Rhumatismes inflammatoires et risques cardio-vasculaires

13ème Symposium Cœur et Cerveau

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CENTRE DE RHUMATOLOGIE | HIRSLANDEN CLINIQUE LA COLLINE

Lecture plan

- Epidemiology
- Pathophysiology
- Effect of therapy
- Management

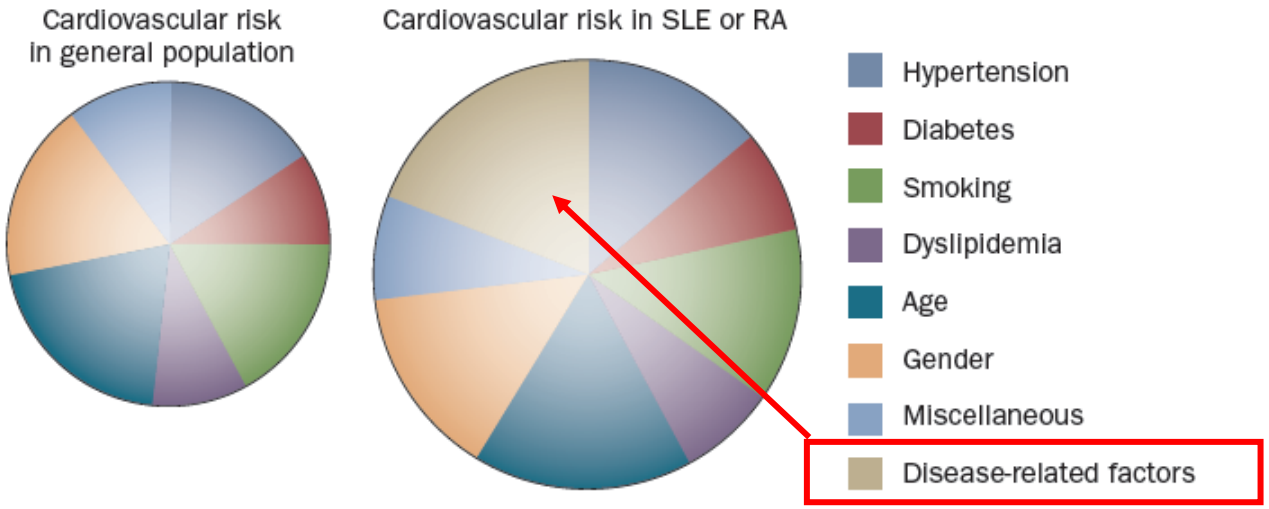
Mortality rate for CV events in RA is increased

Mortality rate for CV events in RA patients is increased by 50-100% compared to the normal population[1,2,3]

Results of a meta-analysis with 111,758 Patients with 22,927 CV events[1]

1 Avina-Zubieta et al., Arthritis & Rheum. 2008;59:1690–1697.
2 Naz et al., Best Practice & Research Clinical Rheumatology. 2007; 21:871–883.
3 Han et al. Arthritis Rheum. 2006;33:2167

CV risk factors in rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) patients vs general population



- RA and SLE patients with greater CVD risk overall vs general population
- relative contribution of traditional CV risk factors is smaller, due to competing risks caused by the presence of inflammatory rheumatic disease.

Symmons et al. Nature Reviews 2011

Cardiovascular Morbidity and Mortality in Women Diagnosed with Rheumatoid Arthritis

Nurses'Health Study:

- 114'342 women free of CV disease at baseline in 1976
- 527 cases of incident RA
- 3622 cases of myocardial infarction (MI) and stroke

Adjusted relative risk for MI: 2.00 (95% CI 1.23 to 3.29), P=0.005

Adjusted relative risk for stroke: 1.47 (95% CI 0.70 to 3.12), P=0.31

D.H. Solomon et al. *Circulation* 2003

Association with CV Events
Rheumatoid arthritis versus Type 2 Diabetes

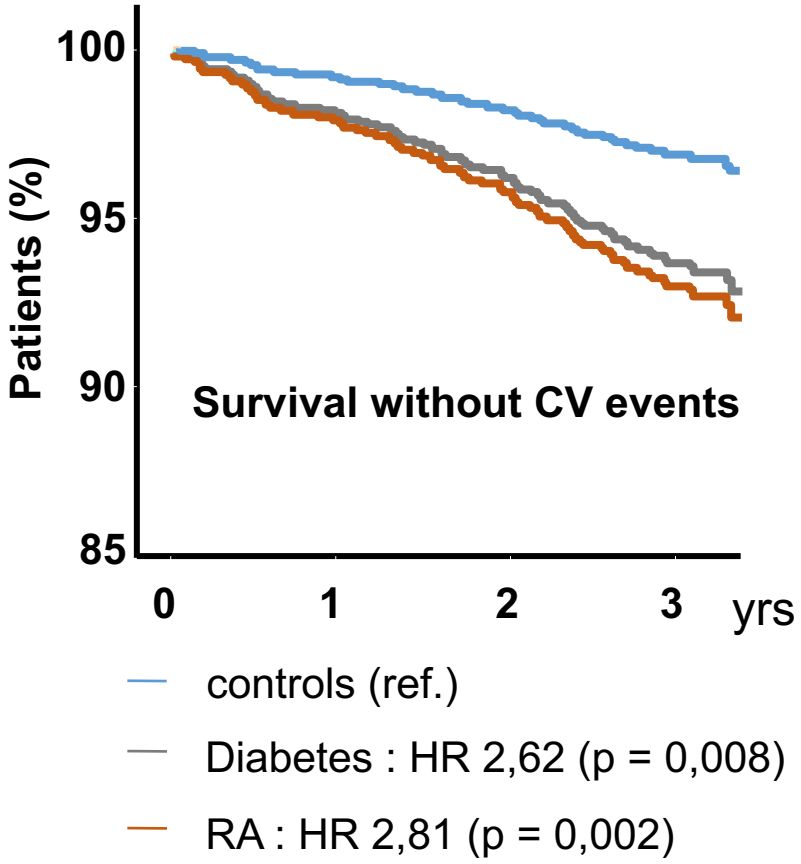


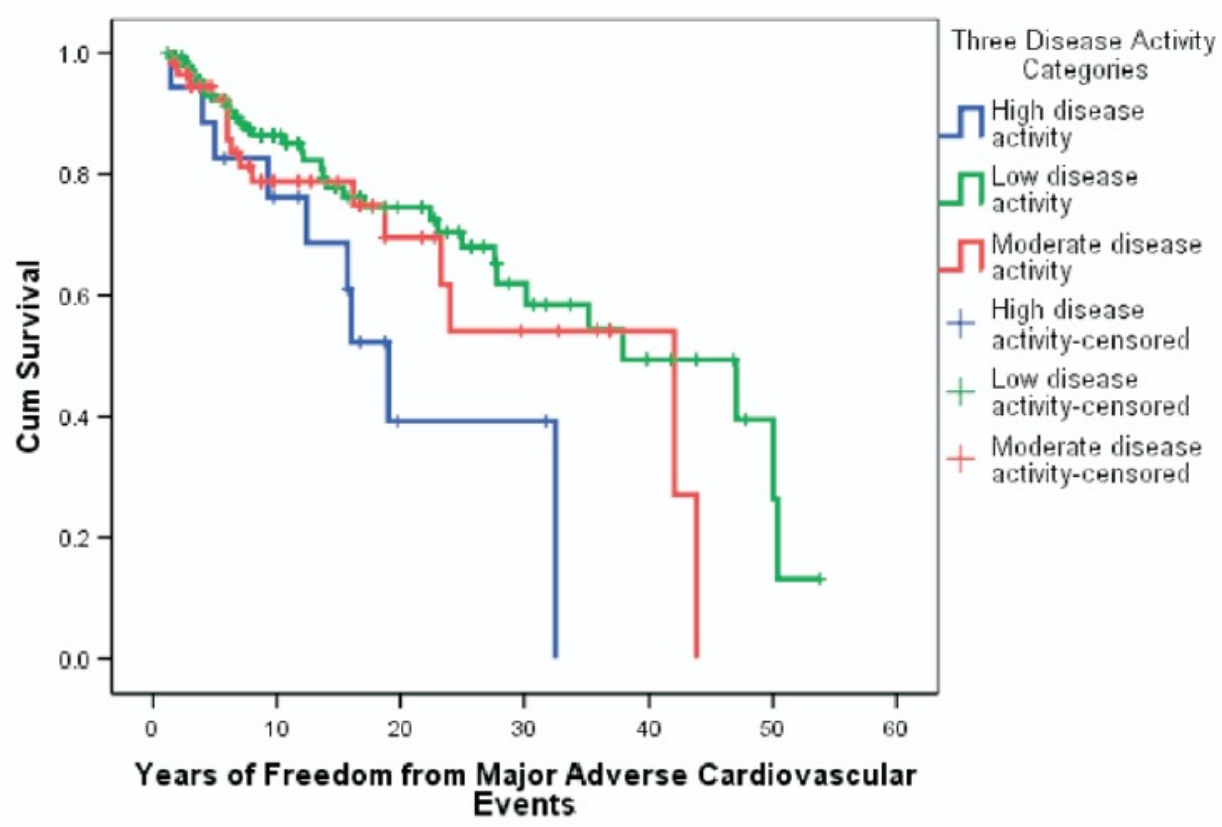
Table 2 Prevalence odds ratios (ORs) for cardiovascular disease using controls as a reference

	OR (95% CI)	p Value
Model I		
Non-diabetic controls	1.00 (reference)	
DM2	2.62 (1.29 to 5.32)	0.008
RA	2.81 (1.46 to 5.42)	0.002
Model II		
Non-diabetic controls	1.00 (reference)	
DM2	2.31 (1.13 to 4.72)	0.022
RA	3.11 (1.59 to 6.08)	0.001
Model III		
Non-diabetic controls	1.00 (reference)	
DM2	2.01 (0.90 to 4.51)	0.090
RA	2.70 (1.24 to 5.86)	0.012

Model I: crude associations
Model II: adjustement for age and sex
Model III: adjustement for CV risk factors

