



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Hot Topic in Rheumatology: Cardio-Rheumatology

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Training	Institution
Medical school	SUNY Downstate Medical Center
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Role	Group
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	Biomedical Informatics (secondary)



Disclosures

- Merck, UCB, consultant

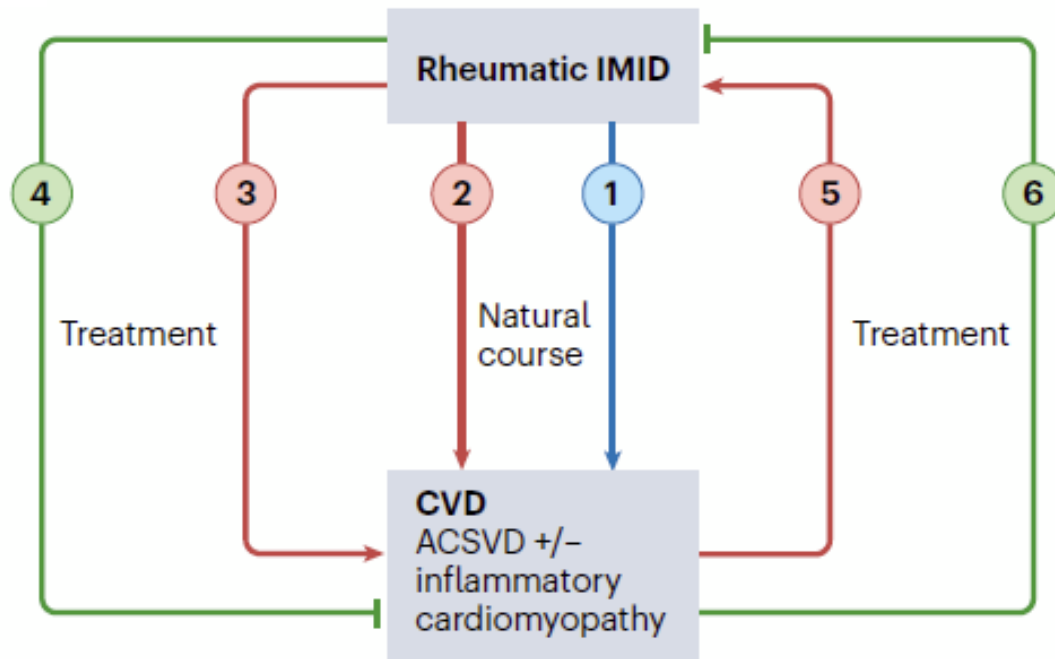


Objectives

- Recall relationship between rheumatic conditions and cardiovascular (CV) risk
- Discuss reasons why routine lipids may be suboptimal markers for CV risk in RA and other inflammatory conditions
- Describe how to consider rheumatic conditions as risk-enhancers for primary prevention



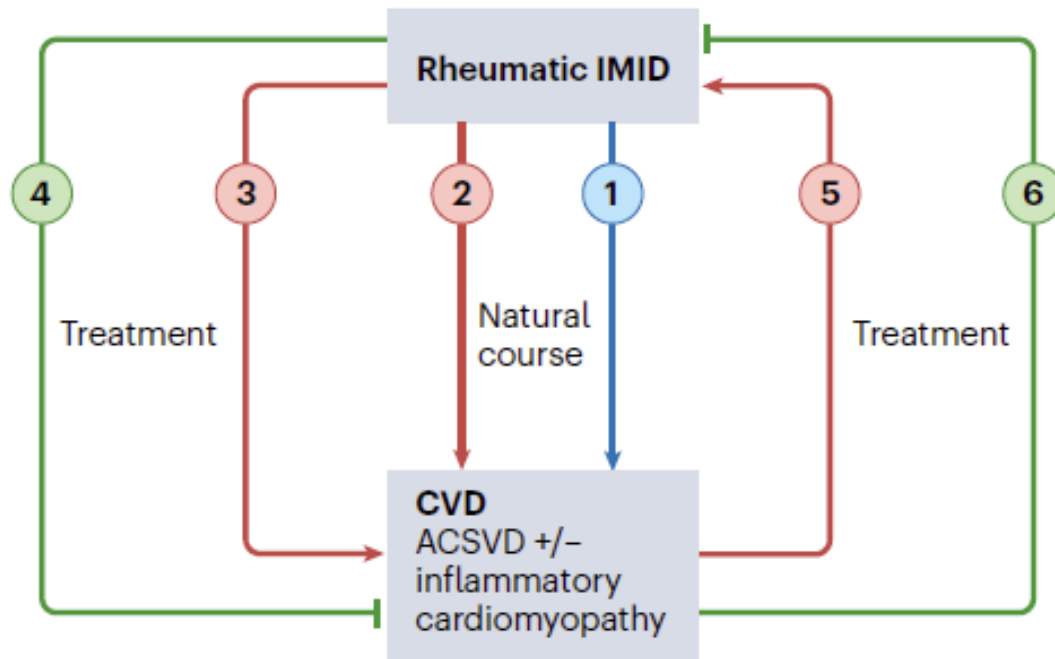
Complex relationships between immune-mediated conditions & cardiovascular disease



- 1 Risk of CVD unrelated to IMID and its course
- 2 IMID increases risk of developing CVD
- 3 Some treatments for IMID might increase CVD
- 4 The treatment of IMID might help to control CVD
- 5 The treatment of CVD might increase IMID
- 6 The treatment of CVD might support control of IMID



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Rheumatoid arthritis (RA)

- Most common autoimmune inflammatory joint disease
 - ~1% prevalence worldwide
- Symmetric small joint arthritis
- Autoantibody
 - Rheumatoid factor
 - Antibodies to cyclic citrullinated peptide (anti-CCP)
- Risk factors
 - Genetic: HLA-DRB1
 - Environmental: Smoking



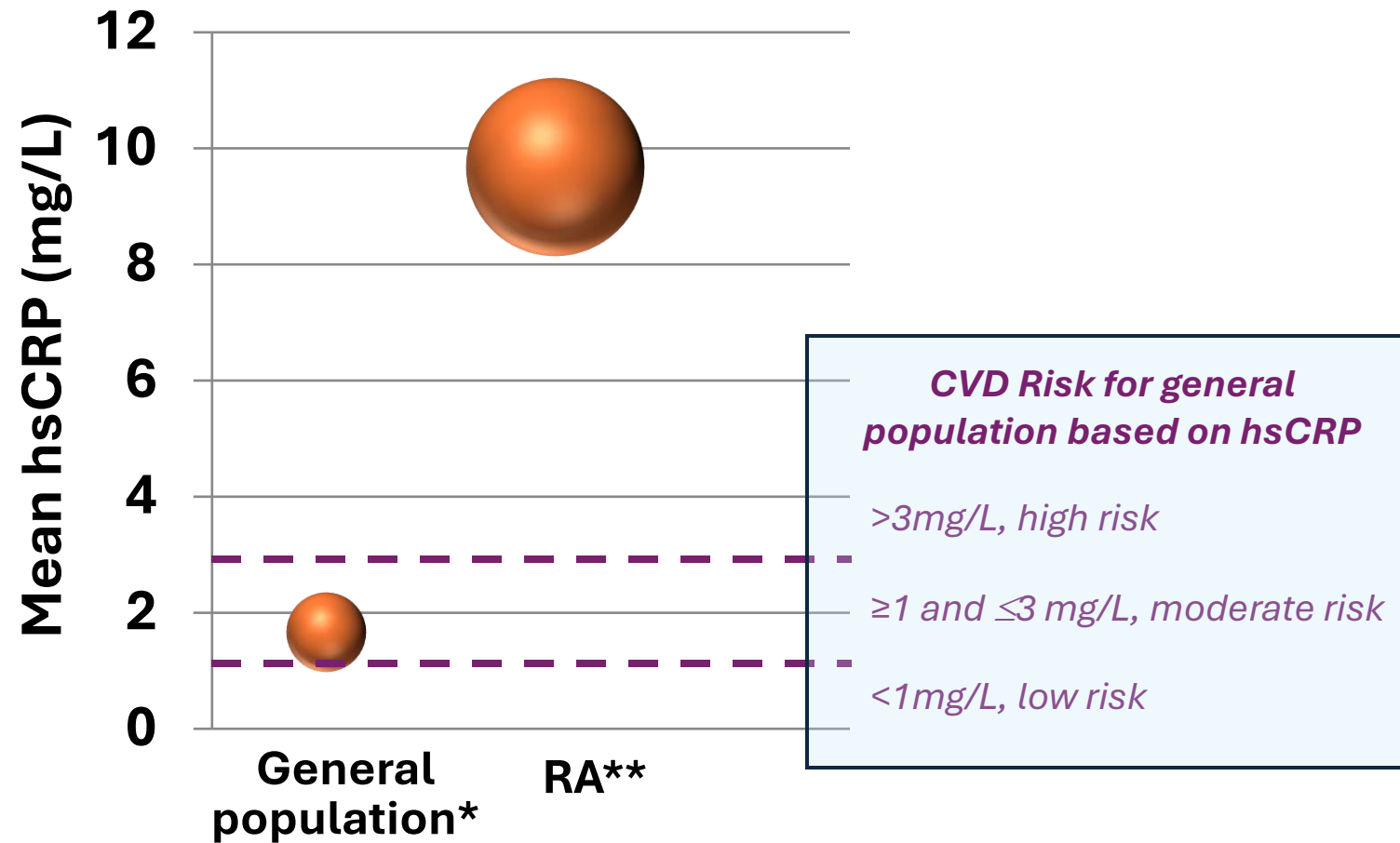
American College of Rheumatology image library

