Rheumatoid Arthritis & the Heart

Advances in Rheumatology
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Disclosures

- Author on UpToDate chapters on RA and cardiovascular disease

Learning objectives

- Recognize limitations of general population-based atherosclerotic cardiovascular disease (ASCVD) risk estimators for patients with RA

- Discuss reasons why routine lipids may be suboptimal markers for cardiovascular (CV) risk in RA

- Impact of key RA treatments on lipids and CV risk
  - JAK inhibitors

Which of these RA pts has the highest CV risk? Who has the lowest?

1. TC, 72M

2. NM, 44F

3. GC, 52F

All have active synovitis, on MTX and TNFi being considered

Pt 1, TC

- 72M w/ seropositive RA
  - Dx 5 yrs ago
- MTX 25mg once a week + folic acid
  - Naproxyn prn
- Past Med Hx
  - OSA, diverticulosis, s/p L ankle fracture, GERD
- Social Hx
  - Quit smoking 23 yrs ago, 25pk-yr history
- Fam Hx
  - Father died of MI in 70s

- Physical
  - BP 156/67, BMI 32.8
  - Swelling in MCPs and PIPs b/l
- Labs
  - BUN 20/creat 1.06
  - WBC 7.5/ Hct 38.9/Plat 152
  - CRP 7.5 mg/L

Pt 2, NM

- 44F w/ seropositive RA
  - Dx 2 yrs ago
- MTX 17.5mg once a week + leucovorin
  - Naproxen prn
- Past Med Hx
  - Asthma
- Social Hx
  - Never smoker, occ EtOH
- Family Hx
  - MGF w/ CAD and MI in 60s

- Physical
  - BP 126/63, BMI 35.8
  - b/l MTP squeeze tenderness, no swelling or tenderness in ankles
- Labs
  - BUN 15/0.82
  - WBC 7.2/ Hct 41.2/Plat 264
  - CRP 4.9 mg/L

Pt 3, GC

- 53F w/ seropos RA
  - Dx 15+ yrs ago
- MTX 20mg once a week + folic acid
- Past Med Hx
  - OA, depression
- Social Hx
  - Never smoked, occ EtOH
- Fam Hx
  - No history of MI

- Physical
  - BP 105/74, BMI 33
  - Swelling in R ankle and wrist
- Labs
  - BUN 12/0.77
  - WBC 9/ Hct 40.1/Plat 274
  - CRP 4.2 mg/L

CV focused summary of TC, NM, GC

	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/dL	7.5	4.9	4.2
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

Which of these RA pts has the highest CV risk? Who has the lowest?

1. TC, 72M, seropos RA x 5 yrs, former smoker, BMI>30, LDL 85mg/dL

2. NM, 46F, seropos RA x 2 yrs, BMI>30, LDL 149mg/dL

3. GC, 55F, seropos RA x 15+ yrs, BMI>30, LDL 140mg/dL

- *Which of these RA pts has the highest CV risk? Who has the lowest?*

AMERICAN COLLEGE *of* CARDIOLOGY

••••

Do not show me this again

App should be used for primary prevention patients (those without ASCVD) only.

Current Age ❶ *

Age must be between 20-79

Sex *

| Male | Female |

Race *

| White | African American | Other |

Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) ○

Value must be between 60-130

Total Cholesterol (mg/dL) *

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

Value must be between 20 - 100

LDL Cholesterol (mg/dL) ❶ ○

Value must be between 30-300

History of Diabetes? *

| Yes | No |

Smoker? ❶ *

| Current ❶ | Former ❶ | Never ❶ |

On Hypertension Treatment? *

| Yes | No |

On a Statin? ❶ ○

| Yes | No |

On Aspirin Therapy? ❶ ○

| Yes | No |

Do you want to refine current risk estimation using data from a previous visit? ❶ ○

| Yes | No |

https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

2018 AHA/ACC et al Guideline on the Management of Blood Cholesterol: Executive Summary

In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7). Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index (ABI) <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5% to 7.5% (borderline risk)

Grundy et al., JACC 2019

CV focused summary of TC, NM, GC

	Pt 1, TC	Pt 2, NM	Pt 3, GC
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Sex	M	F	F
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STUDY RESULTS			
Tchol, mg/dL	171	220	205
LDL, mg/dL	85	149	140
HDL, mg/dL	62	57	54
Tri, mg/dL	59	71	54
10-yr ASCVD risk	**24.2**	**0.8**	**1.2**

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

Stress myocardial perfusion results

Study results

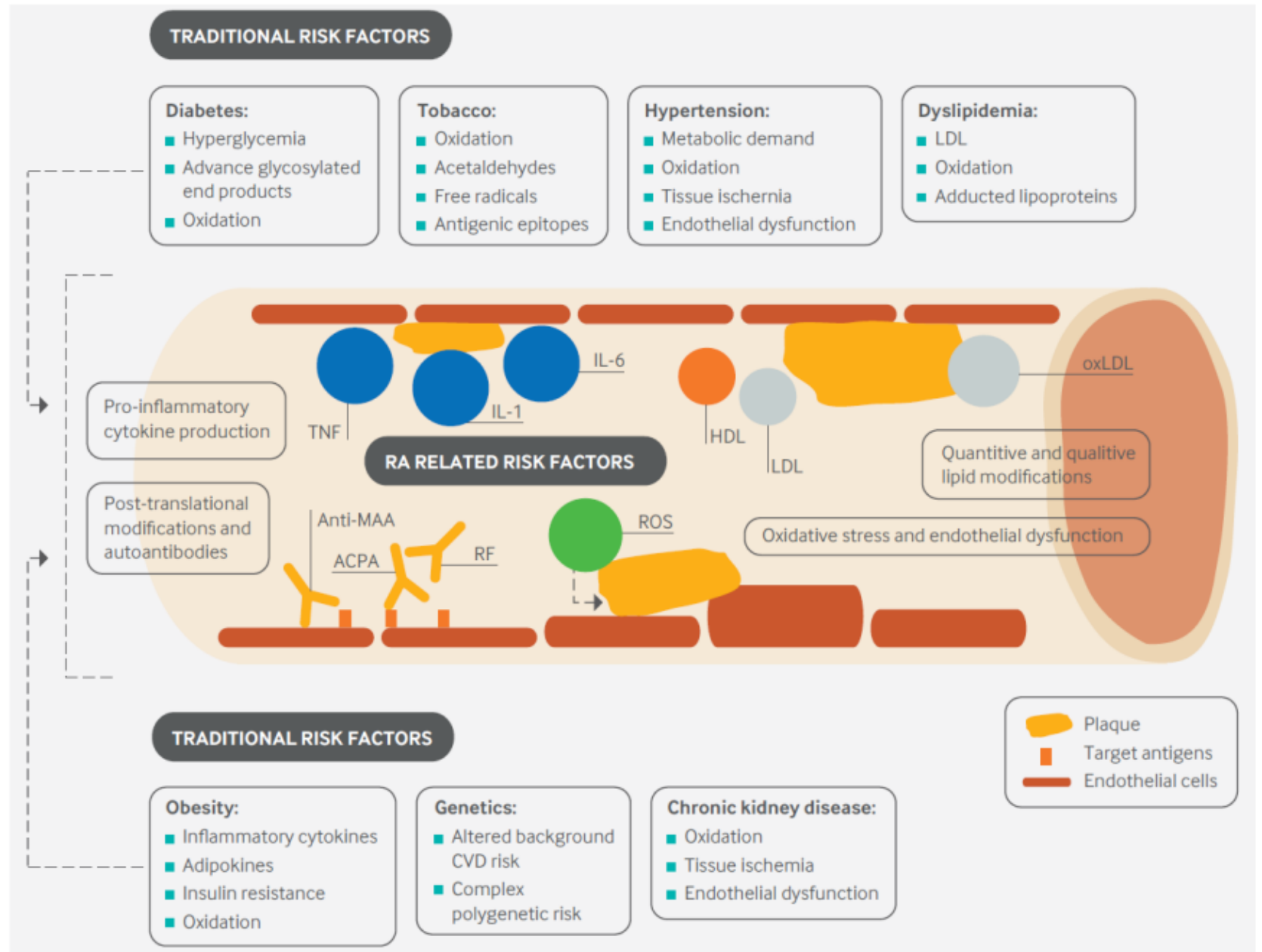|	TC, 72M	NM, 44F	GC, 53F
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10-yr ASCVD risk	24.2	0.8	1.2
CT angio	Severe lesion in the L circumflex coronary artery; mild CAD in the other coronary arteries	Medium amount of calcified/noncalcified plaque, min stenosis of other coronary arteries (1-24%)	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

