Brigham and Women's Hospital
Founding Member, Mass General Brigham

Hot Topic in Rheumatology: Cardio-Rheumatology

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

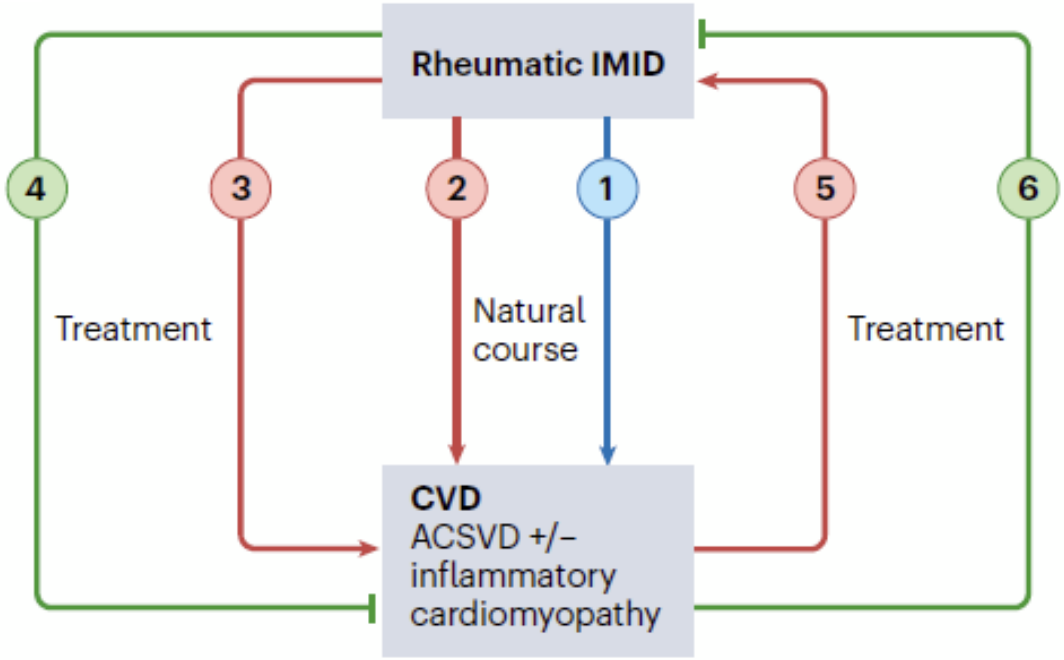
Disclosures

- 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

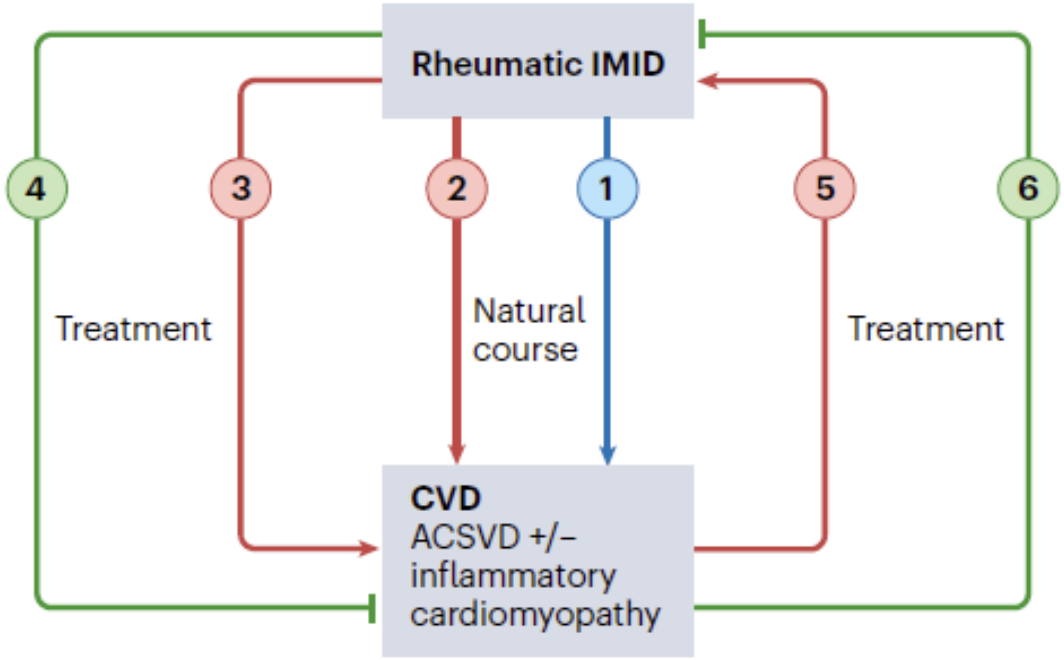
Complex relationships between immune-mediated conditions & cardiovascular disease



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

Buch et al, Nat Rev Rheumatol 2024

Complex relationships between immune-mediated conditions & cardiovascular disease



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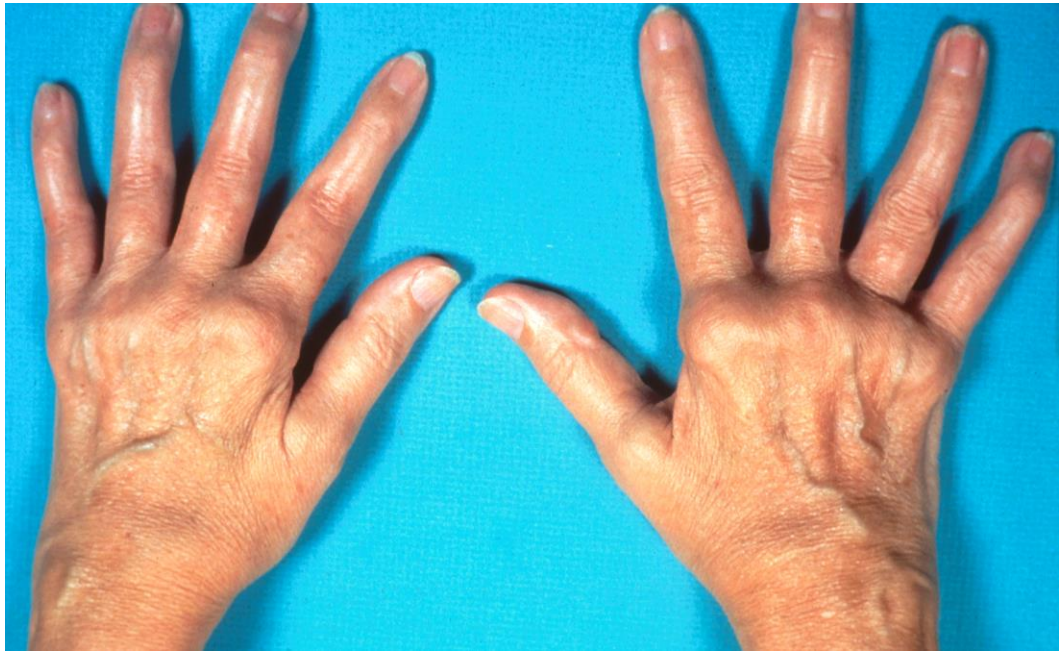
Rheumatoid arthritis (RA)