Management

- Early aggressive therapy
- Acute inflammation
 - Steroids, NSAIDs
- Disease modifying anti-rheumatic drugs (DMARDs)



RA a human model of inflammation

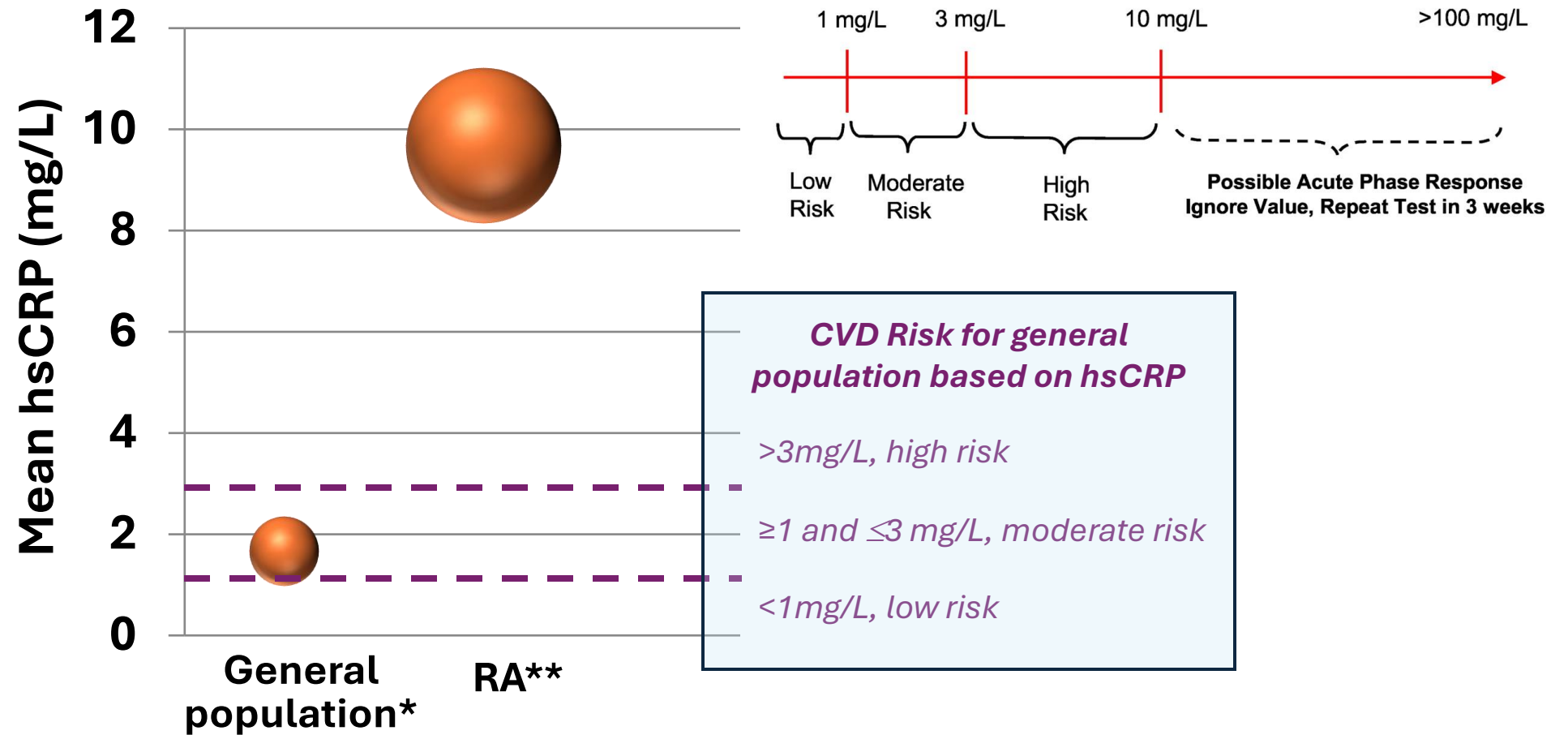


*National Health and Nutrition Examination Survey (NHANES),

**Brigham Rheumatoid Arthritis Sequential Study (BRASS)



RA a human model of inflammation



*National Health and Nutrition Examination Survey (NHANES),

**Brigham Rheumatoid Arthritis Sequential Study (BRASS)



Which of these RA pts has the highest CV risk?

1. TC, 72M
2. NM, 44F
3. GC, 52F

All have active synovitis, on methotrexate and TNFi being considered

None on statin therapy



CV focused summary	Pt 1, TC	Pt 2, NM	Pt 3, GC
Age	72	44	53
Sex	M	F	F
BP	156/67	126/63	105/74
RA duration, yrs	5	2	15
DM	No	No	No
Smoker	Past, quit 23+ yrs ago	Never	Never
CRP mg/L	7.5	4.9	4.2
BMI	32.8	35.8	33
FASTING LIPIDS			
Tchol, mg/dL	171	220	205
LDL, mg/dL	85	149	140
HDL, mg/dL	62	57	54
Tri, mg/dL	59	71	54



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ANSWER: 1



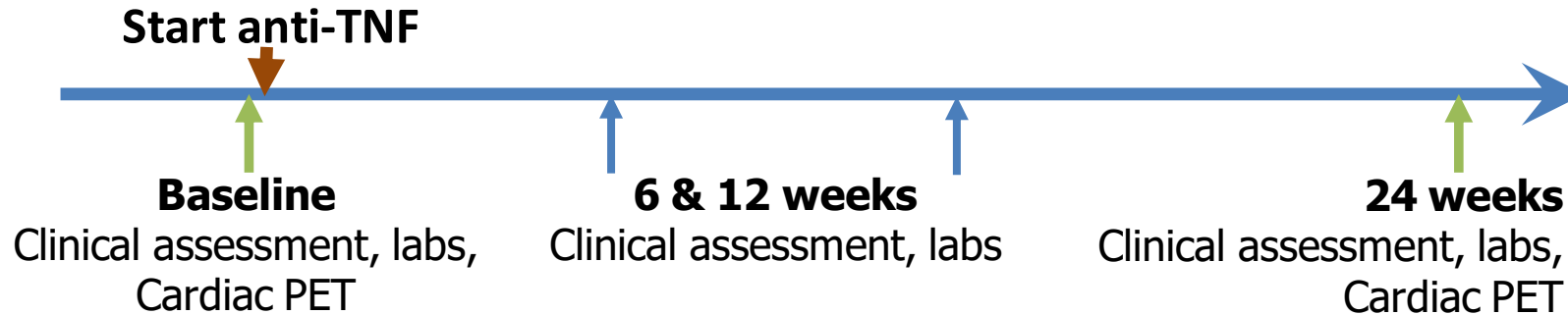
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10-yr ASCVD risk	24.2	0.8	1.2