Van Halm et al *Ann Rheum Dis* 2008

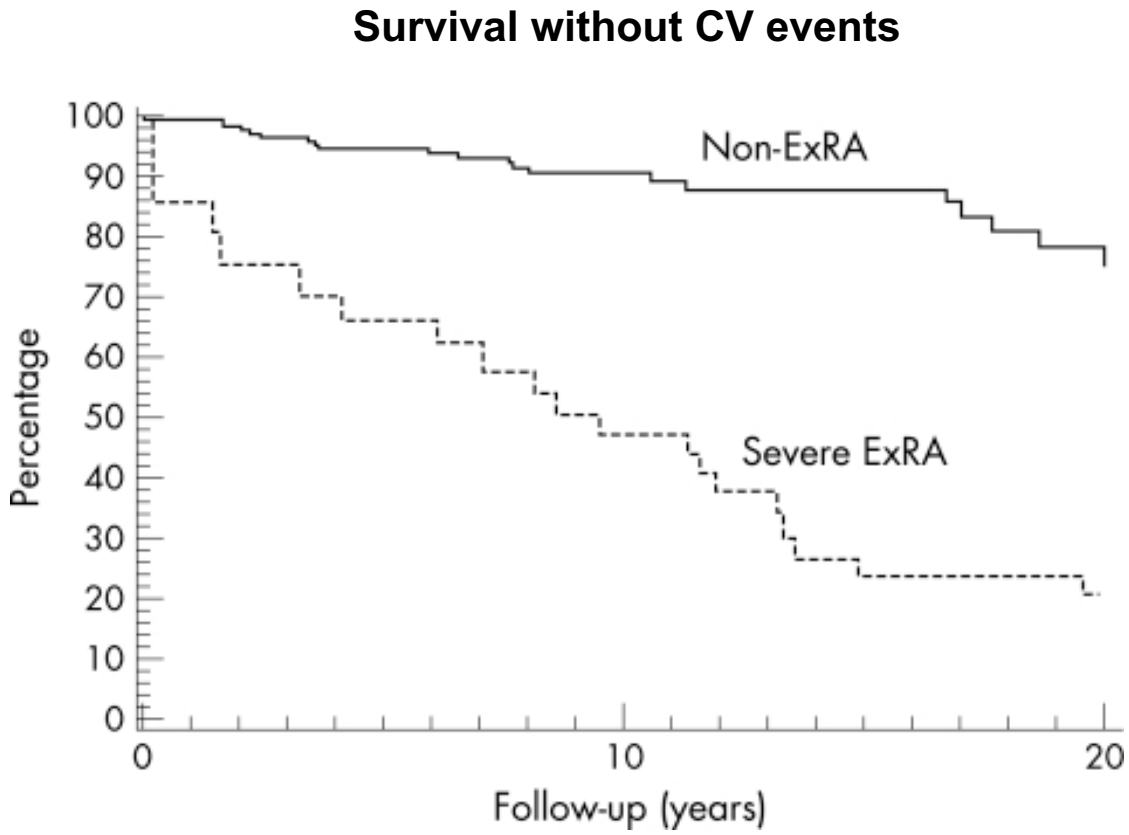
Disease Activity Score is a Significant Predictor of MACEs in RA



- Male US veterans aged >50 years with high risk for MACEs
- Disease activity score = significant predictor of MACEs independent of traditional CV risk factors

Banerjee et al. Am J Cardiol 2008

Significant Effect of Disease Severity as a CV Risk Factor



Turesson et al, *Ann Rheum Dis* 2007

Traditional CV Risk Factors Are Critical in RA

Results from the QUEST Study

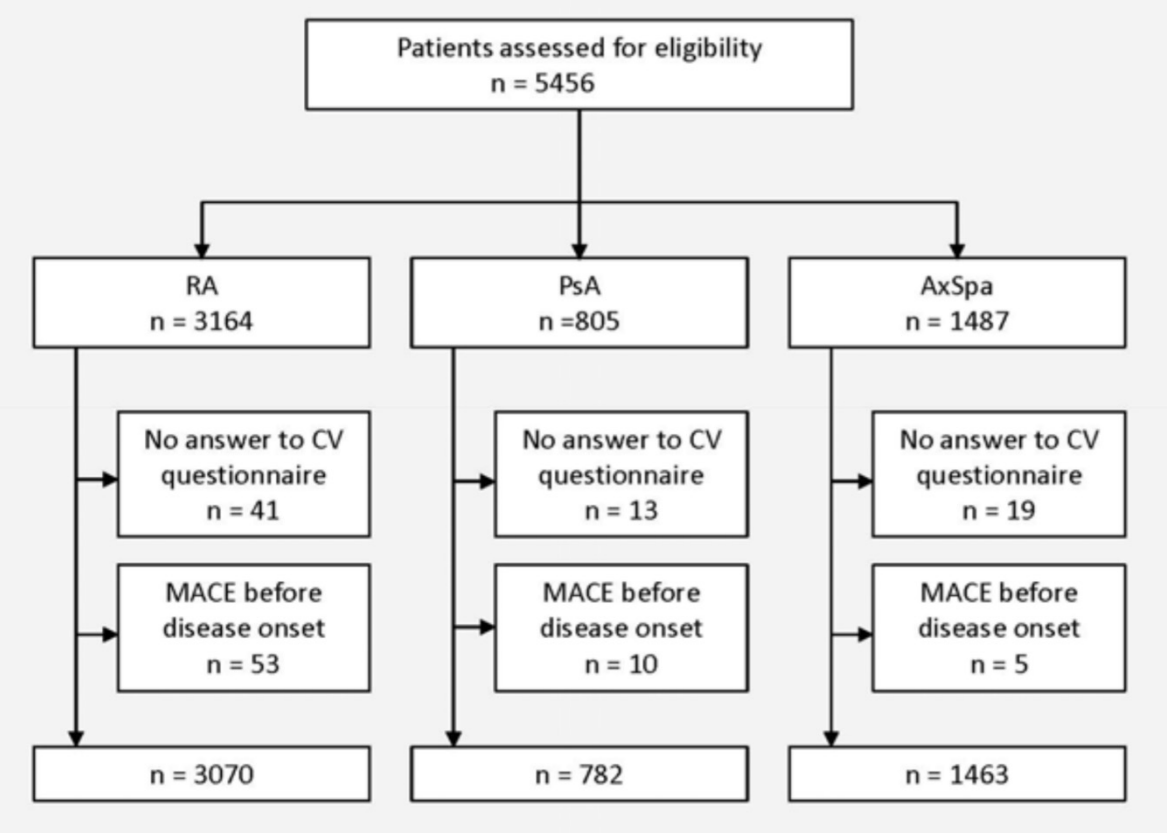
	Myocardial infarction hazard ratio (95% CI)		
	All countries	Countries with high prevalence	Countries with low prevalence
Age	1.05 (1.02–1.08)[c]	1.04 (1.01–1.08)[c]	1.06 (1.00–1.13)[c]
Gender (female)	0.46 (0.27–0.80)[c]	0.55 (0.29–1.06)	0.37 (0.13–1.04)
Rheumatoid factor	0.68 (0.36–1.31)	0.68 (0.31–1.48)	0.82 (0.23–2.91)
Extra-articular disease	2.26 (1.29–3.97)[c]	2.26 (1.17–4.37)[c]	2.13 (0.71–6.35)
Hypertension	1.45 (0.83–2.53)	1.10 (0.57–2.15)	2.19 (0.72–6.71)
Hyperlipidemia	3.51 (1.98–6.21)[b]	3.51 (1.80–6.84)[b]	4.34 (1.41–13.33)[c]
Diabetes	1.18 (0.59–2.38)	1.27 (0.56–2.90)	1.01 (0.24–4.29)
Ever-smoking	3.20 (1.74–5.90)[b]	2.47 (1.22–4.99)[c]	12.14 (2.50–59.05)[c]
Obesity	0.74 (0.34–1.62)	0.59 (0.22–1.57)	1.36 (0.37–5.01)
Physical inactivity	0.88 (0.46–1.65)	0.96 (0.45–2.07)	0.87 (0.24–3.12)

A. Naranjo et al. *Arthritis Res Ther* 2008

Incidence and prevalence of MACE

Results from a patient population with rheumatic diseases

For the analysis of incidence, a total of 5‘315 patients were eligible and contributed a total follow-up time of
37‘495 patient years for RA,
19‘837 for AxSpA,
9‘171 for PsA.
Rheumatic diseases started between 1950 and 2014.



Lauper et al., *Arthritis Care Res* 2018

Prevalence of non-lethal MACE

- Traditional risk factors and disease duration are associated with the prevalence of MACE in a Swiss cohort of patients with rheumatic diseases
- No difference between RA, ankylosing spondylitis and psoriatic arthritis
- Similar results for the incidence of MACE

PR: prevalence ratio, CI: confidence interval, yrs: years. Results from logistic regression.

