 19;43(16):1582-1593

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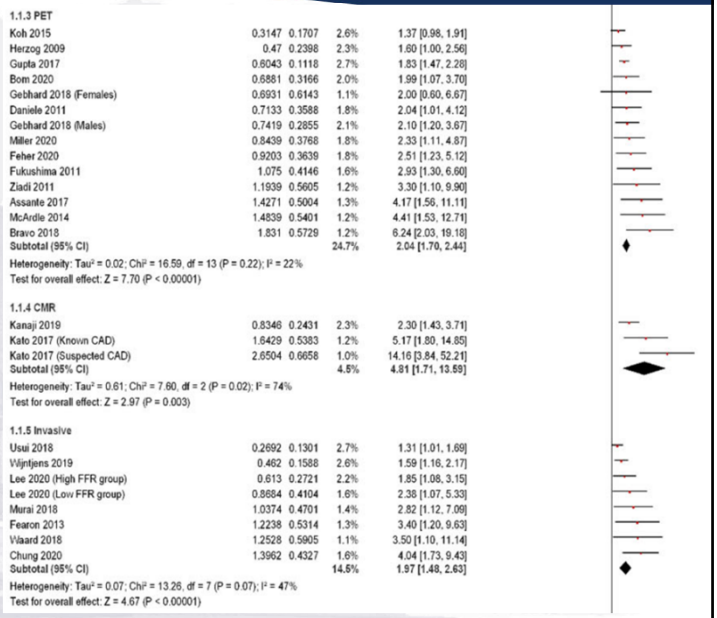
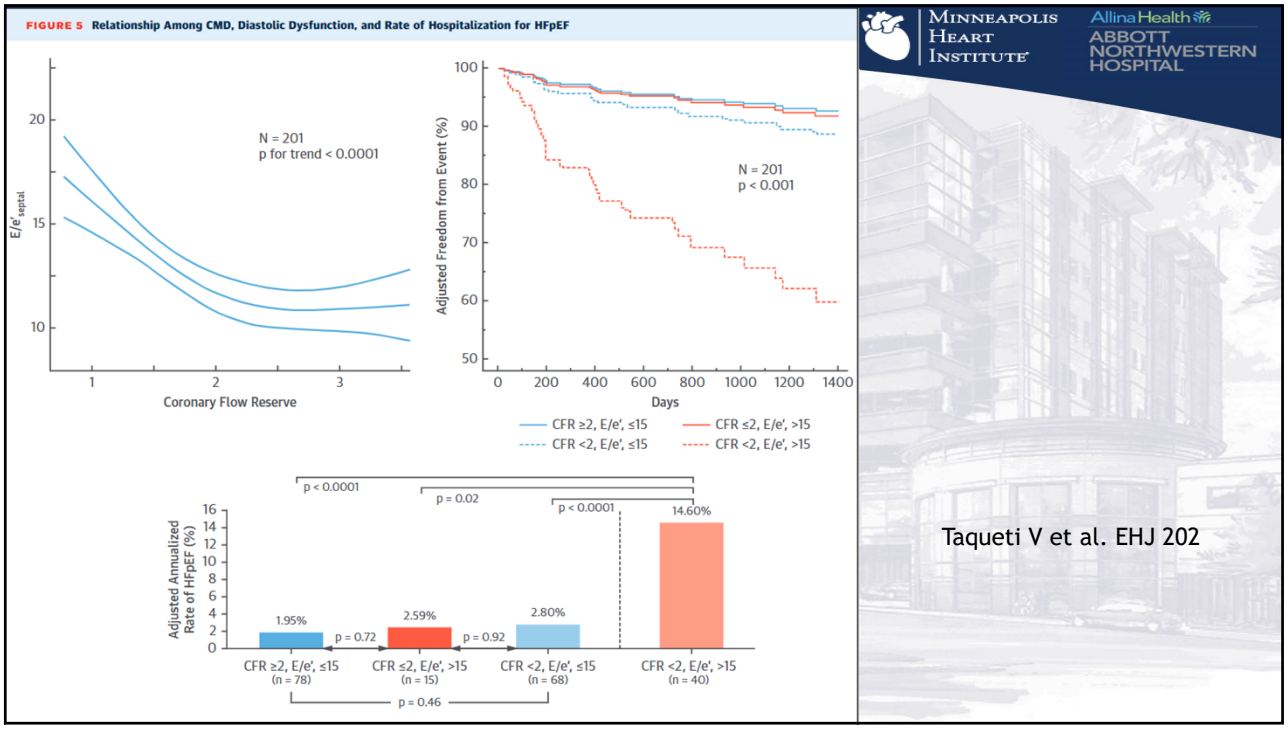
Association of CFR with MACE in several subgroups:

- Acute Coronary Syndromes
- Chronic Coronary Syndromes
- Heart Failure
- Heart Transplant
- Diabetes Mellitus
- Aortic Stenosis
- Systemic Sclerosis
- Sepsis



Kelshiker et al. Eur Heart J 2022 Apr 19;43(16):1582-1593

24



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Taqueti V et al. EHJ 202

25

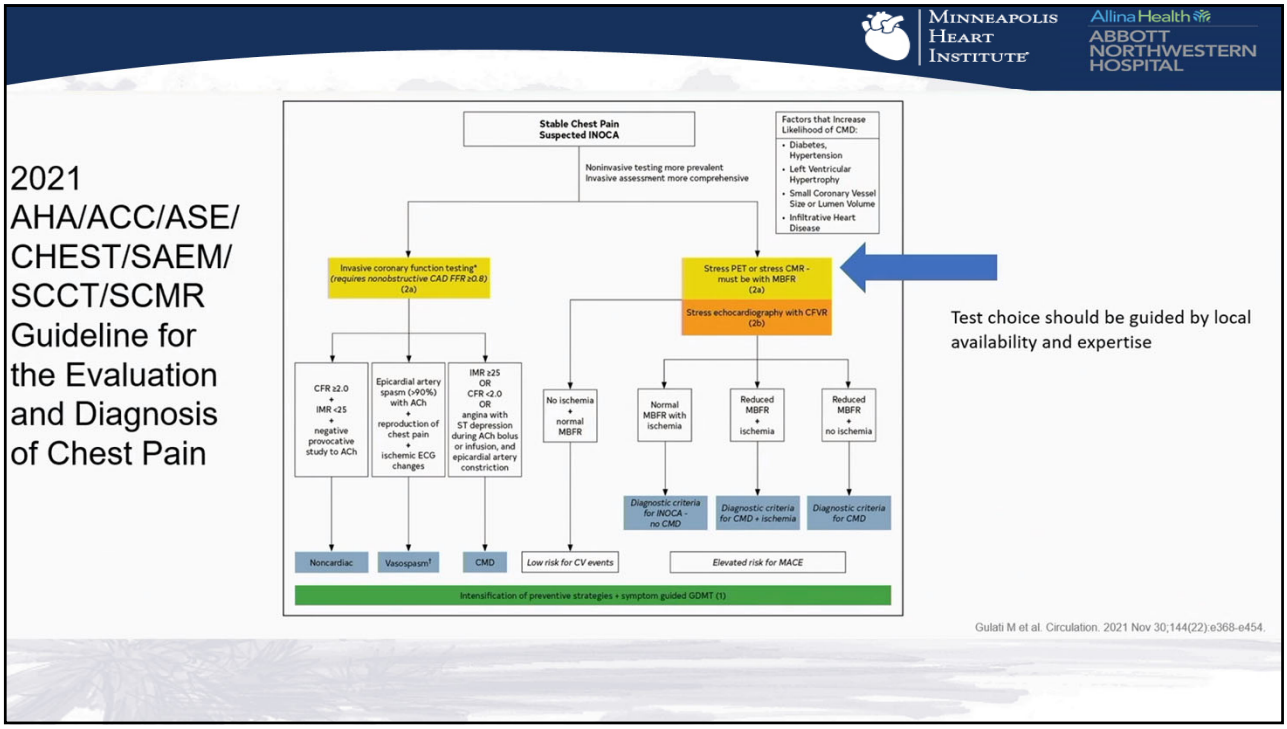

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TABLE 1 Noninvasive Tools for Evaluation of CMD

Modality	Technique	Agent	Parameter	Diagnostic Threshold	Pros	Cons
Echocardiography	Pulsed-wave Doppler on the proximal LAD artery	Adenosine Dipyridamole Regadenoson	CFRV	CFRV <2	• Inexpensive • No radiation exposure • No risks	• Limited to LAD region • Extensive training • Technical pitfalls (poor acoustic window in obese, lung diseases) • Obstructive CAD needs to be excluded • Very limited data with use in non-obstructive CAD
PET	Dynamic rest and vasodilator stress perfusion imaging	Adenosine Dipyridamole Regadenoson ^{13}Nammonia, ^{82}Rb	MPR[a] MBF	MPR <2	• Gold standard for noninvasive assessment of coronary microvascular function • Global evaluation of microvascular function • Low radiation exposure	• Limited availability • Limited spatial resolution • High costs • Obstructive CAD needs to be excluded
CMR	Dynamic first-pass vasodilator stress and then rest perfusion images	Adenosine Dipyridamole Regadenoson Gadolinium-based contrast agents	MPR[a] MBF MPRI	MPRI <2	• No radiation exposure • Excellent spatial resolution • All coronary territories can be evaluated at the same time • Tissue characterization	• High costs • Time-consuming • Poor patient compliance • Limited availability • Limited ability for absolute quantification of MBF • Obstructive CAD needs to be excluded • Imaging artifacts • Contraindicated in patients with severe renal disease, claustrophobia, arrhythmias, and implanted devices • Still under research investigation
CT scan	Dynamic first-pass vasodilator stress and then rest perfusion imaging	Adenosine Dipyridamole Regadenoson Iodine-based contrast agent	MPR[a]	MPR <2	• Combination of coronary anatomy and coronary perfusion data • Evaluation of all coronary territories • CTA-derived FFR	• Radiation exposure • Risk of kidney disease • Overestimation of MBF (caused by the vasodilatory effect of iodinated contrast) • Limited ability for absolute quantification of MBF • Still under research investigation

[a]MPR is preferred to CFR when is not calculated invasively.

CAD = coronary artery disease; CFRV = coronary flow reserve velocity; CMR = cardiac magnetic resonance; CT = computed tomography; FFR = fractional flow reserve; LAD = left anterior descending artery; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; MPRI = myocardial perfusion reserve index; PET = positron emission tomography.

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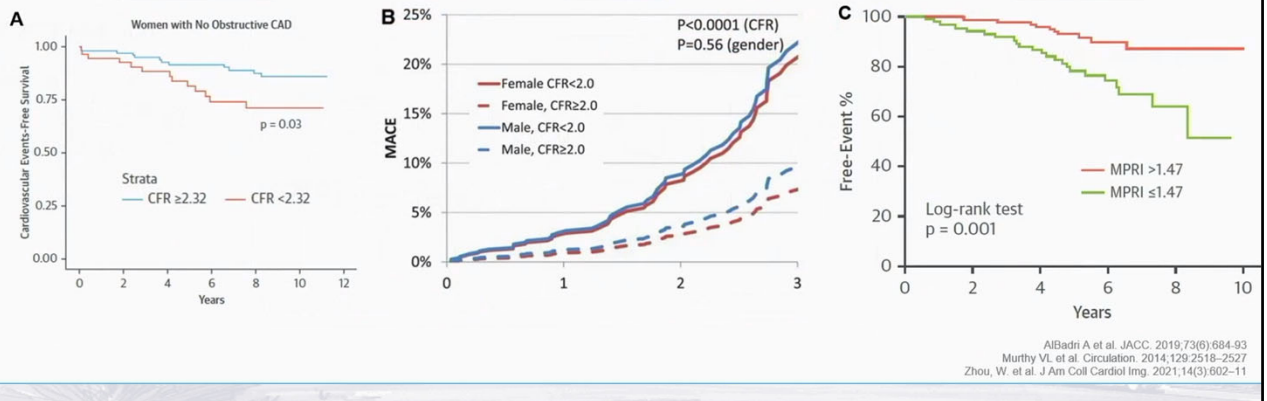
Impaired CFR/MPRI Predicts CVD Outcomes in INOCA

Invasive CFR | PET CFR | CMR MPRI



AlBadri A et al. JACC. 2019;73(6):684-93
Murthy VL et al. Circulation. 2014;129:2518–2527
Zhou, W. et al. J Am Coll Cardiol Img. 2021;14(3):602–11

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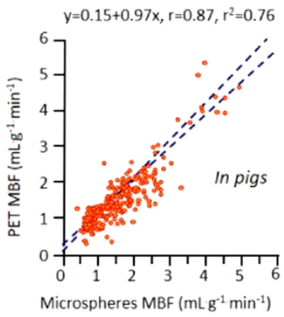
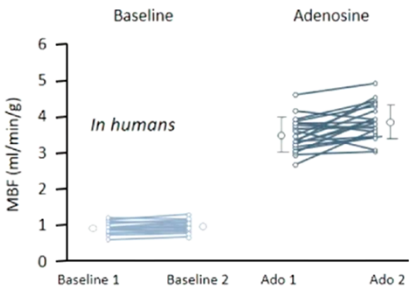
PET: the gold standard for the non-invasive measurement of myocardial blood flow

PET with $H_2{}^{15}O$ or $^{13}NH_3$ allows accurate, reproducible and non-invasive measurement of absolute (ml/min/g) myocardial blood flow in man

Accuracy of PET MBF measurement



Reproducibility of PET MBF measurement



Camici PG, Rimoldi OE. J Nucl Med. 2009; 50:1076–1087.

29

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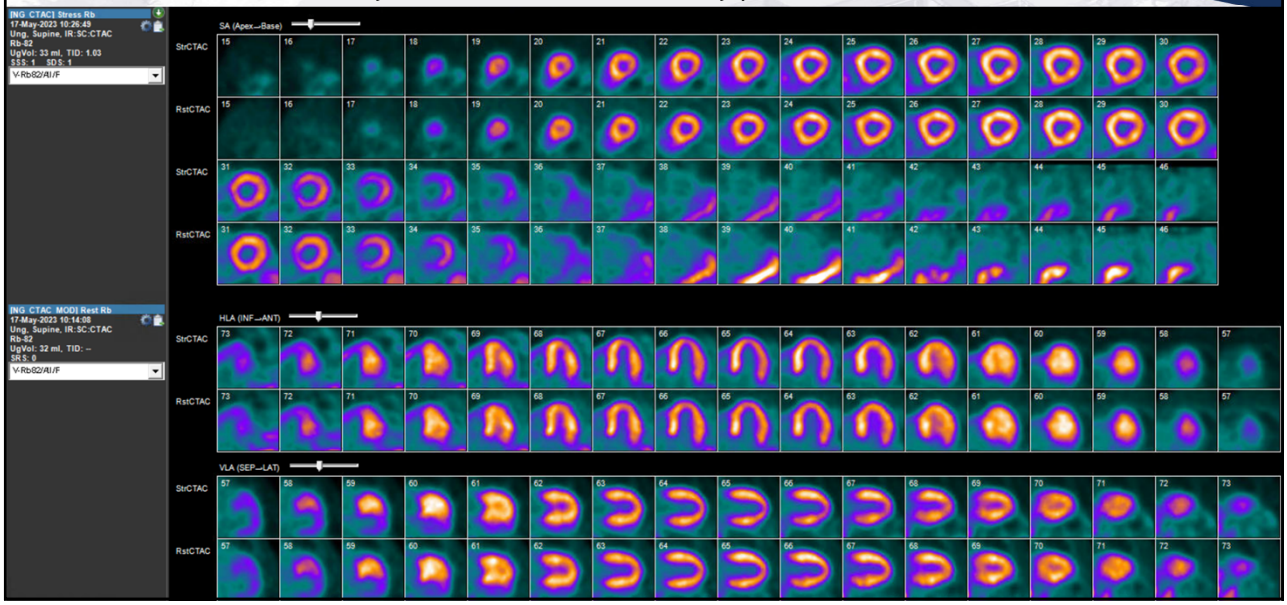
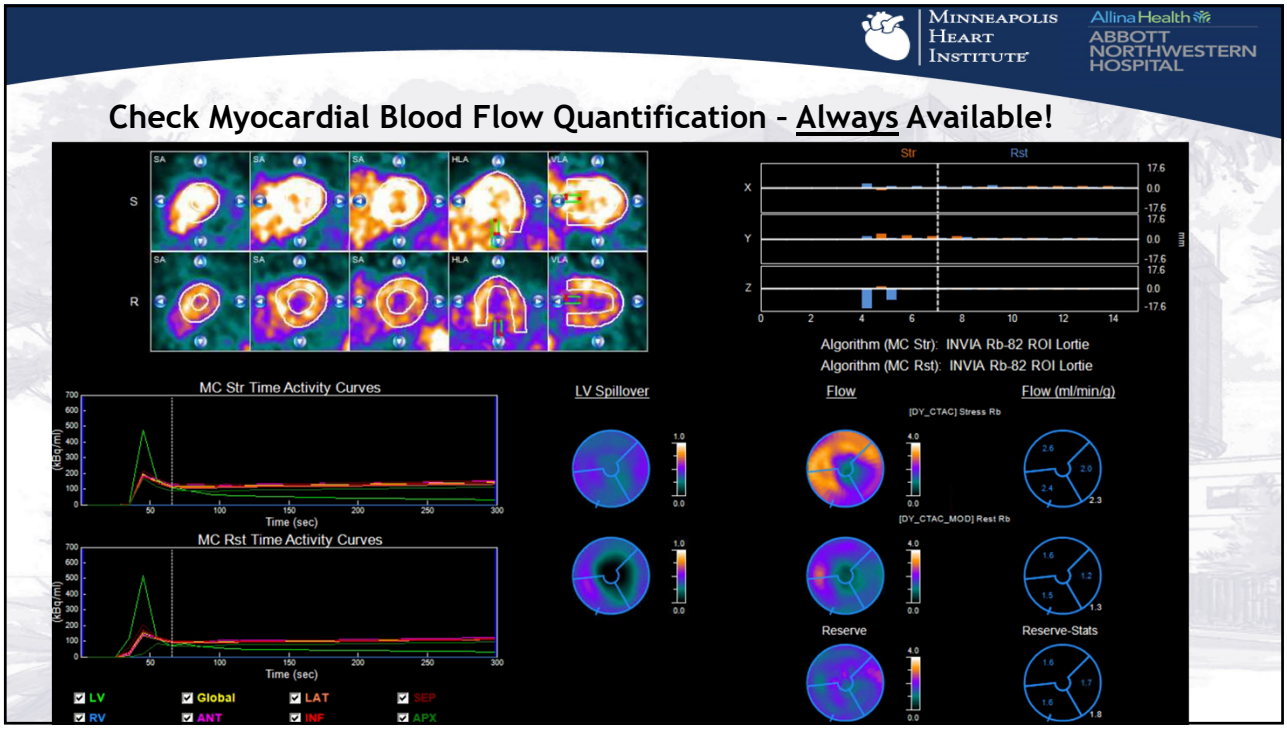
74yo female (BMI=24) with h/o COPD, HTN, prior COVID, mild coronary calcification with exertional dyspnea



30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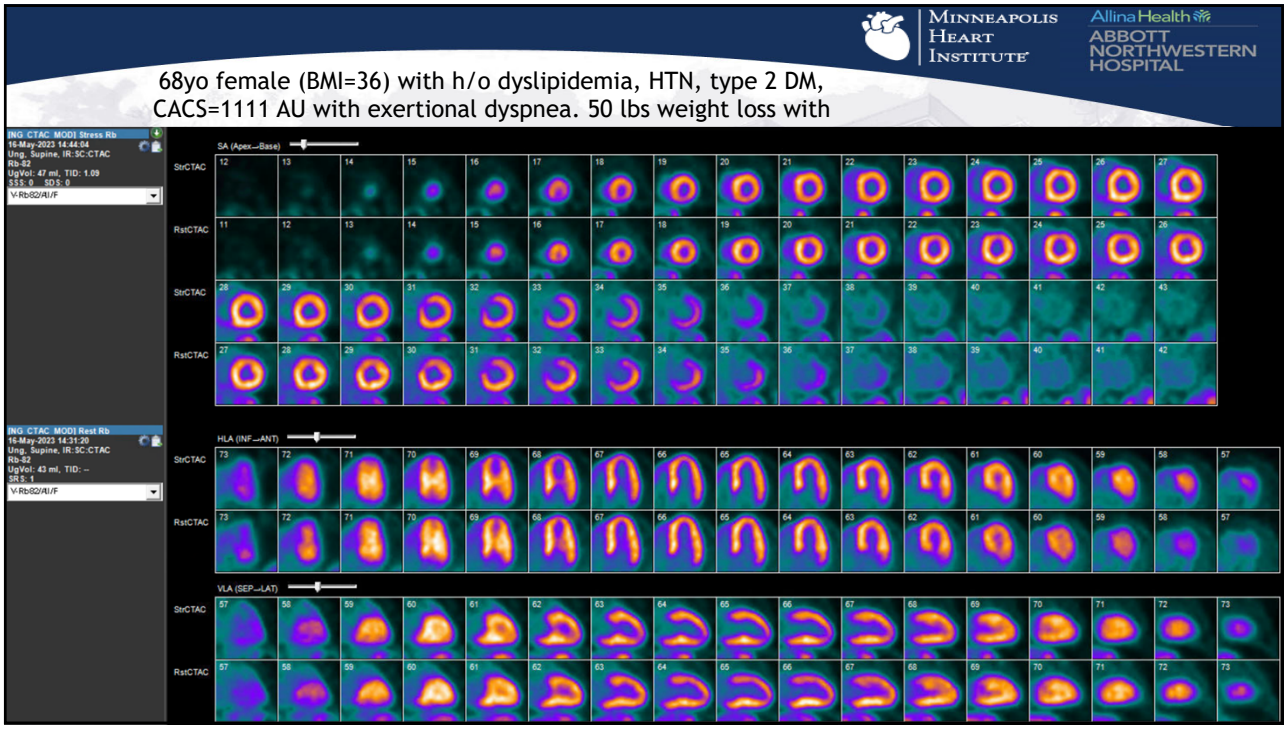
Allina Health
Abbott Northwestern Hospital
Check Myocardial Blood Flow Quantification – Always Available!
Str
Rst
Algorithm (MC Str): INVIA Rb-82 ROI Lortie
Algorithm (MC Rst): INVIA Rb-82 ROI Lortie
MC Str Time Activity Curves
MC Rst Time Activity Curves
Time (sec)
LV Spillover
Flow
Flow (ml/min/g)
[DY_CTAC] Stress Rb
[DY_CTAC_MOD] Rest Rb
Reserve
Reserve-Stats
LV
RV
Global
ANT
LAT
INF
SEP
APX