Lipids, inflammation and CV Risk in RA

NIH R01HL127118



N=73 subjects

- Mean age 55 years, 82% female,
- RA disease duration, mean 7.4 years
- 71% seropositive
- 10-year estimated ASCVD risk median 2.5%

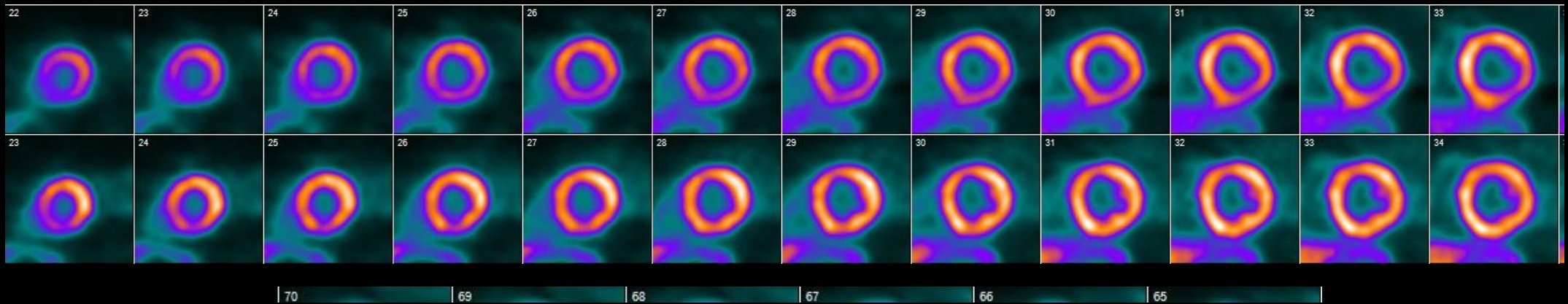


Stress myocardial perfusion results

Study results

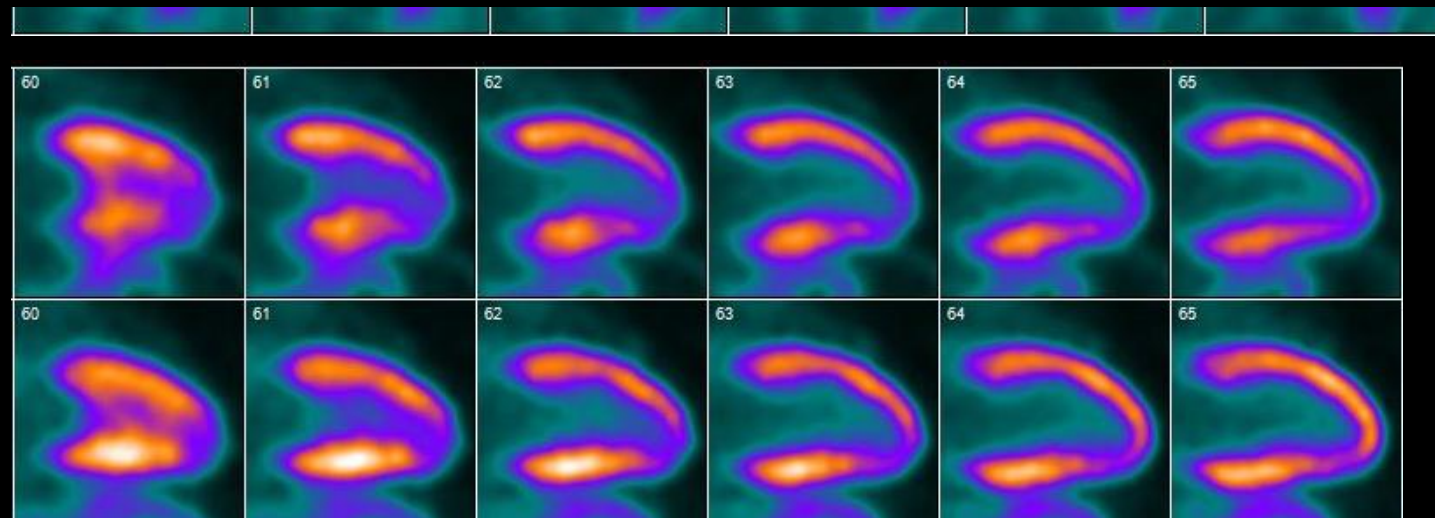
	TC, 72M	NM, 44F	GC, 53F
Follow-up	No evidence of flow limiting CAD Transient LV dilatation in the absence of regional perfusion effect most likely represents subendocardial ischemia from <i>microvascular disease</i>	Medium sized area of moderate stress ischemia in the mid LAD territory	No evidence of flow limiting CAD
10-yr ASCVD risk	24.2	0.8	1.2
Risk Category	High	Low	Low

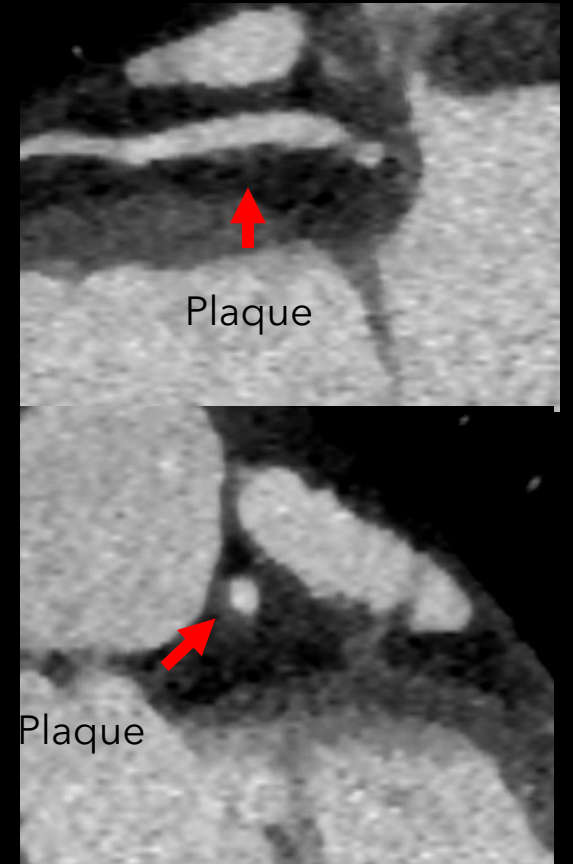
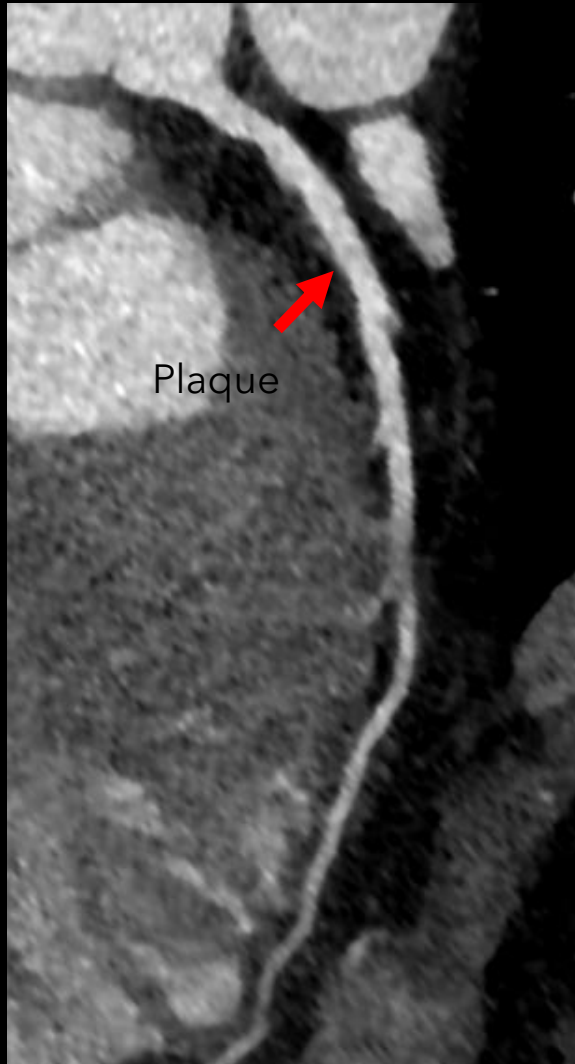