- 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

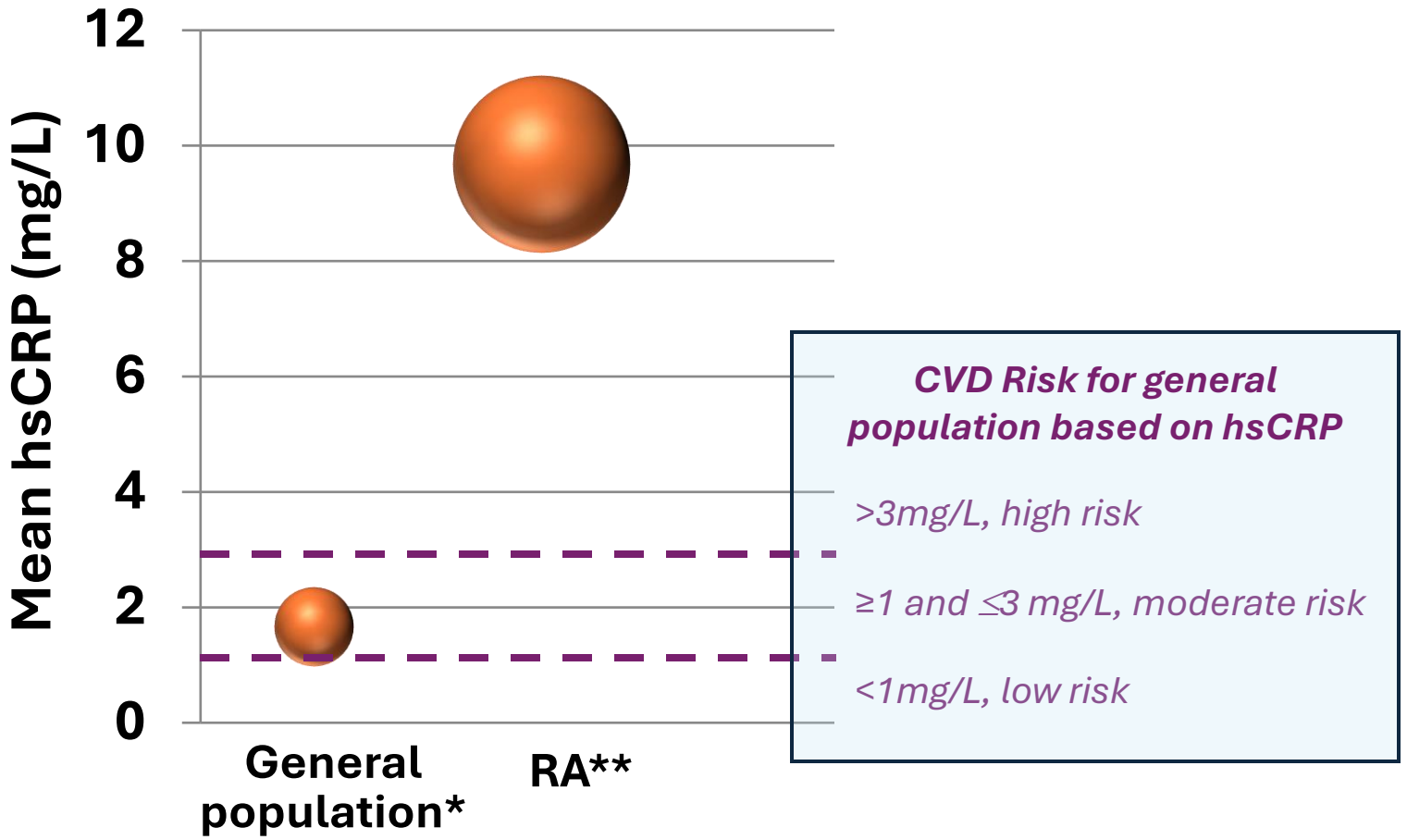


American College of Rheumatology image library

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),
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Liao, Trends Cardiovasc Med 2017; Ridker Circ 2003

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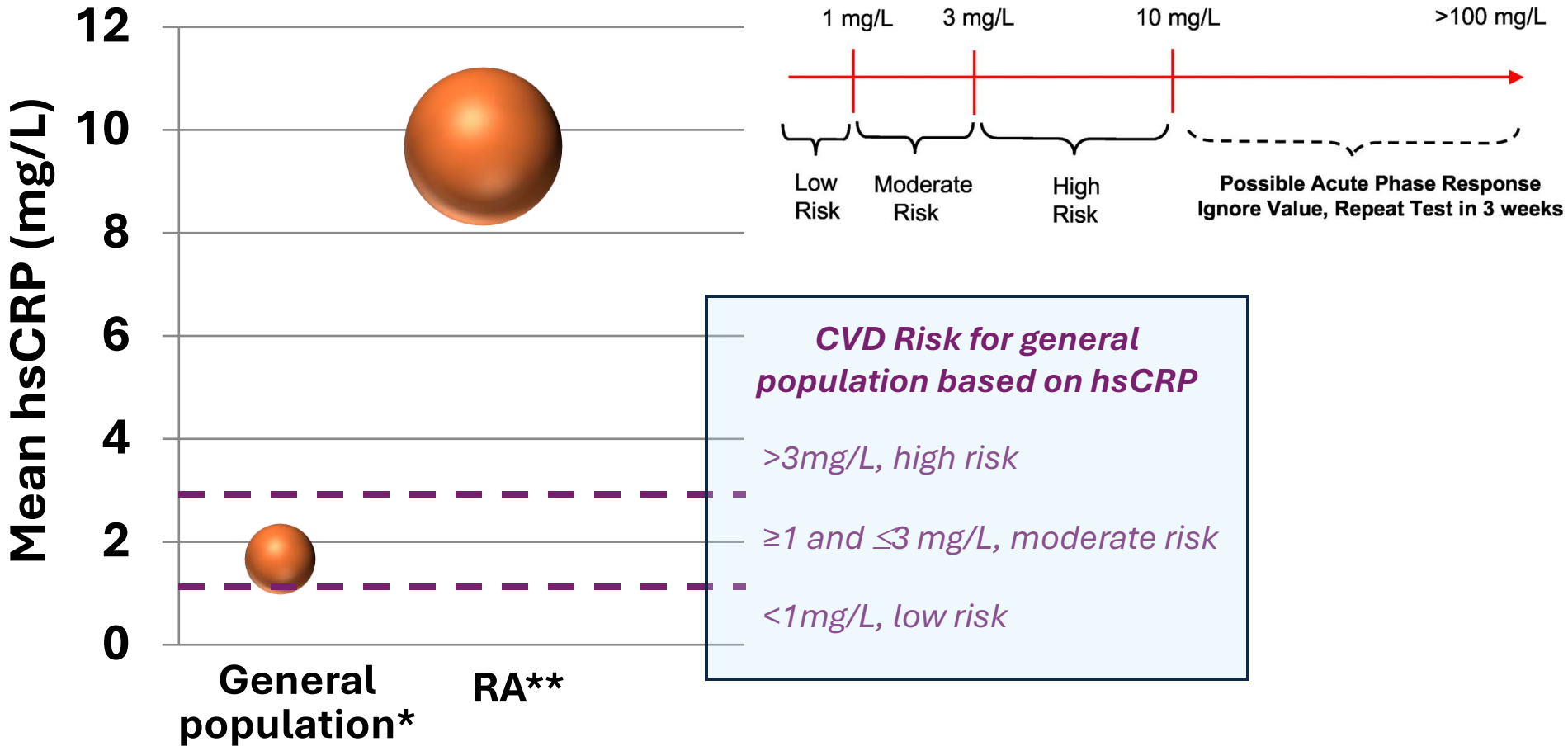