31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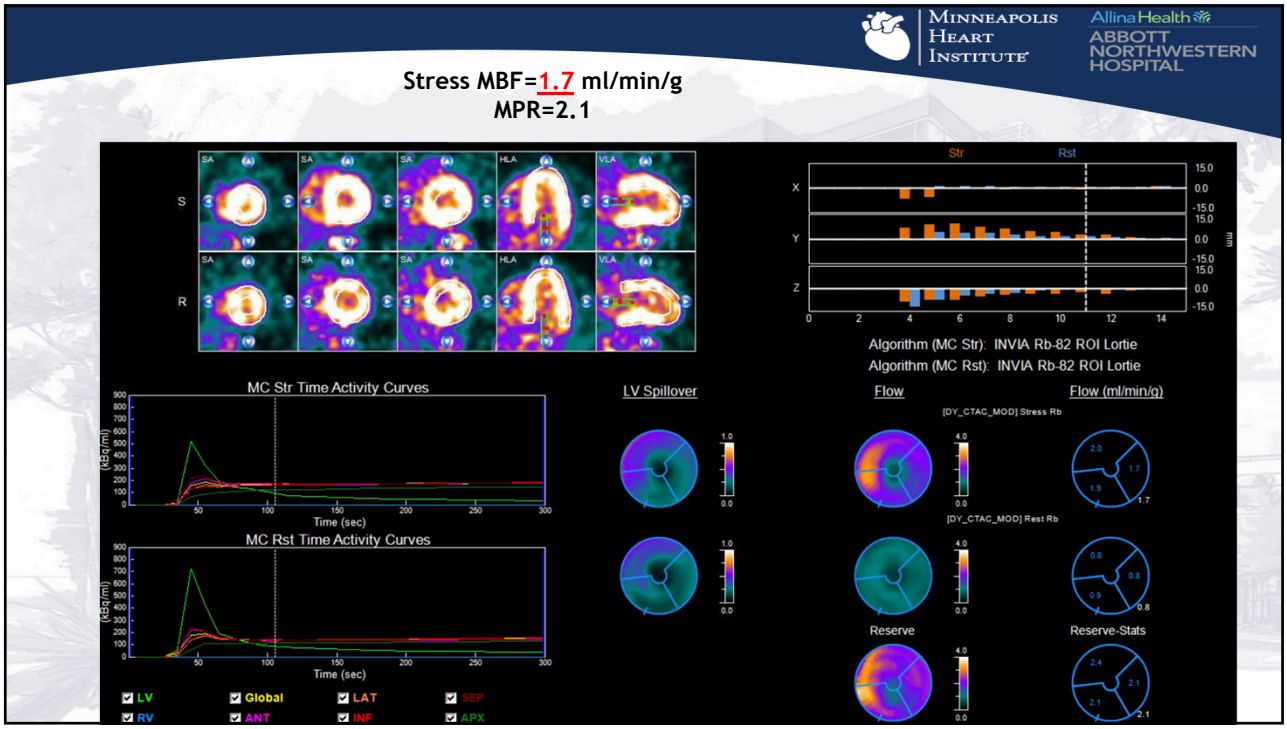
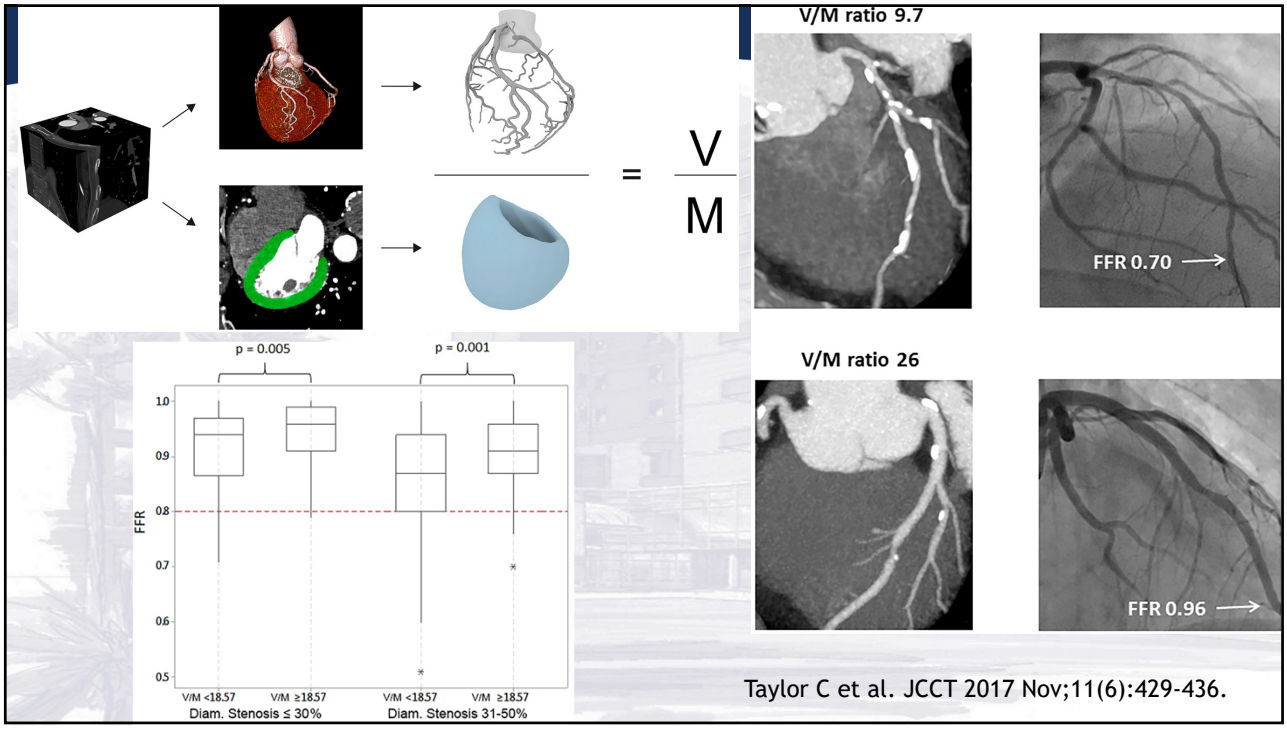
Allina Health
Abbott Northwestern Hospital
68yo female (BMI=36) with h/o dyslipidemia, HTN, type 2 DM,
CACS=1111 AU with exertional dyspnea. 50 lbs weight loss with
SA (Apex→Base)
HLA (INF→ANT)
VLA (SEP→LAT)
StrCTAC
RstCTAC

32


Minneapolis Heart Institute
Allina Health
Abbott Northwestern Hospital
Stress MBF=1.7 ml/min/g
MPR=2.1
Str
Rst
Algorithm (MC Str): INVIA Rb-82 ROI Lortie
Algorithm (MC Rst): INVIA Rb-82 ROI Lortie
MC Str Time Activity Curves
MC Rst Time Activity Curves
Time (sec)
LV Spillover
Flow
Flow (ml/min/g)
[DY_CTAC_MOD] Stress Rb
[DY_CTAC_MOD] Rest Rb
Reserve
Reserve-Stats
LV
RV
Global
ANT
LAT
INF
SEP
APX

33


V
M
V/M ratio 9.7
FFR 0.70
V/M ratio 26
FFR 0.96
p = 0.005
p = 0.001
FFR
V/M <18.57
V/M ≥18.57
Diam. Stenosis ≤ 30%
Diam. Stenosis 31-50%
Taylor C et al. JCCT 2017 Nov;11(6):429-436.

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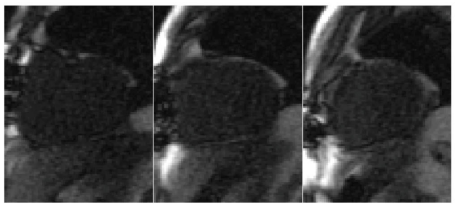
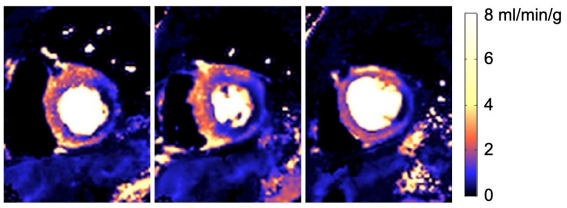
MRI cardiovascular stress testing

myocardial perfusion imaging



quantitative perfusion mapping



visual assessment:
- time consuming
- subjective

quantitative assessment:
- rapid
- objective

Kellman P et al, JCMR 2017; 19:43

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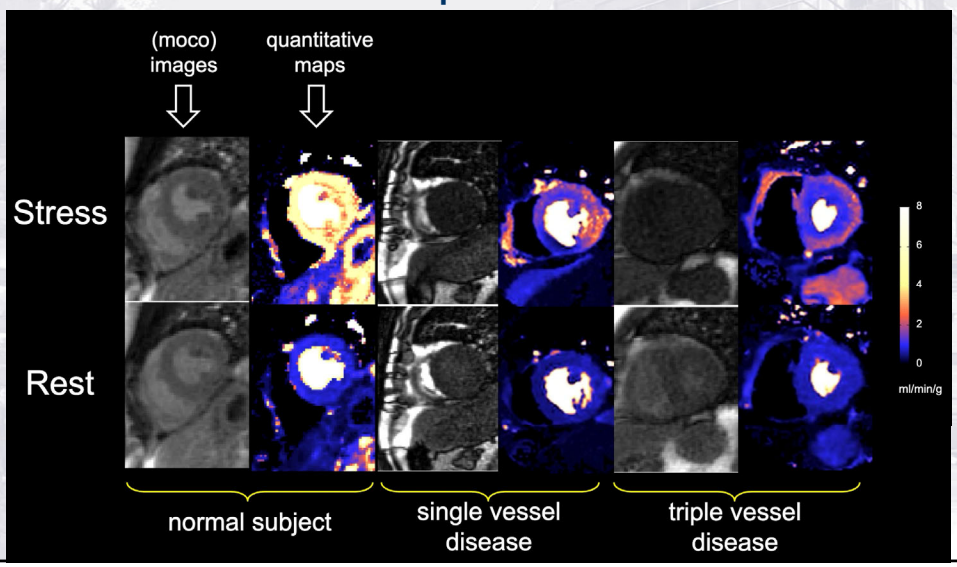
Quantitative Perfusion Improves Identification of 3V CAD



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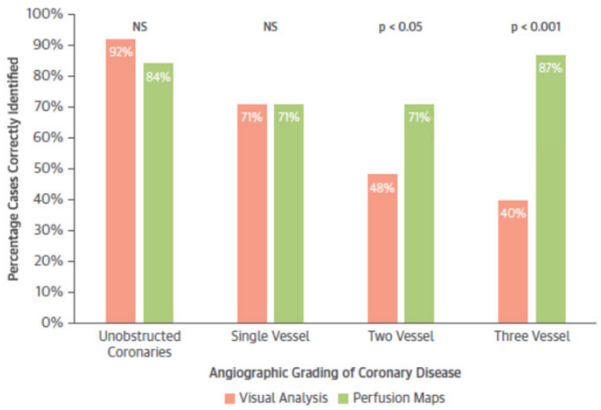
Perfusion Maps improve interpretation accuracy

FIGURE 4 Percentage of Cases Correctly Classified by Perfusion Mapping and VA of First-Pass Perfusion



A significantly higher proportion of 2-vessel and 3-vessel cases are correctly identified compared with visual analysis with no significant difference for single-vessel disease and unobstructed coronaries. NS = nonsignificant; VA = visual assessment.

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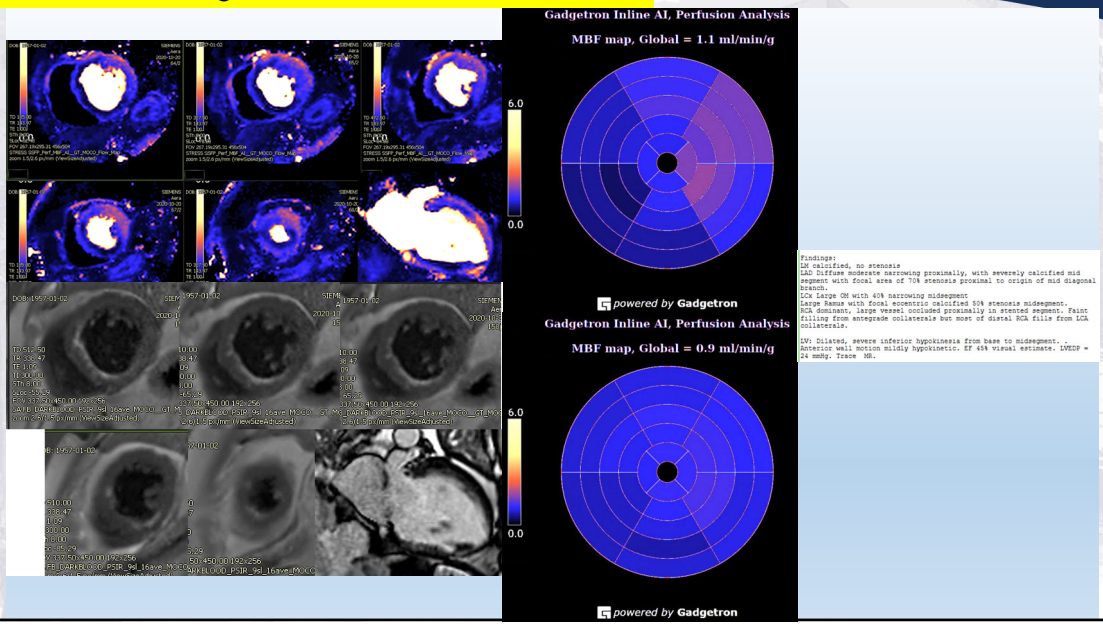
6 slice coverage is now feasible without compromise of the quantification/temporal or spatial resolution
Increases coverage with dedicated 2-chamber



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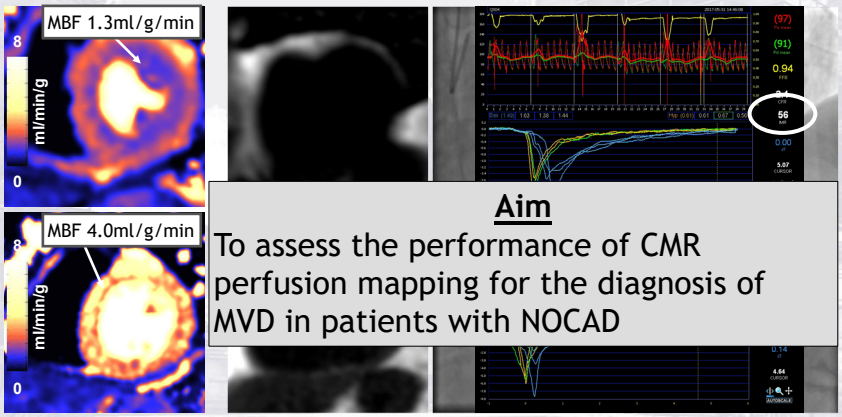
Validation against coronary physiology



Aim

To assess the performance of CMR perfusion mapping for the diagnosis of MVD in patients with NOCAD

Kotecha T …. Fontana M et al, JACC Imaging 2019

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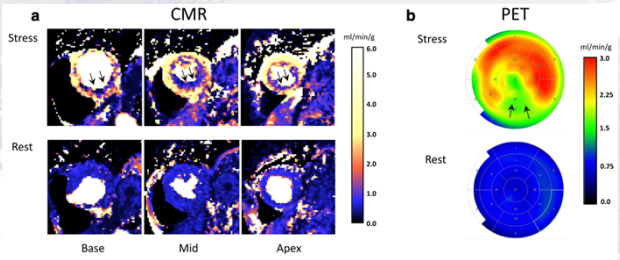
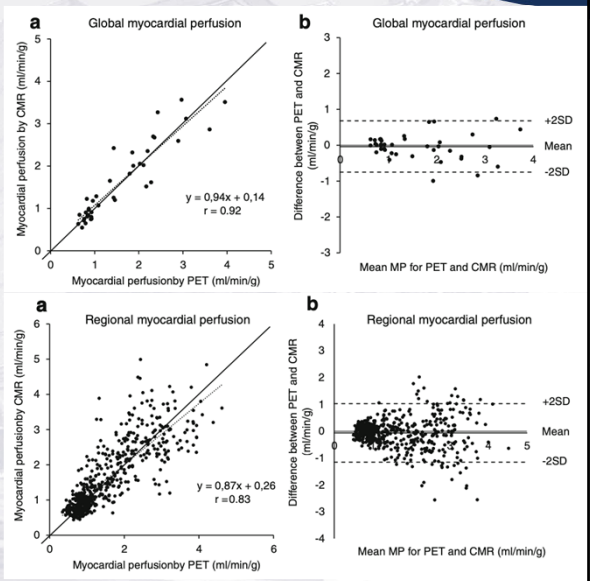
CMR Quantitative Perfusion Correlates well with Cardiac PET



Engblom et al. J Cardiovasc Magn Reson 2017;19(1):78.
doi: 10.1186/s12968-017-0388-9.

N=21 patients



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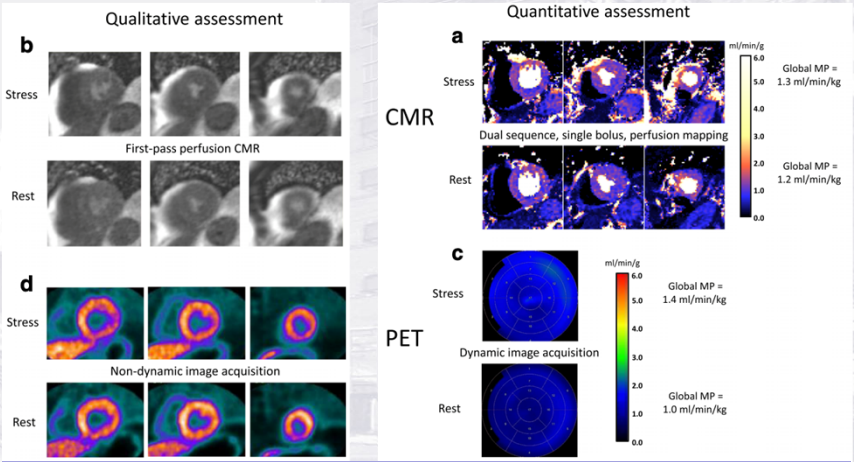
CMR Quantitative Perfusion Correlates well with Cardiac PET

Engblom et al. J Cardiovasc Magn Reson 2017;19(1):78. doi: 10.1186/s12968-017-0388-9.



3 Vessel CAD unmasked by quantitative perfusion by both CMR and PET

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Circulation

ORIGINAL RESEARCH ARTICLE

The Prognostic Significance of Quantitative Myocardial Perfusion

An Artificial Intelligence–Based Approach Using Perfusion Mapping

Editorial, see p 1292

Kristopher D. Knott, MBBS
Andreas Seraphim, MBBS
Joao B. Augusto, MD
Hui Xue, PhD
Liza Chacko, MBBS
Nay Aung, MBBS
Steffen E. Petersen, DPhil
Jackie A. Cooper, MSc
Charlotte Manisty, PhD
Anish N. Bhuva, MBBS
Tushar Kotecha, MBChB
Christos V. Bourantas, PhD
Rhodri H. Davies, PhD
Louise A.E. Brown, MBChB
Sven Plein, PhD
Marianna Fontana, PhD
Peter Kellman, PhD
James C. Moon, MD

BACKGROUND: Myocardial perfusion reflects the macro- and microvascular coronary circulation. Recent quantitation developments using cardiovascular magnetic resonance perfusion permit automated measurement clinically. We explored the prognostic significance of stress myocardial blood flow (MBF) and myocardial perfusion reserve (MPR, the ratio of stress to rest MBF).

METHODS: A 2-center study of patients with both suspected and known coronary artery disease referred clinically for perfusion assessment. Image analysis was performed automatically using a novel artificial intelligence approach deriving global and regional stress and rest MBF and MPR. Cox proportional hazard models adjusting for comorbidities and cardiovascular magnetic resonance parameters sought associations of stress MBF and MPR with death and major adverse cardiovascular events (MACE), including myocardial infarction, stroke, heart failure hospitalization, late (>90 day) revascularization, and death.

RESULTS: A total of 1049 patients were included with a median follow-up of 605 (interquartile range, 464–814) days. There were 42 (4.0%) deaths and 188 MACE in 174 (16.6%) patients. Stress MBF and MPR were independently associated with both death and MACE. For each 1 mL·g^{-1}·min^{-1} decrease in stress MBF, the adjusted hazard ratios for death and MACE were 1.93 (95% CI, 1.08–3.48, P=0.028) and 2.14 (95% CI, 1.58–2.90, P<0.0001), respectively, even after adjusting for age and

Clinical Perspective

What Is New?

- Perfusion mapping uses artificial intelligence to provide instantaneous quantification of myocardial perfusion by cardiovascular magnetic resonance.
- Quantitative myocardial blood flow provides incremental prognostic information in patients with suspected coronary artery disease above traditional cardiovascular risk factors.
- Even in patients without regional perfusion defects, absolute perfusion is prognostic.

What Are the Clinical Implications?

- Absolute perfusion quantification is a likely new biomarker in patient care.
- As there is no user input and no ionizing radiation, early disease and microvascular disease can be studied at scale.
- Impaired global perfusion may be a targetable cardiovascular risk factor.

- Automatically AI-derived MBF and MPR have prognostic relevance beyond the detection of regional ischemia.
- Opportunity for quantitative perfusion analysis to be applied in the routine clinical setting to potentially risk stratify beyond the detection of regional ischemia alone.