Stress myocardial perfusion results

Study results

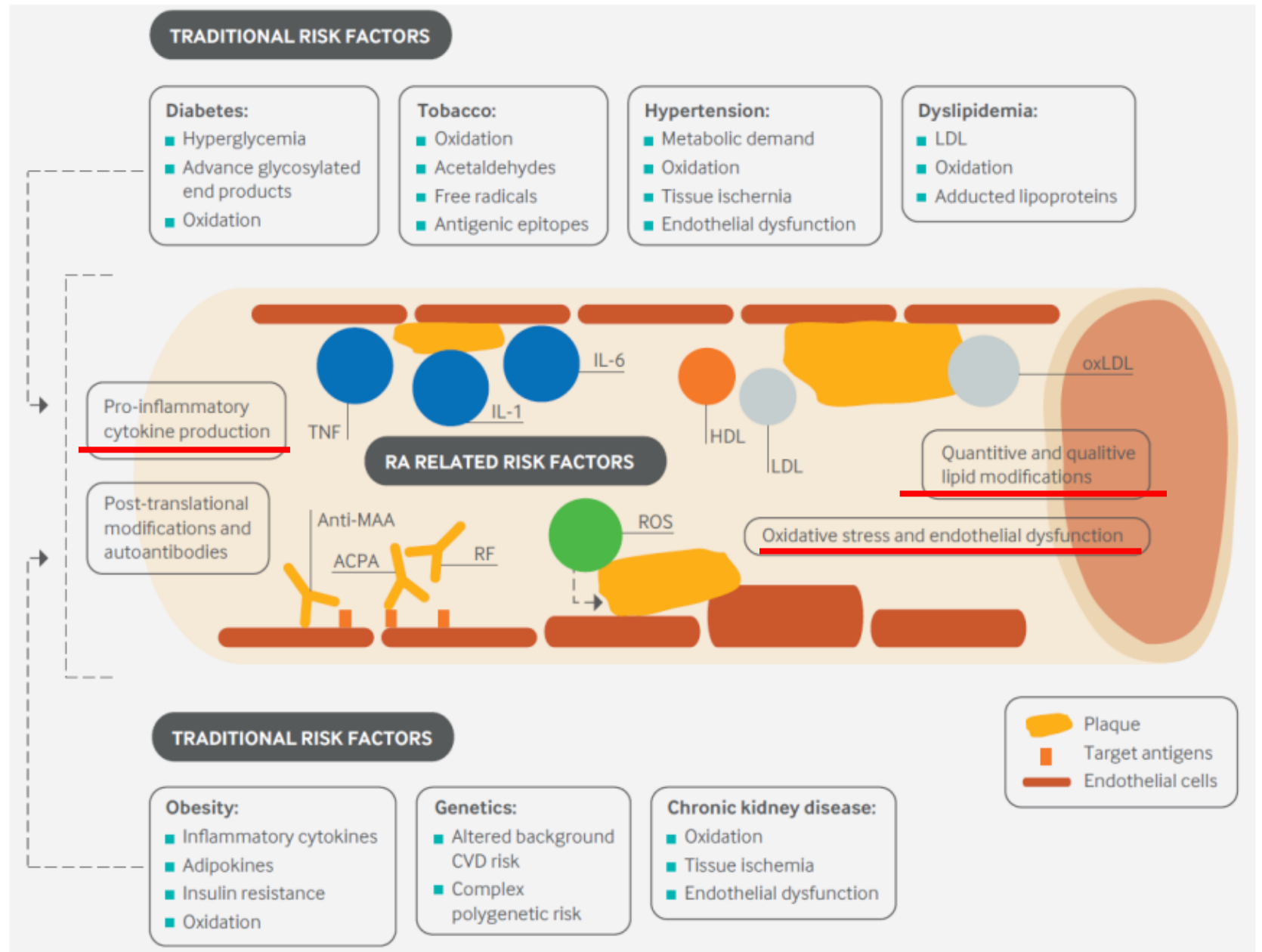|	TC, 72M	NM, 44F	GC, 53F
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RA and Cardiovascular Disease
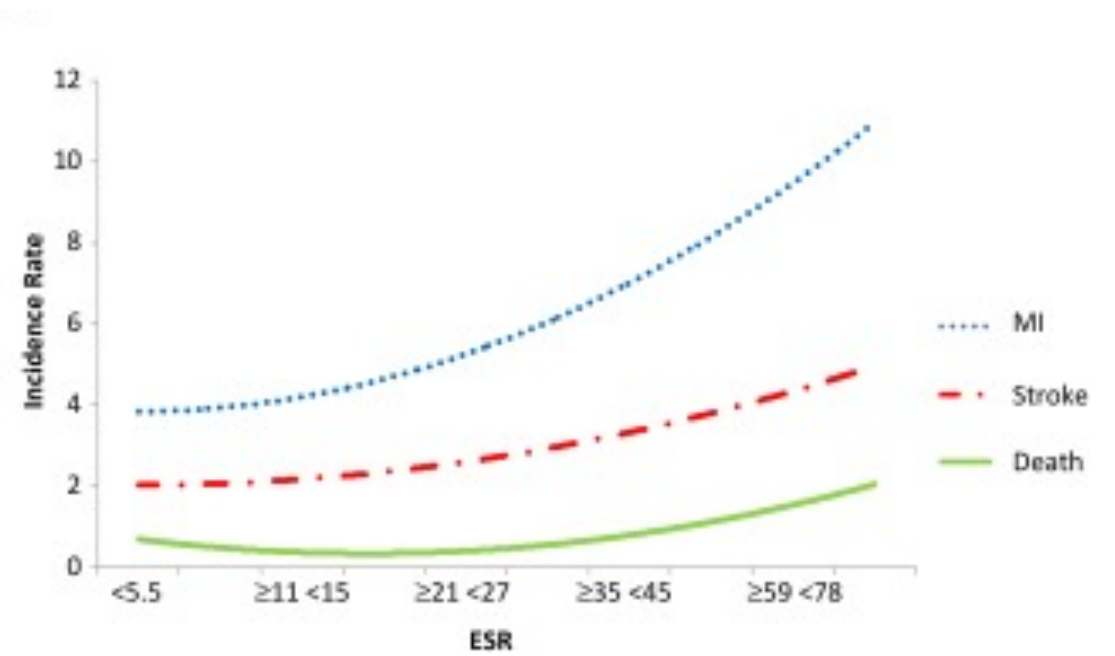
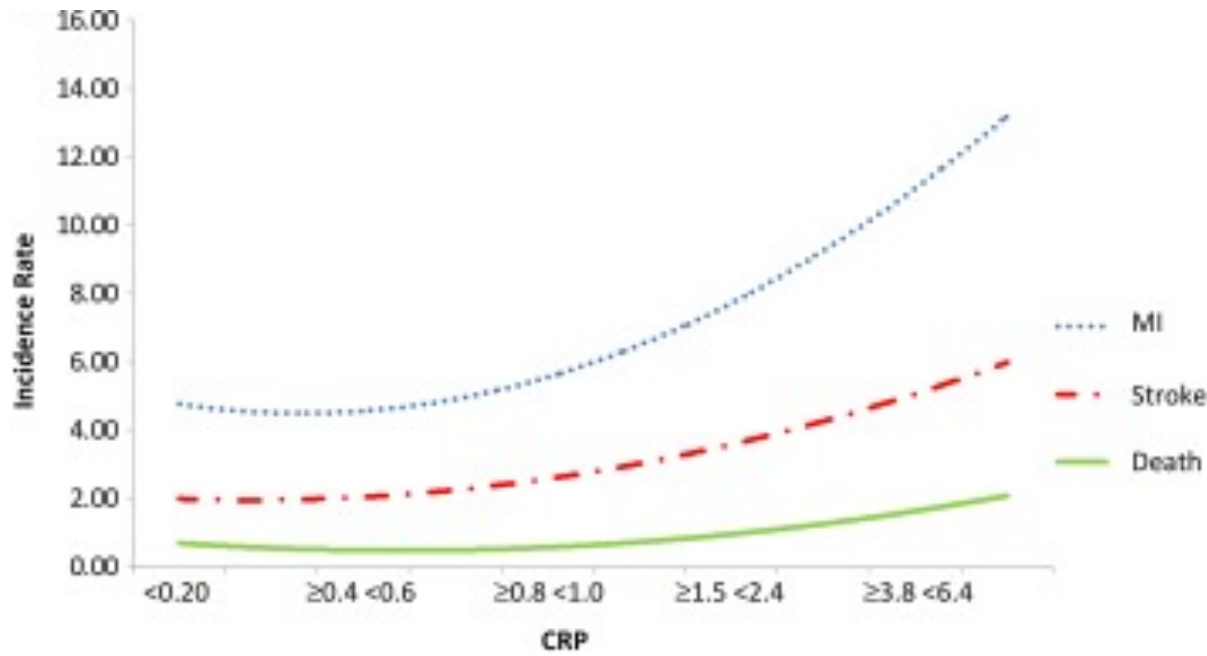## CV risk in RA 1.5-2x higher than the general population