*National Health and Nutrition Examination Survey (NHANES),
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Liao, Trends Cardiovasc Med 2017; Ridker Circ 2003

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

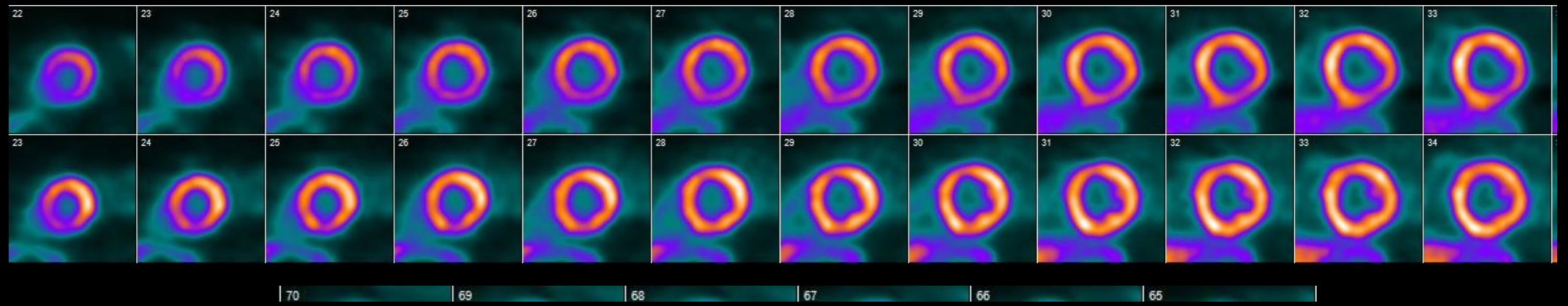
N=73 subjects

- 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

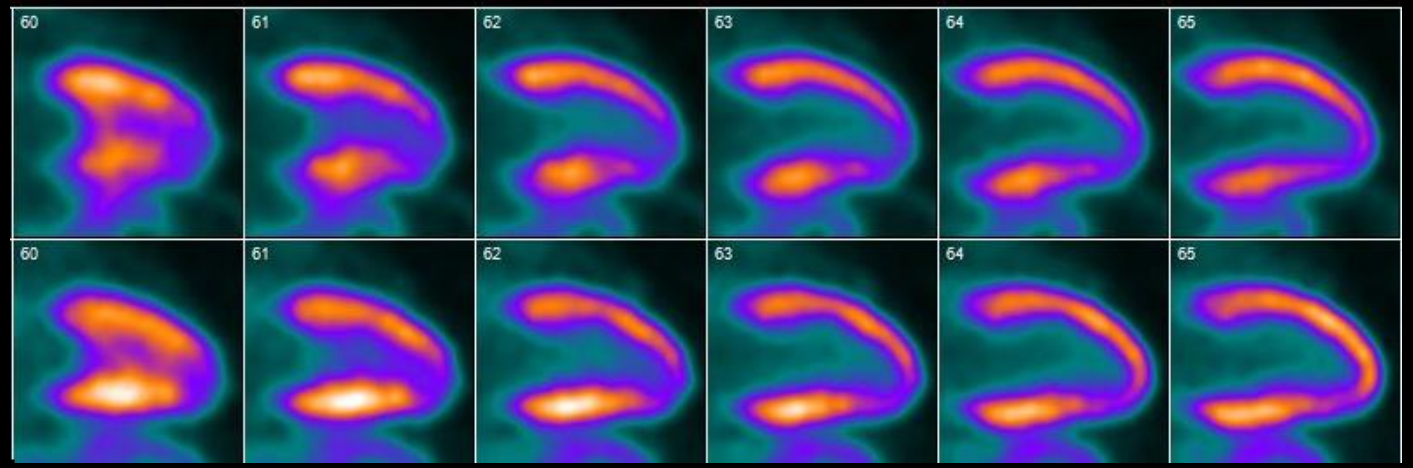
Study results

	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 *microvascular disease*	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