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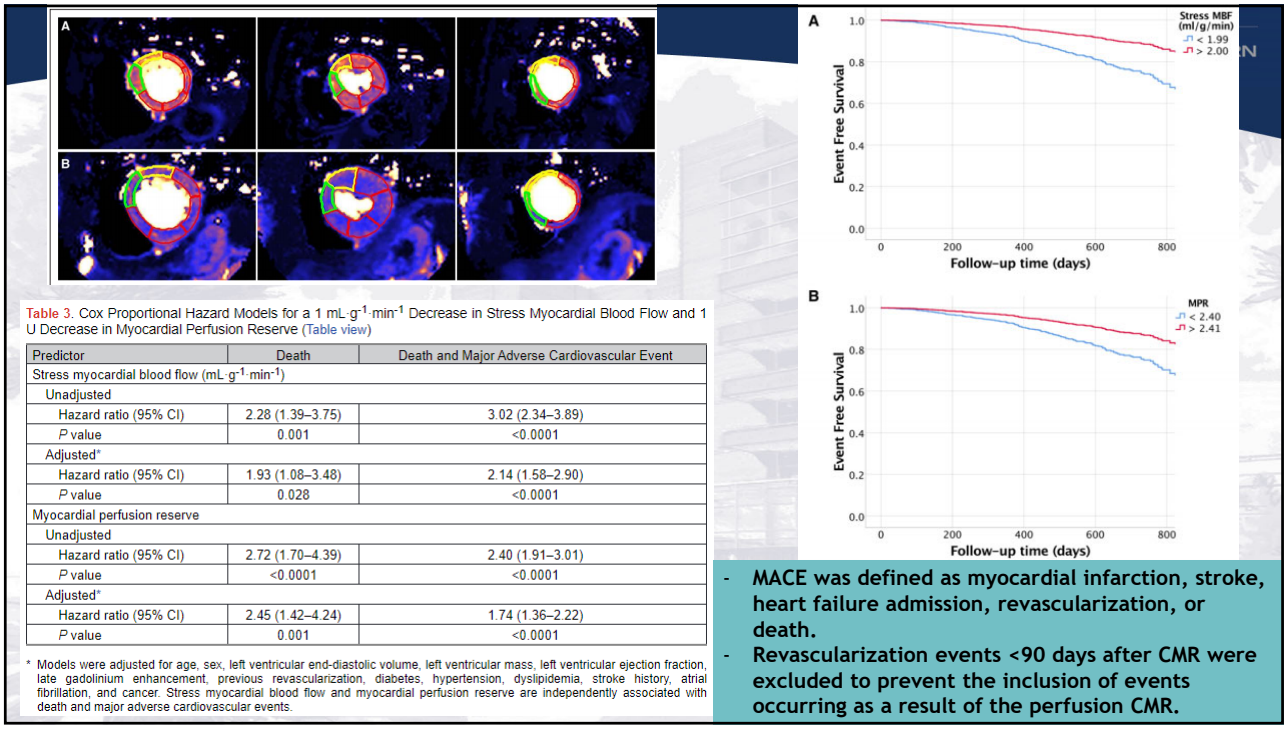

Table 3. Cox Proportional Hazard Models for a 1 mL·g^{-1}·min^{-1} Decrease in Stress Myocardial Blood Flow and 1 U Decrease in Myocardial Perfusion Reserve (Table view)

Predictor	Death	Death and Major Adverse Cardiovascular Event
Stress myocardial blood flow (mL·g^{-1}·min^{-1})		
Unadjusted		
Hazard ratio (95% CI)	2.28 (1.39–3.75)	3.02 (2.34–3.89)
P value	0.001	<0.0001
Adjusted*		
Hazard ratio (95% CI)	1.93 (1.08–3.48)	2.14 (1.58–2.90)
P value	0.028	<0.0001
Myocardial perfusion reserve		
Unadjusted		
Hazard ratio (95% CI)	2.72 (1.70–4.39)	2.40 (1.91–3.01)
P value	<0.0001	<0.0001
Adjusted*		
Hazard ratio (95% CI)	2.45 (1.42–4.24)	1.74 (1.36–2.22)
P value	0.001	<0.0001

* Models were adjusted for age, sex, left ventricular end-diastolic volume, left ventricular mass, left ventricular ejection fraction, late gadolinium enhancement, previous revascularization, diabetes, hypertension, dyslipidemia, stroke history, atrial fibrillation, and cancer. Stress myocardial blood flow and myocardial perfusion reserve are independently associated with death and major adverse cardiovascular events.

- **MACE was defined as myocardial infarction, stroke, heart failure admission, revascularization, or death.**
- **Revascularization events <90 days after CMR were excluded to prevent the inclusion of events occurring as a result of the perfusion CMR.**

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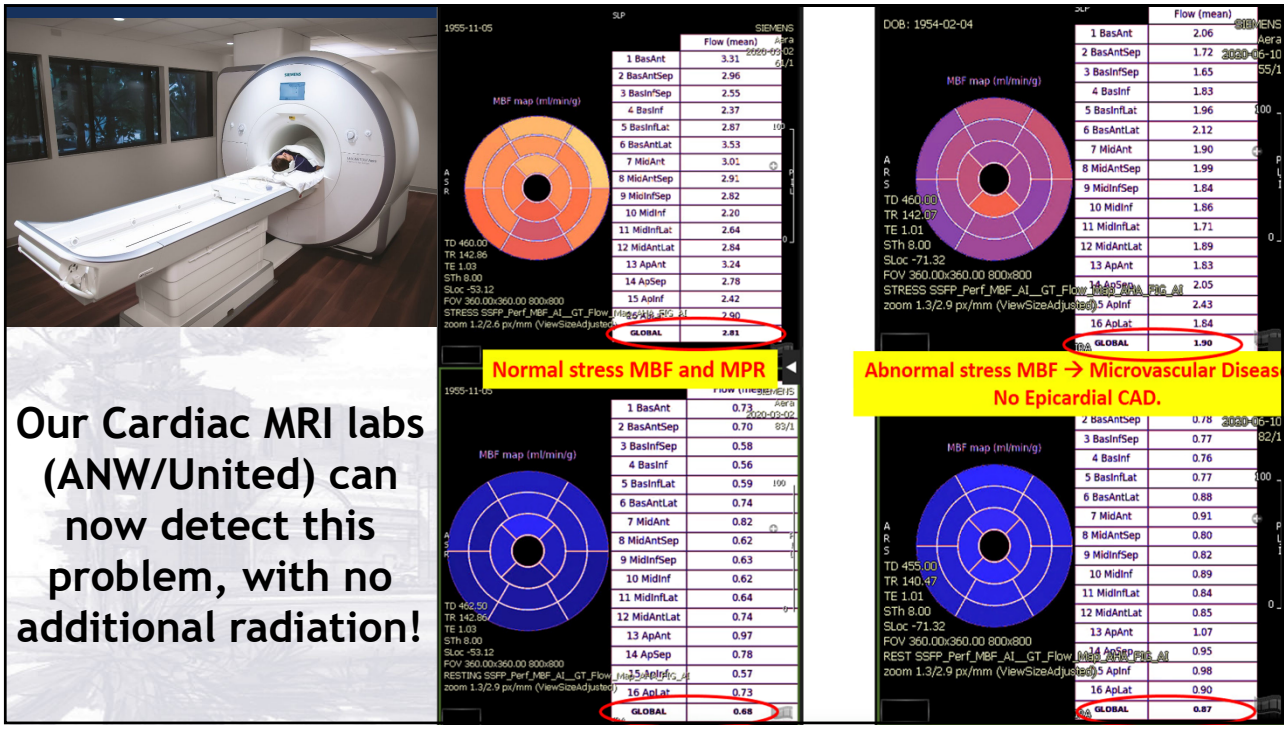

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Clinical Case

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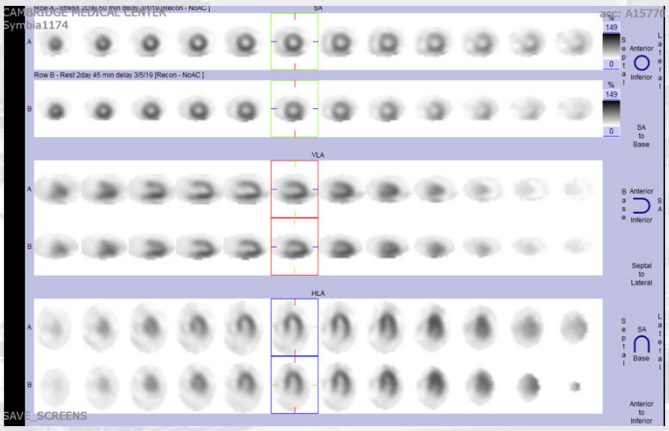
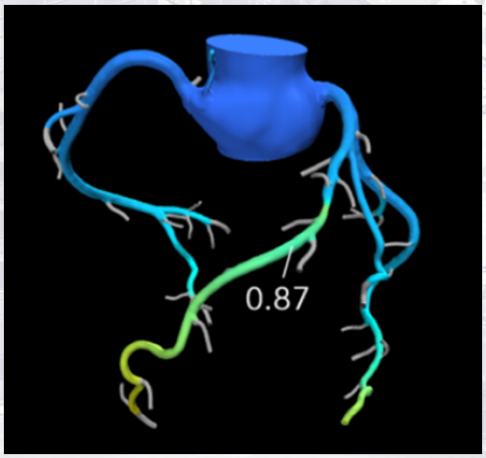
- 75yo female with HTN, dyslipidemia, obesity (BMI=37), prior gastric bypass, CACS=187 AU, presenting with exertional dyspnea and vague retrosternal CP





SPECT IMPRESSION:
1. There is a small area of mild ischemia in the mid and apical anterior septum.
2. Normal left ventricular ejection fraction of 65 percent.

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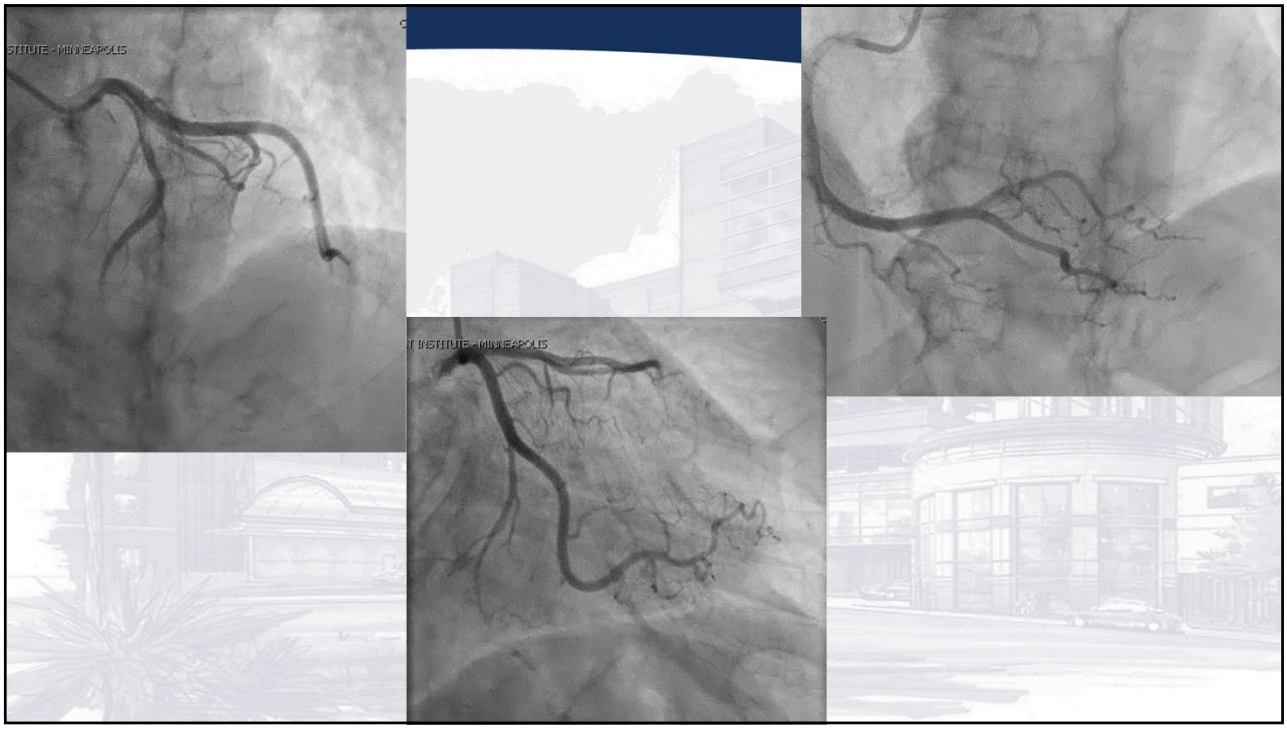

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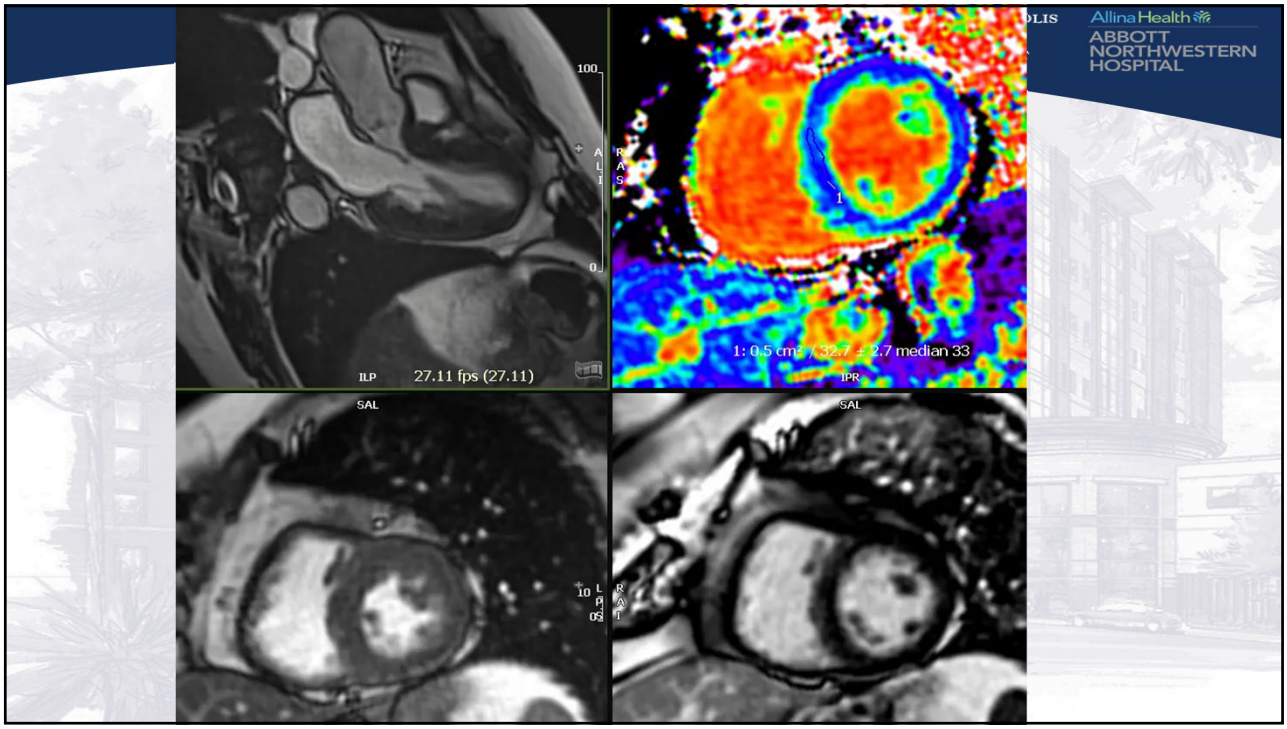
Allina Health
ABBOTT NORTHWESTERN HOSPITAL
27.11 fps (27.11)
SAL
SAL

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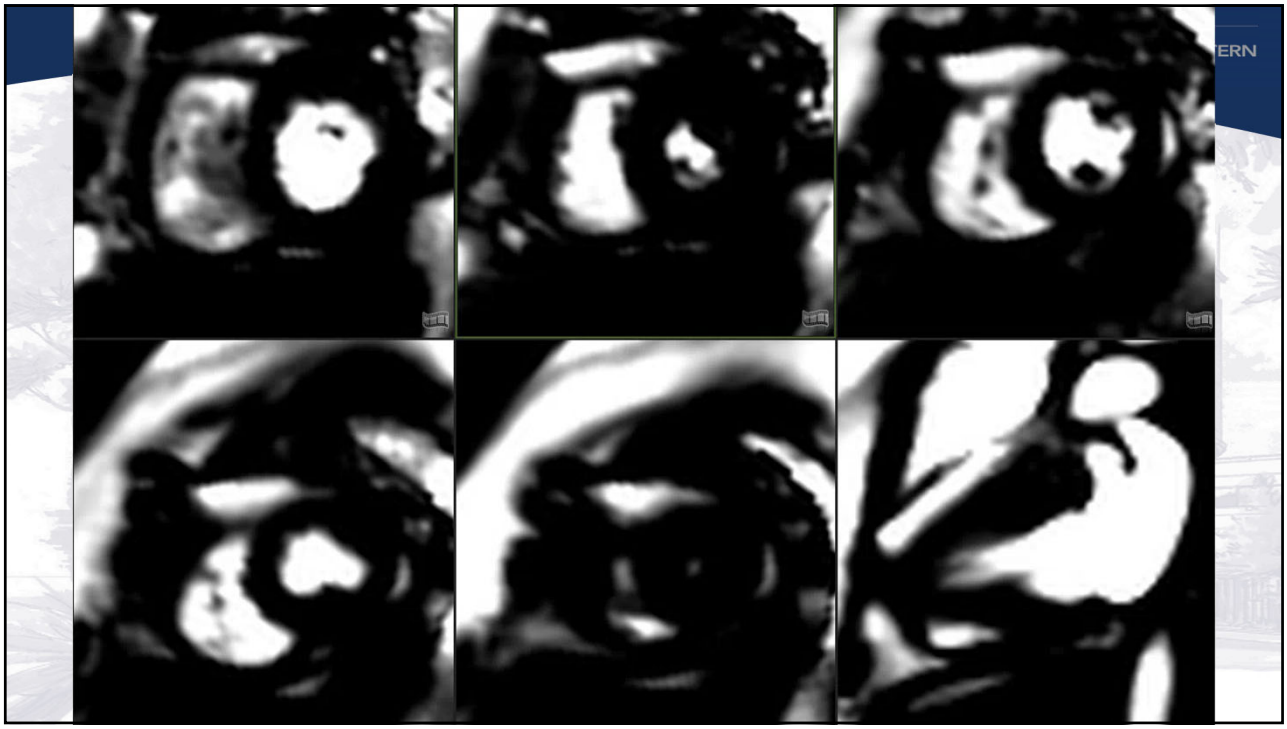
ERN

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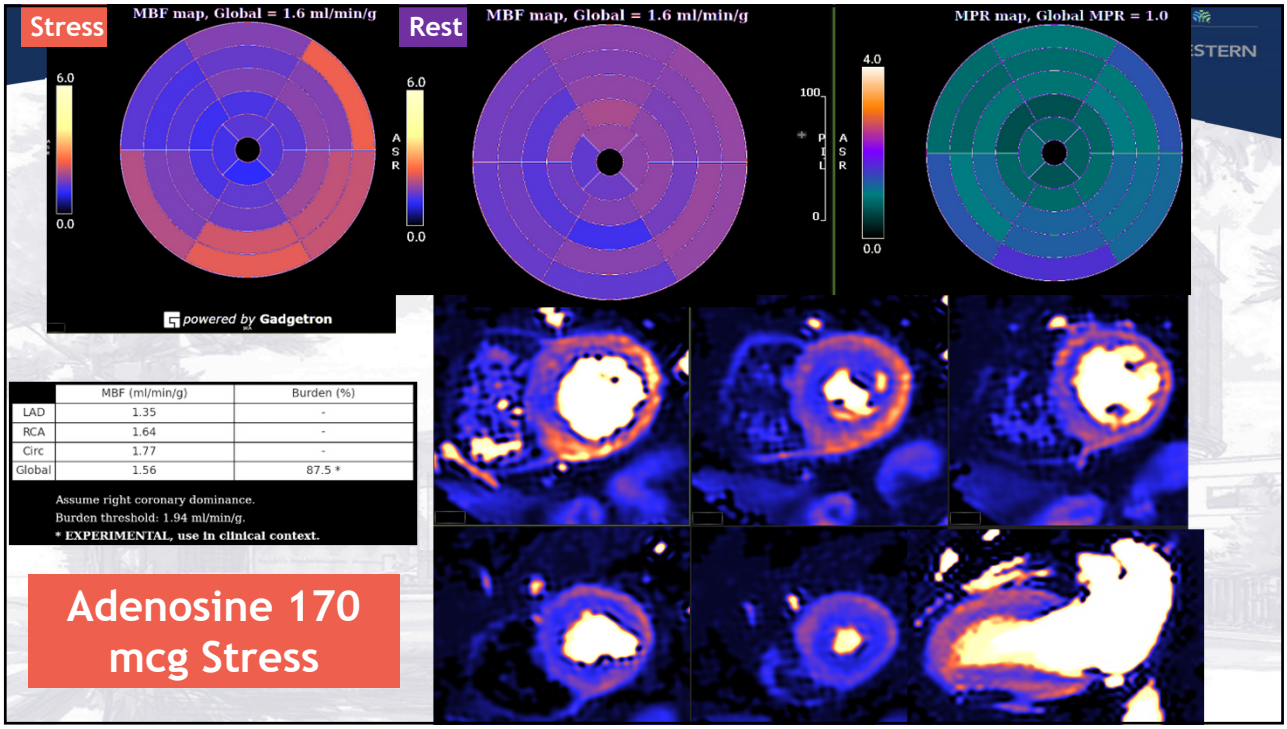
Stress
MBF map, Global = 1.6 ml/min/g
Rest
MBF map, Global = 1.6 ml/min/g
MPR map, Global MPR = 1.0
6.0
0.0
4.0
100
0
powered by Gadgetron
MBF (ml/min/g) Burden (%)
LAD 1.35 -
RCA 1.64 -
Circ 1.77 -
Global 1.56 87.5 *
Assume right coronary dominance.
Burden threshold: 1.94 ml/min/g.
* EXPERIMENTAL, use in clinical context.
Adenosine 170 mcg Stress