NM cardiac PET/stress test:

1. Medium sized area of moderate reversible ischemia in mid-LAD territory
2. Normal global LV systolic function





Medium amount of predominantly noncalcified coronary plaque in the coronary arteries, results in minimal stenosis of the left Main, proximal and mid LAD, proximal LCX, and RCA



Stress myocardial perfusion results

Study results

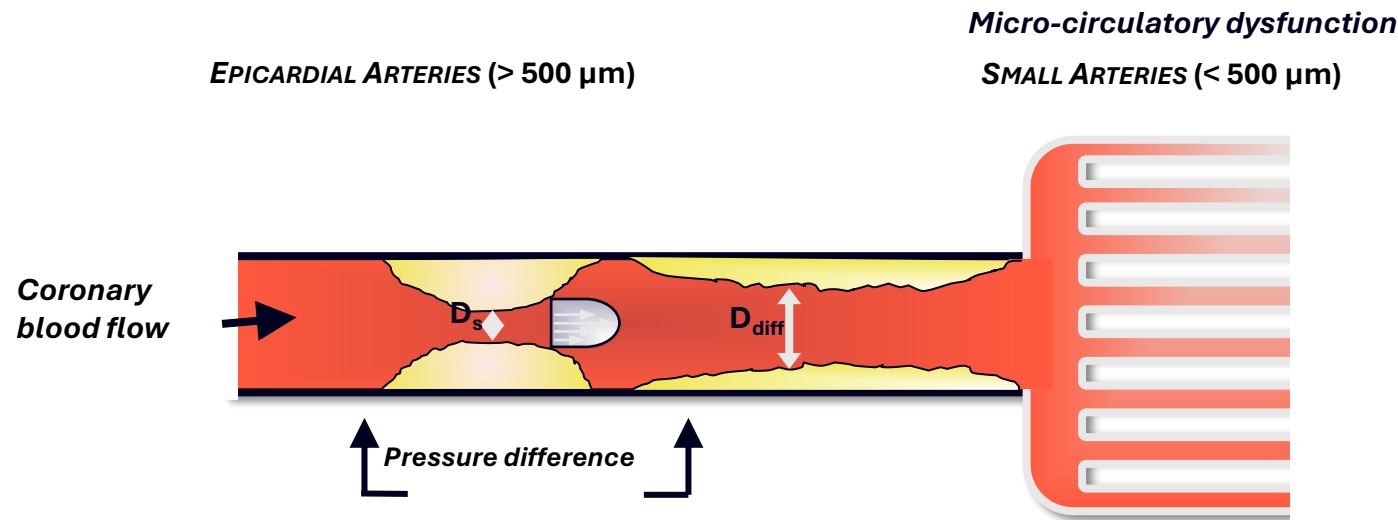
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10-yr ASCVD risk	24.2 High	0.8 Low	1.2 Low
CT angio	Severe lesion in L circumflex coronary artery; mild CAD in other coronary arteries	Medium amount of calcified/noncalcified plaque, min stenosis of other coronary arteries (1-24%)	N/A
Follow-up	Initiated on ASA, statin 1 year later, mild anginal sx s/p cath w/ DES to L main	Initiated on ASA, statin, beta blocker	N/A



Coronary flow reserve (CFR)

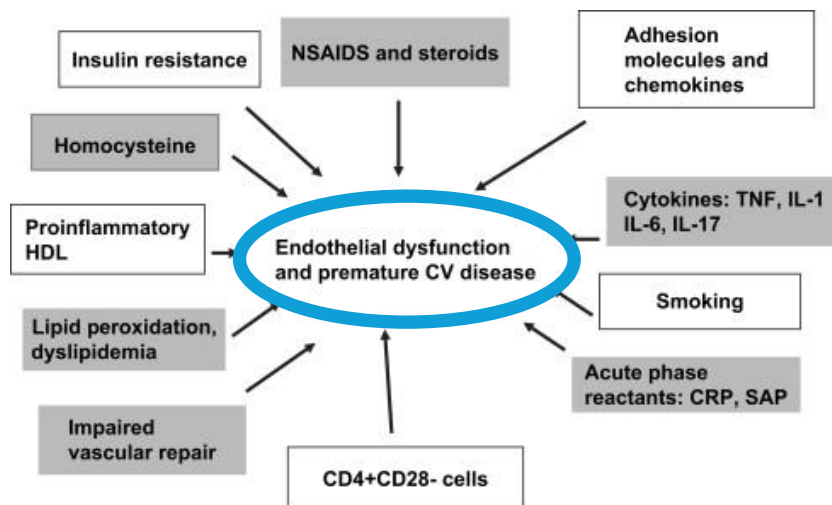
Myocardial flow reserve (MFR)

CFR measures ***integrated*** hemodynamic effects of **epicardial CAD**, **diffuse atherosclerosis**, **vessel remodeling**, and **microvascular dysfunction** on myocardial tissue perfusion

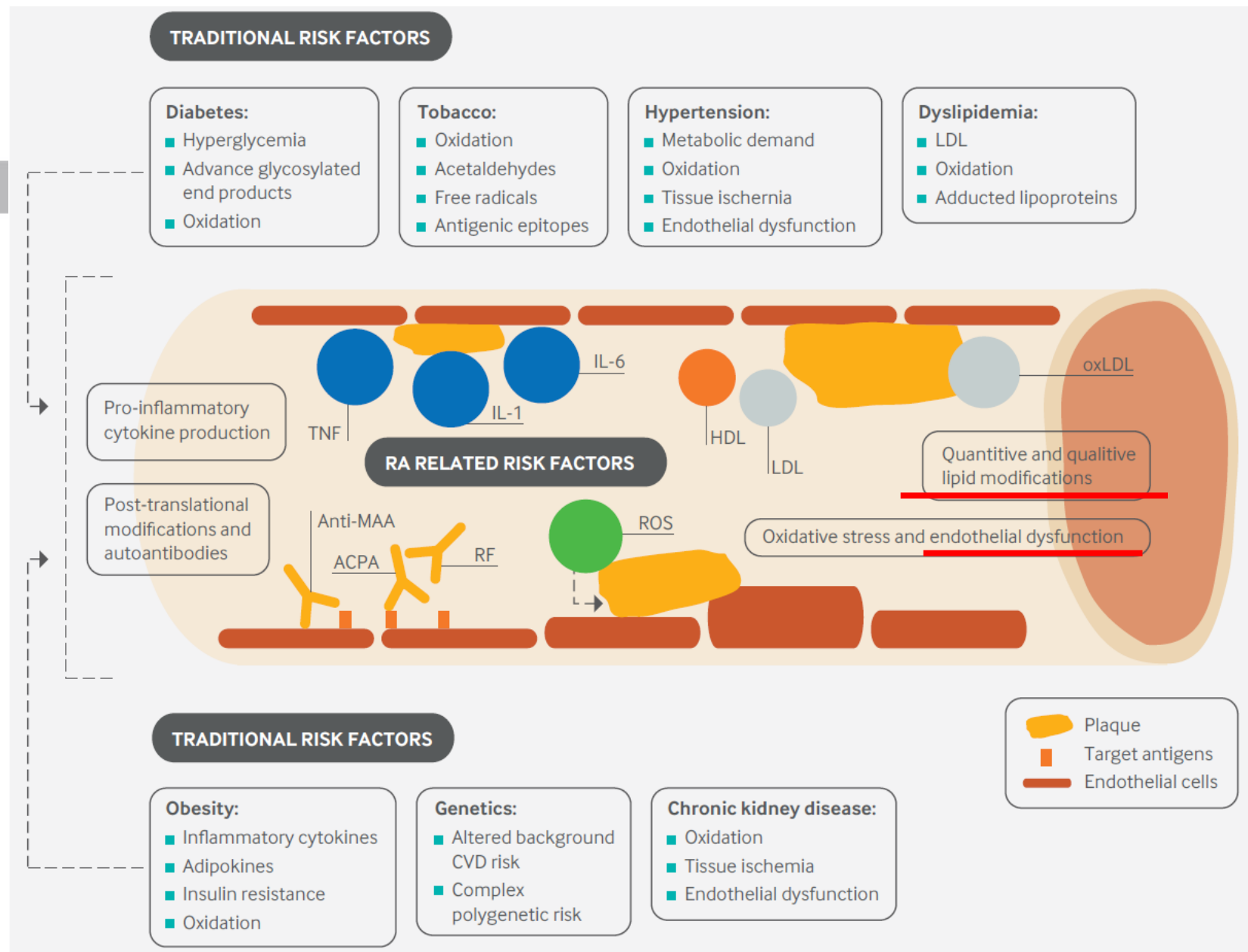


$$CFR = \frac{MBF_{\text{peak hyperemia}}}{MBF_{\text{rest}}}$$





CV risk in RA 1.5-2x higher than the general population



General population US CV risk calculators underestimate risk in rheumatic conditions