Avina-Zubieta et al., Arthr Care & Res 2008; Sparks et al., Arthr Care & Res 2015; England et al., BMJ 2018

RA and Cardiovascular Disease

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
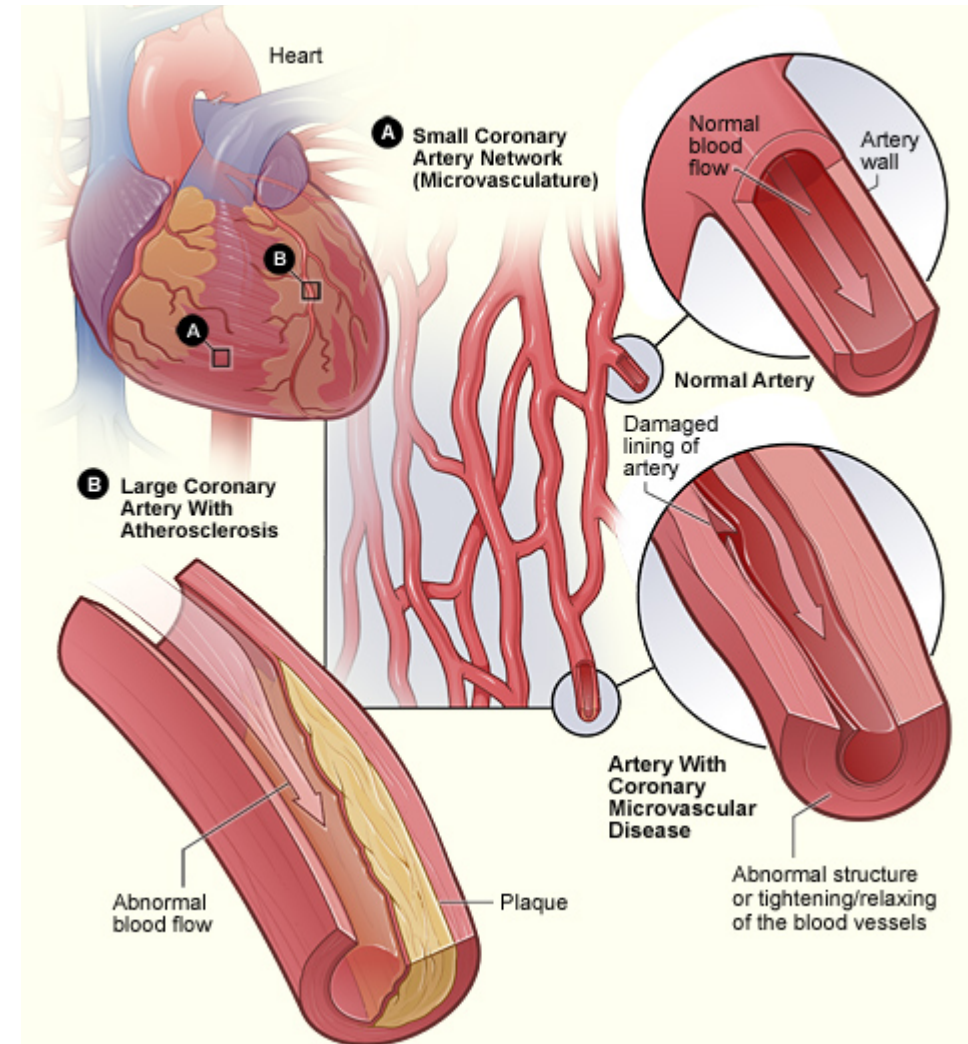
Inflammation and CV risk

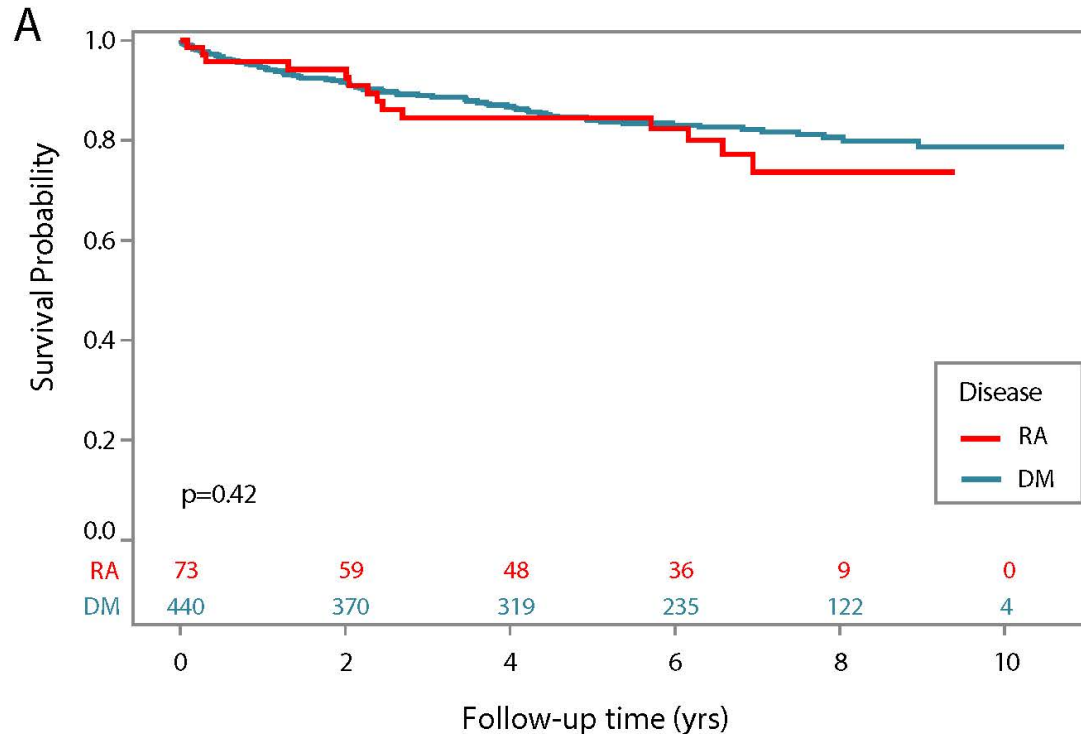# Endothelial dysfunction & coronary microvascular disease (CMD)