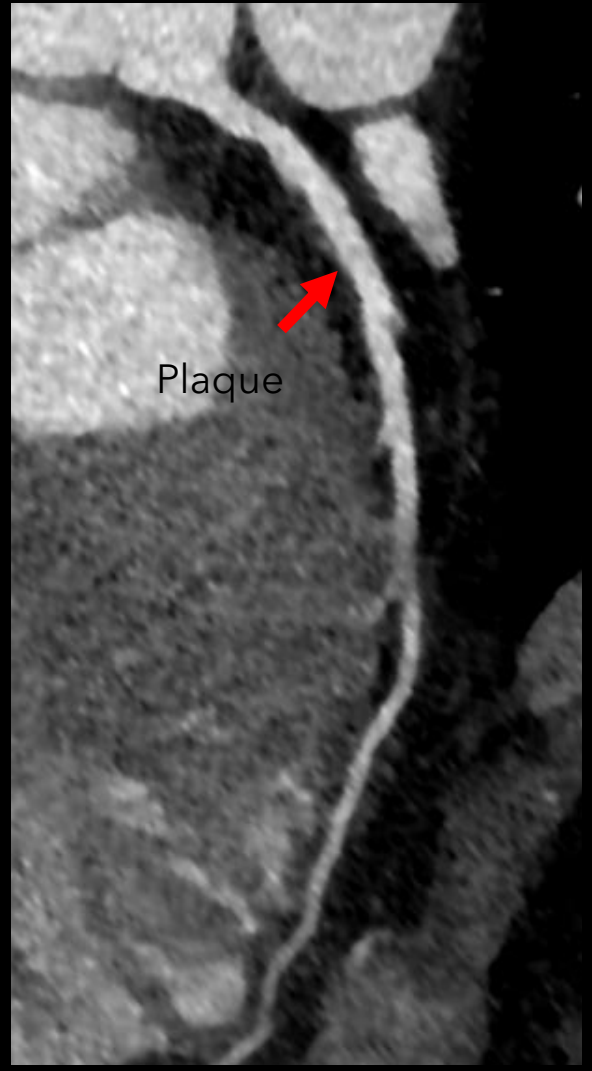


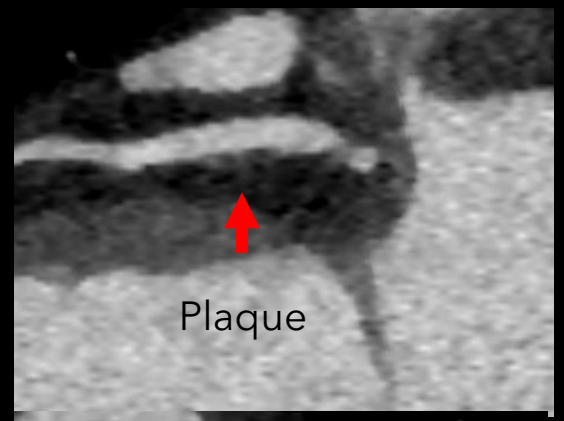
NM cardiac PET/stress test:

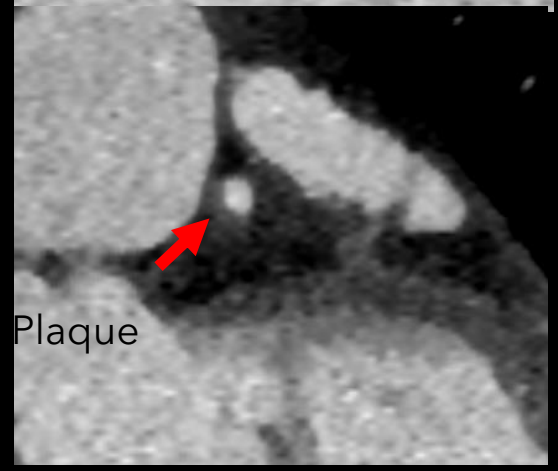
1. Medium sized area of moderate reversible ischemia in mid-LAD territory
2. Normal global LV systolic function



Slide courtesy of Dr. Brittany Weber







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

Slide courtesy of Dr. Brittany Weber via images courtesy from Dr. Emilio Fentanes

Stress myocardial perfusion results

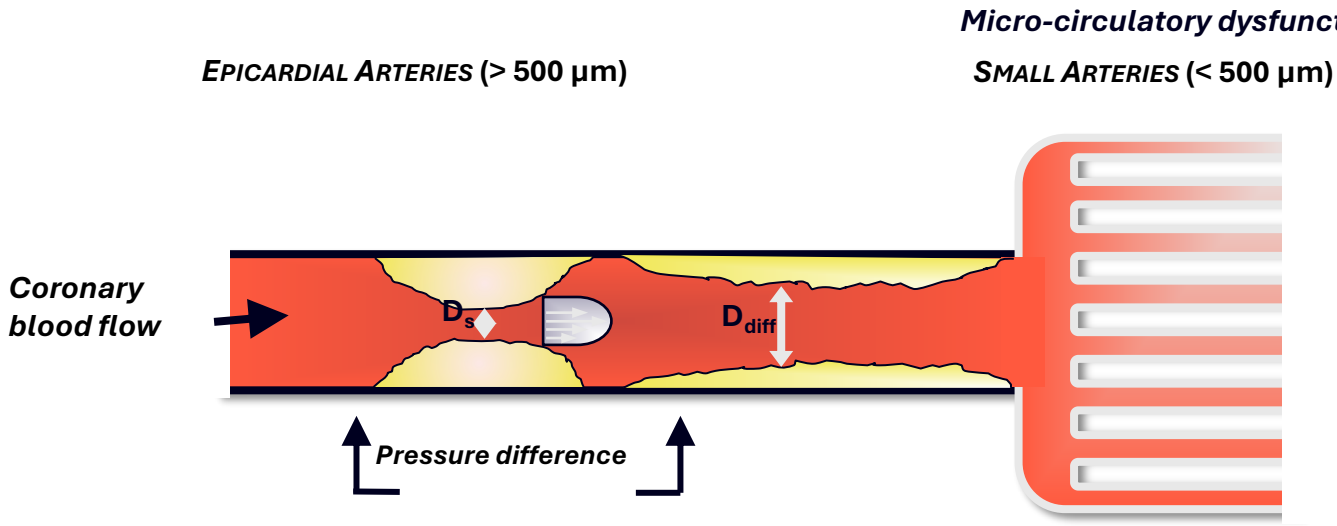
Study results

	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 *microvascular disease*	Medium sized area of moderate stress ischemia in the mid LAD territory	No evidence of flow limiting CAD
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)

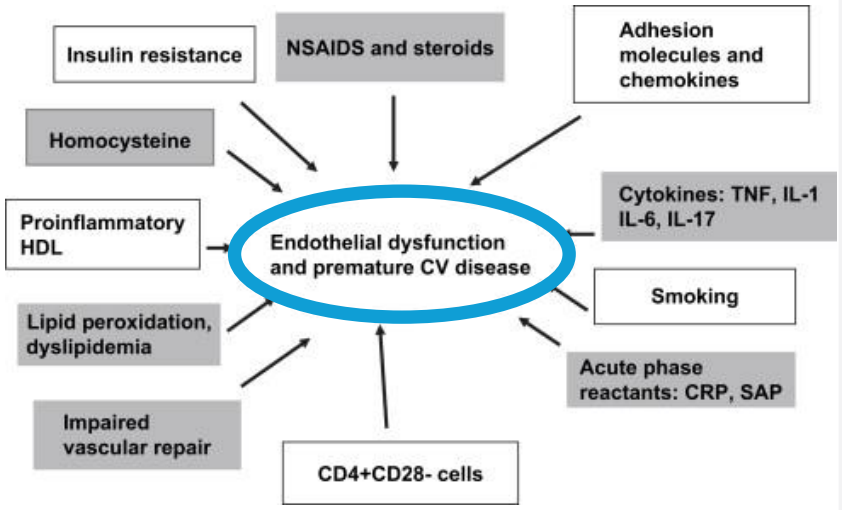
Myocardial flow reserve (MFR)