- 2013 ACC/AHA ASCVD Risk Estimator, aka pooled cohort equation (PCE)

<https://tools.acc.org/ascvd-risk-estimator-plus>

- Underestimate CV risk in RA by as much as 2x

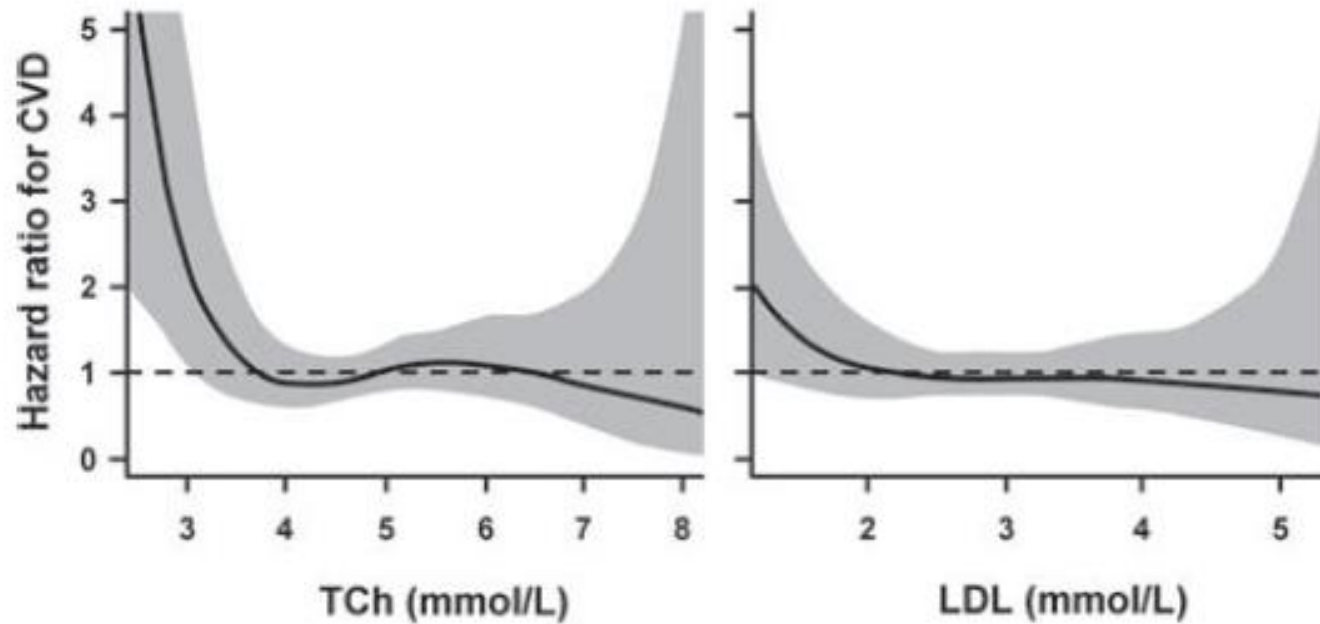
- Predicting Risk of CVD EVENTs (PREVENT) equations

<https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>

- Total CVD
- ASCVD
- Heart failure (HF)
- Early studies in rheumatic disease does not appear to perform better than PCE



The lipid paradox in RA



Mayo Clinic study
N=651 RA patients
Population based cohort



The lipid paradox in RA

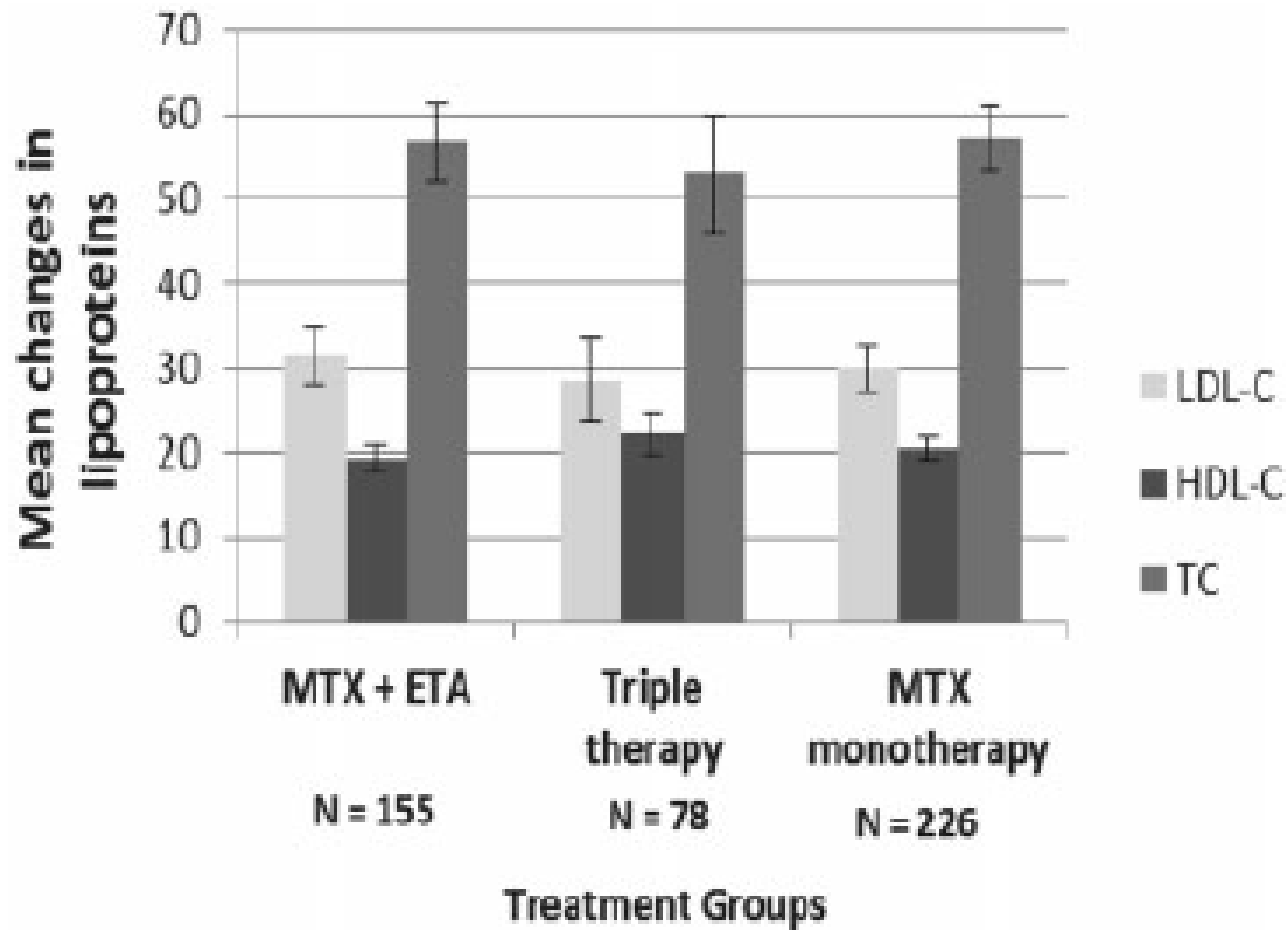
		RA cases		NHANES		
Lipid	Time period	N	Mean (SD), mg/dL	N	Mean (SD), mg/dL	P-value
Tchol	2007-2010	290	186 (20)	4486	200 (64)	0.0002
LDL	2007-2010	297	105 (18)	2027	118 (69)	0.001
HDL	2007-2010	295	58 (10)	4486	59 (30)	0.40