Case 1 TC, Stress test:

No evidence of flow limiting CAD
Transient LV dilatation in the absence of regional perfusion effect most likely represents subendocardial ischemia from *microvascular disease*

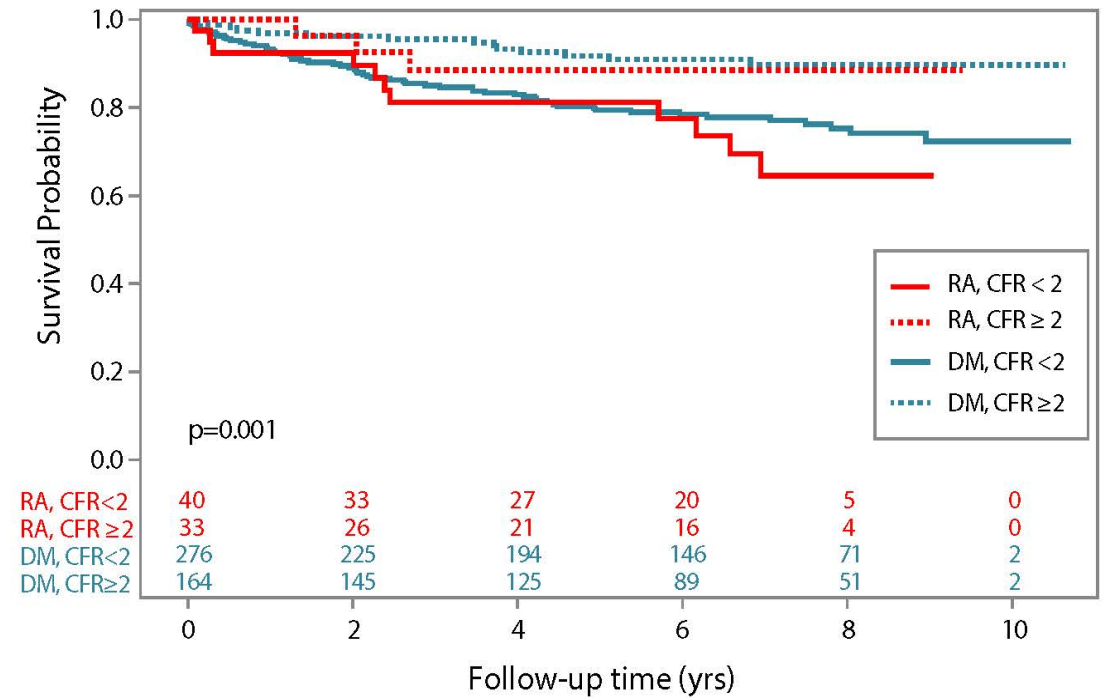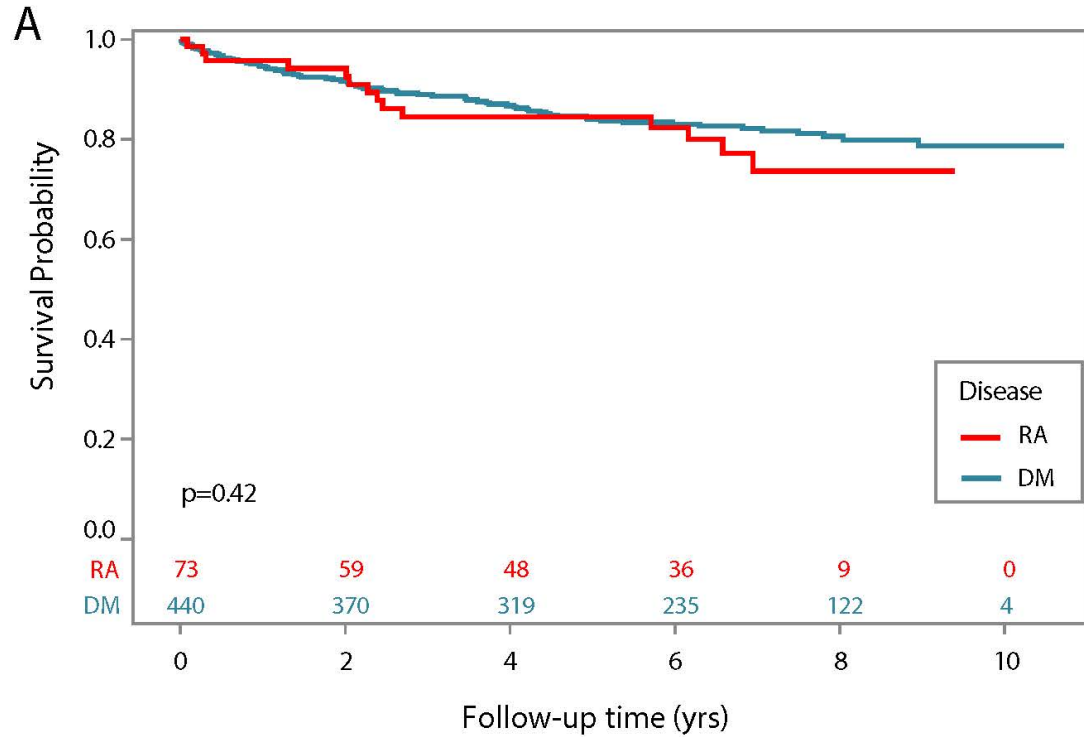Image: https://www.nhlbi.nih.gov/health/health-topics/topics/cmd/

CMD in RA vs DM

- CMD independent risk factor for cardiac mortality in patients with and without diabetes
- Evidence of coronary microvascular disease in ~30% RA patients without clinical CAD

Murthy et al., Circ 2012; Amigues et al., Circ CV Imaging 2019; Liao et al., Arth Care & Res 2021

CMD in RA vs DM


A

CV risk calculators

- Most commonly used in the US
  - ACC/AHA ASCVD Risk Estimator
  - Framingham Risk Score

- Underestimate CV risk in RA by as much as 2x
  - 102% in women with RA
  - 65% in men with RA

- Other
  - QRISK2/3 used in UK
    - May overestimate risk

Crowson et al., Am J Cardiol 2012; Kawai et al., Arth & Rheum 2015; Ozen et al., Rheum 2015; Crowson et al., Rheum 2017

RA specific CV risk estimators

- Expanded Cardiovascular Risk Score for RA (ERS-RA)
  - CV risk calculator developed and internally validated large RA cohort
    - Traditional risk factors + **RA duration + disease activity + prednisone use + functional status**
  - Results of external validation mixed

- European League Against Rheumatism (EULAR)
  - Multiply general guidelines by 1.5 if RA not taken into account
  - No external validation

Solomon et al., Arth & Rheum 2015; Agca et al., Ann Rheum Dis 2017; Crowson et al., Rheum 2017; Ljung et al., RMD Open 2018