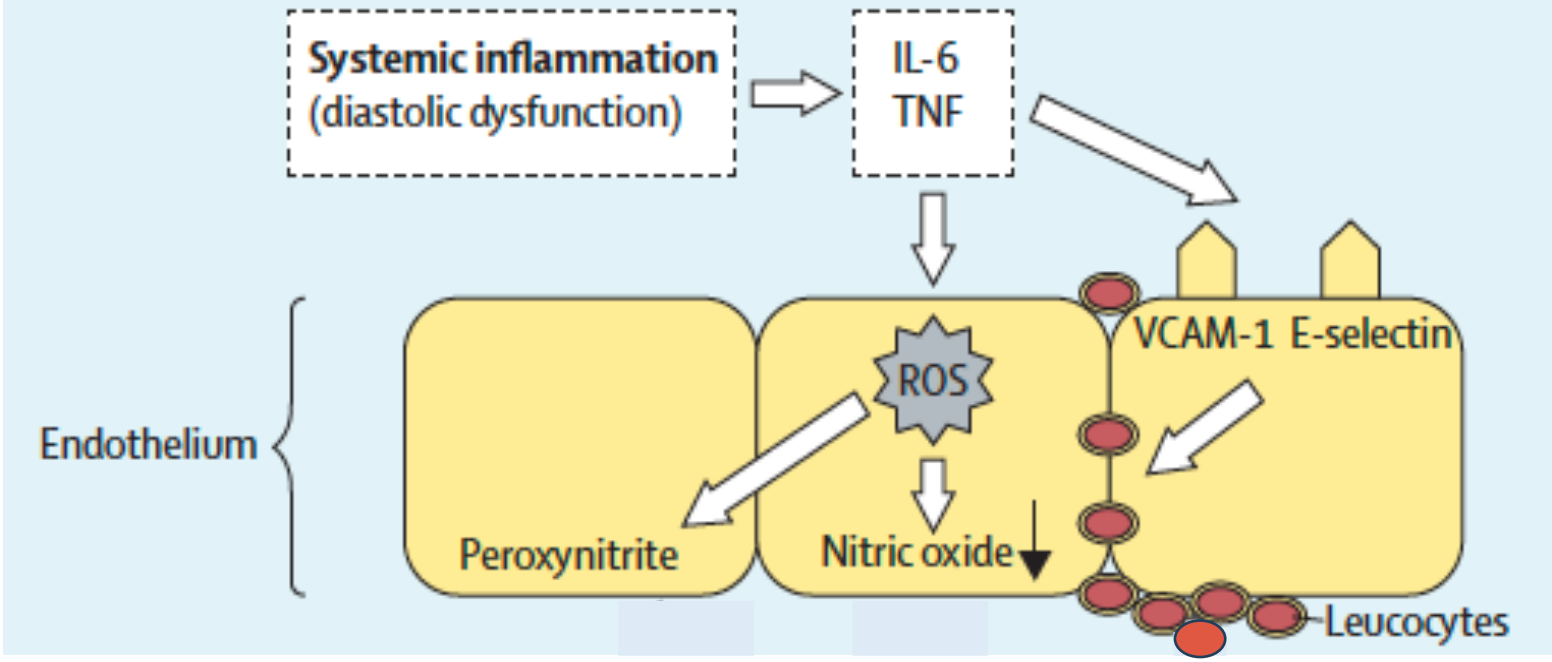
	Events/ patients	Rate (%)	PR	95%CI	*P*-value
Unadjusted					
RA	153/3164	4.84	--	--	--
AxSpA	33/1487	2.22	0.45	0.31-0.65	<0.001
PsA	23/805	2.86	0.58	0.37-0.90	0.02
Adjusted					
RA			--	--	--
AxSpA			0.98	0.58-1.61	0.94
PsA			0.66	0.37-1.12	0.14
Age [yrs]			1.07	1.05-1.09	<0.001
Gender (male)			1.68	1.20-2.35	0.002
Known familial history of MACE			1.66	1.10-2.41	0.01
Ever-smoker			1.80	1.26-2.61	0.001
Hypertension			1.42	1.03-2.07	0.048
Diabetes			0.79	0.47-1.25	0.34
Hyperlipidemia			3.59	2.56-5.03	<0.001
Disease duration [yrs]			1.08	1.06-1.10	<0.001

Lauper et al., *Arthritis Care Res* 2018

Pathophysiology
Inflammation and CV Risk

- Endothelial dysfunction
- Endothelial activation with recruitment of inflammatory cells
- Circulating lipid changes
- Hypercoagulability
- Myocardial dysfunction

Endothelial Activation by Pro-inflammatory Cytokines

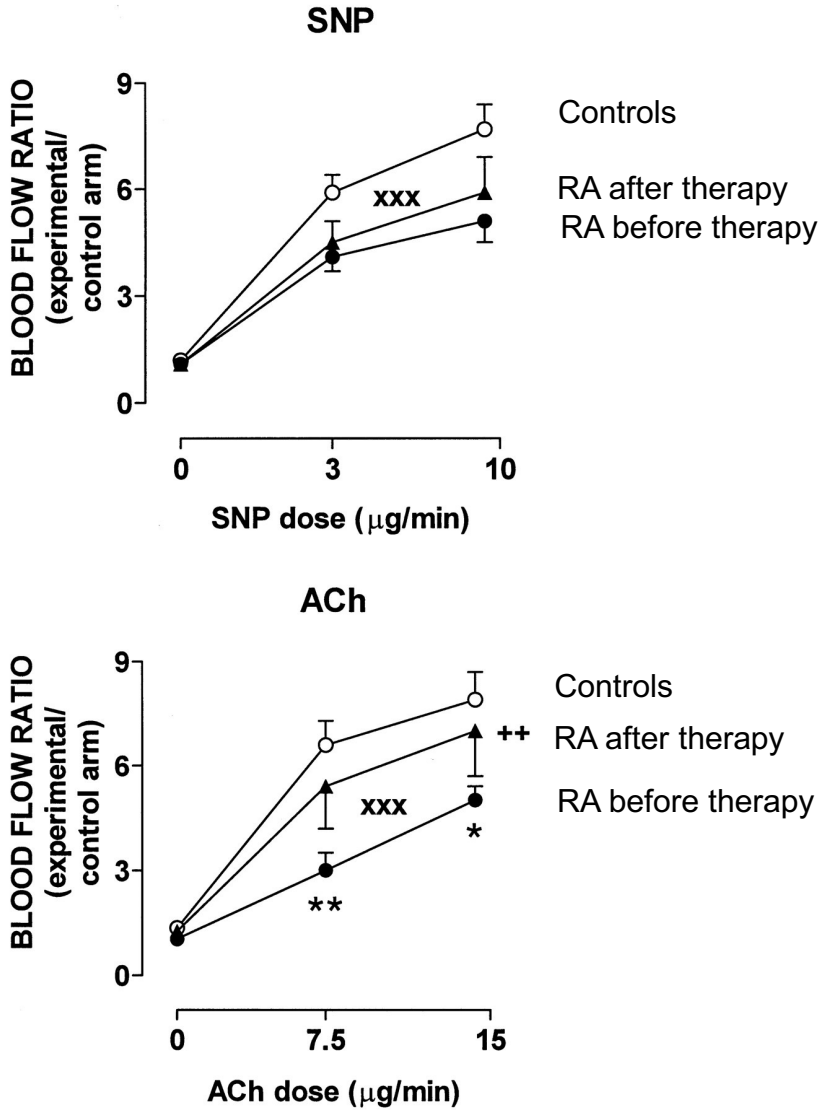


R. Hansildaar et al. *Lancet Rheumatol* 2021

Endothelial Dysfunction in RA

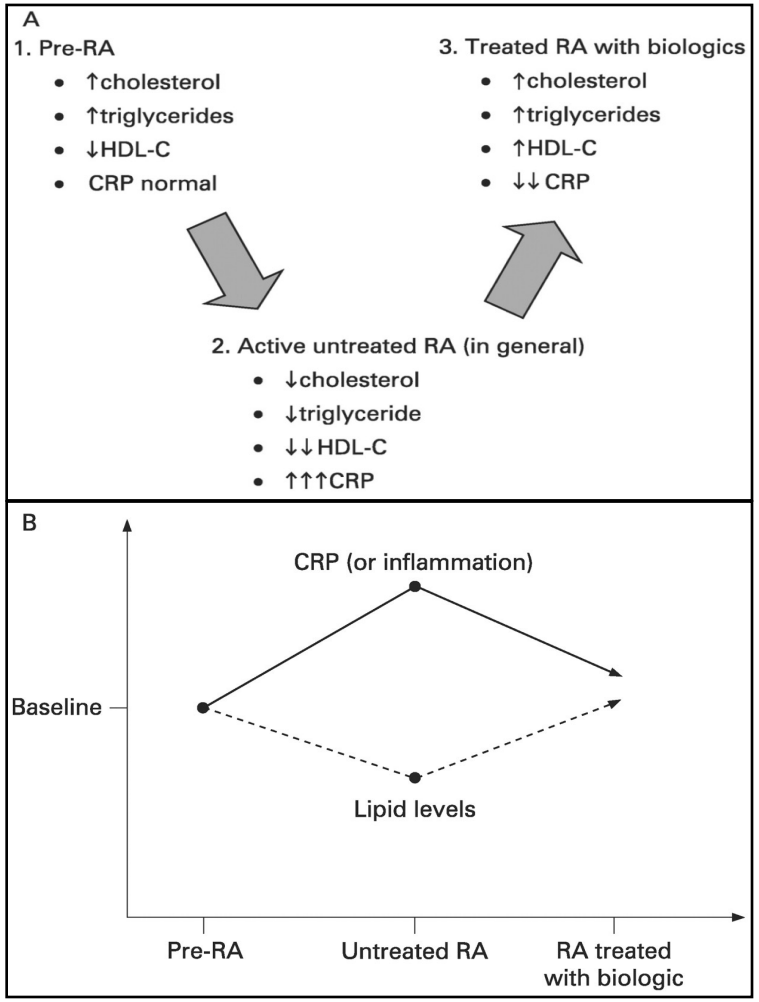
Forearm arterial blood flow measurement in 10 RA and 33 controls

Responsiveness to intrabrachial artery infusion of the endothelial-dependent vasodilator acetylcholine (Ach) and of endothelial independent vasodilator sodium nitroprusside (SNP) before and after anti-inflammatory therapy