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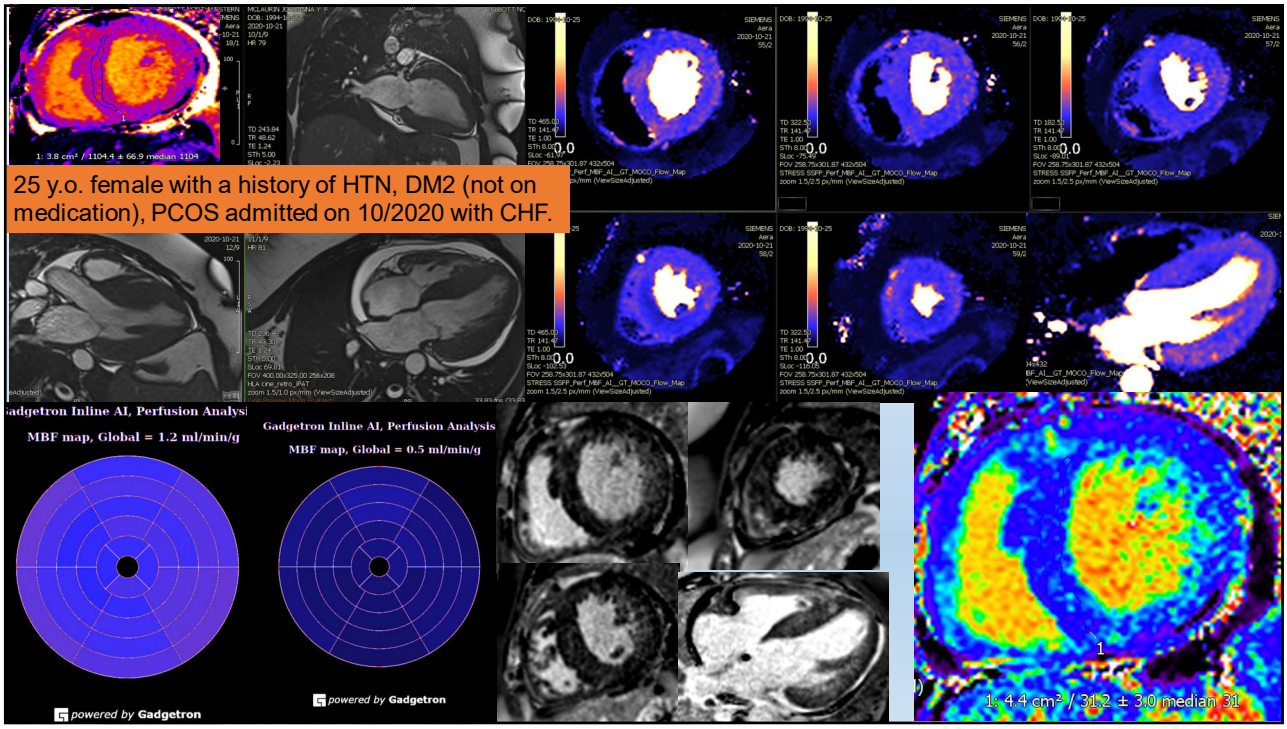
25 y.o. female with a history of HTN, DM2 (not on medication), PCOS admitted on 10/2020 with CHF.
Gadgetron Inline AI, Perfusion Analysis
MBF map, Global = 1.2 ml/min/g
Gadgetron Inline AI, Perfusion Analysis
MBF map, Global = 0.5 ml/min/g
powered by Gadgetron
powered by Gadgetron

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Future Directions

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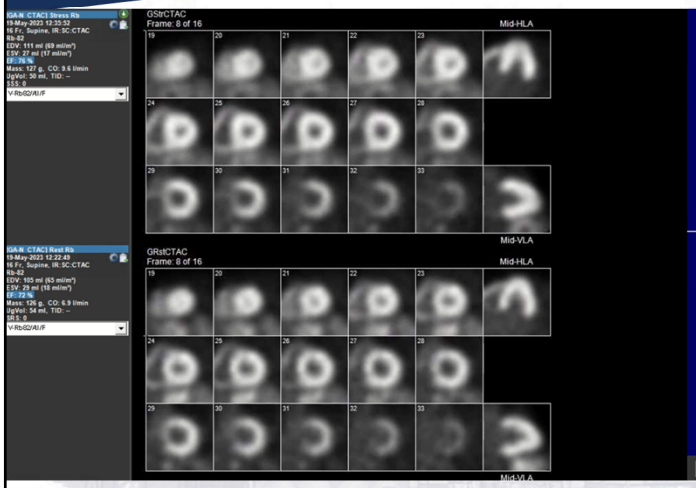

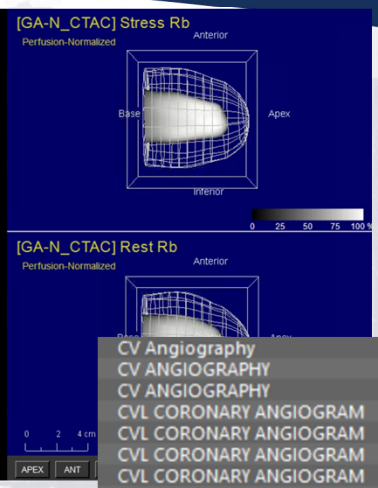

CV Angiography	2013-May-29	09:30:07
CV ANGIOGRAPHY	2005-Mar-18	12:09:57
CV ANGIOGRAPHY	2002-Mar-20	15:41:52
CVL CORONARY ANGIOGRAM	2022-Apr-21	10:34:40
CVL CORONARY ANGIOGRAM	2022-Apr-21	11:51:26
CVL CORONARY ANGIOGRAM	2020-Mar-03	12:27:15
CVL CORONARY ANGIOGRAM	2018-Mar-20	12:51:26
CVL CORONARY ANGIOGRAM	2016-Jun-02	10:29:49
CVL CORONARY ANGIOGRAM	2011-May-25	07:30:00
CVL CORONARY ANGIOGRAM	2011-May-25	09:55:48
CVL CORONARY ANGIOGRAM	2009-May-20	09:28:23
CVL CORONARY ANGIOGRAM	2008-May-23	10:33:32
CVL CORONARY ANGIOGRAM	2007-May-25	09:25:18
CVL CORONARY ANGIOGRAM ...	2010-May-12	07:30:00
CVL CORONARY ANGIOGRAM ...	2010-May-12	09:24:48

72yo female s/p OHTx in 2016 with 20% mid LAD non-obstructive stenosis thought to be cardiac allograft vasculopathy

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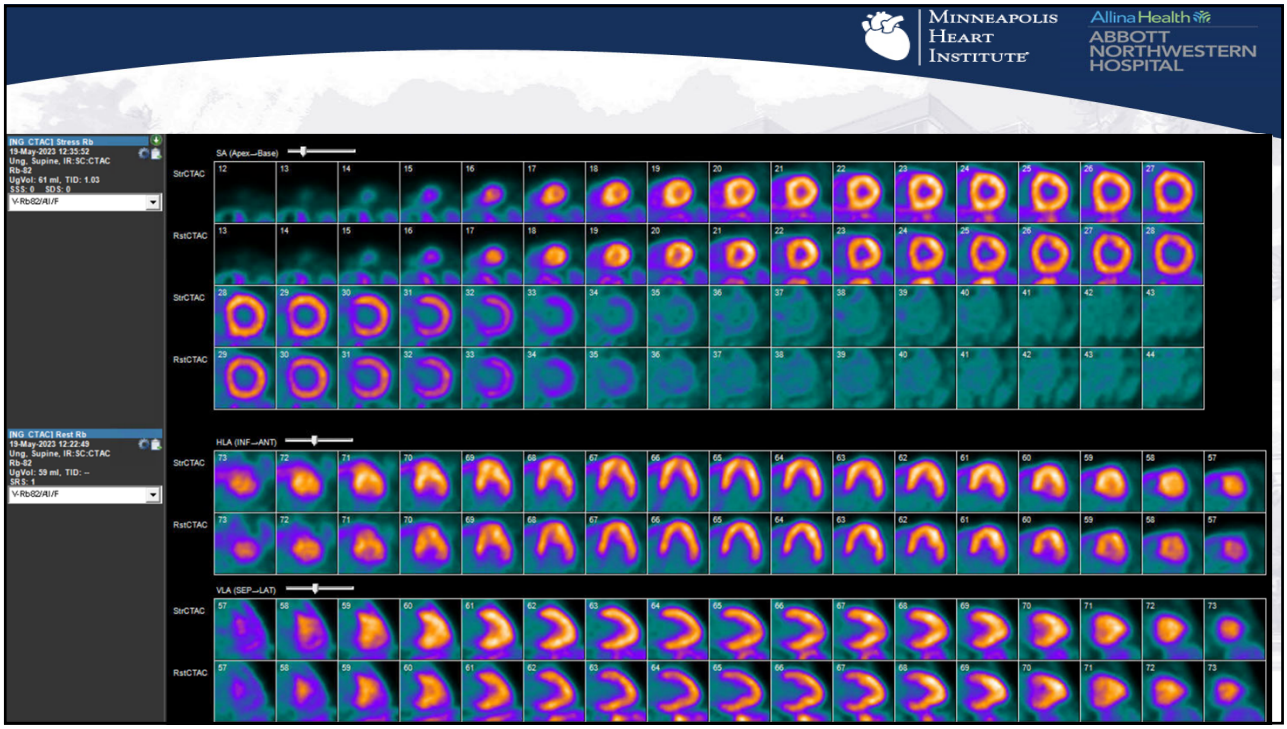
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SA (Apex---Base)
StrCTAC
RstCTAC
HLA (INF---ANT)
VLA (SEP---LAT)

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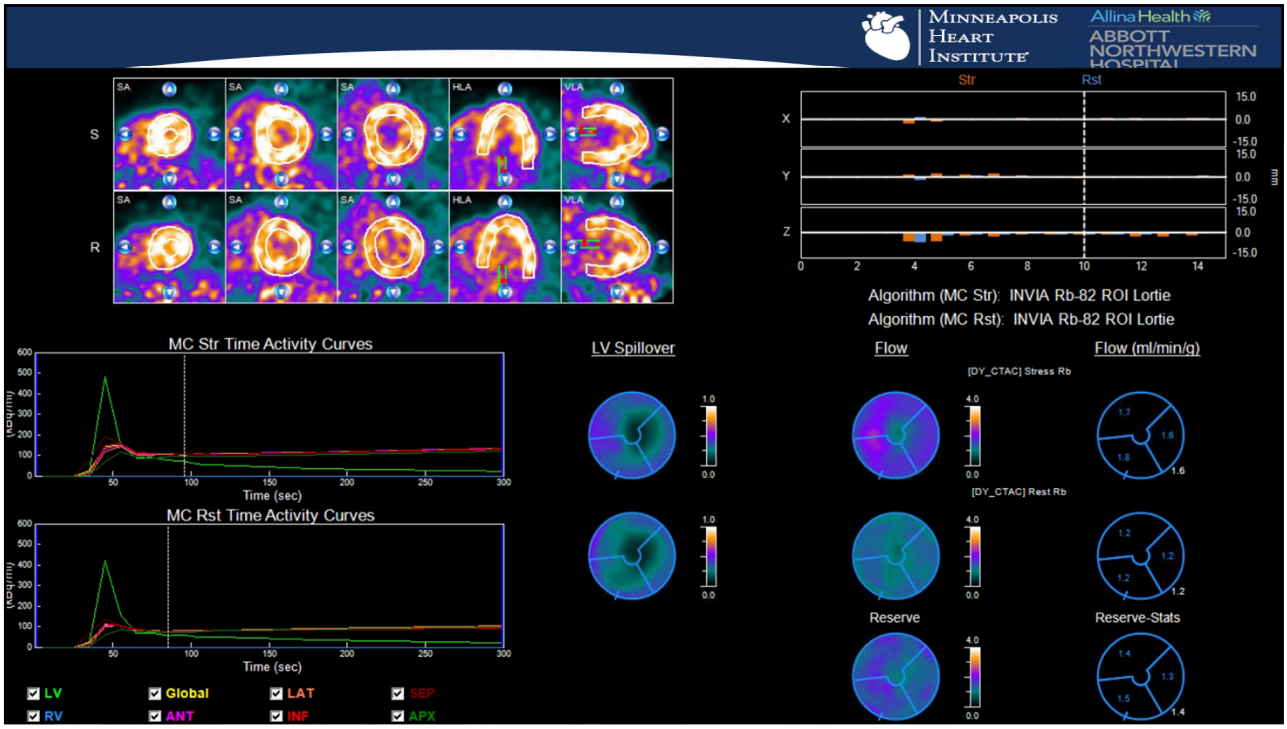
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Str
Rst
Algorithm (MC Str): INVIA Rb-82 ROI Lortie
Algorithm (MC Rst): INVIA Rb-82 ROI Lortie
MC Str Time Activity Curves
MC Rst Time Activity Curves
Time (sec)
LV Spillover
Flow
Flow (ml/min/g)
[DY_CTAC] Stress Rb
[DY_CTAC] Rest Rb
Reserve
Reserve-Stats
LV
RV
Global
ANT
LAT
INF
SEP
APX

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Noninvasive Physiologic Assessment of Cardiac Allograft Vasculopathy Is Prognostic for Post-Transplant Events

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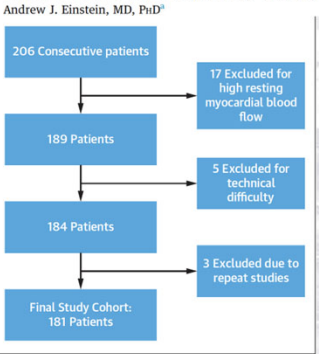

The study included all adult heart transplant recipients who underwent ^{13}N-ammonia positron emission tomography (PET) myocardial perfusion imaging from June 2016 through September 2017, targeting 5 years of follow-up. Patients were excluded for high resting myocardial blood flow, technical difficulties, or patients with repeat studies during the study period.

Patients were classified into 2 groups according to the total MBFR: >2.0 and 2.0. An MBFR value of 2.0 was chosen as the cutoff based on the definition of microvascular dysfunction, prognostic value for stress PET and ROC (1.96).
Then classified into 3 CAV groups: Epicardial CAV → + ischemia (SDS ≥ 2 or ISHLT CAV ≥1, MBFR >2.0; Microvascular CAV: MBFR ≤ 2.0 and no ischemia or epicardial CAV; and Mixed CAV

	All Patients (N = 181)	MBFR >2.0 (n = 110)	MBFR ≤2.0 (n = 71)	P Value
Male	133 (73.5)	76 (69.1)	57 (80.3)	0.10
Age at PET scan, y	62.0 (49-68)	59 (47-67)	65 (56-69)	0.02
Age at transplant, y	54.4 (41-62)	51.5 (37-61)	56 (46-63)	0.06
Time since heart transplant, y	7 (4-11)	7.0 (4.0-10.0)	9.0 (5.0-12.0)	0.11
Donor age, y		29 (21-44)	34 (25-48.5)	0.07
Ethnicity				0.49
White	102 (56.4)	59 (53.6)	43 (60.5)	
Black	38 (21.0)	25 (22.7)	13 (18.3)	
Hispanic	31 (17.1)	18 (16.4)	13 (18.3)	
Other	10 (5.5)	8 (7.3)	2 (2.8)	
HF etiology				0.02
Ischemic	41 (22.6)	18 (16.4)	23 (32.4)	
Nonischemic	122 (67.4)	84 (76.4)	38 (53.5)	
Restrictive/infiltrative	4 (2.2)	2 (1.8)	2 (2.8)	
Retransplant	7 (3.9)	2 (1.8)	5 (7.1)	
Congenital	7 (3.9)	4 (3.6)	3 (4.2)	
Immunosuppression				
CNI	177 (97.8)	108 (98.2)	69 (97.2)	0.66
Tacrolimus	132 (72.9)	86 (78.2)	46 (64.8)	
Cyclosporine	55 (30.4)	22 (20.0)	23 (32.4)	
Proliferation signal inhibitor	48 (26.5)	31 (28.2)	37 (24.3)	0.47
Everolimus	36 (19.9)	25 (22.7)	11 (15.7)	
Sirolimus	12 (6.6)	6 (5.5)	6 (8.6)	
Antimetabolite	112 (61.9)	66 (60.0)	46 (64.8)	0.43
Mycophenolate mofetil	108 (59.7)	63 (57.3)	45 (63.4)	
Azathioprine	4 (2.2)	3 (2.7)	1 (1.4)	
Medication				
ACE inhibitor/ARB/ARNI	62 (34.3)	38 (34.6)	24 (33.8)	0.92
Calcium-channel blocker	72 (40.0)	40 (36.4)	32 (45.1)	0.24
Statin	156 (86.2)	96 (87.3)	60 (84.5)	0.60
Other lipid-lowering agent	42 (23.8)	29 (36.4)	14 (19.7)	0.10
Aspirin	164 (90.6)	105 (95.5)	59 (83.1)	0.005
BMI, kg/m^2	26.7 (23.7-29.2)	26.6 (23.7-28.8)	26.7 (24.0-30.8)	0.42
HTN	127 (70.2)	76 (69.1)	51 (71.8)	0.69
Tobacco use pretransplant	48 (26.5)	29 (26.1)	29 (40.3)	0.04
Insulin-dependent diabetes mellitus	50 (27.6)	20 (18.2)	30 (42.3)	0.0004
Diabetes mellitus	65 (35.9)	31 (28.2)	34 (47.9)	0.007

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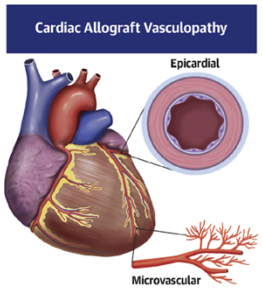
	All Patients (N = 181)	MBFR >2.0 (n = 110)	MBFR ≤2.0 (n = 71)	P Value
Prior stroke	8 (4.4)	2 (1.8)	6 (8.5)	0.03
CKD				0.0002
GFR >60 mL/min	51 (28.2)	39 (35.5)	12 (16.9)	
GFR 30-60 mL/min	85 (47.0)	56 (50.9)	29 (40.9)	
GFR <30 mL/min	33 (18.2)	12 (10.9)	21 (29.5)	
ESRD	12 (6.6)	3 (2.7)	9 (12.7)	
LDL, mg/dL	84.4 ± 24.4	85.4 ± 23.7	82.8 ± 25.6	0.39
Prior ACR	54 (29.8)	26 (23.6)	28 (39.4)	0.02
Prior ACR ≥2R	23 (12.7)	11 (10.0)	12 (16.9)	0.17
Time since ACR	8.2 (2.7-12.2)	6.6 (2.4-9.5)	9.3 (3.3-15.2)	0.05
Prior AMR	14 (7.7)	4 (3.6)	10 (14.1)	0.01
Time since AMR	3.1 (2.5-4.5)	4.0 (3.1-7.7)	2.8 (2.1-3.7)	0.12
Post-transplant DSA	56 (30.9)	30 (27.3)	26 (36.6)	0.19

	MBFR >2.0	MBFR ≤2.0	P Value
Stress agent			0.21
Adenosine	3 (2.8)	2 (2.8)	
Dipyridamole	105 (97.2)	67 (94.4)	
Regadenoson	0 (0.0)	2 (2.8)	
Myocardial blood flow			
Total stress myocardial blood flow	2.32 (2.03-2.62)	1.47 (1.22-1.69)	<0.0001
Total rest myocardial blood flow	0.94 (0.85-1.03)	0.90 (0.82-1.0)	0.08
Total myocardial flow reserve	2.60 (2.20-3.0)	1.63 (1.35-1.80)	<0.0001
Resting ejection fraction, %	60.1 ± 7.4	57.3 ± 10.4	0.06
Stress ejection fraction, %	63.0 ± 7.0	59.4 ± 10.6	0.03
Any ischemia	6 (5.5)	12 (16.9)	0.02
<5% of myocardium	4 (3.6)	2 (2.8)	
5%-10% of myocardium	1 (0.9)	5 (7.0)	
>10% of myocardium	1 (0.9)	5 (7.0)	
Transient ischemic dilation	0 (0.0)	1 (1.4)	0.21
Coronary calcium			0.01
No coronary calcium	85 (80.2)	40 (62.5)	
Any coronary calcium	21 (19.8)	24 (37.5)	
VECAC			
0	85 (80.2)	40 (62.5)	0.11
1-99	5 (4.7)	8 (12.5)	
10-99	7 (6.6)	7 (10.9)	
100-399	7 (6.6)	6 (9.4)	
400-999	2 (1.9)	3 (4.7)	

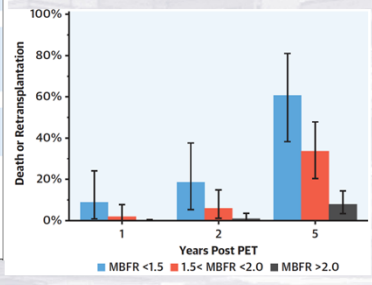
CENTRAL ILLUSTRATION 5-Year Outcomes According to Myocardial Blood Flow Reserve

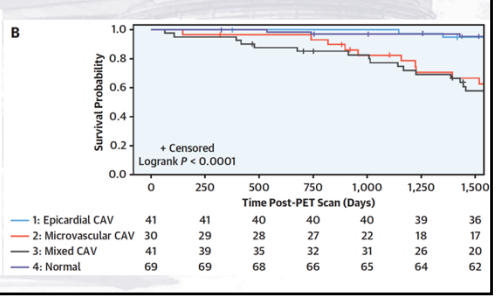


	MBFR ≤2.0	MBFR >2.0	HR
5-Year Death or Retransplant	41.9%	8.1%	↑7.1
5-Year CV Death or Retransplant	17.2%	2.6%	↑12.0
5-Year CV Hospitalization	31.5%	3.9%	↑10.1

Clerkin KJ, et al. J Am Coll Cardiol. 2022;80(17):1617-1628.

Patients with a myocardial blood flow reserve (MBFR) ≤2.0 have a 7-fold increased 5-year risk of death or retransplantation, 12-fold increased risk of cardiovascular (CV) death or retransplantation, and 10-fold increased risk of CV hospitalization.