Routine lipids

- Total cholesterol (Tchol)
- Low density lipoprotein cholesterol (LDL-C)
- High density lipoprotein cholesterol (HDL-C)
- Triglycerides (Tri)
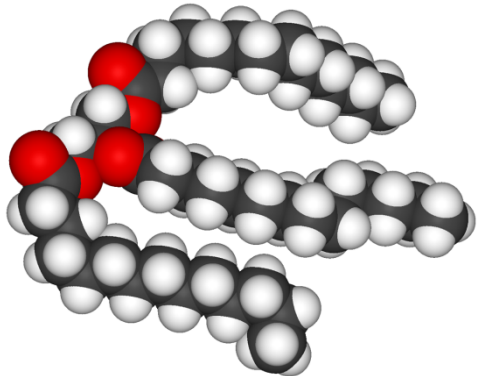
The lipid paradox in RA
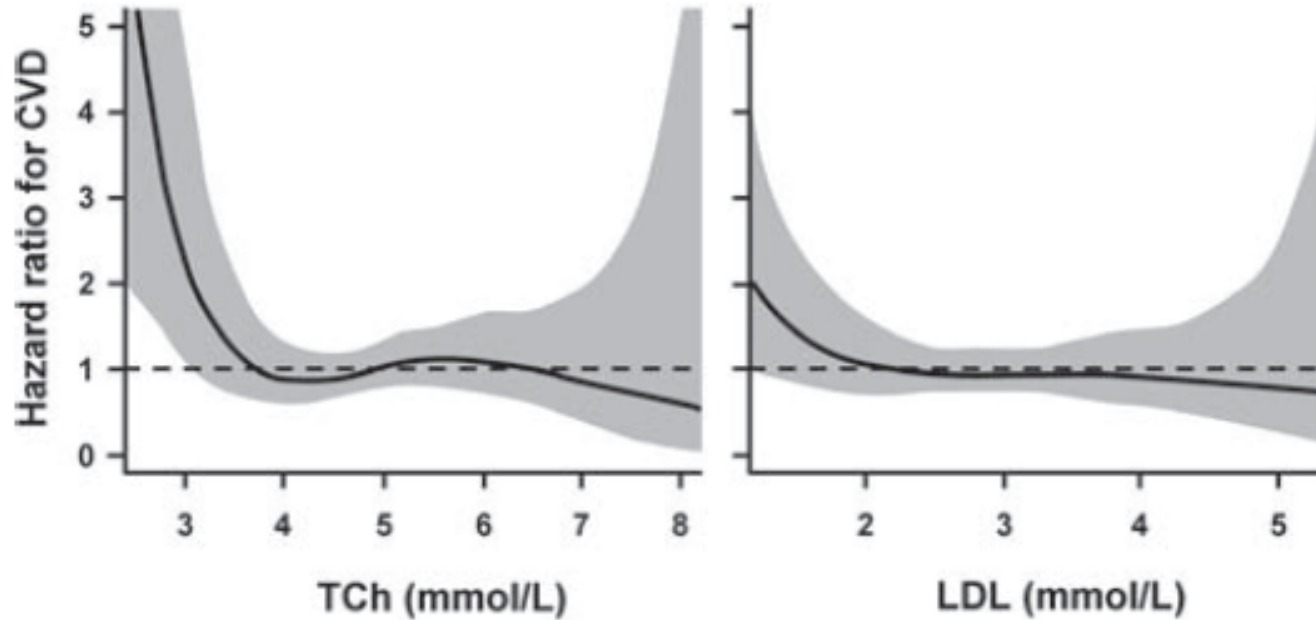
Mayo Clinic study
N=651 RA patients
Population based cohort

The lipid paradox in RA

Lipid	Time period	RA cases		NHANES		
		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 women 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

CV focused summary of TC, NM, GC

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RA duration, yrs	5	2	15
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10-yr ASCVD risk	**24.2**	**0.8**	**1.2**

Summary: Routine lipids

- Despite "better" lipid profile, RA patients have elevated CV risk
  - Elevated CV risk attributed to inflammation
    - May explain lower TC and LDL-C levels

- Do lipid values change with changes in inflammation?

RA treatments associated with lipid changes

Treatment of Early RA (TEAR) Trial

- 2 year randomized, 4 arm, placebo controlled
- N=755 early RA, DMARD naïve
- Arms
  - MTX monotherapy w/ step up to:
    - Etanercept
    - Triple therapy, add sulfasalazine (SSZ) and hydroxychloroquine (HCQ)
  - MTX + etanercept
  - Triple therapy (MTX, SSZ, HCQ)
- Tchol, LDL and HDL measured at 0 and 24 weeks

Moreland et al., Arth & Rheum 2012

Lipids in the TEAR study
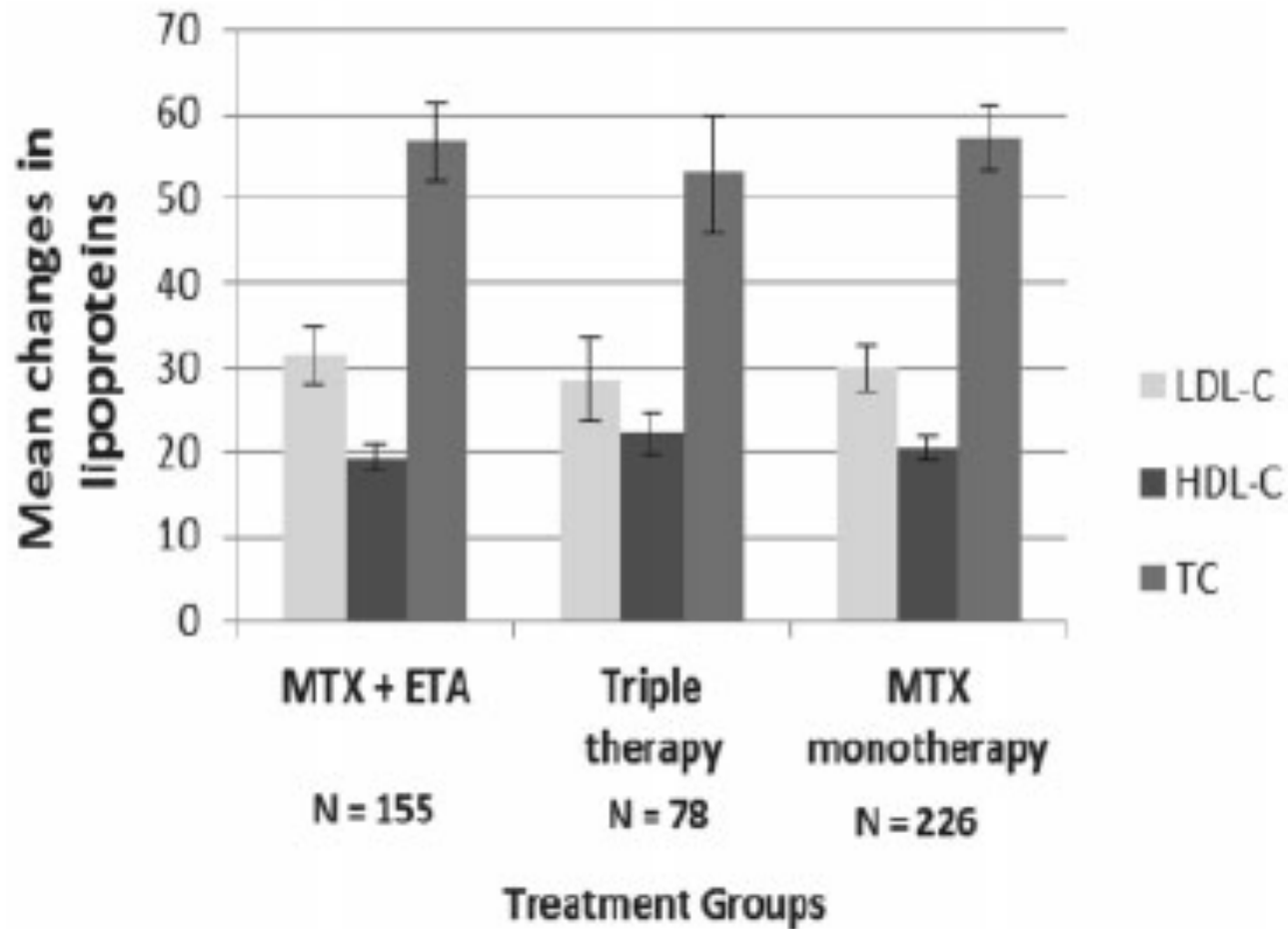
- Changes between baseline and 24 weeks sig in all 3 groups (p<0.0001)

- Increase in LDL-C by as much as 30% in ETA arm

Navarro-Milan et al., Arth & Rheum 2013

Inflammation associated with lipid changes

- Brigham Rheumatoid Arthritis Sequential Study (BRASS)
  - Prospective cohort study, n=~1300 RA subjects

- Inclusion criteria for lipid substudy
  - Subjects with ≥10mg/L reduction hsCRP
  - Two consecutive time points 1 year
  - Routine lipids measured at both time points + HDL cholesterol efflux capacity