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

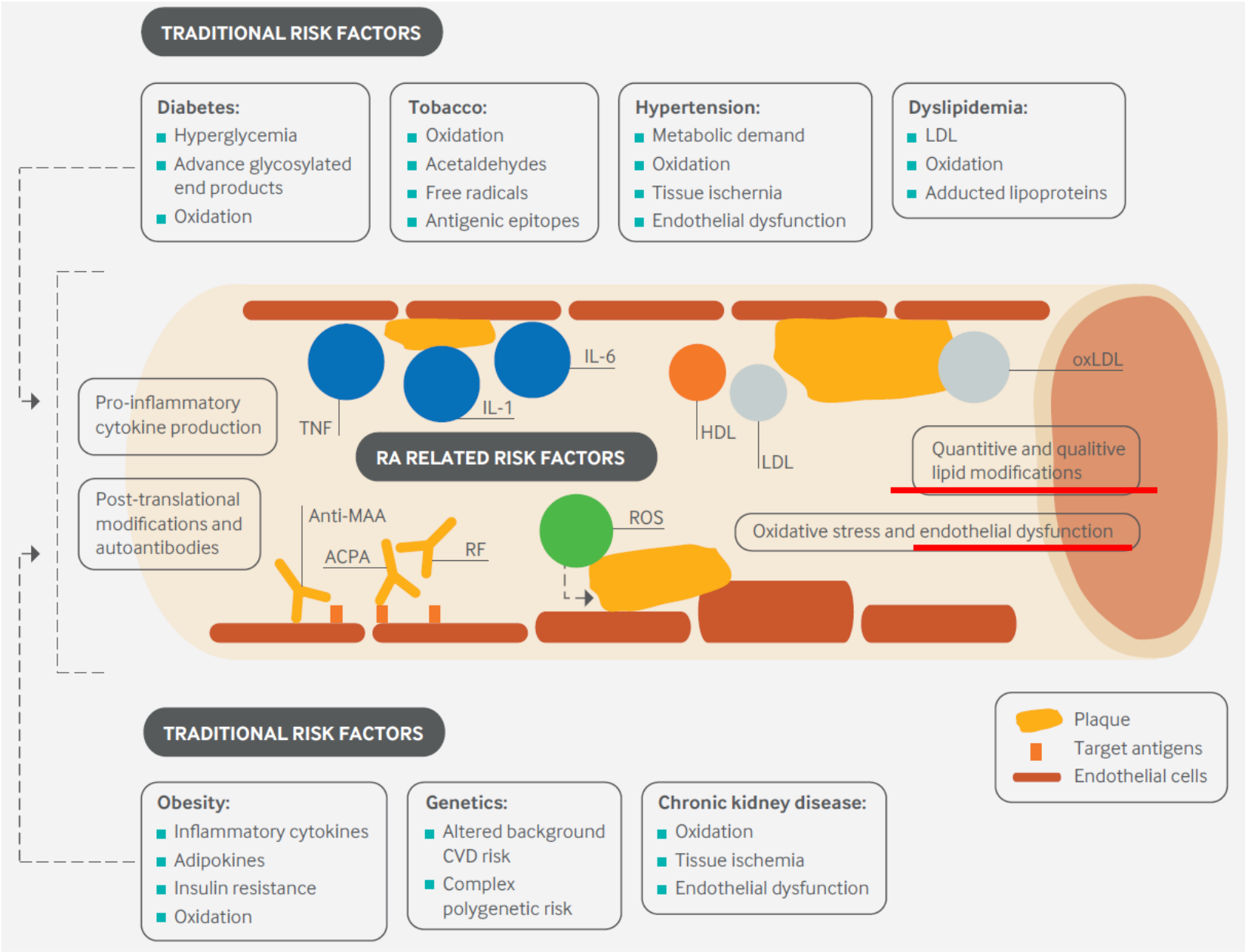


$$CFR = \frac{MBF_{peak\ hyperemia}}{MBF_{rest}}$$

Slide courtesy of Dr. Marcelo Di Carli



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



Avina-Zubieta et al., Arthr Care & Res 2008; Sparks et al., Arthr Care & Res 2015; England et al., BMJ 2018; Kaplan et al.., Rheum Dis Clin North Am. 2010

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

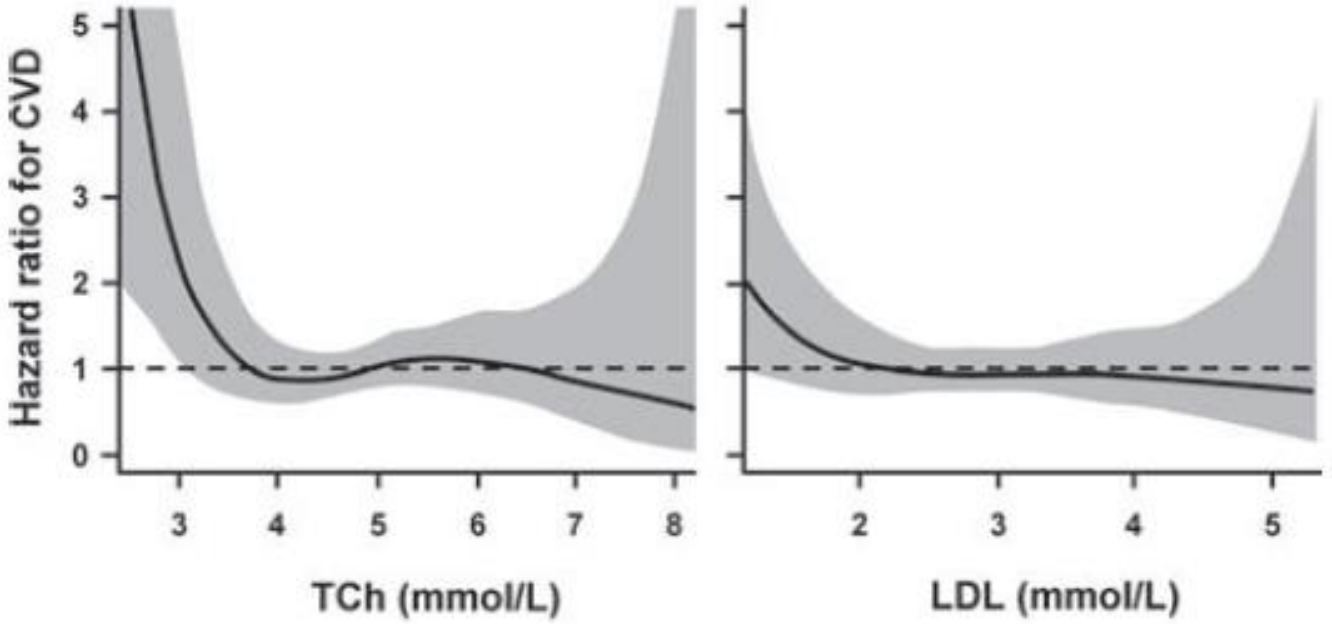
- Predicting Risk of CVD EVENTs (PREVENT) equations

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

  - Total CVD
  - ASCVD
  - Heart failure (HF)
  - Several studies in progress in rheumatic conditions; does not appear to perform better than PCE

Goff et al., Circ. 2013; Crowson et al., Am J Cardiol 2012; Kawai et al., Arthritis Rheumatol 2015; Ozen et al., Rheum 2015; Crowson et al., Rheum 2017; Arnett et al, Circ 2019; Khan et al., Circ. 2023