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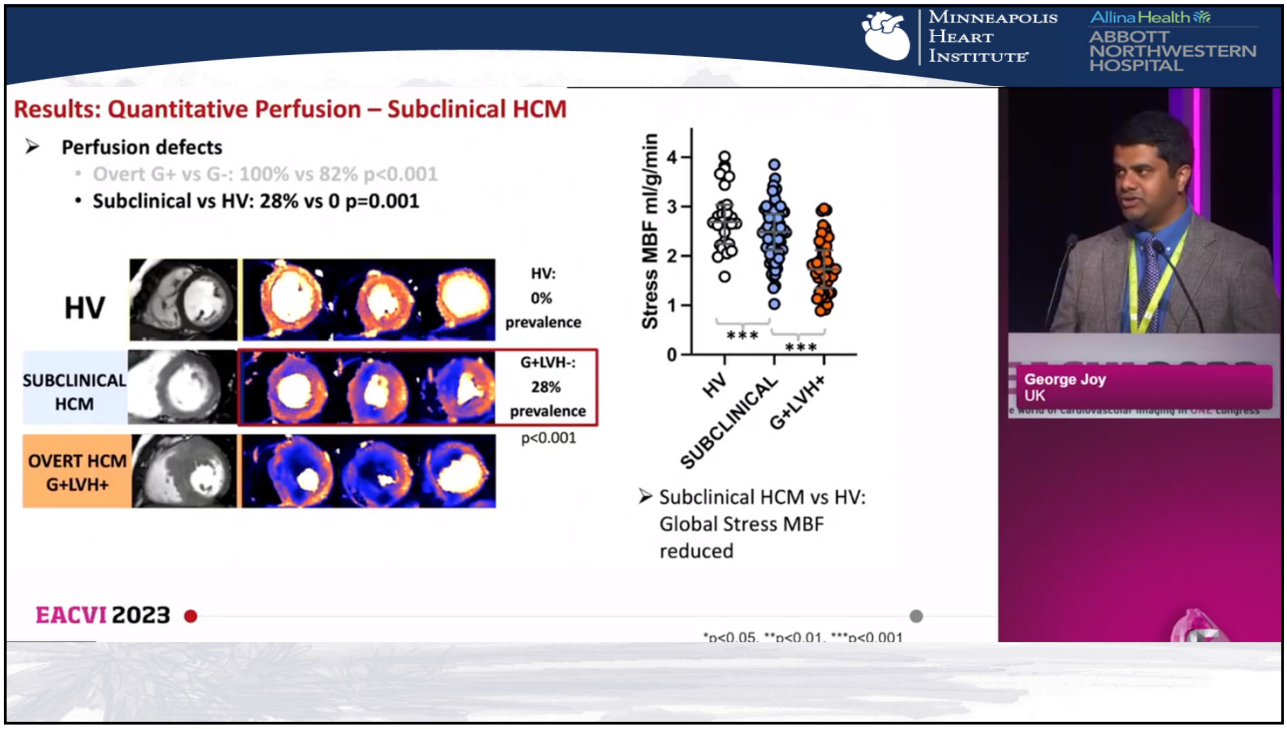
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Results: Quantitative Perfusion – Subclinical HCM
Perfusion defects
Overt G+ vs G-: 100% vs 82% p<0.001
Subclinical vs HV: 28% vs 0 p=0.001
HV
SUBCLINICAL HCM
OVERT HCM G+LVH+
HV: 0% prevalence
G+LVH-: 28% prevalence
p<0.001
Stress MBF ml/g/min
HV
SUBCLINICAL
G+LVH+
Subclinical HCM vs HV: Global Stress MBF reduced
EACVI 2023
*p<0.05, **p<0.01, ***p<0.001
George Joy
UK

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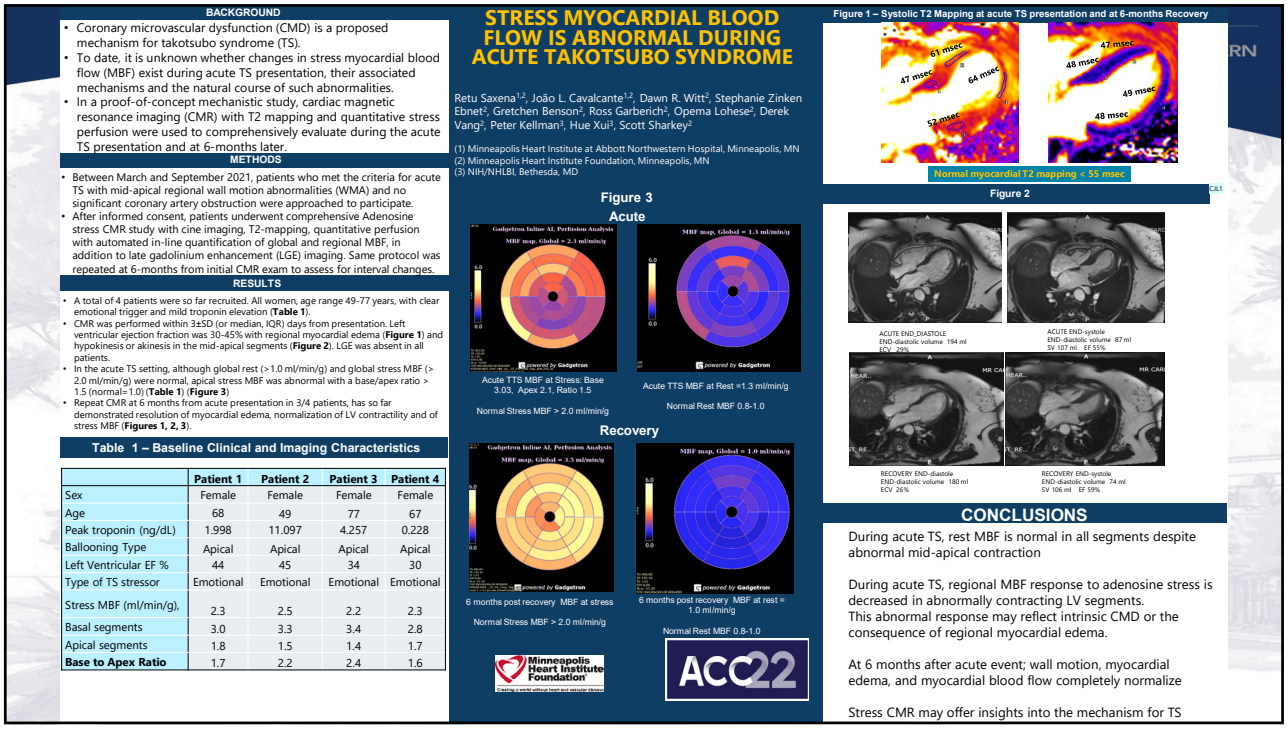
BACKGROUND
Coronary microvascular dysfunction (CMD) is a proposed mechanism for takotsubo syndrome (TS).
To date, it is unknown whether changes in stress myocardial blood flow (MBF) exist during acute TS presentation, their associated mechanisms and the natural course of such abnormalities.
In a proof-of-concept mechanistic study, cardiac magnetic resonance imaging (CMR) with T2 mapping and quantitative stress perfusion were used to comprehensively evaluate during the acute TS presentation and at 6-months later.
METHODS
Between March and September 2021, patients who met the criteria for acute TS with mid-apical regional wall motion abnormalities (WMA) and no significant coronary artery obstruction were approached to participate.
After informed consent, patients underwent comprehensive Adenosine stress CMR study with cine imaging, T2-mapping, quantitative perfusion with automated in-line quantification of global and regional MBF, in addition to late gadolinium enhancement (LGE) imaging. Same protocol was repeated at 6-months from initial CMR exam to assess for interval changes.
RESULTS
A total of 4 patients were so far recruited. All women, age range 49-77 years, with clear emotional trigger and mild troponin elevation (Table 1).
CMR was performed within 3±SD (or median, IQR) days from presentation. Left ventricular ejection fraction was 30-45% with regional myocardial edema (Figure 1) and hypokinesis or akinesis in the mid-apical segments (Figure 2). LGE was absent in all patients.
In the acute TS setting, although global rest (>1.0 ml/min/g) and global stress MBF (>2.0 ml/min/g) were normal, apical stress MBF was abnormal with a base/apex ratio >1.5 (normal=1.0) (Table 1) (Figure 3)
Repeat CMR at 6 months from acute presentation in 3/4 patients, has so far demonstrated resolution of myocardial edema, normalization of LV contractility and of stress MBF (Figures 1, 2, 3).
Table 1 – Baseline Clinical and Imaging Characteristics
Patient 1 Patient 2 Patient 3 Patient 4
Sex Female Female Female Female
Age 68 49 77 67
Peak troponin (ng/dL) 1.998 11.097 4.257 0.228
Ballooning Type Apical Apical Apical Apical
Left Ventricular EF % 44 45 34 30
Type of TS stressor Emotional Emotional Emotional Emotional
Stress MBF (ml/min/g), 2.3 2.5 2.2 2.3
Basal segments 3.0 3.3 3.4 2.8
Apical segments 1.8 1.5 1.4 1.7
Base to Apex Ratio 1.7 2.2 2.4 1.6
STRESS MYOCARDIAL BLOOD FLOW IS ABNORMAL DURING ACUTE TAKOTSUBO SYNDROME
Retu Saxena[1,2], João L. Cavalcante[1,2], Dawn R. Witt[2], Stephanie Zinken Ebnet[2], Gretchen Benson[2], Ross Garberich[2], Opema Lohese[2], Derek Vang[2], Peter Kellman[3], Hue Xui[3], Scott Sharkey[2]
(1) Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN
(2) Minneapolis Heart Institute Foundation, Minneapolis, MN
(3) NIH/NHLBI, Bethesda, MD
Figure 3
Acute
Acute TTS MBF at Stress: Base 3.03, Apex 2.1, Ratio 1.5
Normal Stress MBF > 2.0 ml/min/g
Acute TTS MBF at Rest =1.3 ml/min/g
Normal Rest MBF 0.8-1.0
Recovery
6 months post recovery MBF at stress
Normal Stress MBF > 2.0 ml/min/g
6 months post recovery MBF at rest = 1.0 ml/min/g
Normal Rest MBF 0.8-1.0
Minneapolis Heart Institute Foundation
ACC22
Figure 1 – Systolic T2 Mapping at acute TS presentation and at 6-months Recovery
61 msec
47 msec
64 msec
52 msec
47 msec
48 msec
49 msec
48 msec
Normal myocardial T2 mapping < 55 msec
Figure 2
ACUTE END_DIASTOLE
END-diastolic volume 194 ml
ECV 29%
ACUTE END-systole
END-diastolic volume 87 ml
SV 107 ml EF 55%
RECOVERY END-diastole
END-diastolic volume 180 ml
ECV 26%
RECOVERY END-systole
END-diastolic volume 74 ml
SV 106 ml EF 59%
CONCLUSIONS
During acute TS, rest MBF is normal in all segments despite abnormal mid-apical contraction
During acute TS, regional MBF response to adenosine stress is decreased in abnormally contracting LV segments. This abnormal response may reflect intrinsic CMD or the consequence of regional myocardial edema.
At 6 months after acute event; wall motion, myocardial edema, and myocardial blood flow completely normalize
Stress CMR may offer insights into the mechanism for TS

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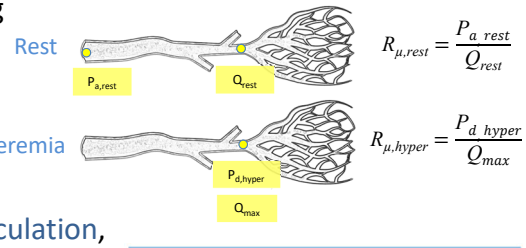
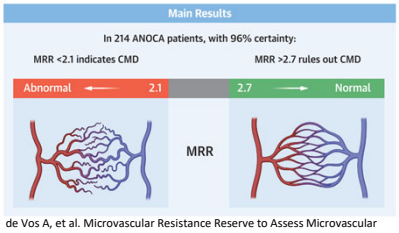
What did we study?

- Microvascular resistance reserve (MRR) (De Bruyne, Pijls et al. 2021) is the ratio of ***true*** resting microvascular resistance to hyperemic microvascular resistance:

$$\text{MRR} = \frac{R_{\mu,rest}}{R_{\mu,hyper}} = \frac{Q_{max}}{Q_{rest}} \cdot \frac{P_{a,rest}}{P_{d,hyper}}$$



- MRR is a reflection of disease only in the microcirculation, even in the presence of epicardial disease
  - MRR in the "normal" group was 3.4 compared with a mean MRR of 1.9 in the "abnormal" group.
  - MRR >2.7 ruled out coronary microvascular dysfunction (CMD) with a certainty of 96%, whereas MRR <2.1 indicated the presence of CMD with a similar high certainty of 96%.



de Vos A, et al. Microvascular Resistance Reserve to Assess Microvascular Dysfunction in ANOCA Patients. J Am Coll Cardiol Intv. 2023

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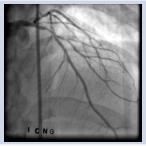
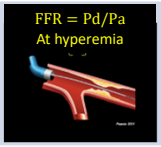
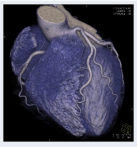
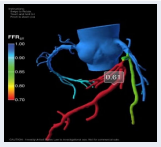
What did we study?

- The CCTA+FFR_{CT} pathway enables non-invasive evaluation of epicardial disease
- We propose a **non-invasively computed MRR (MRR_{CT})** using a model built from CCTA imaging, and using total LV flow at rest and stress from [^{15}O]H_2O-PET MPI
- As a proof-of-principle, we evaluated MRR_{CT} and FFR_{CT} in different patient groups

	Anatomy	Epicardial function	Microvascular function
Invasive			
Non-invasive			

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Slide 59

0 Add animations
, 2023-04-04T20:58:34.106

1 Explain the importance of MRR, and why evaluating microvascular resistance is important
, 2023-04-04T21:05:42.753

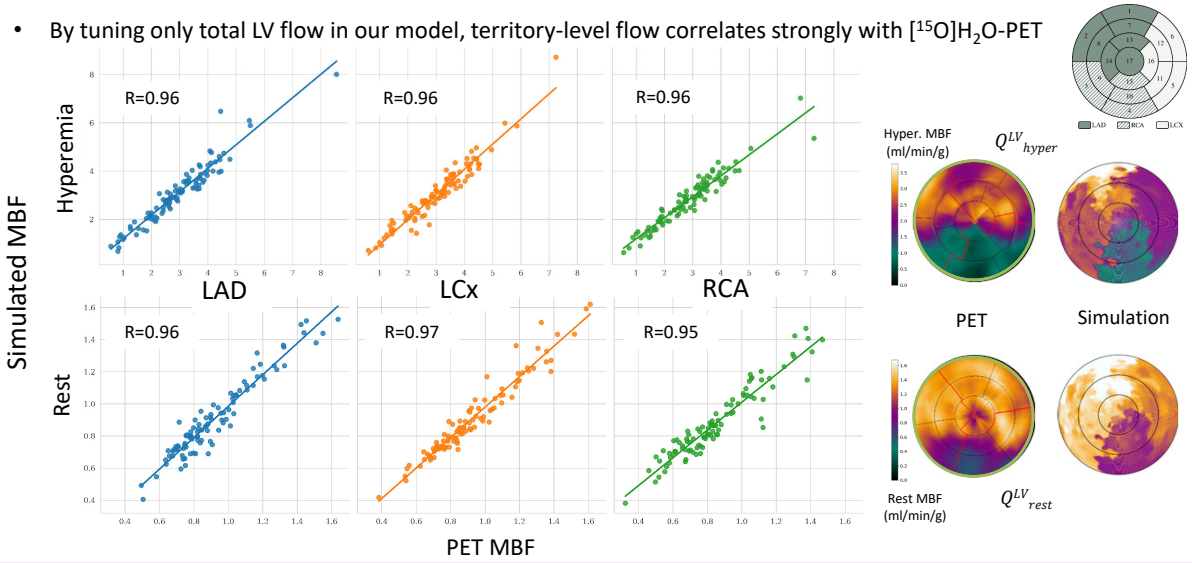
2 Replace text with illustrations ideally, and explain clinical relevance
, 2023-04-04T21:06:25.947

3 Explain how MRR-CT and FFR-CT allows us to evaluate epicardial and microvascular disease non-invasively
, 2023-04-04T21:14:58.734

4 Add table showing how certain metrics would typically require invasive measurements (FFR for epicardial, MRR for microvascular evaluation), with a new row showing how we can do this non-invasively
, 2023-04-04T21:17:53.582

What are the essential results?

- By tuning only total LV flow in our model, territory-level flow correlates strongly with [^{15}O]H_2O-PET



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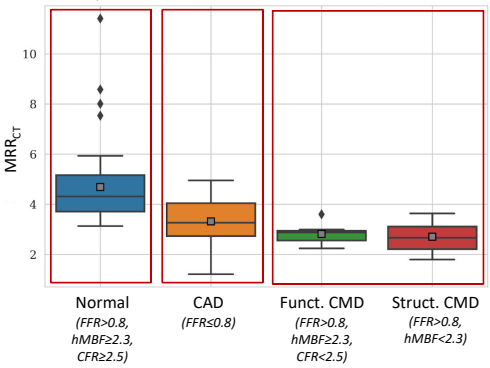
What are the essential results?

- MRR_{CT} was significantly different between disease categories, with the lowest values found in CMD patients, and highest values in Normal patients
- MRR_{CT} displays a range of values for CAD patients, which could stratify patients for treatment

MRR_{CT} computed for different Disease Categories, N=92



70 y.o. Female with typical angina, CMD, No CAD, and *low* MRR_{CT}

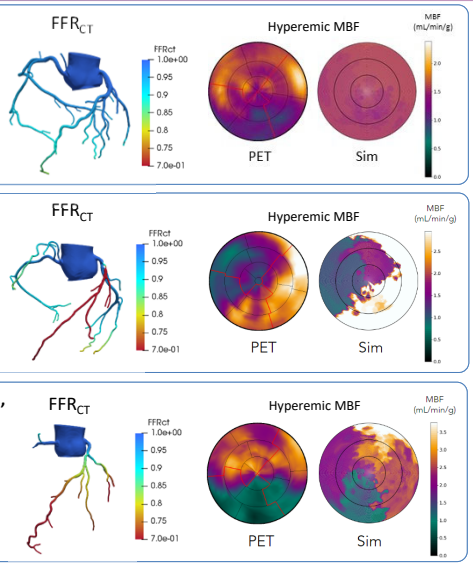
	FFR_{CT}	FFR	MRR_{CT}
RCA	0.95	1	2.19
LAD	0.90	0.94	2.21
LCX	0.98	1	2.19

58 y.o. Male with atypical angina, CAD and *normal* MRR_{CT}

	FFR_{CT}	FFR	MRR_{CT}
RCA	0.91	1.0	4.08
LAD	0.47	0.43	4.00
OM	0.90	0.91	4.18

55 y.o. Female with atypical angina, CAD, CTO and *low* MRR_{CT}

	FFR_{CT}	FFR	MRR_{CT}
RCA	CTO	CTO	N/A
LAD	0.68	0.72	2.22
LCX	0.72	0.73	2.15



62

Slide 62

0 Animate cases to appear 1 at a time
, 2023-04-04T21:00:24.240

1 Point out that predicted MBF distribution of simulated polarmaps match well with the PET imaging, where we can see clearly the local perfusion deficits
, 2023-04-04T21:01:19.989

2 Patient 1: mention patient conditions, highlighting normal epicardial vessels
, 2023-04-04T21:02:09.487

3 Add any additional clinical context for the patient in a pop-up box in the purple section at the bottom
, 2023-04-04T21:02:36.312

4 Update MRR -> MRRct in plot (bottom left)
, 2023-05-12T17:17:37.034

The essentials to remember

CCTA-derived Microvascular Resistance Reserve (MRR_{CT}) enables non-invasive evaluation of coronary microvascular function

- **Why?** MRR overcomes issues with CFR and IMR for evaluating CMD, but is invasive
- **What?** MRR_{CT} is a non-invasive MRR assessment as derived from CCTA and PET MPI
- **How?** MRR_{CT} uses geometry from CCTA, total LV rest and stress flow from MPI, and is computed at measurement sites from the resulting simulated pressure and flow
- **Results?** MRR_{CT} distinguishes Normal subjects from CMD patients, and stratifies CAD patients into those with normal *vs* abnormal microvascular function
- **Why is this important?** MRR_{CT} is the first non-invasive and specific approach to CMD

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Closing Thoughts

- CMD is common (25-40%) of patients without obstructive CAD and symptoms. Female:male ratio (3:1). Comorbidities increase the risk.
- Stress Cardiac PET has been validated decades ago and accurate detection of CMD. Quantification with stress MBF and CFR (MPR) are reimbursable and available. Importantly, strongly linked with comorbidities and outcomes.
- Stress Cardiac MRI with now in-line automated quantitative perfusion – akin to stress PET – is available on both campuses and opens the possibility to provide objective assessment of CMD.
- Several new developments in imaging will continue to add value to this complex field and ultimately benefiting patients by providing an answer and tailored targeted medications.

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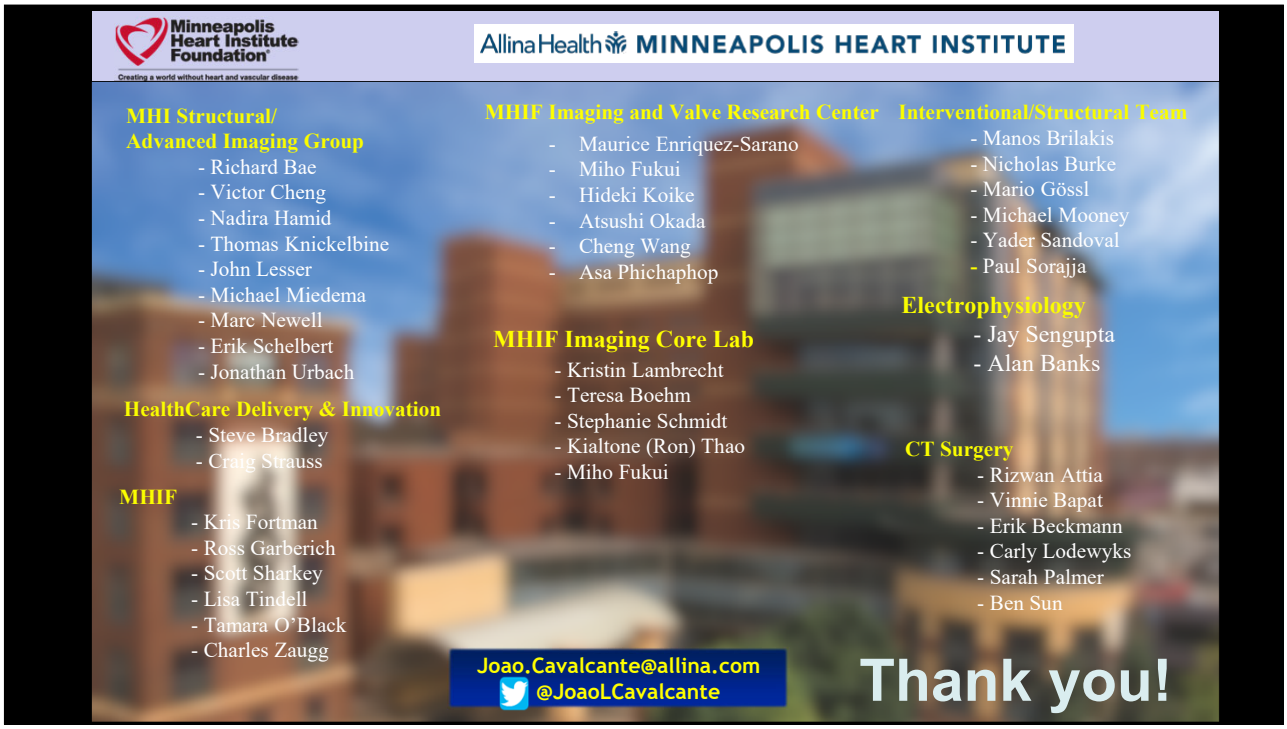
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- Nadira Hamid
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Thank you!