R. Bergholm et al. *Aterioscl Thromb Vasc Biol* 2002

Inflammation-Dependent Metabolic Changes



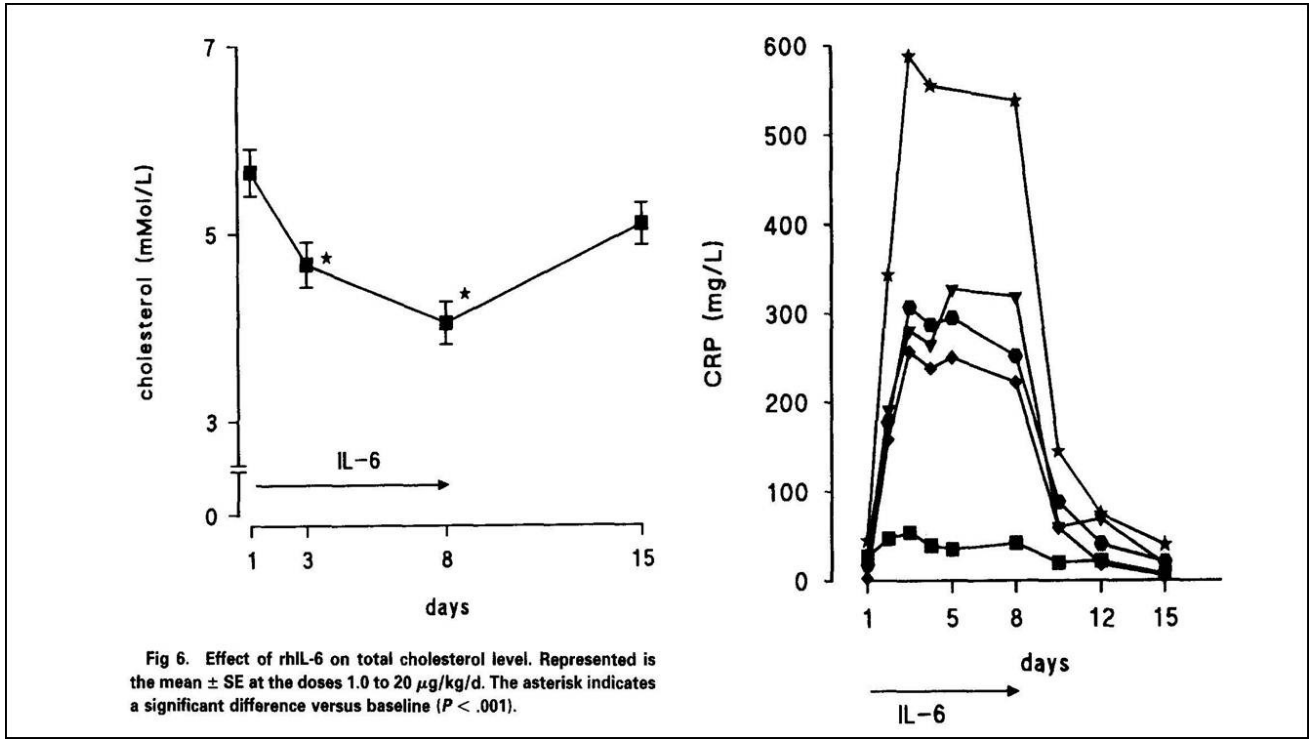
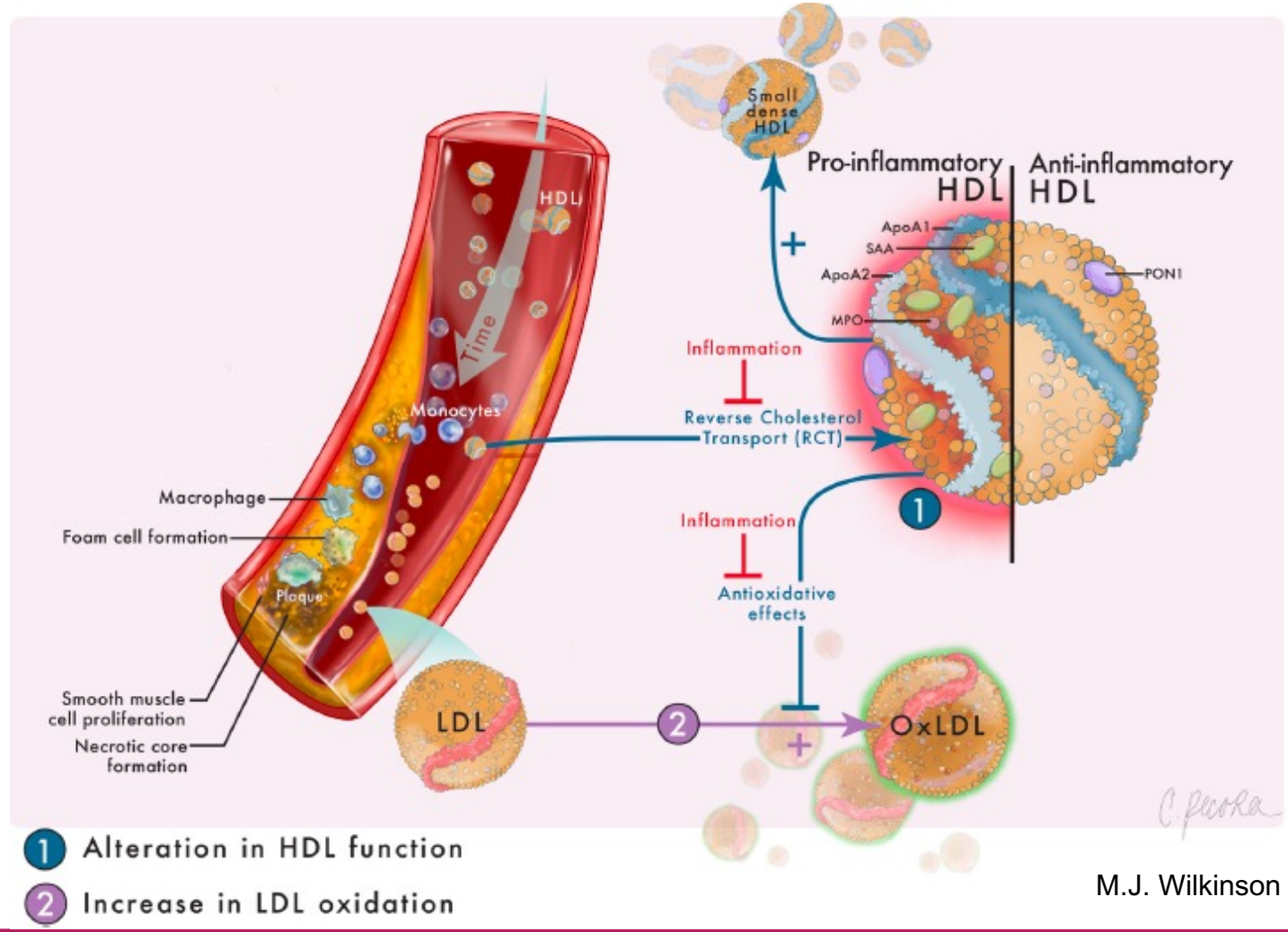


Fig 6. Effect of rhIL-6 on total cholesterol level. Represented is the mean ± SE at the doses 1.0 to 20 μg/kg/d. The asterisk indicates a significant difference versus baseline ($P < .001$).

E Choy and N Sattar. *Ann Rheum Dis* 2009;68:460-469.

van Gameren MM, et al. *Blood* 1994; 84(5):1434–1441

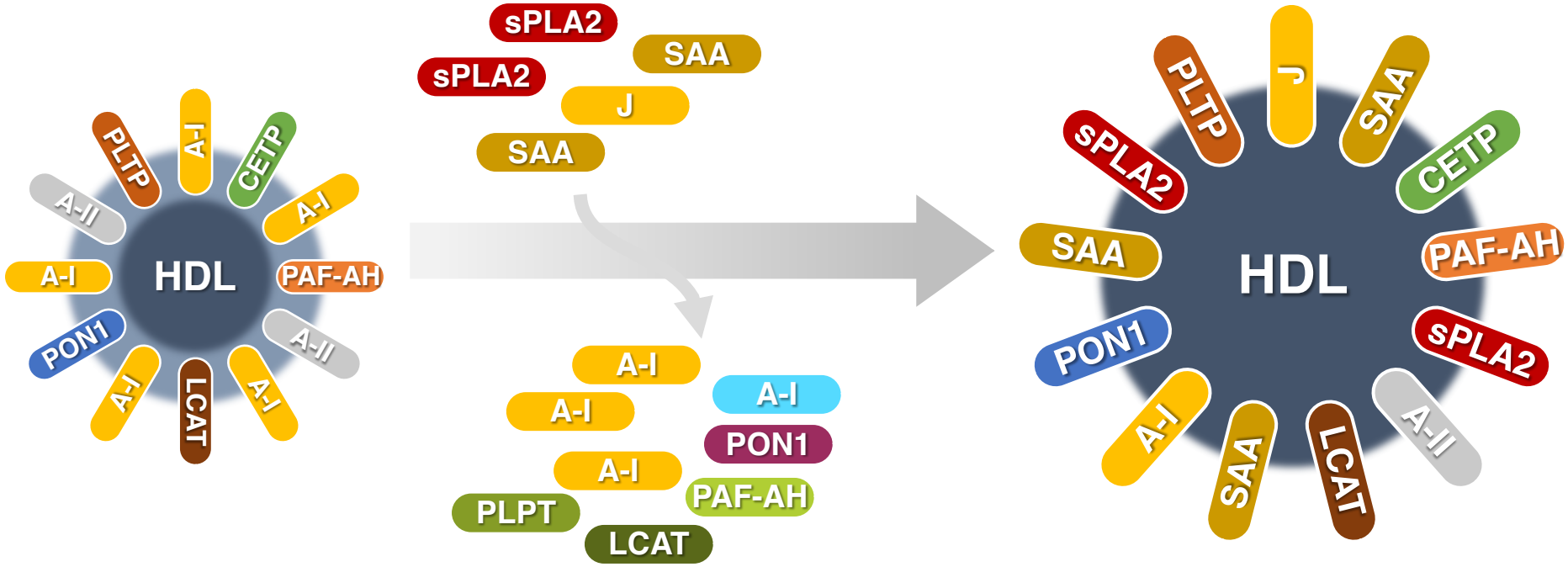
Changes in Circulating Lipids in Inflammatory Diseases



M.J. Wilkinson et al. *Arterioscl Thromb Vasc Biol* 2024

HDL Changes to Proinflammatory Composition

HDL particles become atherogenic and proinflammatory by associating with specific acute-phase reactants, including SAA, apolipoproteins and phospholipases