The lipid paradox in RA



Mayo Clinic study
N=651 RA patients
Population based cohort

Myasoedova et al. Ann Rheum Dis 2011

The lipid paradox in RA

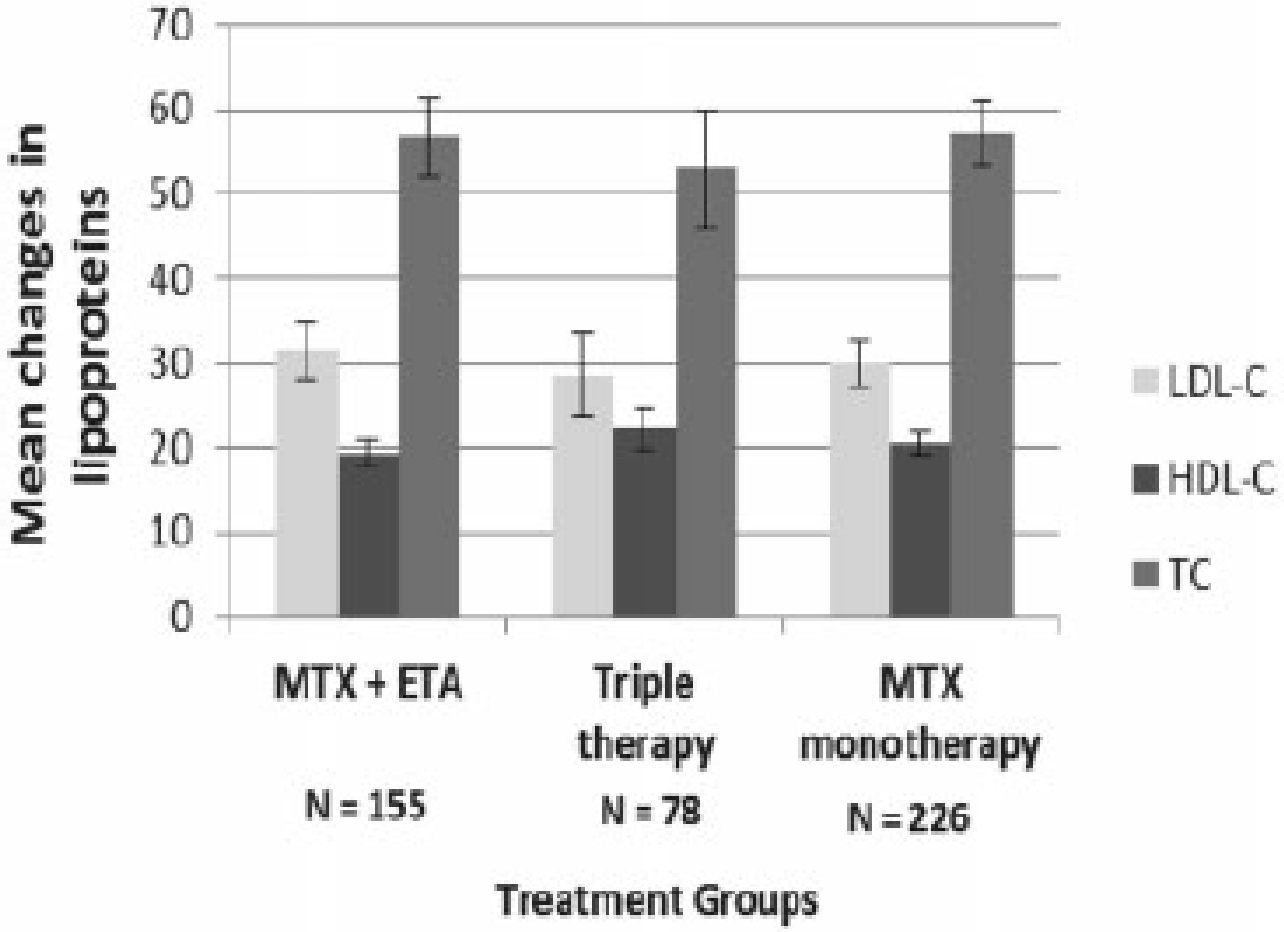
		RA cases		NHANES		
Lipid	**Time period**	**N**	**Mean (SD), mg/dL**	**N**	**Mean (SD), mg/dL**	**P-value**
Tchol	2007-2010	290	186 (20)	4486	200 (64)	0.0002
LDL	2007-2010	297	105 (18)	2027	118 (69)	0.001
HDL	2007-2010	295	58 (10)	4486	59 (30)	0.40

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

Liao et al., Arth Care & Res 2013

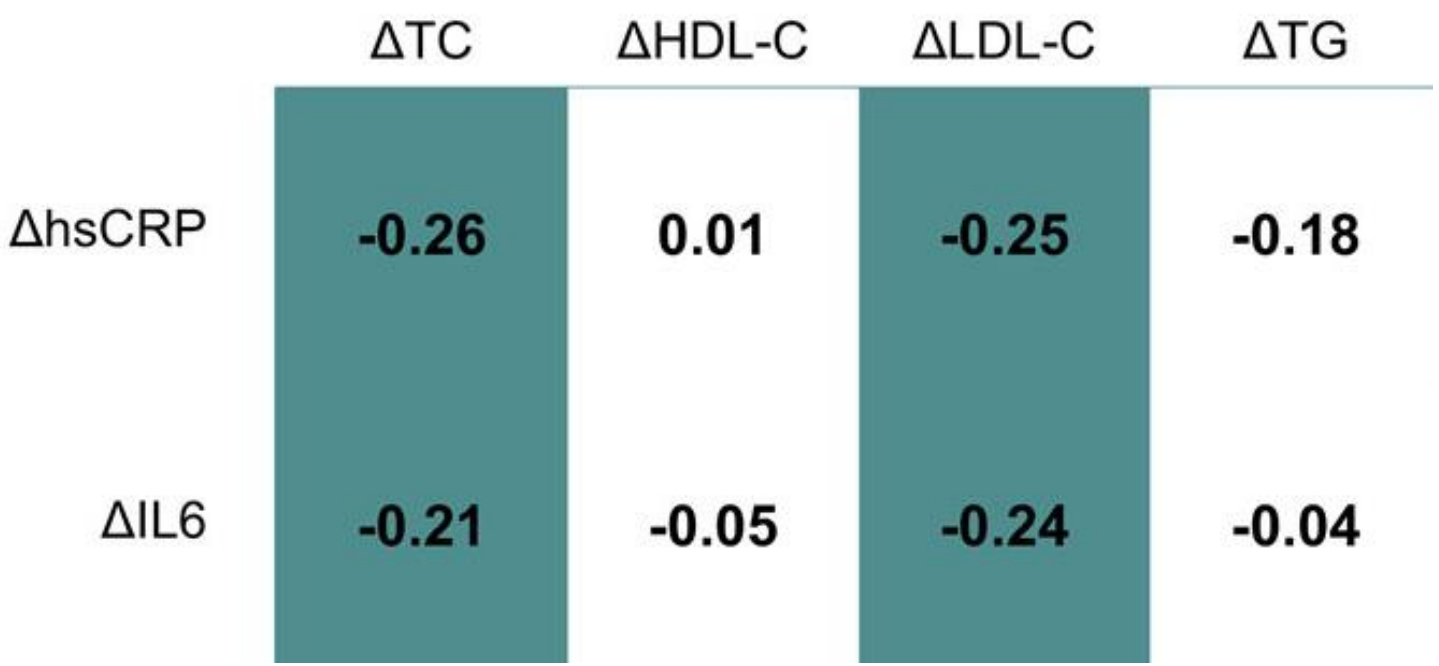
Lipids in the Treatment of Early RA (TEAR) trial