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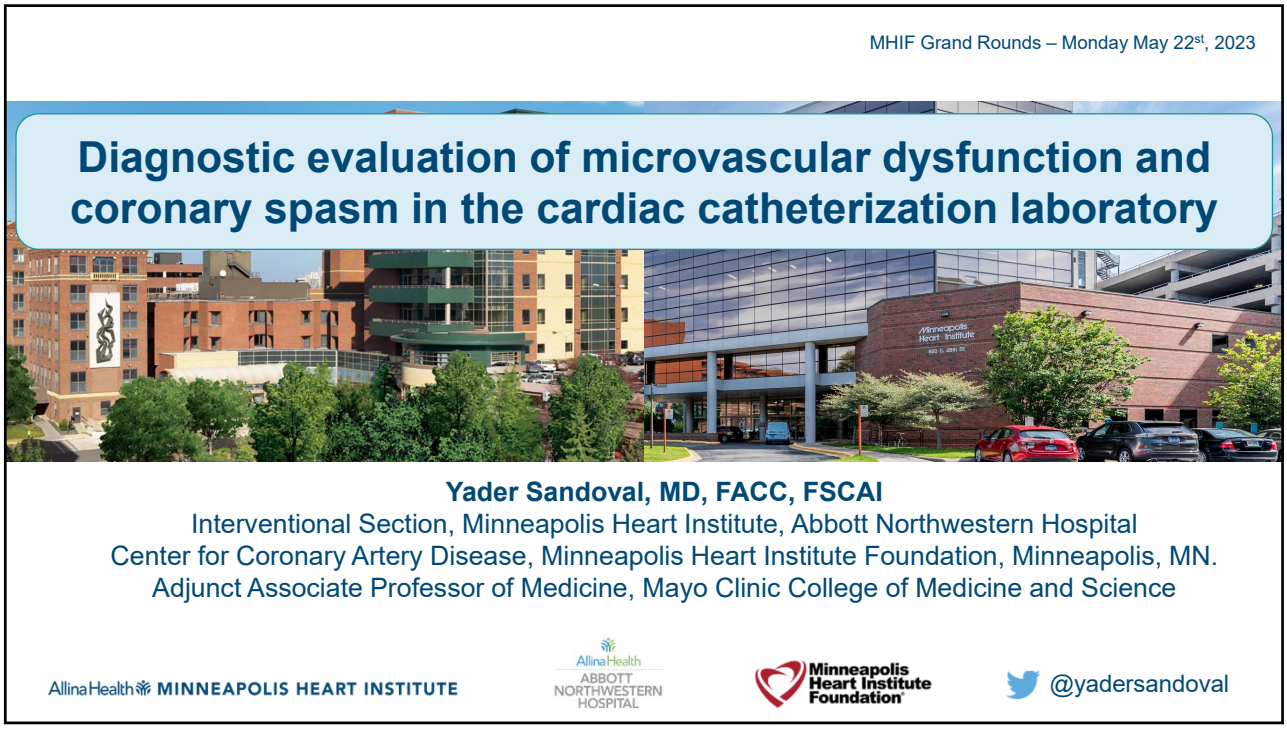
MHIF Grand Rounds – Monday May 22st, 2023
Diagnostic evaluation of microvascular dysfunction and coronary spasm in the cardiac catheterization laboratory
Yader Sandoval, MD, FACC, FSCAI
Interventional Section, Minneapolis Heart Institute, Abbott Northwestern Hospital
Center for Coronary Artery Disease, Minneapolis Heart Institute Foundation, Minneapolis, MN.
Adjunct Associate Professor of Medicine, Mayo Clinic College of Medicine and Science
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DISCLOSURES

- Abbott Diagnostics (advisory board), Roche Diagnostics (advisory board, speaker), Zoll (advisory board), Phillips (advisory board), Patent #20210401347 (machine learning models for ECG-based troponin level detection)

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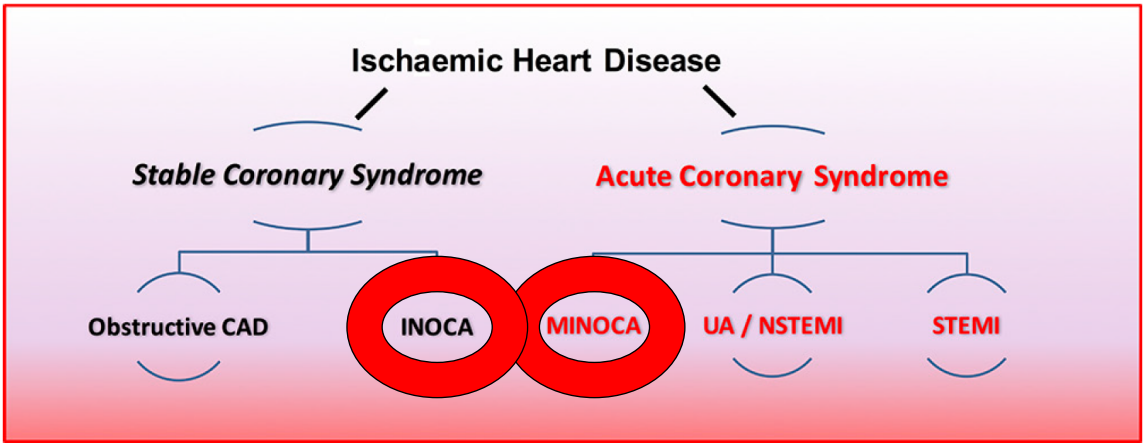
Nomenclature: INOCA and MINOCA



Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. Heart. 2018 Feb;104(4):284-292.

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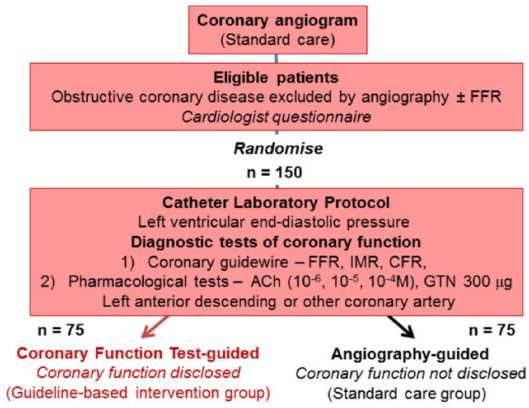
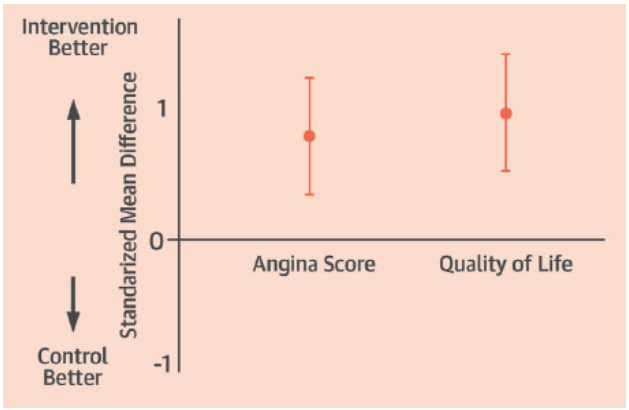
CorMicA: Coronary Microvascular Angina RCT





CONCLUSIONS Coronary angiography often fails to identify patients with vasospastic and/or microvascular angina. Stratified medical therapy, including an IDP with linked medical therapy, is routinely feasible and improves angina in patients with no obstructive CAD. (CORonary MICrovascular Angina [CorMicA]; NCT03193294) (J Am Coll Cardiol 2018;72:2841-55) © 2018 by the American College of Cardiology Foundation.

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Guideline recommended (class 2) approaches for MVD

2a	B-NR	1. For patients with persistent stable chest pain and nonobstructive CAD and at least mild myocardial ischemia on imaging, it is reasonable to consider invasive coronary function testing to improve the diagnosis of coronary microvascular dysfunction and to enhance risk stratification.[1-4]
2a	B-NR	2. For patients with persistent stable chest pain and nonobstructive CAD, stress PET MPI with MBFR is reasonable to diagnose microvascular dysfunction and enhance risk stratification.[5-11]
2a	B-NR	3. For patients with persistent stable chest pain and nonobstructive CAD, stress CMR with the addition of MBFR measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.[12-14]
2b	C-EO	4. For patients with persistent stable chest pain and nonobstructive CAD, stress echocardiography with the addition of coronary flow velocity reserve measurement may be reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.

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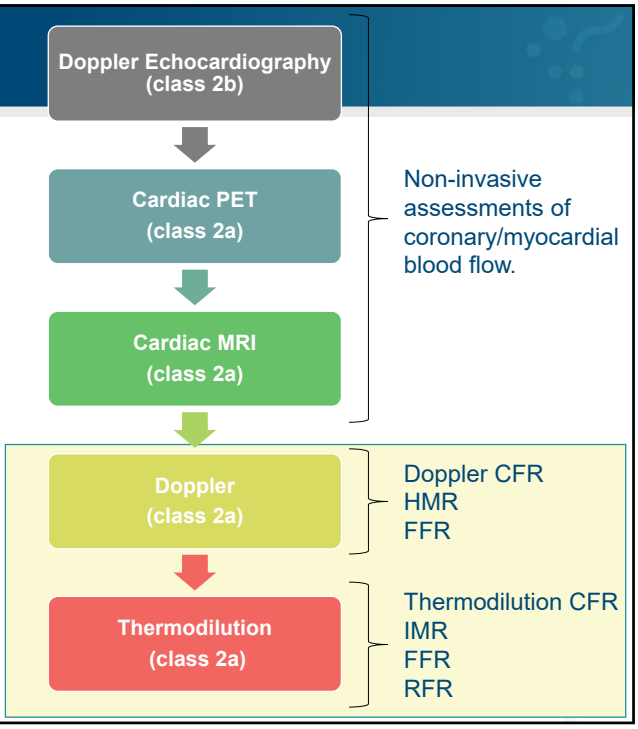

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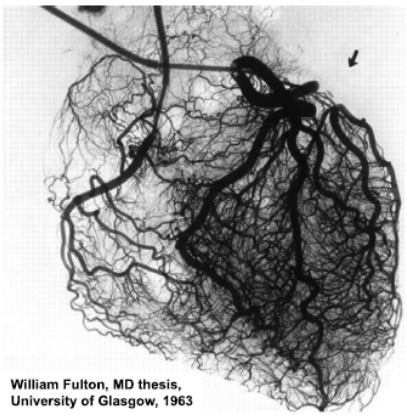
Coronary angiography and microvasculature

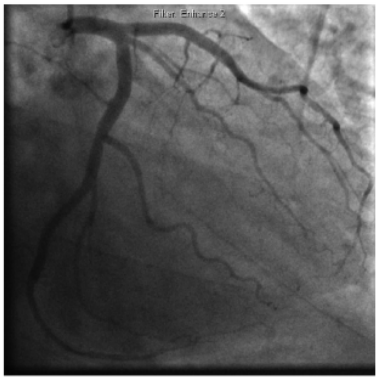
Imaging resolution

30 µm



William Fulton, MD thesis,
University of Glasgow, 1963

300 µm +



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Modified clinical classification of CMD

CMVD	Definition
Type 1	Primary, i.e. in the absence of structural heart disease
Type 2	In the presence of cardiomyopathies such as LVH, HCM, DCM, amyloidosis.
Type 3	In the presence of obstructive CAD (including ACS)
Type 4	After coronary interventions
Type 5	After cardiac transplantation

Modifiers	
Duration	Acute or chronic
Symptoms	Asymptomatic or symptomatic
Therapy	None, minimal, moderate, or maximal level

Herrmann J, Kaski JC, Lerman A. Coronary microvascular dysfunction in the clinical setting: from mystery to reality. Eur Heart J 2012; 33: 2771-2781.

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Invasive evaluation of microvascular dysfunction

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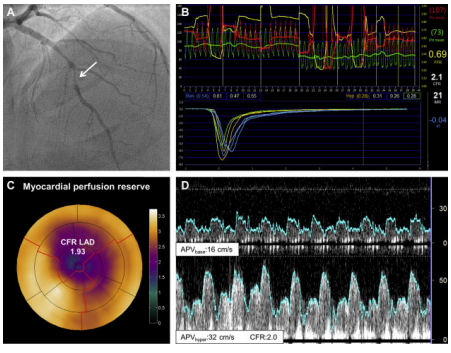
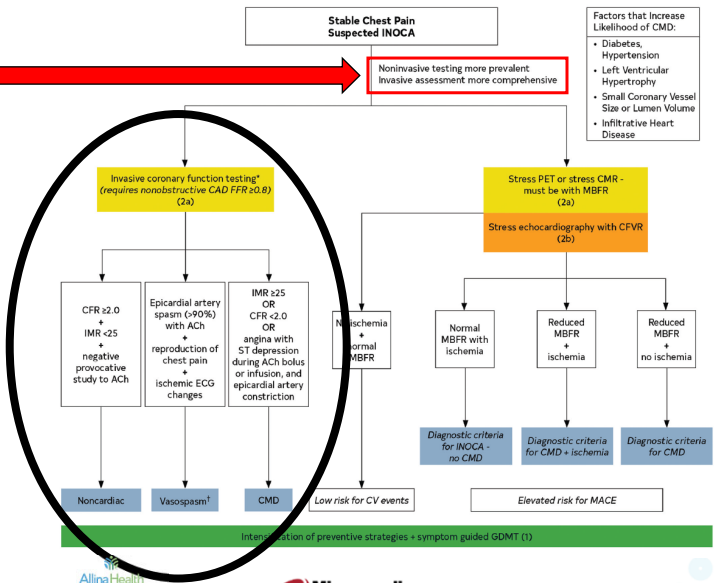
Ischemia and No Obstructive CAD (INOCA)

Noninvasive testing more prevalent
Invasive assessment more comprehensive





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Invasive evaluation of microvascular function and coronary spasm

Testing

Non-endothelium dependent microvascular function	Endothelium dependent vasomotion assessment
Adenosine & coronary flow reserve	Acetylcholine for spasm provocation

Conditions

INOCA

MINOCA

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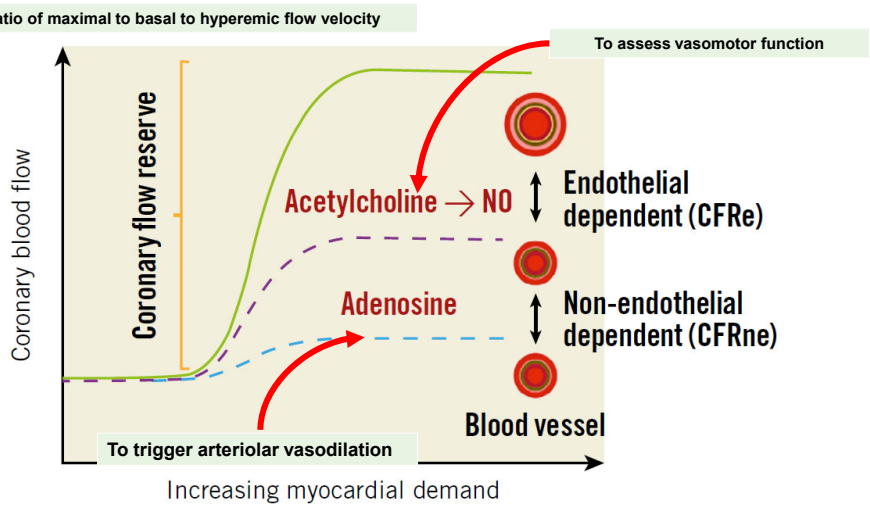

What is coronary flow reserve (CFR)? CFR relates to the ability of the coronary circulation to increase blood flow in response to alterations in oxygen demand.

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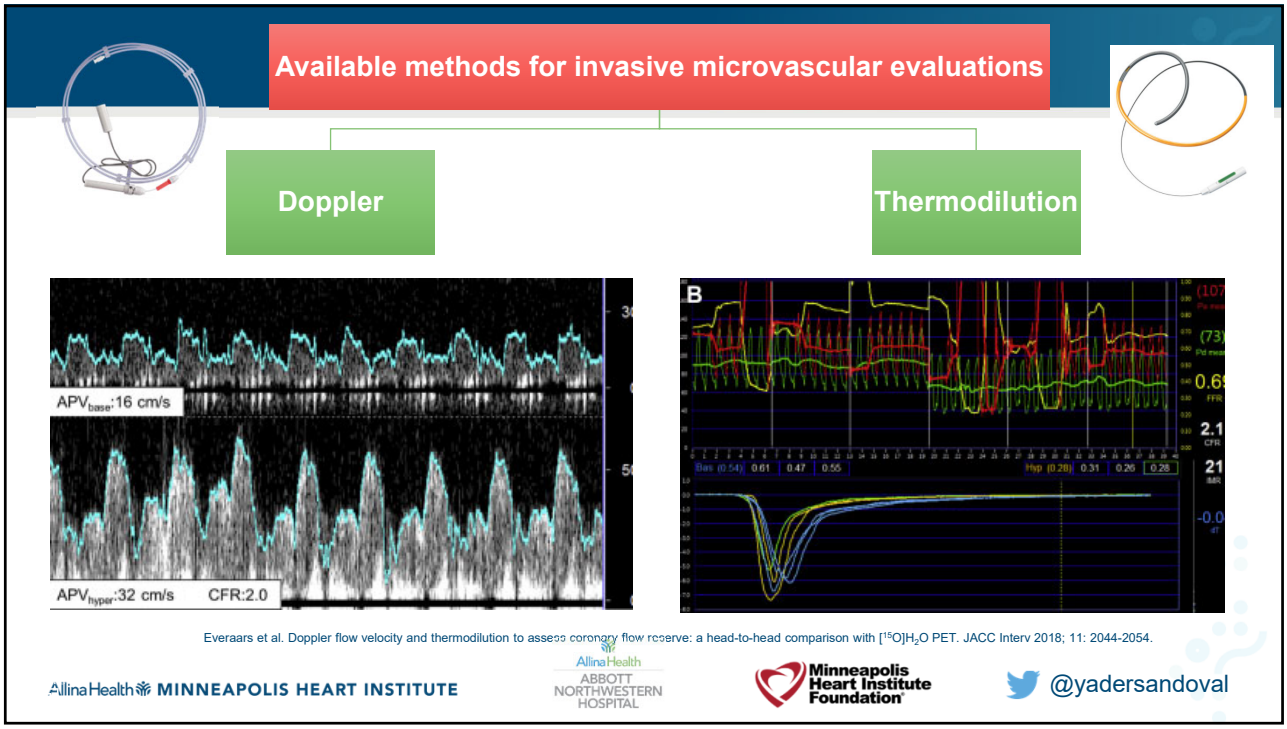

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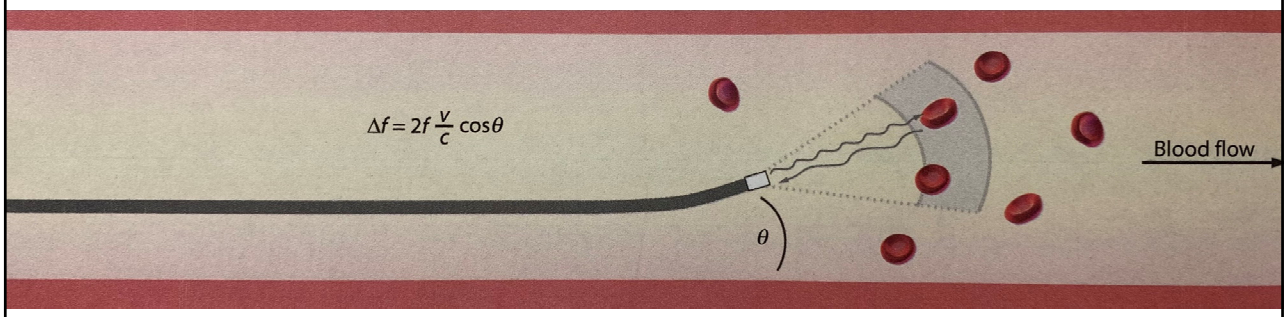
Doppler Flow Velocity



- Flow velocity is extracted from these data by detecting the instantaneous peak velocity, which represents the maximum velocity within the sample volume.
- The average of instantaneous peak velocity over one or multiple heartbeats is termed **average peak velocity** (APV).

Escaned & Davies. Physiological assessment of coronary stenoses and the microcirculation.

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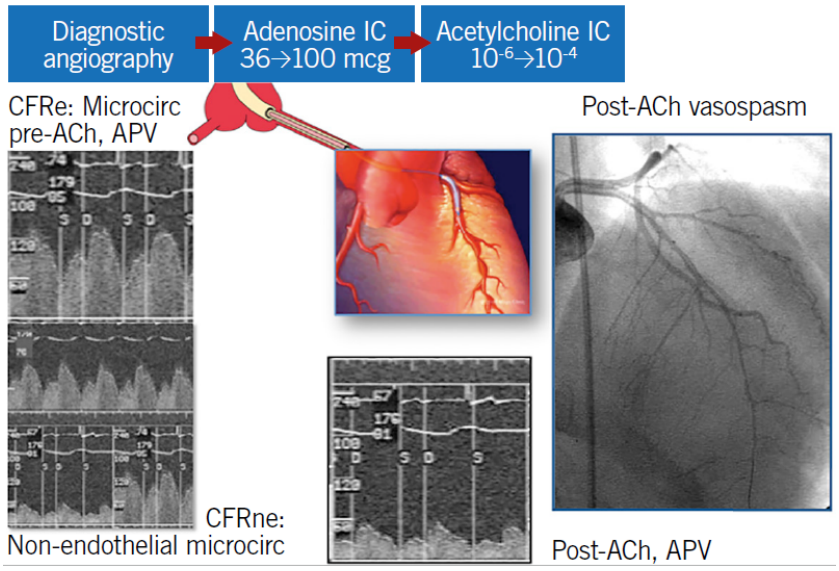

Widmer et al. The functional assessment of patients with non-obstructive coronary artery disease: expert review from an international microcirculation working group. EuroIntervention 2019; 14: 1694-1702.