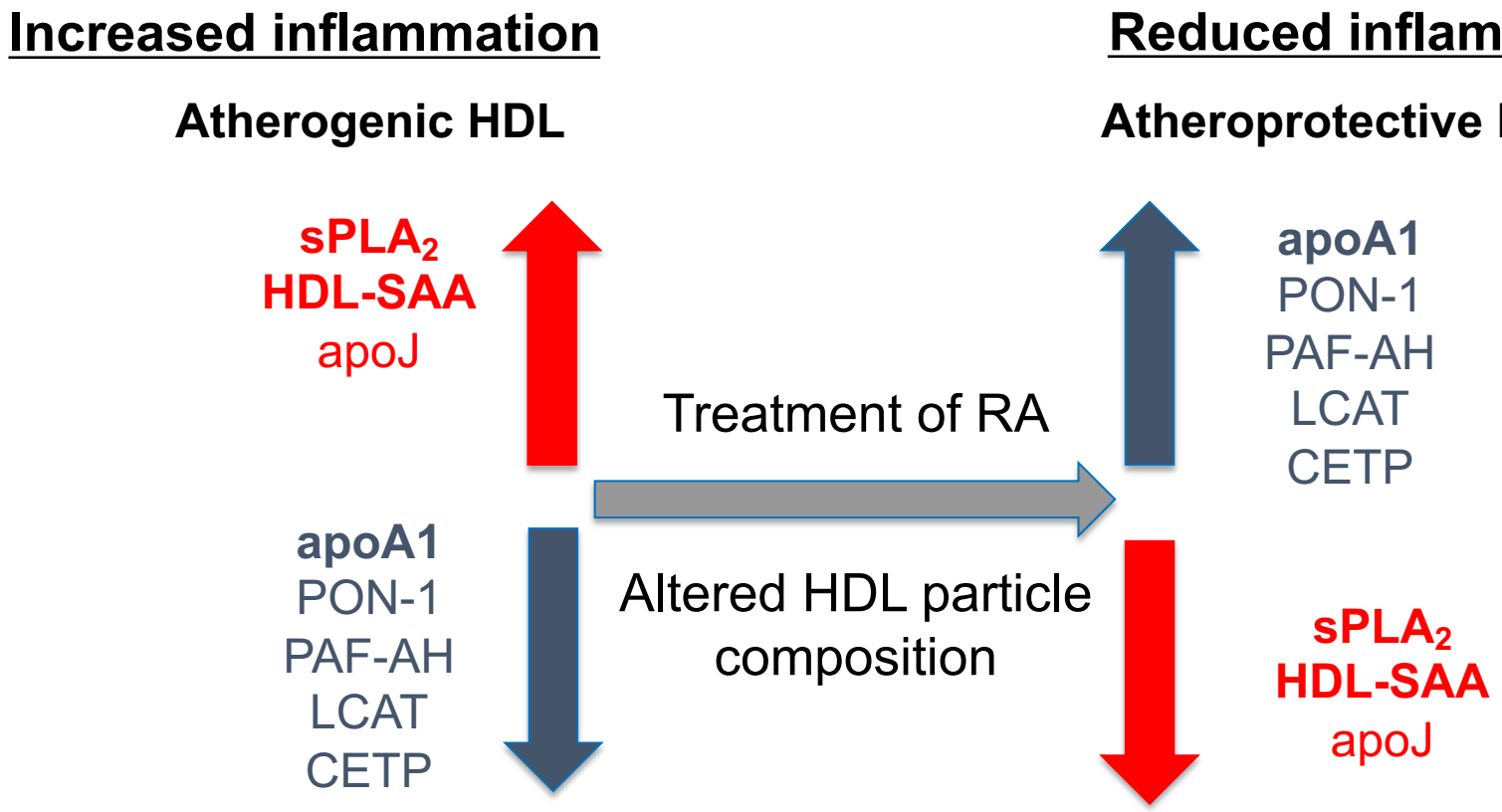


A-I, apolipoprotein A-I; CETP, cholesteryl ester transfer protein; LCAT, lecithin: cholesterol acyltransferase; PAF-AH, platelet activating factor acyl hydrolase; PLTP, phospholipid transfer protein; PON, paraoxonase

Adapted from Rohrer L, et al. *Curr Opin Lipidol* 2004;15:269–78

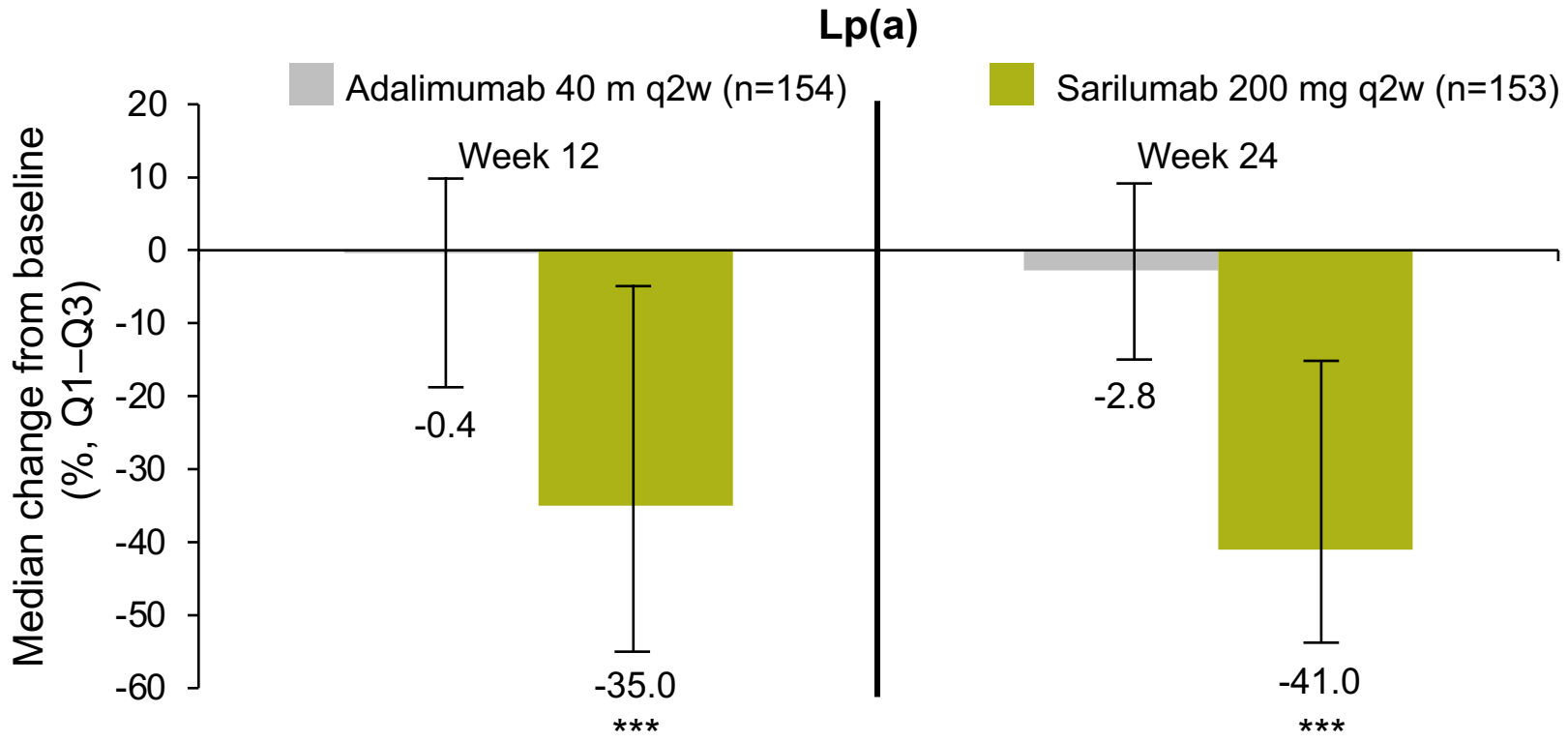
Changes in HDL Composition

Change in Cardiovascular Inflammatory Markers with Treatment of RA



Apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL-SAA, HDL-associated serum amyloid A; LCAT, lecithin:cholesterol acyltransferase; MI, myocardial infarction; PAF-AH, platelet-activating factor acetylhydrolase; PON-1, paraoxonase 1; $sPLA_2$, secretory phospholipase A_2.

Sarilumab (Anti-IL-6R) decreased Lp(a), a marker of cardiovascular risk, compared to adalimumab (Anti-TNF) monotherapy