Change in lipid values, BRASS

Measurement	Baseline	1 year follow-up	P-value
Total cholesterol (mg/dL)	187.2	183.2	0.14
LDL (mg/dL)	102.0	109.0	0.02*
HDL (mg/dL)	65.3	66.3	0.50
HDL cholesterol efflux capacity	1.05	1.11	0.0005*
CRP, median (mg/L)	28.6	4.3	P<0.0001

Note: Higher value for HDL cholesterol efflux capacity = improved HDL function to efflux cholesterol from macrophages

- ↑LDL by 7.2%
- Improvement in cholesterol efflux capacity by 5.7%
  - Estimated 15% reduction in CV risk

Liao et al., JAHA 2015; Rohatgi et al., NEJM 2014

Recommendations for lipids in RA

- Reduction in inflammation associated with ↑LDL-C
  - ↑LDL-C not necessarily a sign of ↑CV risk
  - Observed across all bDMARDs
  - Other measures, e.g. HDL cholesterol efflux capacity suggest reduced inflammation → reduced atherogenicity

- 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; Barber et al., Arth Care & Res 2015; Charles-Schoeman et al., Arthr Rheumatol 2015; Agca et al., Ann Rheum Dis 2016; Ormseth et al., Arthr Rheumatol 2016; Grundy et al., JACC 2019

RA therapies with package insert info for lipids

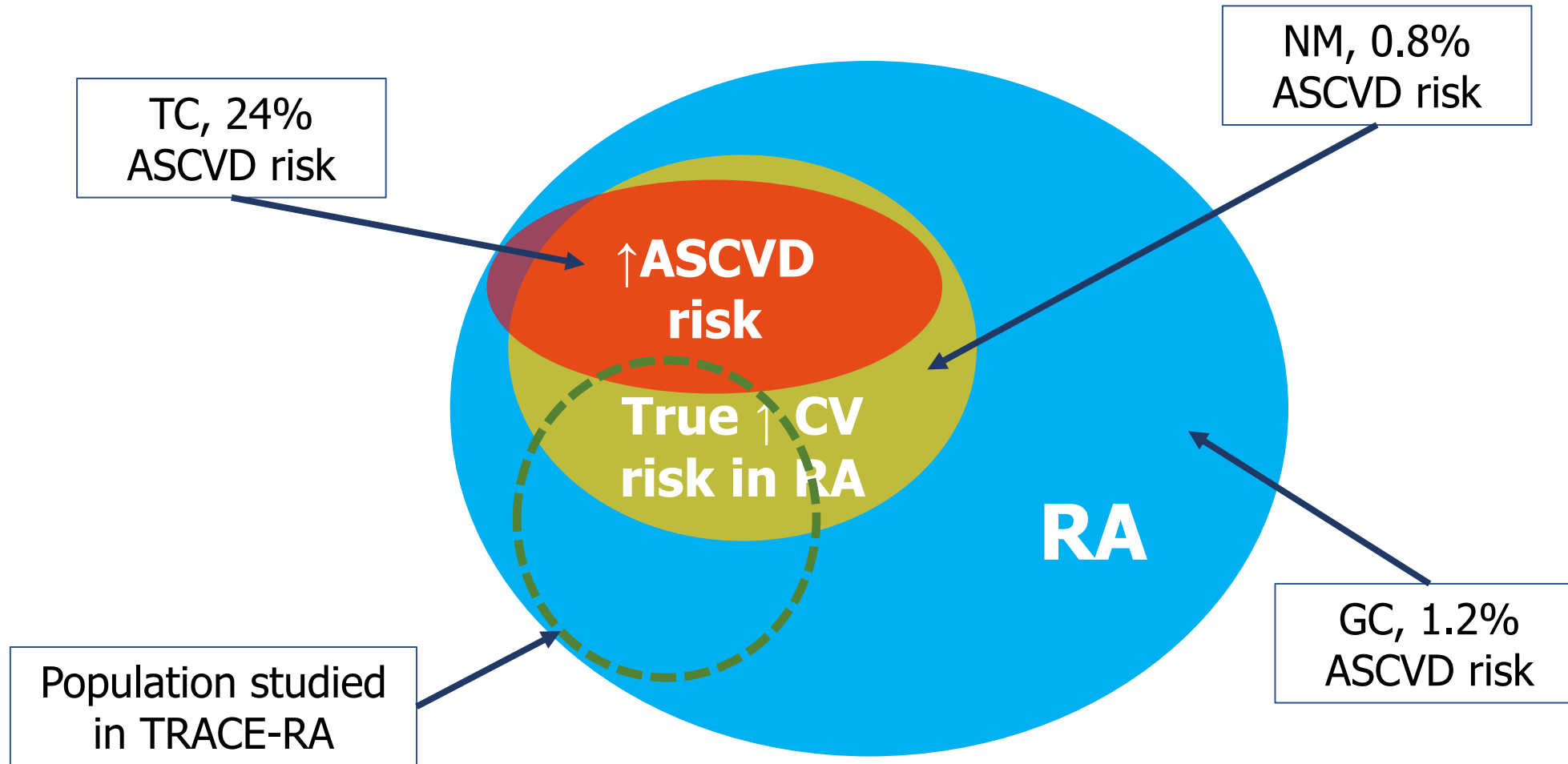| Class	Generic	Trade	Dyslipid (%)	TC	LDL-C	HDL-C	Trig	When to recheck lipids
JAKi	Tofacitinib	Xeljanz	1-10	↑	↑	↑		4-8 weeks after initiation
	Baricitinib	Olumiant	NR	↑	↑	↑		12 weeks "
	Upadacitinib	Rinvoq	NR	↑	↑	↑		12 weeks "
IL6R	Tocilizumab	Actemra	>10	↑	↑	↑		4-8 weeks after initiation, then at ~24 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

- Median f/u 2.5 years

- LDL-C in atorvastatin group, ↓41.4 mg/dL
  - Placebo ↓ 5.4 mg/dL

- HR 0.66 (95% CI 0.40-1.11), p=0.119

- Trial terminated early due to low event rates
  - 0.76% vs. anticipated 1.80%

- Adverse events similar between 2 groups (p=0.927)
  - 19.7%, atorvastatin vs. 19.5%, placebo group

Kitas et al., Arthr Rheum 2019

Summary: CV risk in RA

TC, 24%
ASCVD risk

NM, 0.8%
ASCVD risk

↑ASCVD
risk

True ↑ CV
risk in RA

RA

Population studied
in TRACE-RA

GC, 1.2%
ASCVD risk

Inflammation as a modifiable CV risk factor

Potential role of RA treatments

Modifiable CV risk factors

Risk factor
Dyslipidemia
Hypertension
Diabetes
Smoking
Inflammation

Non-modifiable= age, gender, family history of CVD

↓inflammation→↓CV risk: CANTOS Trial

Canakinumab Anti-inflammatory Thrombosis Outcome Study

- Randomized, double-blind, placebo controlled trial

- Inclusion: h/o MI and CRP≥2mg/L despite aggressive 2° prevention

- Primary outcome: non-fatal MI, non-fatal stroke, CV death

- Treatment arms
  - Canakinumab 50mg, 150, and 300mg SC q 3months
    - Monoclonal targeting IL-1β
   - Indicated for CAPS, FMF, sJIA
  - Placebo

CANTOS trial

- N=10,061 randomized
  - Pts on anti-inflammatory therapy excluded

- Key secondary endpoint= hospitalization for unstable angina leading to revasc

- Incidence rate of fatal infx higher in canakinumab vs placebo

- Canakinumab at 150mg q3 months led to significant lower rate of CV events compared to placebo, independent of lipid-lowering