- 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 ($p<0.0001$)

Navarro-Milan et al., Arthritis Rheum 2013; Moreland et al., Arthritis Rheum 2012

Inverse correlation between Δinflammation and Δ in routine lipids in RA



Significant correlation

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

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

Weber et al., Arthritis Rheum 2021

Summary: recommendations for lipids in RA

- 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

Jacobson et al., J Clin Lipodol 2015; Grundy et al., JACC 2019

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

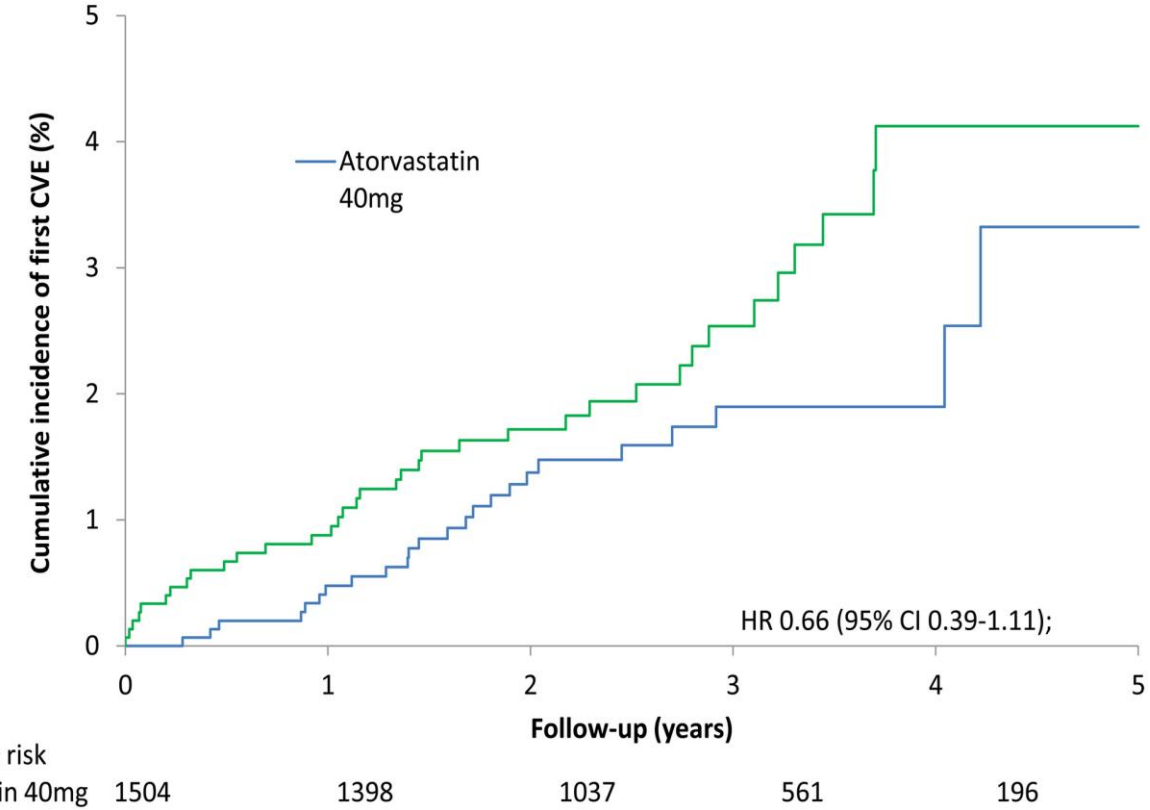
Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with RA (TRACE RA)