Data above for female only, age >20, not on statins

- RA patients appear to have a “better” lipid profile than controls
 - Lower Tchol and LDL; HDL was comparable



Lipids in the Treatment of Early RA (TEAR) trial



- 4 arm, placebo controlled
- N=755 early RA, DMARD naïve
 - MTX monotherapy w/ step up to:
 - Etanercept
 - Triple therapy
 - MTX + etanercept
 - Triple therapy (MTX, SSZ, HCQ)
- Lipids measured at 0 and 24 weeks
- Changes between baseline and 24 weeks sig in all 3 groups ($p < 0.0001$)



Inverse correlation between Δ inflammation and Δ in routine lipids in RA

N=196 RA
Brigham Rheumatoid
Arthritis Sequential
Study (BRASS)

Subjects with
 ≥ 10 mg/L increase or
decrease in hsCRP at
2 consecutive time
points

	Δ TC	Δ HDL-C	Δ LDL-C	Δ TG
Δ hsCRP	-0.26	0.01	-0.25	-0.18
Δ IL6	-0.21	-0.05	-0.24	-0.04

 Significant correlation



Summary: recommendations for lipids in RA

Relationship hypothesized to be similar for other rheumatic conditions

- Reduction in inflammation associated with ↑LDL-C
 - ↑LDL-C not necessarily a sign of ↑CV risk
- Assess lipids during remission or low disease activity
 - Alternative stable disease
 - At minimum screening frequency per general population guidelines
- General population CV risk calculators underestimate
 - Incorporate recommendations w/ risk enhancers



DMARDs with package insert info for lipids

Class	Generic	Trade	Dyslipid (%)	TC	LDL-C	HDL-C	Trig	Rec for lipid check
JAKi	Tofacitinib	Xeljanz	1-10	↑	↑	↑		4-8 weeks after initiation
	Baricitinib	Olumiant	NR	↑	↑	↑		12 weeks “
	Upadacitinib	Rinvoq	NR	↑	↑	↑		12 weeks “
IL6Ri	Tocilizumab	Actemra	>10	↑	↑	↑		4-8 weeks after initiation, then at ~24 week intervals
	Sarilumab	Kevzara	1-10		↑	↑	↑	“



TRACE RA

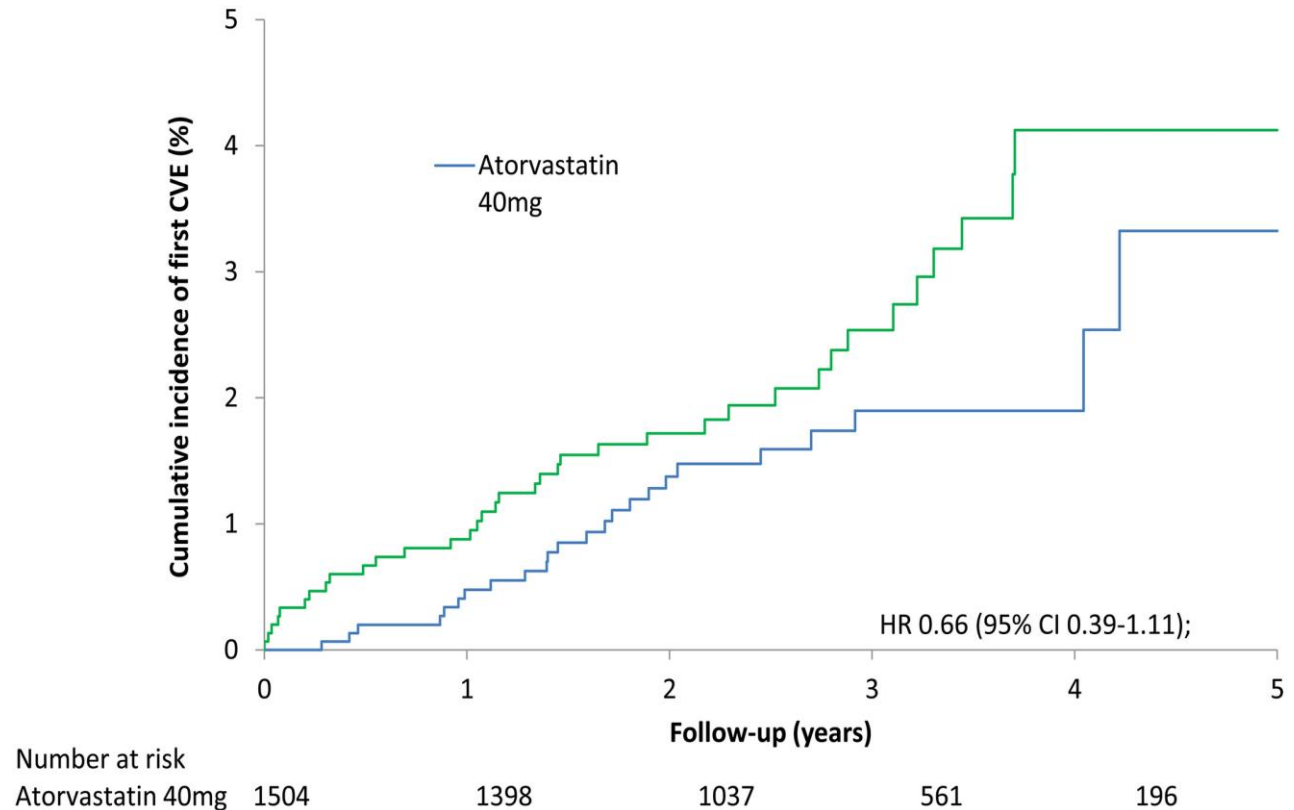
Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with RA (TRACE RA)

- Randomized multi-center double-blind placebo-controlled trial
- Inclusion: RA subjects age >50 or with disease duration >10 years
- Exclusion: on statin, known risk CVD where statins indicated, e.g. DM
- Hypothesis: atorvastatin 40mg daily superior to placebo for primary prevention of CVD events in RA
- Primary outcome: composite of CVD death, non-fatal MI, CVA (excluding haemorrhagic stroke), TIA, hospitalized angina, coronary and non-coronary revascularization