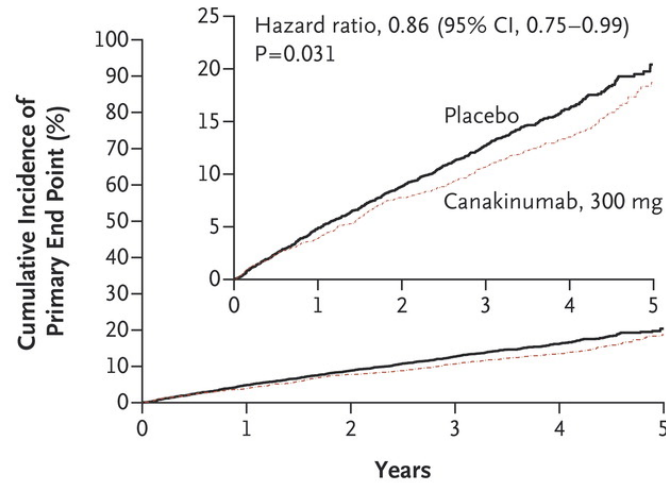A Primary End Point with Canakinumab, 50 mg, vs. Placebo

Hazard ratio, 0.93 (95% CI, 0.80–1.07)
P=0.30
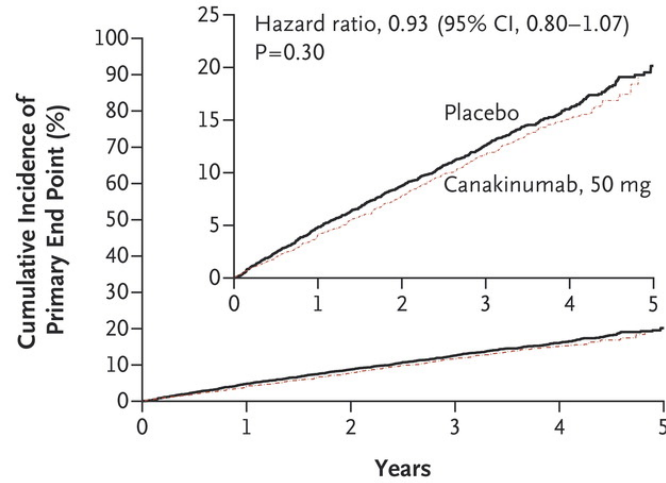
Placebo
Canakinumab, 50 mg

No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2170	2057	1950	1713	762	47

B Primary End Point with Canakinumab, 150 mg, vs. Placebo

Hazard ratio, 0.85 (95% CI, 0.74–0.98)
P=0.021
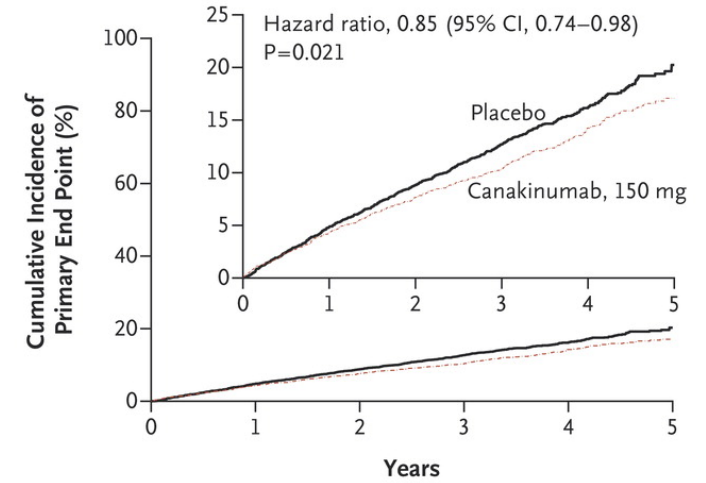
Placebo
Canakinumab, 150 mg

No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

C Primary End Point with Canakinumab, 300 mg, vs. Placebo

Hazard ratio, 0.86 (95% CI, 0.75–0.99)
P=0.031

Placebo
Canakinumab, 300 mg

No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2263	2149	2038	1819	938	199

D Key Secondary End Point with Canakinumab, 150 mg, vs. Placebo

Hazard ratio, 0.83 (95% CI, 0.73–0.95)
P=0.005

Placebo
Canakinumab, 150 mg
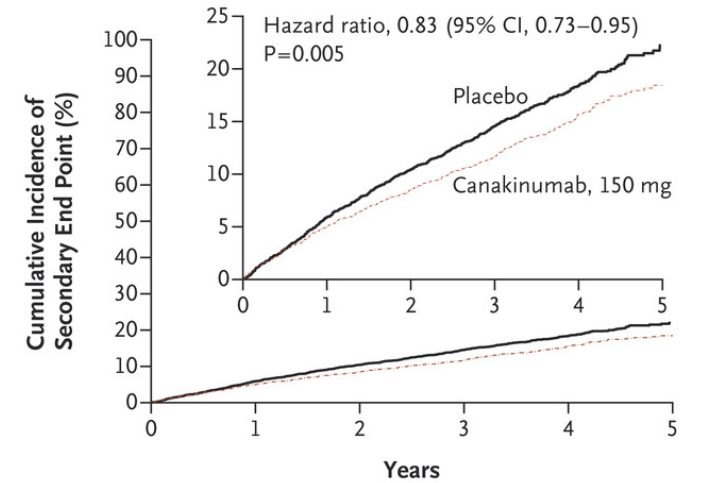
No. at Risk

Placebo	3344	3107	2921	2578	1238	206
Canakinumab	2284	2135	2039	1824	892	201

Ridker et al., NEJM 2017

Modifiable CV risk factors

Risk factor	Therapeutic intervention
Dyslipidemia	Statins
Hypertension	Beta blockers, ACE inhibitors
Diabetes	Metformin, insulin
Smoking	Buproprion, varenicline
Inflammation	**?role of bDMARDs and small molecules**

Lifestyle intervention most important component of treatment!

RA treatments and CV risk

RA treatments and CV risk : TNFi

- British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

- Prospective observational study

- Compared rates of MI in TNFi vs non-biologic DMARD

- Inclusion:
  - on TNFi (DAS >5.1 at 2 time points)
  - nbDMARD DAS>4.1

(*PD=Deciles of propensity score)

Table 2 Risk of MI compared between sDMARD and TNFi cohorts

	sDMARD; n=3058	TNFi; n=11 200
Median duration of follow-up per patient, years (IQR)	3.5 (1.8, 4.9)	5.3 (3.6, 6.4)
Total person-years of exposure, pyrs	10 337	55 636
Primary drug exposure model: on-TNFi+90 days		
Number of verified first MIs	58	194
Crude incidence rate of verified first MI per 10 000 pyrs (95% CI)	56 (43 to 73)	35 (30 to 40)
Unadjusted HR (95% CI)	Referent	0.78 (0.58 to 1.05)
HR adjusted for age and gender (95% CI)		1.19 (0.89 to 1.59)
HR after adjusting for PD* (95% CI)		0.61 (0.41 to 0.89)

Low et al., Ann Rheum Dis 2017

RA treatments and CV risk : biologic DMARDs

- Comparative effectiveness of abatacept vs other biologic DMARDs
- Medicare, n=47,193 RA patients

	HR	LCL	UCL
Tocilizumab	0.64	0.40	1.01
Rituximab	0.94	0.75	1.17
Infliximab	1.07	0.90	1.28
Golimumab	0.77	0.43	1.38
Etanercept	1.04	0.83	1.29
Certolizumab	0.79	0.52	1.22
Adalimumab	1.00	0.80	1.26

Favors Alternative   Favors Abatacept
0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2
Hazard Ratio and 95% CL

	HR	LCL	UCL
Tocilizumab	0.64	0.41	0.99
Rituximab	0.93	0.74	1.17
Anti-TNF	1.01	0.87	1.17

Favors Alternative   Favors Abatacept
0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2
Hazard Ratio and 95% CL

Interest in IL6 blockade to ↓CV risk

- In RA, despite increased in LDL-C, HDL function improved w/ tocilizumab therapy

- Genomic studies potential causal association between impaired IL6R function and ↓risk of coronary heart disease (CHD)

- IL-6 inhibition w/ ziltivekimab in patients at high atherosclerotic risk (RESCUE)
  - Phase 2, randomized, double-blind, placebo controlled trial
  - N=264, age>18, mod to severe CKD, hsCRP≥2mg/L
  - Significant reduction for biomarkers of inflammation and thrombosis