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Normal diagnostic parameters: Doppler-based approach

	Non-endothelium dependent function (CFRne)	Epicardial endothelial function	Microcirculatory endothelial function (CFRe)
Adenosine (microcirculation)	% Δ in ratio of hyperaemic to rest APV (i.e., CFR) >2.5	-	-
Acetylcholine (epicardial and microcirculation)	-	% Δ in coronary artery diameter >20%	% Δ in CBF >50%
NTG (epicardial)	% Δ in coronary artery diameter QCA >20%	-	-

Coronary blood flow (CBF) = 0.5 x velocity x area
Coronary blood flow (CBF) = 0.5 × APV × (radius^2×π)

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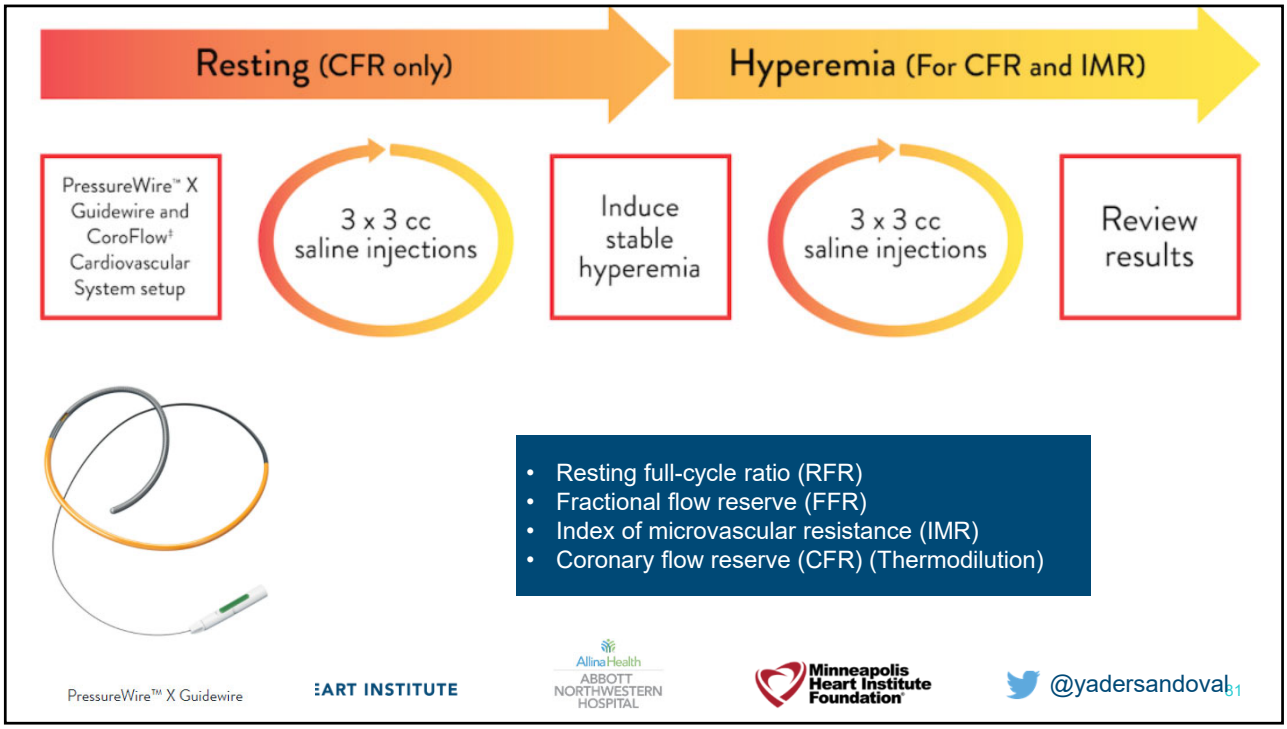
Resting (CFR only)
Hyperemia (For CFR and IMR)
PressureWire™ X Guidewire and CoroFlow‡ Cardiovascular System setup
3 x 3 cc saline injections
Induce stable hyperemia
3 x 3 cc saline injections
Review results
PressureWire™ X Guidewire
• Resting full-cycle ratio (RFR)
• Fractional flow reserve (FFR)
• Index of microvascular resistance (IMR)
• Coronary flow reserve (CFR) (Thermodilution)
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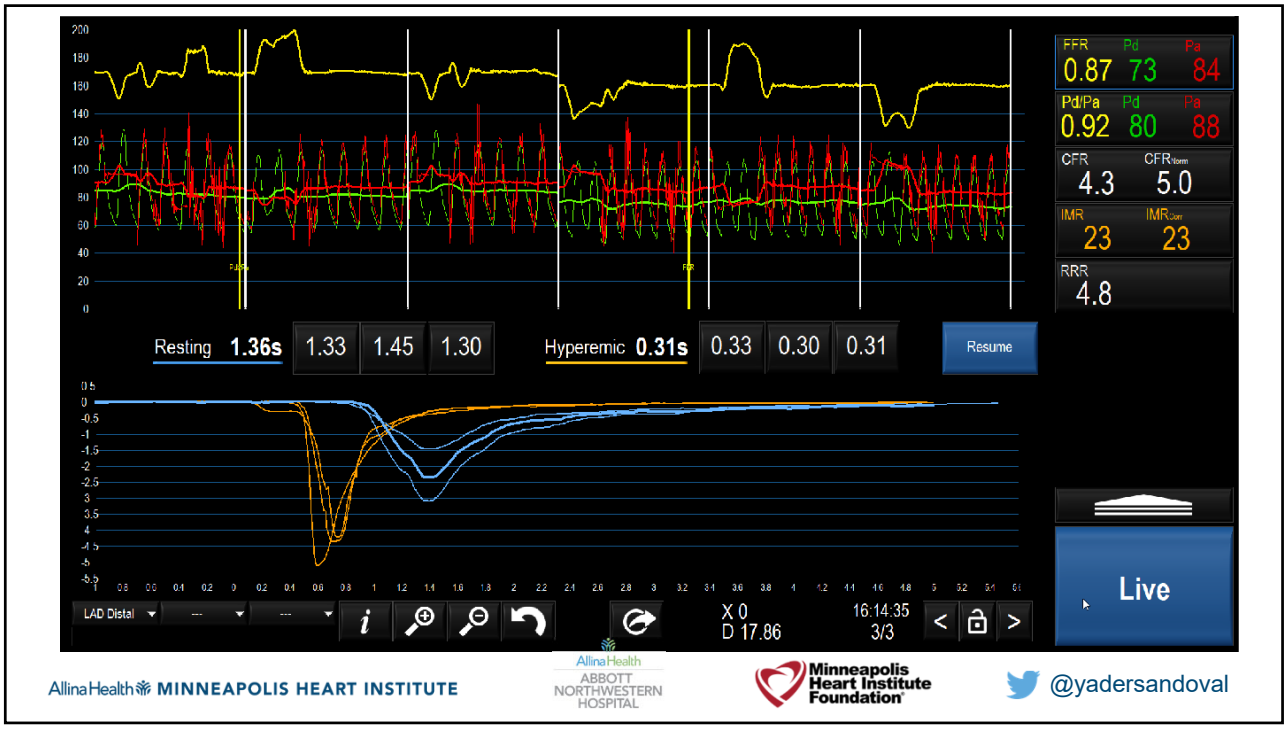
FFR 0.87 Pd 73 Pa 84
Pd/Pa 0.92 Pd 80 Pa 88
CFR 4.3 CFR 5.0
IMR 23 IMR 23
RRR 4.8
Resting 1.36s 1.33 1.45 1.30
Hyperemic 0.31s 0.33 0.30 0.31
Resume
Live
LAD Distal
X 0
D 17.86
16:14:35
3/3
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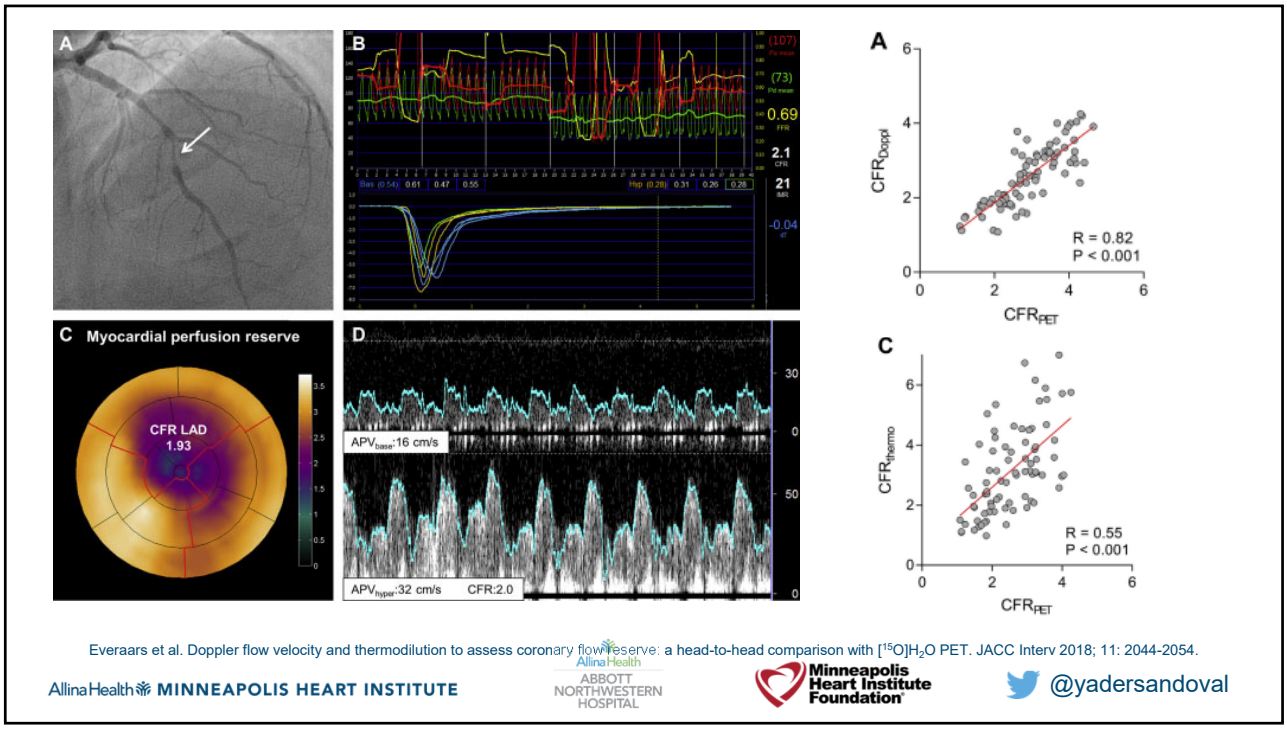

Everaars et al. Doppler flow velocity and thermodilution to assess coronary flow reserve: a head-to-head comparison with [^{15}O]H_2O PET. JACC Interv 2018; 11: 2044-2054.

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Assessment of microcirculation

- Instrument LAD with Doppler wire and infusion catheter
- Adenosine 36-100 µg to obtain CFR
- *Equipment: Doppler wire set up, infusion catheter, and adenosine*

Assessment of endothelium

- ACh (10^{-6} M → 10^{-4} M)
- Calculate Δ diameter and Δ blood flow
- *Equipment: ACh and infusion pump*

Widmer et al. The functional assessment of patients with non-obstructive coronary artery disease: expert review from an international microcirculation working group. EuroIntervention 2019; 14: 1694-1702.

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Risk of invasive coronary reactivity testing: low risk (1%) of adverse events

Safety of Coronary Reactivity Testing in Women With No Obstructive Coronary Artery Disease

Results From the NHLBI-Sponsored WISE (Women's Ischemia Syndrome Evaluation) Study

293 women, mean age 54 years (SD 10)

Results CRT-SAEs occurred in 2 women (0.7%) during the procedure; 1 had coronary artery dissection, and 1 developed MI associated with coronary spasm. CRT-AEs occurred in 2 women (0.7%) and included 1 transient air microembolism and 1 deep venous thrombosis. There was no CRT-related mortality. In the mean follow-up period of 5.4 years, the MACE rate was 8.2%, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%).

Conclusions In women undergoing CRT for suspected MCD, contemporary testing carries a relatively low risk compared with the MACE rate in these women. These results support the use of CRT by experienced operators for establishing definitive diagnosis and assessing prognosis in this at-risk population. (Women's Ischemia Syndrome Evaluation [WISE]; NCT00832702) (J Am Coll Cardiol Intv 2012;5:646–53) © 2012 by the American College of Cardiology Foundation

Wei J et al. JACC Cardiovasc Interv 2012; 5: 646-53.

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ORIGINAL INVESTIGATIONS

Safety of Provocative Testing With Intracoronary Acetylcholine and Implications for Standard Protocols

Tatsunori Takahashi, MD,[a] Bruce A. Samuels, MD,[b] Weijia Li, MD,[a] Manish A. Parikh, MD,[c] Janet Wei, MD,[b] Jeffery W. Moses, MD,[d] William F. Fearon, MD,[e] Timothy D. Henry, MD,[f] Jennifer A. Tremmel, MD, MS,[a] Yuhei Kobayashi, MD,[c] on behalf of the Microvascular Network

ABSTRACT

BACKGROUND Heterogeneity in diagnostic criteria and provocation protocols has posed challenges in understanding the safety of coronary provocation testing with intracoronary acetylcholine (ACh) for the contemporary diagnosis of epicardial and microvascular spasm.

OBJECTIVES We examined the safety of testing and subgroup differences in procedural risks based on ethnicity, diagnostic criteria, and provocation protocols.

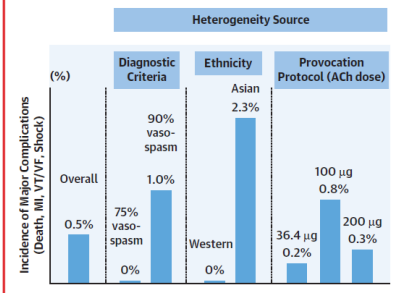
METHODS PubMed and Embase were searched in November 2021 to identify original articles reporting procedural complications associated with intracoronary ACh administration. The primary outcome was the pooled estimate of the incidence of major complications including death, myocardial infarction, ventricular tachycardia/fibrillation, and shock.

RESULTS A total of 16 studies with 12,585 patients were included in the meta-analysis. The overall pooled estimate of the incidence of major complications was 0.5% (95% CI: 0.0%-1.3%) without any reports of death. Exploratory subgroup analyses revealed that the pooled incidence of major complications was significantly higher in the studies that followed the contemporary diagnosis criteria for epicardial spasm defined as ≥90% diameter reduction (1.0%; 95% CI: 0.3%-2.0%) but significantly lower in Western populations (0.0%; 95% CI: 0.0%-0.45%). The rate of positive epicardial spasm and the incidence of major complications were similar between provocation protocols using the maximum ACh doses of 100 μg and 200 μg.

CONCLUSIONS Intracoronary ACh administration for the contemporary diagnosis of epicardial and microvascular spasm is a safe procedure. Moreover, excellent safety records are observed in Western populations primarily presenting with myocardial ischemia and/or infarction with nonobstructive coronary arteries. This study will help standardize ACh testing to improve clinical diagnosis and ensure procedural safety. (J Am Coll Cardiol 2022;79:2367-2378)

16 studies, 12585 patients
Pooled estimate of incidence of major complications was 0.5% without any reports of death.

CENTRAL ILLUSTRATION Procedural Safety of Provocative Spasm Testing With Intracoronary Acetylcholine



Takahashi T, et al. J Am Coll Cardiol. 2022;79(24):2367-2378.

Summary

- No death reported in the published data
- ACh test extremely safe in the Western studies
- Max ACh 100 μg vs. 200 μg did not show major differences in safety and positivity rate

Future Direction

- Creating physician-lead network
- Provocation protocol standardization
- Standardized complication reporting

Although the overall incidence of major complications was 0.5%, the rate of major complications can vary depending on diagnostic criteria, ethnicity, and acetylcholine dose. These results help us standardize the provocation protocol as well as a complication reporting system. ACh = acetylcholine; MI = myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

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Case presentation

- 70 year-old female with a history of hypertension and dyslipidemia with dyspnea on exertion and chest discomfort.
- Previous CCTA ~3 years ago with no significant obstructive CAD, CAC 100.
- RHC: RA 11, PA 45/18 (30), PCWP 18, CO 5.8, CI 2.6
- LVEDP 17 mmHg

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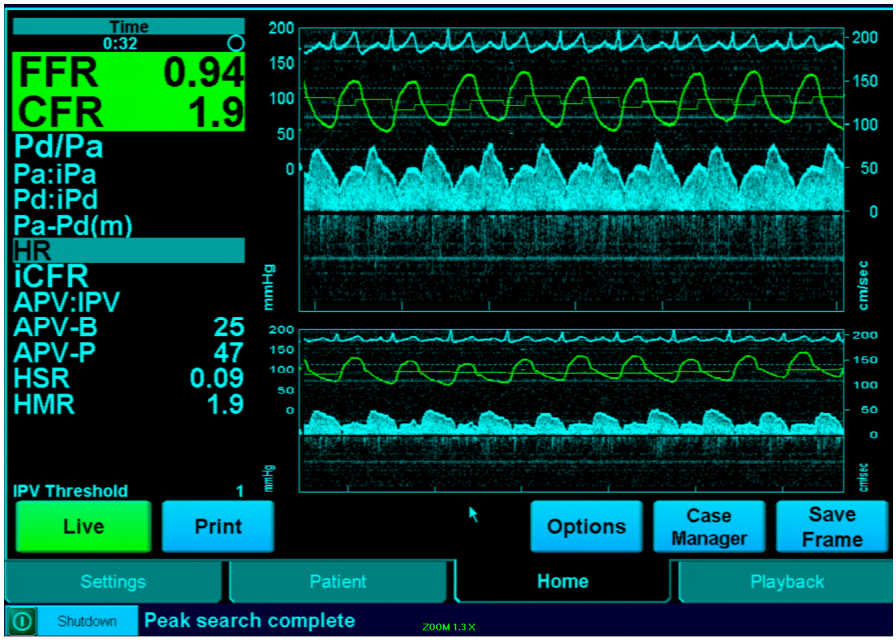
Intracoronary adenosine

FFR

Doppler CFR

HMR
Hyperemic microvascular resistance



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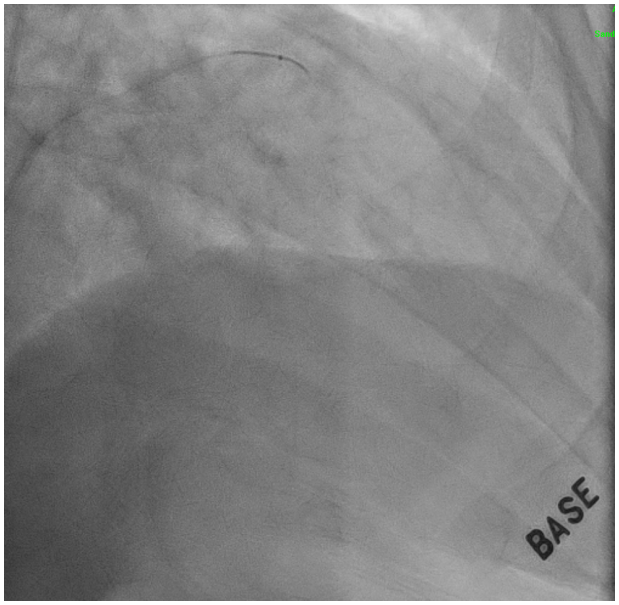

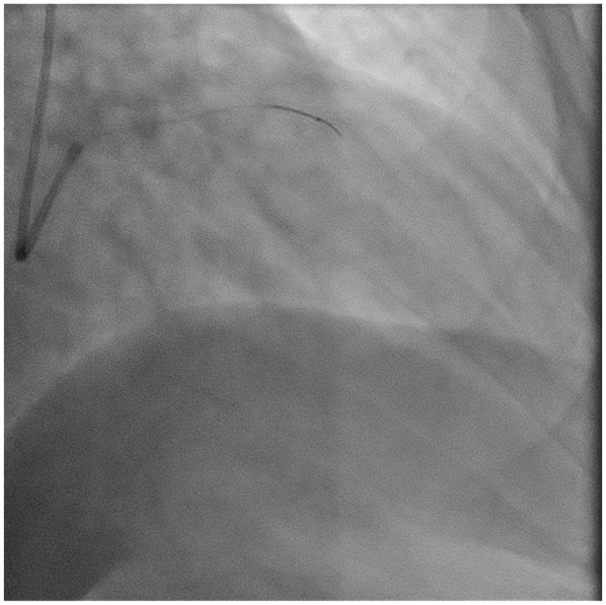

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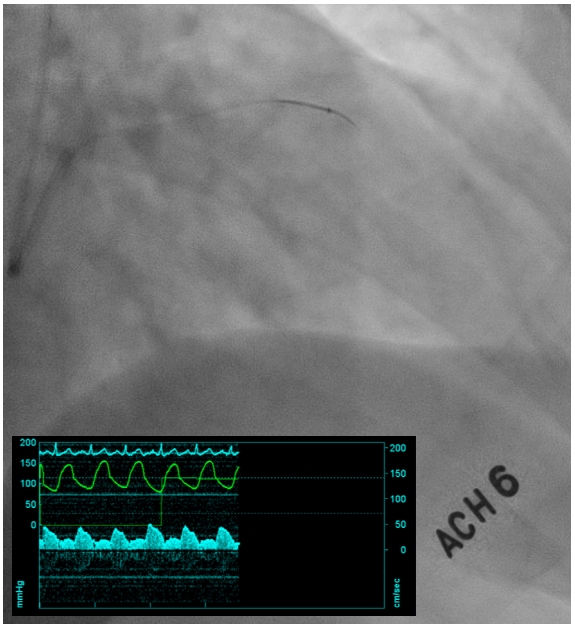