- 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

Kitas et al., Arthritis Rheumatol 2019

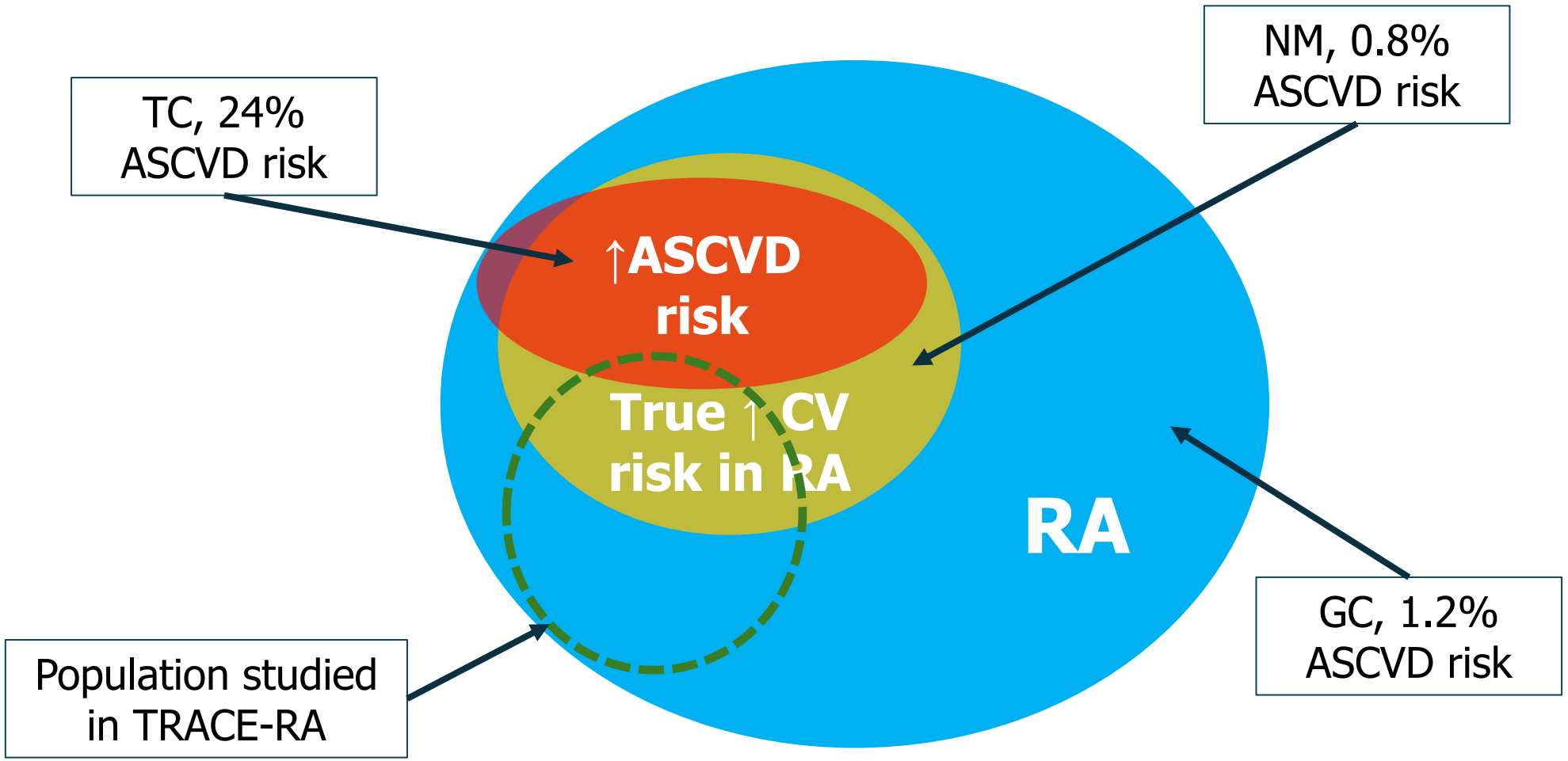
TRACE RA

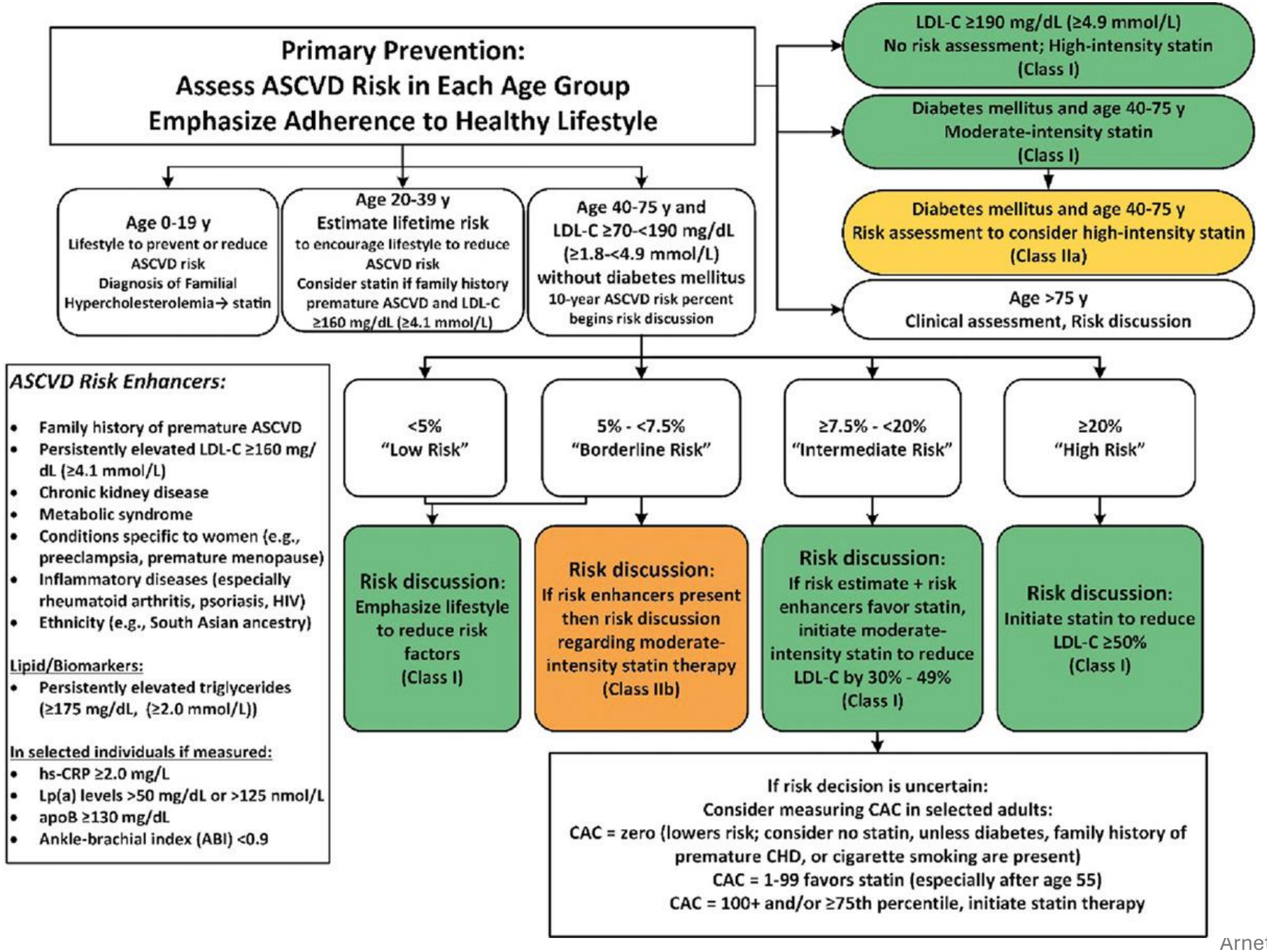
- N=2,986 subjects randomized
- Trial terminated early
  - Low event rate 0.76%
- Superiority not observed
  - Median f/u 2.5 years
- LDL-C
  - atorvastatin group, ↓41.4 mg/dL
  - placebo ↓ 5.4 mg/dL
- Atorvastatin well-tolerated
  - Adverse events similar between 2 groups (p=0.927)



Kitas et al., Arthritis Rheumatol 2019

Summary: CV risk in RA





Arnett et al., Circ 2019

ASCVD risk enhancers

Family history of premature ASCVD (males, age <55 y; females, age <65 y)

Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*

Metabolic syndrome (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)

Chronic kidney disease (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)

Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS

History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia

High-risk race/ethnicity (eg, South Asian ancestry)

Lipids/biomarkers: associated with increased ASCVD risk

Persistently elevated* primary hypertriglyceridemia (≥175 mg/dL, nonfasting)

If measured:

Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)

Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).

Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor

ABI (<0.9)

Statin recommendations

2019 ACC/AHA Guideline on the Primary Prevention of ASCVD + risk enhancer

Risk category	Estimated 10-year ASCVD risk	Risk discussion
High	≥20%	Initiate statin
Intermediate	≥7.5 to 20%	Favor statin
Borderline	≥5 to >7.5%	Discuss statin
Low	<5%	Emphasize lifestyle, no statin discussion recommended

MOC Reflective Statement

- 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 and cardiac PET can assist with CV 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 (ACC/AHA) 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

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?

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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 two risk-enhancers, RA and a CRP≥2.0mg/L according to the 2019 ACC/AHA guidelines for the primary prevention of ASCVD. With a risk enhancer discussion regarding the potential benefit of statin is recommended of individuals with a 10-year estimated ASCVD risk of 5% 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 2019 ACC/AHA 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.

References

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Thank you

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