IL6R Mendelian Randomisation Analysis Consortium, Lancet 2012; IL6R Genetics Consortium Emerging Risk Factors Collaboration, Lancet 2012
Ormseth et al., Arthr Rheumatol 2016; Liao et al., JAMA Card 2018; Ridker et al., Lancet 2021

FDA email Sept 1, 2021

- Boxed warning, FDA's most prominent warning, for all 3 JAKi's
  - Serious heart-related events, cancer, blood clots, and death
    - Bariticinib and upadacitinib without data at this time

- Limit JAKi for RA to patients who are not treated effectively or who have side effects to other treatments, e.g. TNFi

JAKi and CVD: ORAL surveillance

- Post-marketing safety study
- Randomized controlled trial
  - Tofacitinib 5mg or 10mg vs TNFi
- Inclusion
  - RA
  - Age ≥50
  - ≥1 CV risk factor
  - Background MTX
- Co-primary endpoints
  - Major adverse cardiovascular events (MACE)
    - CV death, non-fatal MI, non-fatal stroke
  - Malignancies, excluding non-melanoma skin cancer
- Prespecified risk margin of HR 1.8 for above endpoints on tofacinitib vs TNFi

NEWS / Pfizer Shares Co-Primary Endpoint Results from Post-Marketing Required Safety Study of XELJANZ® (tofacitinib) in Subjects with Rheumatoid Arthritis (RA)

PFIZER SHARES CO-PRIMARY ENDPOINT RESULTS FROM POST-MARKETING REQUIRED SAFETY STUDY OF XELJANZ® (TOFACITINIB) IN SUBJECTS WITH RHEUMATOID ARTHRITIS (RA)

Wednesday, January 27, 2021 - 06:45am

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today co-primary endpoint results from a recently completed post-marketing required safety study, ORAL Surveillance (A3921133; NCT02092467). The primary objective of this study was to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily)

Data from ORAL Surveillance on MACE
Mean age 60 yrs, 78% female, 77% White, median on-study follow-up 4 years

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID**	Tofacitinib Doses Combined	TNFi
Total number of subjects	1455	1456	2911	1451
# subjects with 1st event within the risk period*** (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Person-years	5166.32	4871.96	10038.28	5045.27
IR (95% CI) (# subjects w/ event/100 person-years)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) for tofacitinib vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	**1.33 (0.91, 1.94)******	

Adjudicated MACE*

BID=twice daily; CI=confidence interval; HR=hazard ratio; IR=incidence rate; MACE=major adverse cardiovascular event; TNFi=Tumor Necrosis Factor inhibitor.
(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
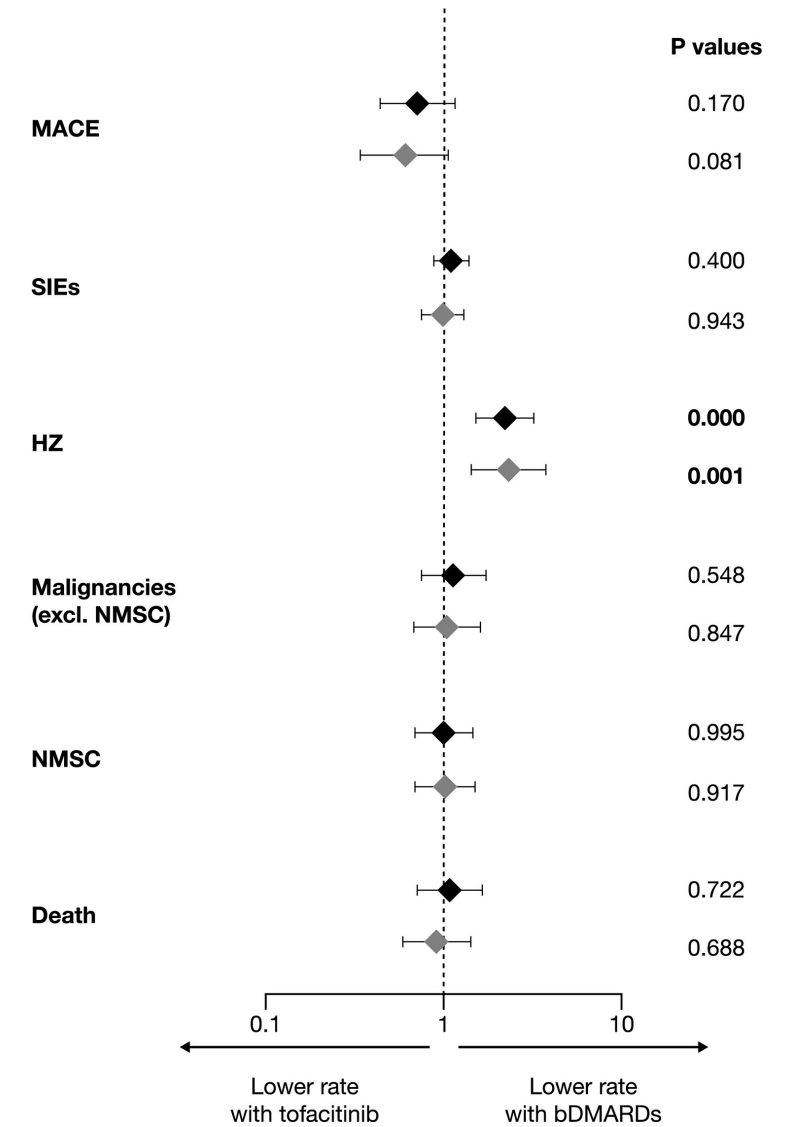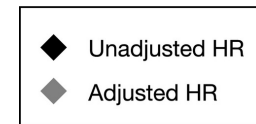*(***) The risk period was from start of therapy up to 60 days past last dose.*
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 1.94 >1.8.

Observational studies

- Comparative safety tofacitinib vs bDMARD in RA
  - N=1999 tofa vs n=8358 bDMARD initiators, CORRONA
  - No difference in MACE, serious infection (SIE), VTE, malignancy; Herpes zoster (HZ) rates higher

- Similar findings for PsA
  - N=686
  - Higher HZ rates

- Meta-analyses and pooled trial data for tofacitinib
  - Incident rates stable over median f/u period up to 3 yrs for MACE, mortality
  - No comparison group

- Unselected patients in contrast to ORAL

Xie et al., Ann Rheum Dis 2019; Cohen et al., RMD Open 2020; Burmester et al., Drug Saf 2020; Kremer et al., ACR Open Rheumatol 2021

RA treatments and CV risk: Caveats

- Observational data
- CVD outcomes vary
- Different length of exposure to treatments
- Dosing varies
- Different comparator groups
- Information on CV and RA related factors vary
- Measured and unmeasured confounding

- THM: pathway targeted may matter for CV risk w/ RA treatments

Modifiable CV risk factors

Risk factor	Therapeutic intervention
Dyslipidemia	Statins
Hypertension	Beta blockers, ACE inhibitors
Diabetes	Metformin, insulin
Smoking	Buproprion, varenicline
Inflammation	Favor specific bDMARDs while avoiding others?

Summary

- RA patients 1.5-2x risk for CVD compared to the general population
- Screening for CVD and CV risk factors in RA at minimum per general population guidelines
  - However, current risk estimator underestimate CV risk in RA
  - Need for additional methods to risk stratify beyond risk enhancers
- Routine lipids suboptimal markers of CV risk with active RA
  - Recommend checking fasting lipids when patient is in remission or stable disease

Summary

- RA treatments and association with CV risk may depend on pathway
  - TNFi and IL6R blockade w/ some evidence of ↓CV risk; limited data on abatacept, rituximab
  - Concern for JAKi and ↑CV risk in comparison to TNFi
- Statins safe and effective for lowering LDL-C in RA
  - First line treatment for dyslipidemia
  - Optimal RA population for primary prevention without dyslipidemia remains to be seen

Thank you

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