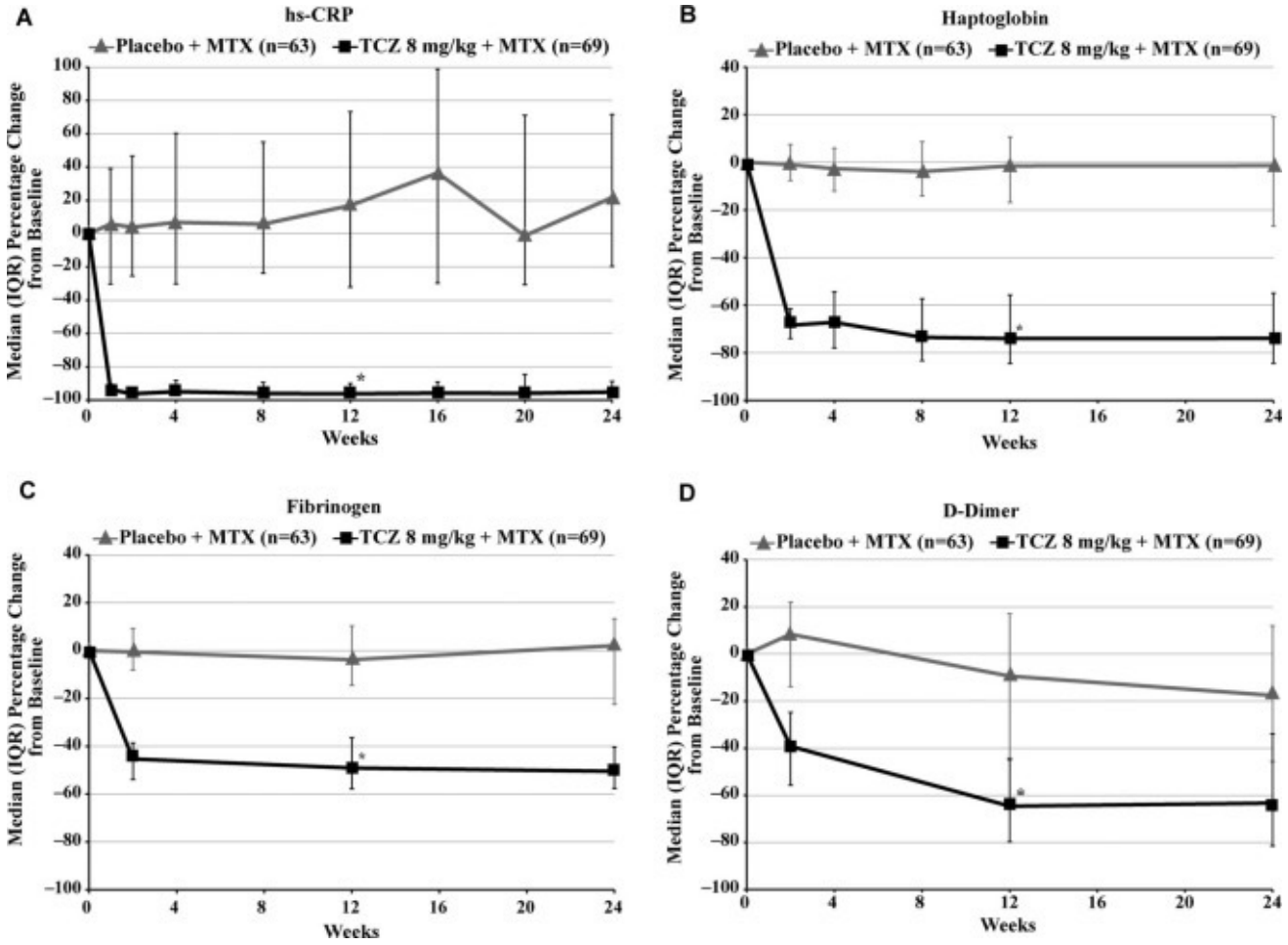
- Elevated Lp(a) levels are associated with increased risk of CVD and CHD[1]
- Sarilumab may attenuate CV risk by decreasing Lp(a) levels compared with adalimumab

***Adjusted p < 0.0001 vs. adalimumab (Benjamini–Hochberg procedure). CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; Lp(a), lipoprotein (a); ; Q, quartile; q2w, every 2 weeks

1. Nordestgaard BG, et al. *Eur Heart J* 2010;31:2844–53

Gabay, et al. *Arthritis Res Ther* 2020 Apr 7;22(1):70

IL-6 Inhibition Reverses the Hypercoagulability State in RA



IL-6 inhibition also decreases inflammation-dependent elevated platelet levels

I.B. McInnes et al. *Ann Rheum Dis* 2015

Effect of Anti-inflammatory Therapy
Prednisone

- Prednisone was associated with subsequent MI in RA[1]
- Prednisone use was associated with a dose-dependent increased risk for CV events (p=0.04)[2]
- Prednisone > 7.5 mg/d significantly associated with CV events[2,3]
- Cumulative prednisone exposure was associated with plaque progression[4]
- Use of corticosteroids in RA patients was associated with future development of diabetes and hypertension[1]

1 Wolfe & Michaud. *Arthritis Rheum* 2008; 2 Greenberg et al. *Ann Rheum Dis* 2011; 3 Davis et al. *Arthritis Rheum* 2007; 4 Giles et al. *Arthritis Rheum* 2011

Effect of Anti-inflammatory Therapy

Conventional Synthetic Disease Modifying Antirheumatic Drugs (csDMARDs)

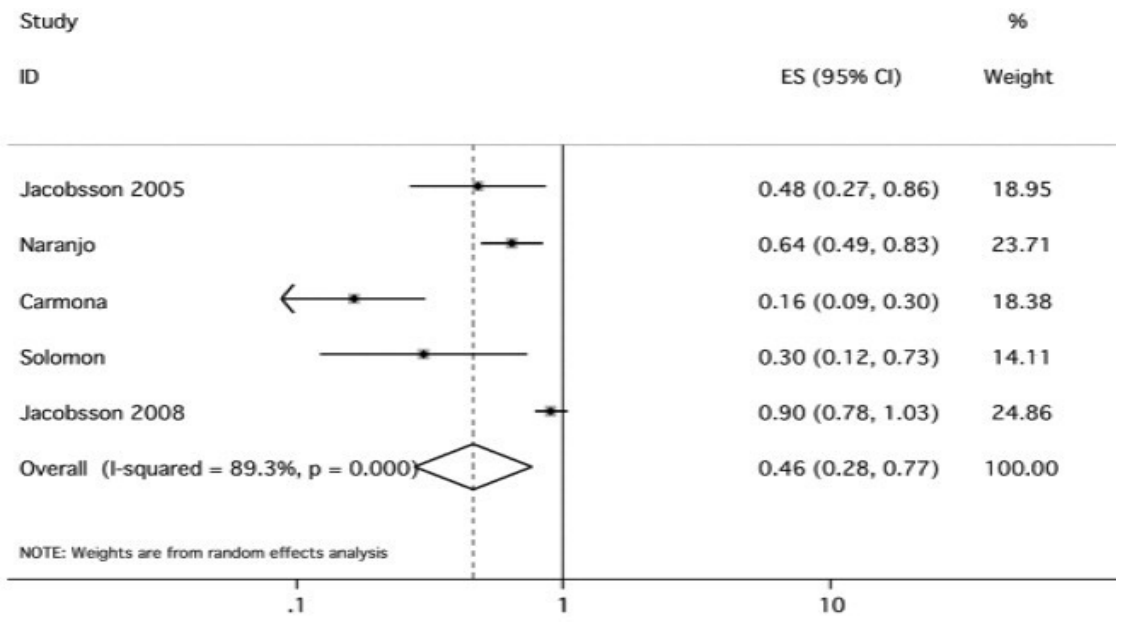
- Methotrexate (MTX) reduces CV mortality[1]
- MTX & Leflunomide are associated with a reduction in acute MI risk[2]
- MTX use is associated with a reduced risk of CV events[3]
- MTX, leflunomide, salazopyrine are associated with reduced CV risk[4]

➡ The protective effect of MTX is consistently observed in studies in RA

1 Choi et al. Lancet 2002
2 Suissa Arthritis & Rheum 2006
3 Westlake et al. Review. Rheumatology 2010
4 Naranjo et al. *Arthritis Res Ther* 2008

Effect of Anti-inflammatory Therapy
Biological Disease Modifying Antirheumatic Drugs (bDMARDs)

- Anti-TNF therapy is associated with a reduced risk of all cardiovascular events* in observational cohorts
- RCTs demonstrated a trend toward decreased risk (point estimate of the effect from RCTs underpowered with wide 95% CIs and CV events were secondary outcomes)



*all events, myocardial infarction, congestive heart failure, and cerebrovascular accident

C. Bernabe et al. *Arthritis Care & Research* 2011

Incidence of MACE in a Collaboration of Registries

JAK Inhibitors vs Biologics

Table 4. Crude and adjusted incidence and IRRs of MACEs for within-registry and combined data analysis in the randomized controlled trial duplicate cohort (aged ≥50 years and with at least one cardiovascular risk factor)

	PYs	MACEs	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Within-registry analysis[a]					
TNFi	21,628	258	11.93 (10.52–13.48)	1 (ref)	1 (ref)
JAKi	9,027	91	10.08 (8.12–12.38)	1.02 (0.80–1.32)	0.57 (0.12–2.66)
bDMARD-OMA	13,256	224	16.90 (14.76–19.26)	1.46 (1.22–1.75)[b]	1.11 (0.43–2.94)
Combined data analysis[c]					
TNFi	21,136	94	4.45 (3.59–5.44)	1 (ref)	1 (ref)
JAKi	11,440	41	3.58 (2.57–4.86)	0.81 (0.56–1.17)	1.11 (0.55–2.22)
bDMARD-OMA	12,933	70	5.41 (4.22–6.84)	1.22 (0.89–1.66)	1.36 (1.07–1.72)[b]