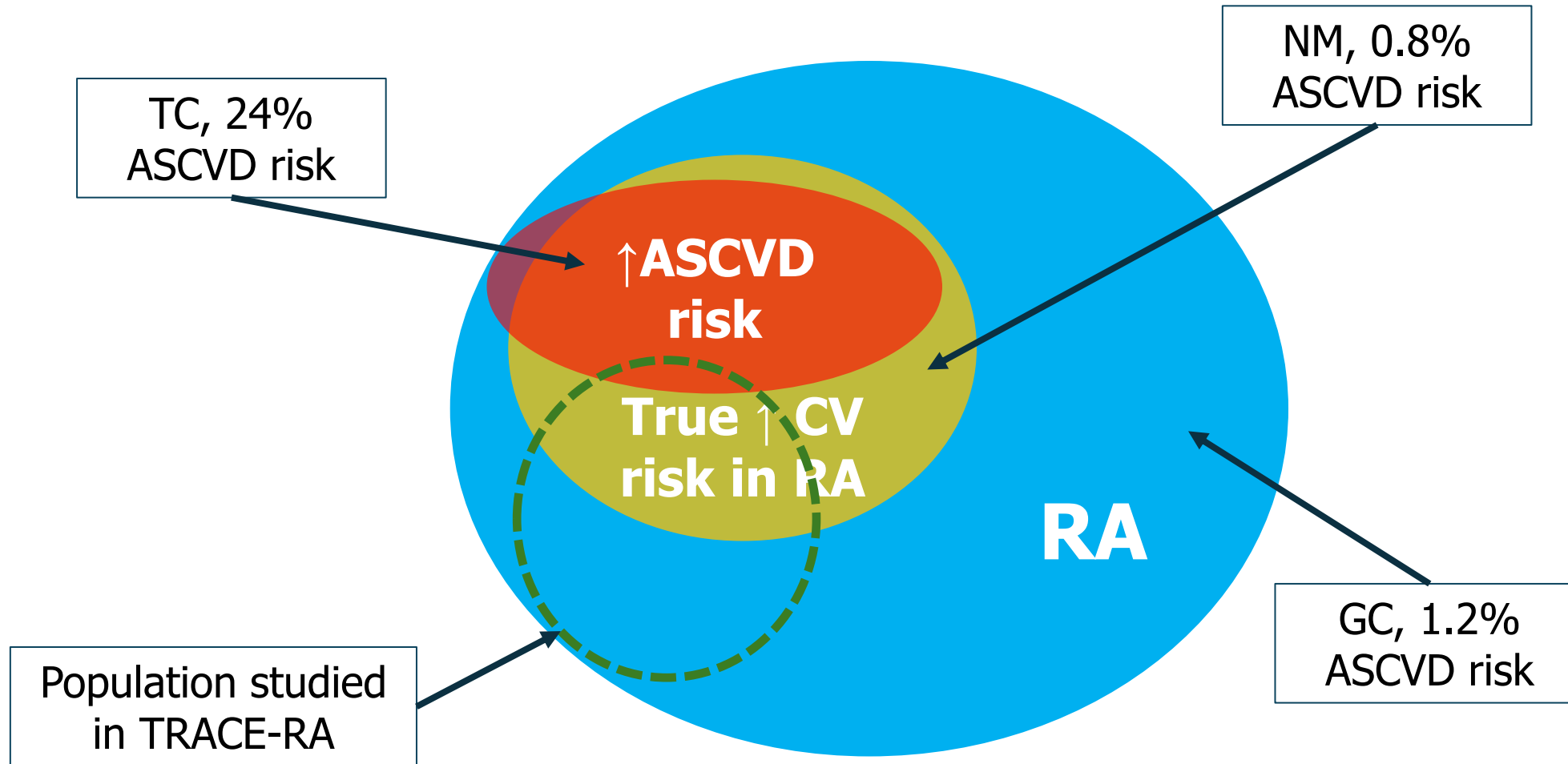


TRACE RA

- N=2,986 subjects randomized
- Trial terminated early
 - Low event rate 0.76%
- Superiority not observed
 - Median f/u 2.5 years
- LDL-C
 - atorvastatin group, ↓41.4 mg/dL
 - placebo ↓ 5.4 mg/dL
- Atorvastatin well-tolerated
 - Adverse events similar between 2 groups (p=0.927)



Summary: CV risk in RA



Operationalizing the 2026 Dyslipidemia Guidelines in rheumatic disease

Practical considerations



CPR Framework for Risk Evaluation

LEGEND

- COR 1
- COR 2a
- COR 2b
- COR 3-No Benefit
- COR 3-Harm
- (Class of Recommendation)

Calculate and Classify

Estimate 10-y risk with
PREVENT-ASCVD

1

Low risk
0%–<3%

Borderline risk
3%–<5%

Intermediate risk
5%–<10%

High risk
≥10%

Personalize

Discuss risk estimate
and therapy options
with patient

1

Discuss risk estimate
and therapy options
with patient

1

AND

Evaluate risk enhancers

2a

Discuss risk estimate
and therapy options
with patient

1

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1

Reclassify and Reassess

If clinical or patient
uncertainty, consider
CAC score and revise
results

1

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1

Decide and Treat

Lifestyle modification

1

Treat with lifestyle
modification and
potential lipid-lowering
therapy

2a

Lifestyle modification
and lipid-lowering
therapy

1



2026 Dyslipidemia

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CPR=calculate-
personalize-
reclassify



Updated ASCVD risk categories

- 10-year ASCVD risk estimate categories
 - low-risk (<3%)
 - borderline-risk (3% to <5%)
 - intermediate-risk (5% to <10%)
 - high-risk ($\geq$ 10%)
- Prior thresholds: <5 (low), $\geq$ 5 to <7.5 (borderline), $\geq$ 7.5 to <20 (intermediate), $\geq$ 20% (high)



CPR Framework for Risk Evaluation

LEGEND

- COR 1
 - COR 2a
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 - COR 3-No Benefit
 - COR 3-Harm
- (Class of Recommendation)

Calculate and Classify

<5% considered low risk
before new guidelines!

Estimate 10-y risk with
PREVENT-ASCVD

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3%–<5%

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2026 Dyslipidemia

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Blumenthal et al., Circ 2026

Risk enhancers

Risk Enhancers
History of premature ASCVD in a parent or sibling (onset age <55 y for men, <65 y for women)
Higher risk ancestry (eg, South Asian, Filipino)
High polygenic risk (if measured) (Section 4.2.3.5, "Polygenic Risk Scores")
Chronic inflammatory diseases (eg, systemic lupus, rheumatoid arthritis, advanced psoriasis, inflammatory arthritis)
Lp(a) ≥ 125 nmol/L or ≥ 50 mg/dL
hsCRP ≥ 2 mg/L on >1 occasion (if measured)
TG persistently ≥ 175 mg/dL (2 mmol/L) (if nonfasting) and ≥ 150 mg/dL (1.7 mmol/L) (if fasting)
CKM syndrome
LDL-C persistently ≥ 160 – 189 mg/dL (4.1–4.9 mmol/L), non-HDL-C ≥ 190 – 219 mg/dL or apoB ≥ 120 mg/dL*
Reproductive risk markers (premature menopause, preeclampsia, gestational diabetes, gestational hypertension, preterm delivery; Section 4.2.3.4, "Reproductive Risk Marker")



ASCVD risk enhancers

Threshold for lipid lowering therapy (LLT) at borderline risk

2018

- In patients at borderline risk...the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy

2026

- In adults without ASCVD with a borderline...risk estimate (3% to <5%) by the PREVENT-ASCVD equations consideration of risk enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk



CPR Framework for Risk Evaluation

Same category to discuss statin in risk enhancer but at a lower 10-year estimated risk

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Estimate 10-y risk with
PREVENT-ASCVD