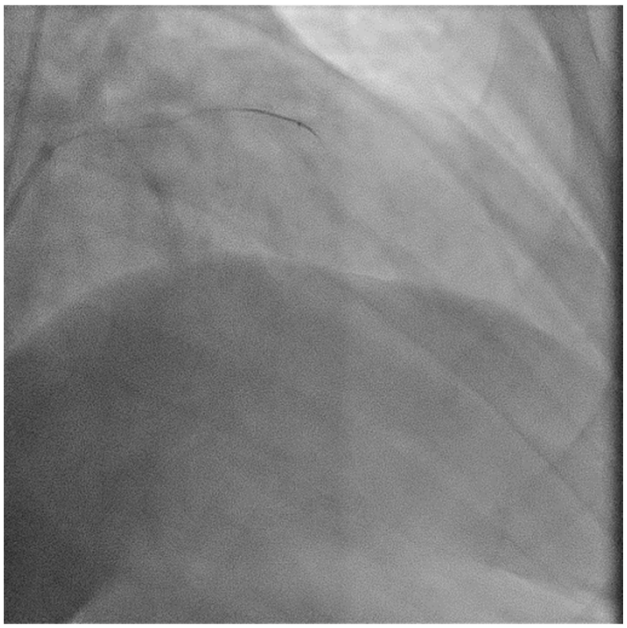

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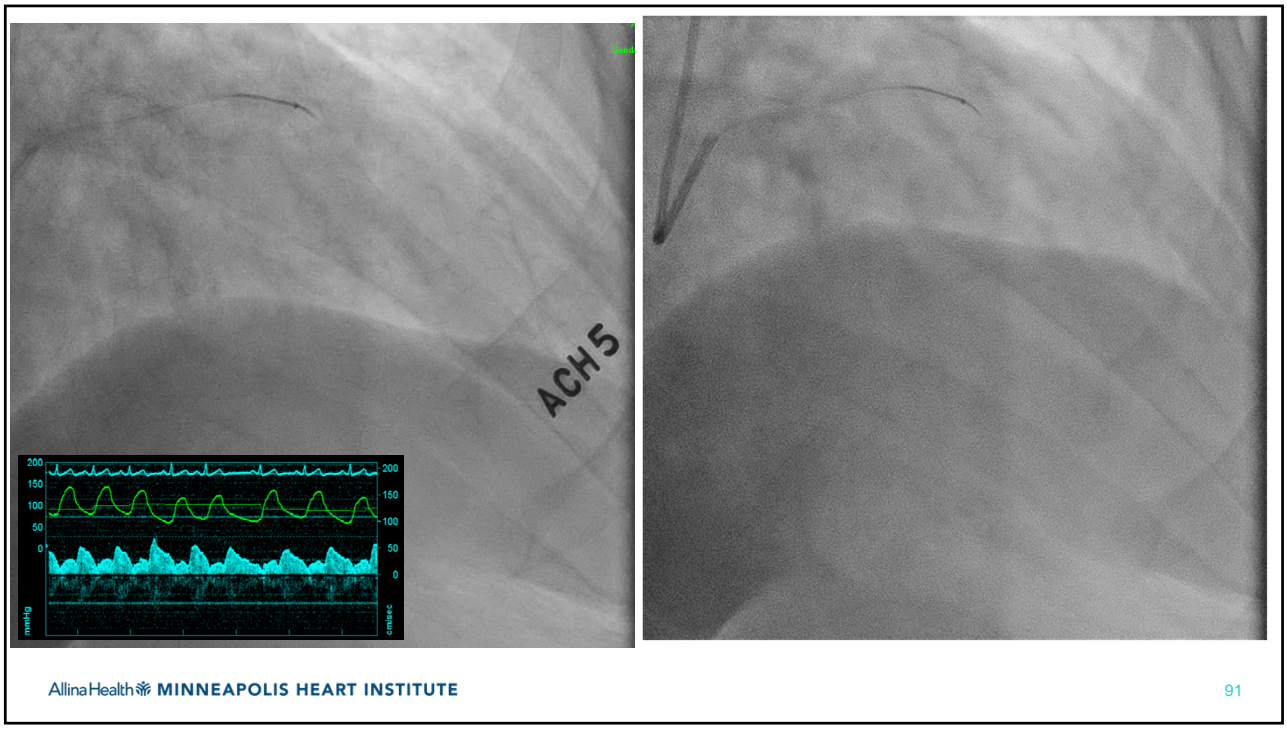
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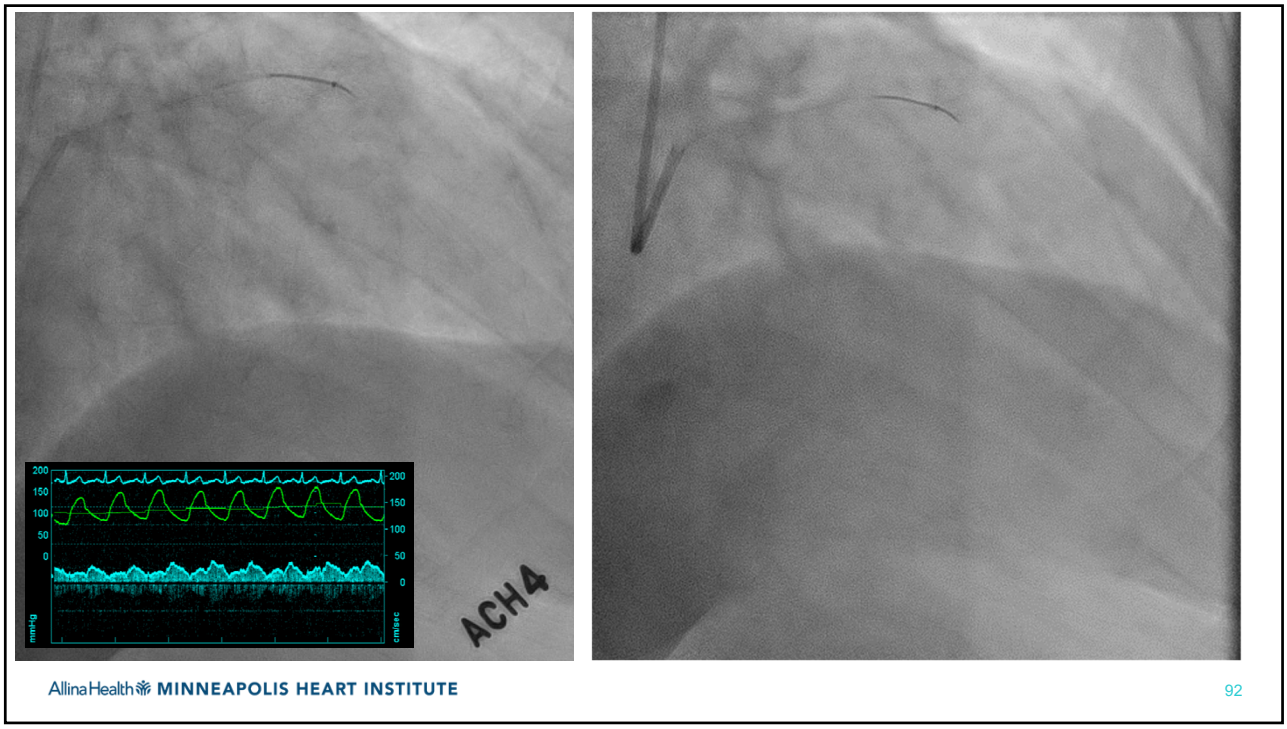
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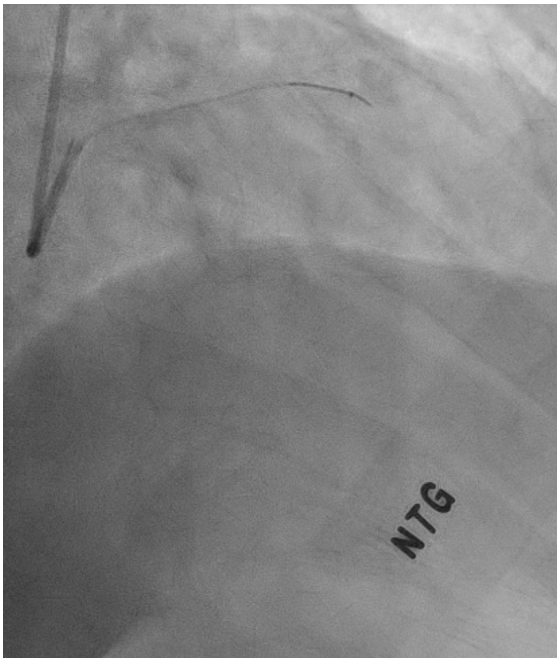

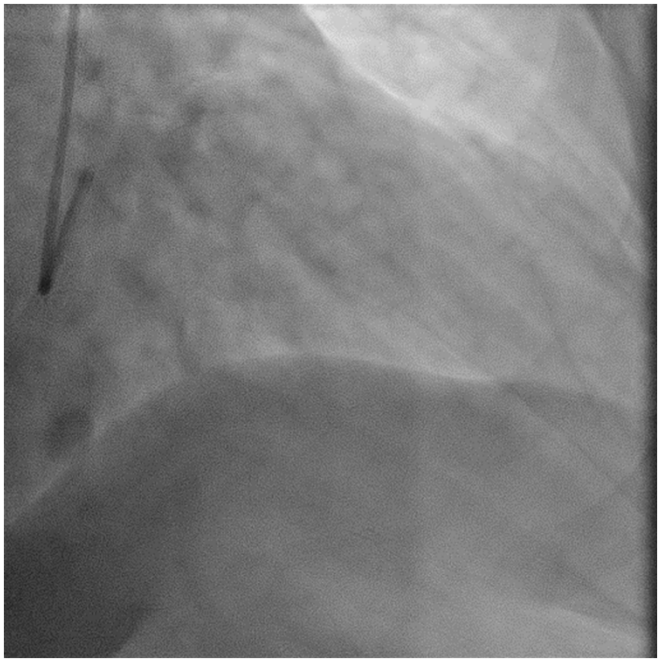

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Putting it all together

Symptoms	• Reproduction of index symptoms
ECG	• Ischemic ECG findings
CFR (Adenosine)	• Normal CFR: 2.5 Doppler, 2.0 TD
CBF response (ACH)	• Normal % delta CBF>50% (Doppler)
Microvasculature	• TD → IMR ; Doppler → HMR
Epicardial coronary vasomotion (ACH/ NTG)	• Normal >20% diameter (dilation)

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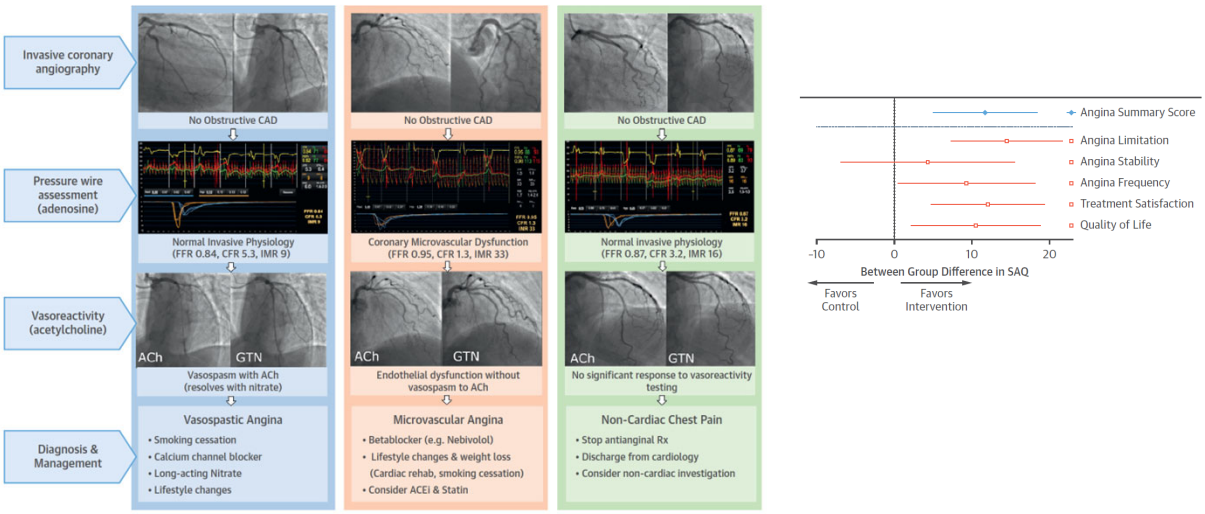
Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

The CorMicA Trial



Ford TJ et al. Stratified medical therapy using invasive coronary function testing in angina: The CorMicA trial. JACC 2018; 72: 2841-2855.

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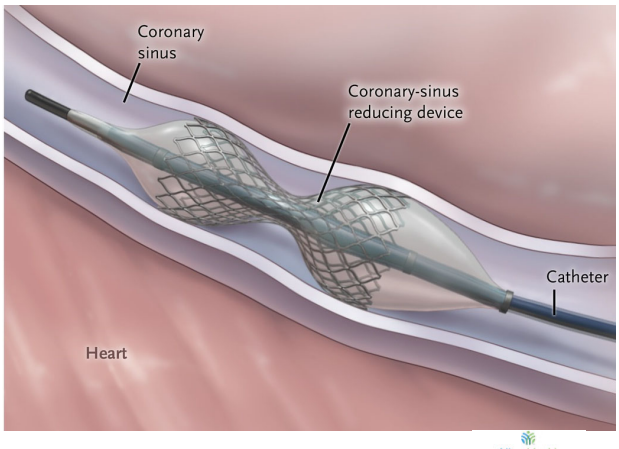
Save this study

COSIMA: COronary SInus Reducer for the Treatment of Refractory Microvascular Angina (COSIMA)



ClinicalTrials.gov Identifier: NCT04606459

Recruitment Status : Recruiting
First Posted : October 28, 2020
Last Update Posted : March 31, 2022

See Contacts and Locations

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Circulation Research

ORIGINAL RESEARCH

IMPROvE-CED Trial: Intracoronary Autologous CD34+ Cell Therapy for Treatment of Coronary Endothelial Dysfunction in Patients With Angina and Nonobstructive Coronary Arteries

Michel T. Corban, Takumi Toya, Diana Albers, Faten Sebaali, Bradley R. Lewis, John Bois, Rajiv Gulati, Abhiram Prasad, Patricia J.M. Best, Malcolm R. Bell, Charanjit S. Rihal, Megha Prasad, Ali Ahmad, Lilach O. Lerman, Mary L. Solseth, Jeffrey L. Winters, Allan B. Dietz, Amir Lerman

BACKGROUND: Coronary endothelial dysfunction (CED) causes angina/ischemia in patients with nonobstructive coronary artery disease (NOCAD). Patients with CED have decreased number and function of CD34+ cells involved in normal vascular repair with microcirculatory regenerative potential and paracrine anti-inflammatory effects. We evaluated safety and potential efficacy of intracoronary autologous CD34+ cell therapy for CED.

METHODS: Twenty NOCAD patients with invasively diagnosed CED and persistent angina despite maximally tolerated medical therapy underwent baseline exercise stress test, GCSF (granulocyte colony stimulating factor)-mediated CD34+ cell mobilization, leukapheresis, and selective 1×10^5 CD34+ cells/kg infusion into left anterior descending. Invasive CED evaluation and exercise stress test were repeated 6 months after cell infusion. Primary end points were safety and effect of intracoronary autologous CD34+ cell therapy on CED at 6 months of follow-up. Secondary end points were change in Canadian Cardiovascular Society angina class, as-needed sublingual nitroglycerin use/day, Seattle Angina Questionnaire scores, and exercise time at 6 months. Change in CED was compared with that of 51 historic control NOCAD patients treated with maximally tolerated medical therapy alone.

RESULTS: Mean age was 52±13 years; 75% were women. No death, myocardial infarction, or stroke occurred. Intracoronary CD34+ cell infusion improved microvascular CED (%acetylcholine-mediated coronary blood flow increased from 7.2 [−18.0 to 32.4] to 57.6 [16.3–98.3]%; P=0.014), decreased Canadian Cardiovascular Society angina class (3.7±0.5 to 1.7±0.9, Wilcoxon signed-rank test, P=0.00018), and sublingual nitroglycerin use/day (1 [0.4–3.5] to 0 [0–1], Wilcoxon signed-rank test, P=0.00047), and improved all Seattle Angina Questionnaire scores with no significant change in exercise time at 6 months of follow-up. Historic control patients had no significant change in CED.

CONCLUSIONS: A single intracoronary autologous CD34+ cell infusion was safe and may potentially be an effective disease-modifying therapy for microvascular CED in humans.

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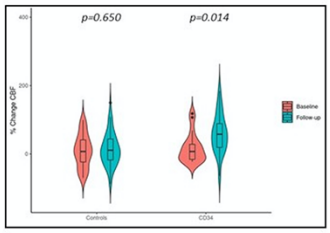
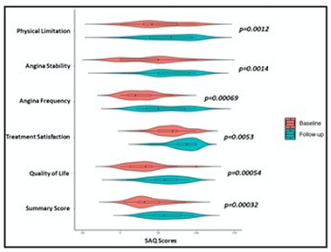
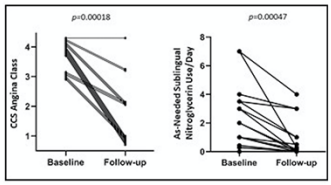
Improved microvascular endothelial function



Improved SAQ Angina and Quality of Life Scores



Improved CCS Angina Class and SL Nitro Use



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Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Autologous CD34+ Stem Cell Therapy Increases Coronary Flow Reserve and Reduces Angina in Patients With Coronary Microvascular Dysfunction

Timothy D. Henry, MD; C. Noel Bairey Merz, MD; Janet Wei, MD; Michel T. Corban, MD; Odayme Quesada, MD; Sandy Joung, MHDS; Christine L. Kotynski, BS; Jian Wang, ScM, MD; Michelle Lewis, BS; Ann M. Schumacher, RN, MSN, CCRA; Ronnda L. Bartel, PhD; Hiroshi Takagi, DVM; Vishal Shah, MS; Anna Lee, PhD; William K. Sietsema, PhD; Douglas W. Losordo, MD; Amir Lerman, MD

BACKGROUND: Coronary microvascular dysfunction results in angina and adverse outcomes in patients with evidence of ischemia and nonobstructive coronary artery disease; however, no specific therapy exists. CD34+ cell therapy increases microvasculature in preclinical models and improves symptoms, exercise tolerance, and mortality in refractory angina patients with obstructive coronary artery disease. The objective of this research was to evaluate the safety, tolerability, and efficacy of intracoronary CD34+ cell therapy in patients with coronary microvascular dysfunction.

METHODS: We conducted a 2-center, 20-participant trial of autologous CD34+ cell therapy (protocol CLBS16-P01; NCT03508609) in patients with ischemia and nonobstructive coronary artery disease with persistent angina and coronary flow reserve ≤2.5. Efficacy measures included coronary flow reserve, angina frequency, Canadian Cardiovascular Society angina class, Seattle Angina Questionnaire, SF-36, and modified Bruce exercise treadmill test obtained at baseline and 6 months after treatment. Autologous CD34+ cells (CLBS16) were mobilized by administration of granulocyte-colony stimulating factor 5μg/kg/day for 5 days and collected by leukapheresis. Participants received a single intracoronary left anterior descending infusion of isolated CD34+ cells in medium that enhances cell function.

RESULTS: Coronary flow reserve improved from 2.08±0.32 at baseline to 2.68±0.79 at 6 months after treatment (P<0.005). Angina frequency decreased (P<0.004), Canadian Cardiovascular Society class improved (P<0.001), and quality of life improved as assessed by the Seattle Angina Questionnaire (P≤0.03, all scales) and SF-36 (P≤0.04, all scales). There were no cell-related serious adverse events.

CONCLUSIONS: In this pilot clinical trial of microvascular angina, patients with ischemia and nonobstructive coronary artery disease receiving intracoronary infusion of CD34+ cell therapy had higher coronary flow reserve, less severe angina, and better quality of life at 6 months. The current study supports a potential therapeutic role for CD34+ cells in patients with microvascular angina.

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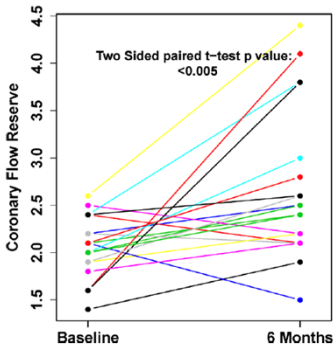

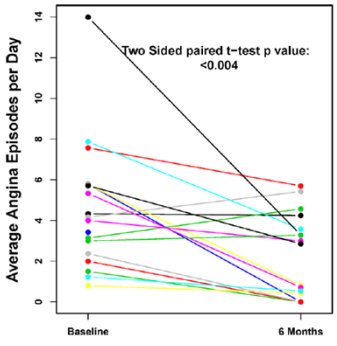

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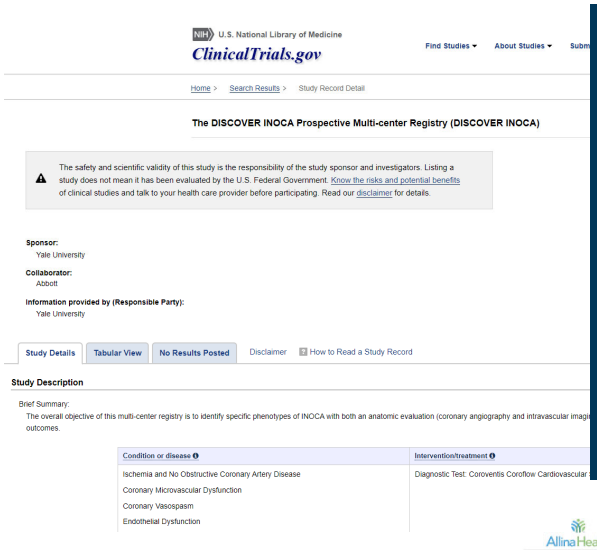
DISCOVER INOCA (NCT05288361): 500 participants over 2-years at 10 US sites



DISCOVER INOCA: adult patients >18 years of age with suspected ischemic heart disease referred to undergo clinically indicated invasive coronary angiography, with no obstructive CAD (angiographically normal, <50% CAD, or ≥50 but <70% with FFR≥0.81 or RFR≥0.90

Diagnostic assessment: coronary angiography, acetylcholine provocation, coronary physiology, intra-coronary imaging.

Patient reported outcomes: SAQ, EQ-5D-5L, PHQ-8, GAD-7

Study follow-up: 30-days, 6-months, 12-months, annually for 5-years.

Primary endpoint: major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction, hospitalization for cardiovascular causes, or coronary revascularization at a follow-up of 5-years.

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Take home points

- Microvascular disease is common and nomenclature is evolving with terms such as INOCA and MINOCA used to refer to patients with stable and unstable presentations.
- MVD represents a spectrum of those with epicardial coronary spasm to those with abnormal microcirculation without spasm.
- Non-invasive MBF can be assessed using PET or CMRI
- The gold-standard comprehensive approach remains invasive evaluation, which can be performed using either Doppler or Thermodilution with ACH spasm provocation.
- Randomized data emerging to support diagnosis and tailored therapies.

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