Similar results when analyzing patients with history of CV disease

R. Aymon et al. *Arthritis Rheumatol* 2025

Management of CV Risk in Patients with Inflammatory Rheumatic Diseases

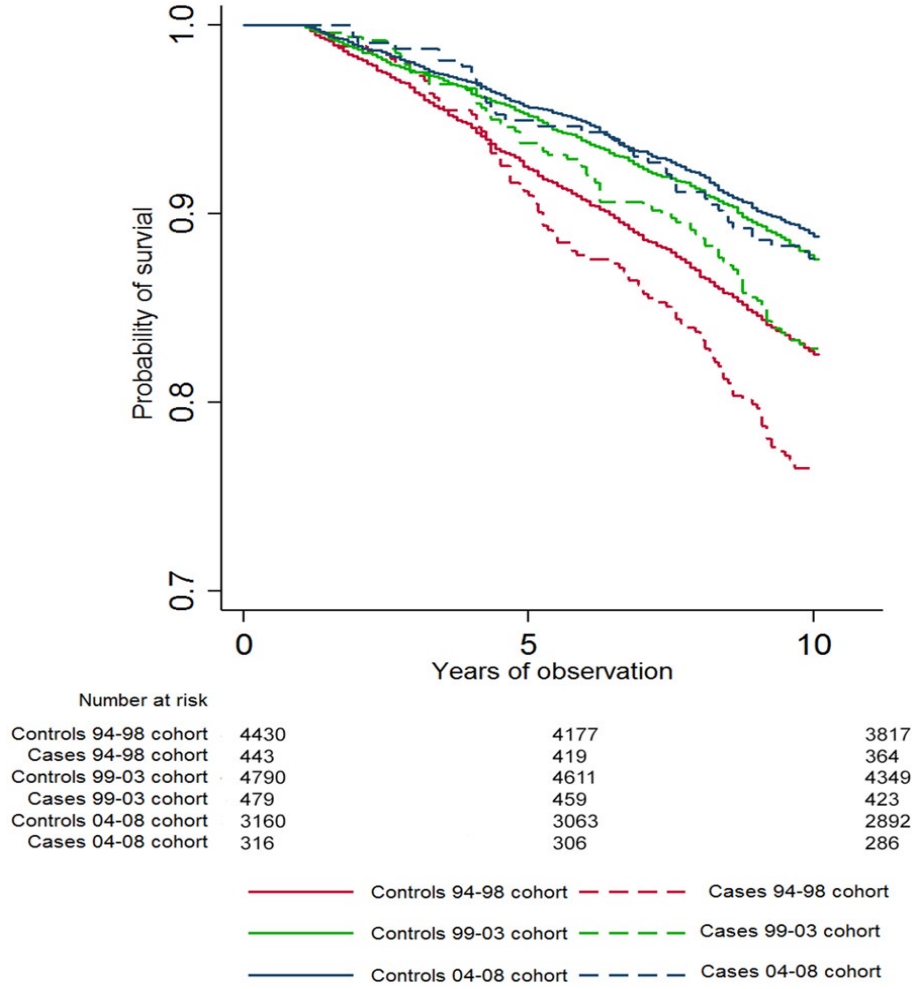
EULAR 2015-16 Updated Recommendations

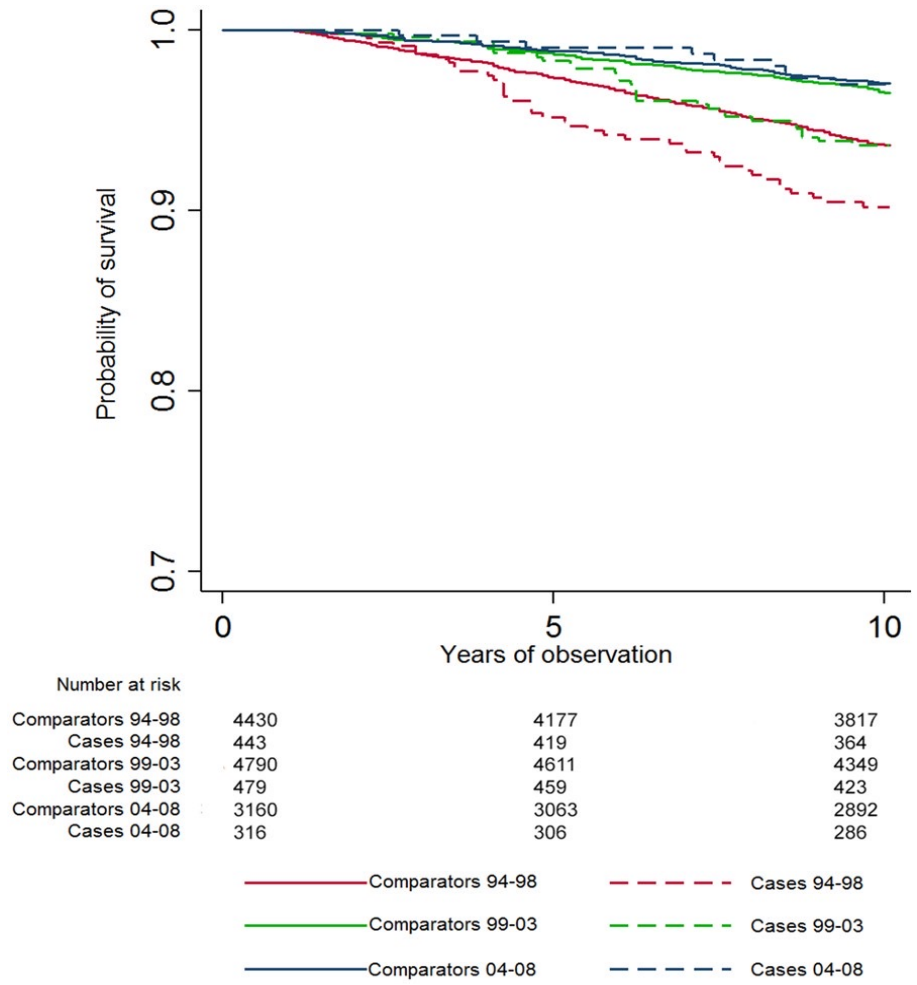
	Level of evidence	Strength of recommendation	Level of agreement (SD)
Overarching principles A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA. B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD. C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS			
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

R. Agca et al. *Ann Rheum Dis* 2017

Kaplan–Meyer survival curves

All-cause and CV mortality over 10 years.





S.A. Provan et al. Rheumatology 2020

Conclusion

Cardiovascular risk in patients with inflammatory rheumatic diseases requires an appropriate management of traditional risk factors and the inflammatory condition

IL-6 is a major inducer of the acute-phase response

- RA inflammation can be accompanied by a systemic reaction that leads to an increase or decrease in acute phase reactant (APR) by at least 25%[1]
- IL-6 is a major inducer of the production of most acute-phase proteins in human liver cells[2]
- CRP accelerates the chronicity of disease by promoting IL-6R shedding by human neutrophils and enhancing complement function in mice and humans[3,4]

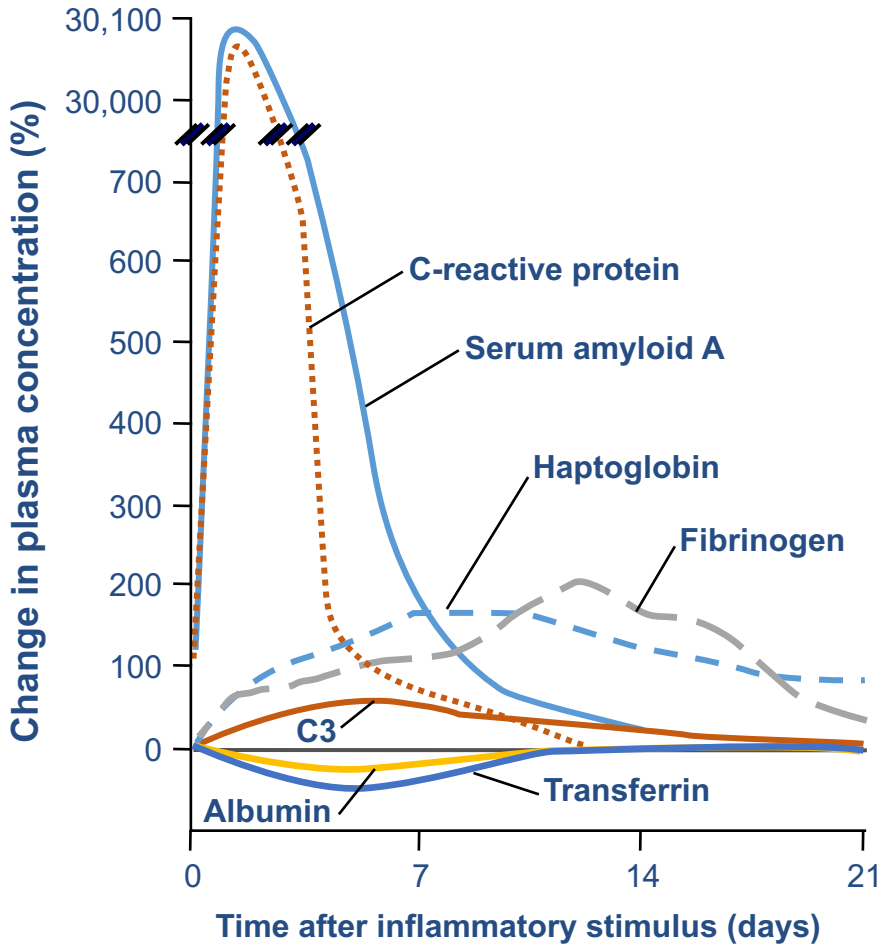
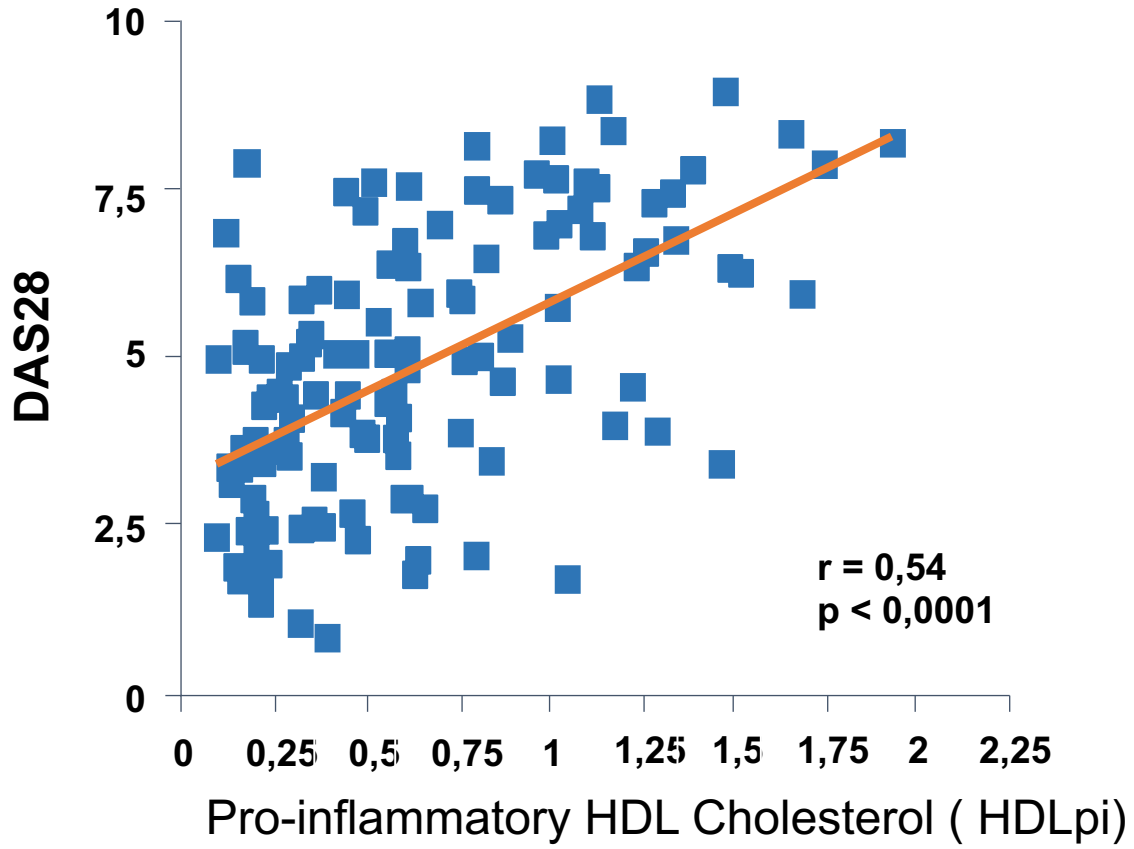


Figure adapted from Gabay C, Kushner I. *N Engl J Med*. 1999;340:448-454.