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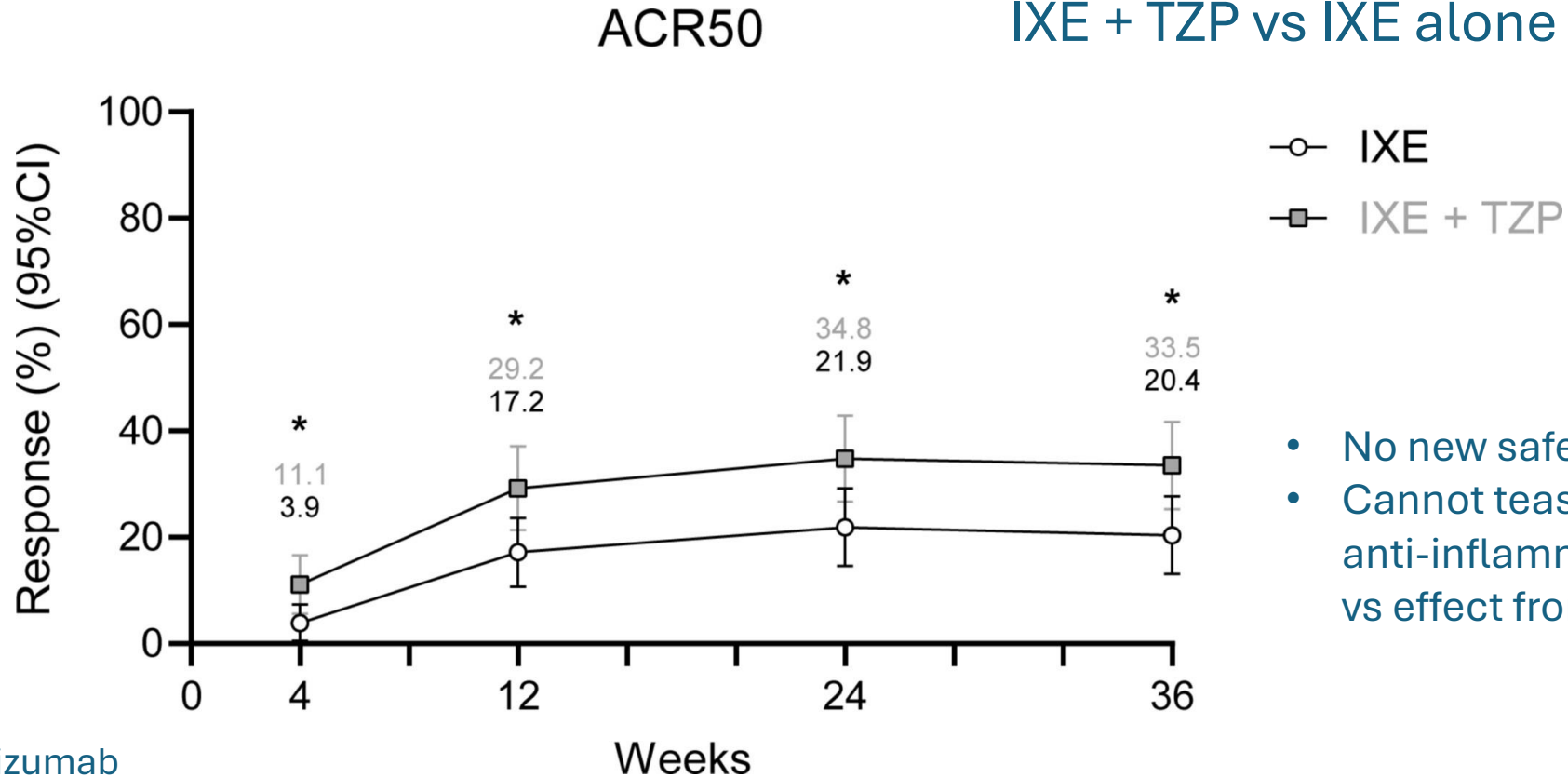
Glucagon-like peptide 1 (GLP1) receptor agonist

- Tested in psoriasis and psoriatic arthritis (PsA)
 - Higher prevalence of metabolic syndrome and obesity vs other rheumatic conditions, e.g., RA, systemic lupus erythematosus
- TOGETHER-PsA: Randomized open-label safety and efficacy trial
Inclusion: active PsA and BMI ≥ 27 or < 30
 - Hypothesis: Ixekizumab (IXE) vs IXE+tirzepitide (TZP)
 - Ixekizumab is a biologic that inhibits IL17A
 - Co-primary endpoint, 36 weeks
 - 50% improvement in the American College of Rheumatology response criteria (ACR50)
 - $\geq 10\%$ weight reduction



TOGETHER-PsA

Greater improvement in ACR50 in
IXE + TZP vs IXE alone



- No new safety concerns
- Cannot tease out direct anti-inflammatory effects vs effect from weight loss

IXE=ixekizumab
TZP=tirzepatide



MOC Take Home Summary

- Inflammation contributes to excess CV risk in patients with rheumatic conditions
- TChol and LDL-C may be lower than “baseline” with active inflammation
- Chronic inflammatory conditions are risk enhancers for ASCVD
 - Lower bar to either initiate or discuss statins
- Statins well tolerated
 - Adverse events in well-treated RA population similar in statin vs placebo
- Future work needed to better identify rheumatic disease population at true elevated risk
 - CV imaging, e.g., CAC to improve risk stratification



Question 1

A 58-year-old woman with seropositive rheumatoid arthritis (RA) is being evaluated for cardiovascular risk. Her LDL-C is 133 mg/dL and her hsCRP is 4.5 mg/L. She has hypertension and is on anti-hypertensive therapy with a blood pressure of 140/86. Her 10-year ASCVD risk 4.3%. Which of the following best reflects the current ACC/AHA guidelines for primary prevention of ASCVD for this patient?

- A. No statin therapy is needed because her 10-year ASCVD risk is borderline (≥ 3 and $< 5\%$ 10-year risk)
- B. Statin therapy is indicated because she meets the definition of metabolic syndrome
- C. Statin therapy should be discussed because she has an ASCVD risk-enhancers
- D. Statin therapy should be avoided due to the potential side effects when used in combination with RA treatments



Question 1

A 58-year-old woman with seropositive rheumatoid arthritis (RA) is being evaluated for cardiovascular risk. Her LDL-C is 133 mg/dL, and her hsCRP is 4.5 mg/L. She has hypertension and is on treatment with a blood pressure of 140/86. Her 10-year ASCVD risk by Pooled Cohort Equations is 5.3%. Which of the following best reflects the current ACC/AHA guidelines for primary prevention of ASCVD for this patient?

- A. No statin therapy is needed because her 10-year ASCVD risk is borderline (≥ 5 and $< 7.5\%$ 10-year risk)
- B. Statin therapy is indicated because she meets the definition of metabolic syndrome
- C. Statin therapy should be discussed because she has ASCVD risk-enhancers**
- D. Statin therapy should be avoided due to the potential side effects when used in combination with RA treatments

Correct Answer: C. The patient has RA as a risk enhancer per the 2026 Dyslipidemia guidelines. With a risk enhancer discussion regarding the potential benefit of statin is recommended of individuals with a 10-year estimated ASCVD risk of 3% or greater. A large randomized clinical trial of statins in RA demonstrated safety with a similar percentage of adverse events among individuals randomized to the statin and placebo arms.



Question 2

A 62-year-old man with RA on methotrexate has a baseline hsCRP of 10.2 mg/L and LDL-C of 90 mg/dL. Six months later, after initiating anti-TNF therapy, his hsCRP has decreased to 2.1 mg/L, and his LDL-C has increased to 117 mg/dL. What is the most likely explanation for the rise in LDL-C?

- A. Hepatotoxicity due to methotrexate use
- B. Medication non-adherence
- C. Improved inflammatory control with the initiation of anti-TNF
- D. His cardiovascular risk increased after initiation of anti-TNF



Question 2

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- B. Medication non-adherence
- C. Improved inflammatory control with the initiation of anti-TNF**
- D. His cardiovascular risk increased after initiation of anti-TNF

Correct Answer: C. In RA, inflammation is associated with lower LDL-C levels, and reducing inflammation can paradoxically raise LDL-C. Some RA therapies are also associated with increased lipid levels. This increase is not necessarily a sign of increased cardiovascular risk.



Question 3

A 67-year-old woman with longstanding RA with no history of cardiovascular disease presents with recurrent atypical chest pain. A stress echo performed 5 years ago was unremarkable. Her 10-year estimated ASCVD risk is 7.5%. She does not want to add another medication to her already complex RA regimen of methotrexate, folic acid, and an anti-TNF. Which imaging studies might be considered for further CV risk stratification?

- A. Repeat stress echo
- B. Coronary artery calcium (CAC) scan
- C. CT angiogram
- D. Cardiac MRI



Question 3

A 67-year-old woman with longstanding RA with no history of cardiovascular disease presents with recurrent atypical chest pain. A stress echo performed 5 years ago was unremarkable. Her 10-year estimated ASCVD risk is 7.5%. She is not interested in adding a statin due to already needing to take methotrexate, folic acid, and an anti-TNF. Which imaging studies might be considered for further CV risk stratification?

- A. Repeat stress echo
- B. Coronary artery calcium (CAC) scan**
- C. CT angiogram
- D. Stress myocardial perfusion PET

Correct Answer: B. She is considered intermediate risk for ASCVD and statins would be favored per the 2026 Dyslipidemia Management Guidelines for primary prevention since RA is a risk-enhancer. In cases where the risk decision is uncertain, a CAC scan is recommended. Evidence of CAC provides evidence of existing plaque and can assist discussions for statin initiation. While not part of the guidelines, stress myocardial perfusion PET (cardiac PET) can be considered to assess for both flow limiting abnormalities and microvascular disease which can cause atypical chest pain.



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Thank you

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