1. Kushner I. *Ann NY Acad Sci*. 1982;389:39-48.
2. Gabay C, Kushner I. *N Engl J Med*. 1999;340:448-454.
3. Marnell L et al. *Clin Immmunol*. 2006;117:104-111.
4. Jones SA et al. *J Exp Med*. 1999;189:599-604.

Lipids and Inflammation

Correlation between Pro-inflammatory HDL levels and Disease Activity Score



Mc Mahon et al, *Arthritis Rheum* 2006;54:2541-9

Changes in HDL Composition (ADACTA Study)

Changes in acute phase reactant levels from baseline to week 8

Subgroup	Statistic	Change From Baseline at Week 8 in HDL-SAA, mg/L		Change From Baseline at Week 8 in $sPLA_2$, ng/mL	
		ADA	TCZ	ADA	TCZ
All patients	n	62	55	86	73
	Mean (SD)	–4.4 (12.3)	–9.3 (18.3)	–1.8 (9.2)	–7.8 (12.8)
	Median (min, max)	–1.1 (–42.4, 26.5)	–3.2 (–112.6, 9.1)	–1.3 (–43.8, 29.7)	–4.1 (–70.6, 1.6)
	Quartiles [25%, 75%]	–7.1, 0.6	–11.1, –1.0	–2.9, 0.8	–7.8, –1.1
	p[a]	0.0077		<0.0001	

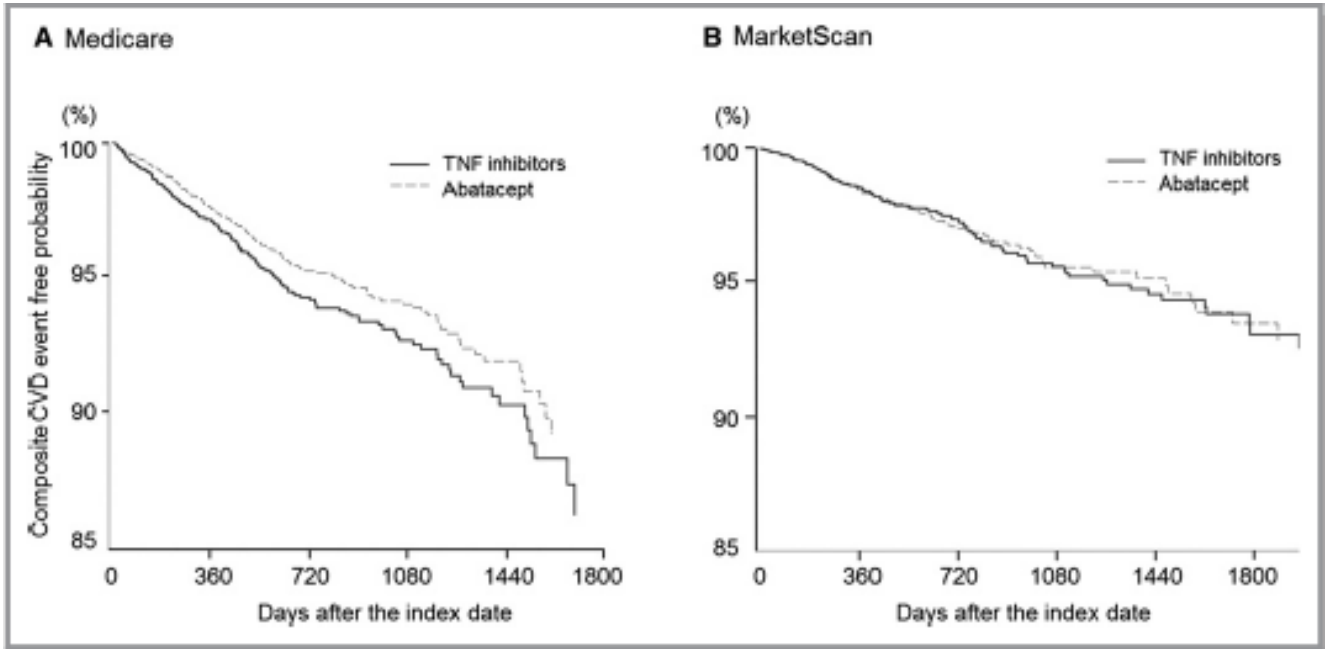
[a]Kruskal-Wallis analysis comparing difference between median values (ADA vs TCZ)
TCZ: Tocilizumab Anti-IL-6R antibody
ADA: adalimumab Anti-TNF antibody

Gabay C, et al. *Ann Rheum Dis* 2016;75:1806–1812

Effect of Anti-inflammatory Therapy

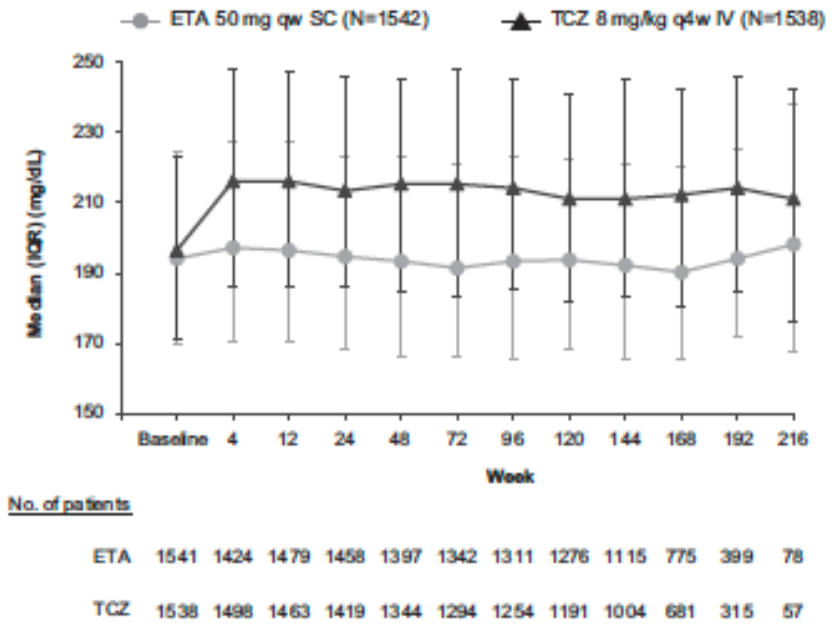
Biological Disease Modifying Antirheumatic Drugs (bDMARDs)

- Abatacept is associated with reduced CV
- Abatacept vs anti-TNF and occurrence of CV events were compared using MediCare and MediScan databases
- Abatacept offered a better protection in MediCare RA patients with diabetes



E.H. Kang et al. *J Am Heart Assoc* 2018

Cardiovascular Safety of Tocilizumab vs Etanercept in RA Patients



End point	First event: Etanercept No. (%) first events	Etanercept No. first events/ 100 person-years (95% CI)	Tocilizumab No. (%) first events	Tocilizumab No. first events/ 100 person-years (95% CI)	HR†	95% CI†
Primary end point of MACE, including undetermined cause of death						
ITT population‡	78 (5)	1.70 (1.35–2.10)	83 (5)	1.82 (1.46–2.24)	1.05	0.77–1.43
On-treatment population§	52 (3)	1.28 (0.97–1.66)	57 (4)	1.44 (1.10–1.85)	1.11	0.76–1.62
Sensitivity analysis of primary end point (ITT population)						
MACE, excluding undetermined cause of death	72 (5)	1.57 (1.24–1.97)	74 (5)	1.63 (1.29–2.03)	1.01	0.73–1.40
MACE, before last direct contact	46 (3)	1.00 (0.74–1.33)	49 (3)	1.06 (0.79–1.40)	1.04	0.70–1.56
Secondary end points (ITT population)						
Nonfatal MI	31 (2)	0.65 (0.45–0.92)	28 (2)	0.59 (0.40–0.85)	0.89	0.54–1.49
Nonfatal and fatal MI	32 (2)	0.67 (0.46–0.95)	29 (2)	0.61 (0.41–0.87)	0.90	0.54–1.48
Nonfatal stroke, all types	15 (1)	0.33 (0.19–0.53)	24 (2)	0.49 (0.31–0.73)	1.53	0.80–2.92
Nonfatal and fatal stroke, all types	16 (1)	0.35 (0.20–0.56)	26 (2)	0.53 (0.35–0.78)	1.55	0.83–2.90
Cardiovascular-related death	35 (2)	0.72 (0.50–1.00)	36 (2)	0.73 (0.51–1.02)	1.03	0.64–1.63
Death from any cause	64 (4)	1.31 (1.01–1.67)	64 (4)	1.31 (1.01–1.67)	0.99	0.70–1.41
Expanded composite end point¶	84 (5)	1.98 (1.61–2.42)	84 (6)	1.90 (1.53–2.33)	0.99	0.73–1.34
Exploratory end points (ITT population)						
MACE and HHF	85 (6)	1.90 (1.53–2.33)	90 (6)	2.12 (1.73–2.57)	1.05	0.78–1.41
HHF	8 (1)	0.20 (0.10–0.38)	12 (1)	0.31 (0.17–0.50)	1.50	0.61–3.67

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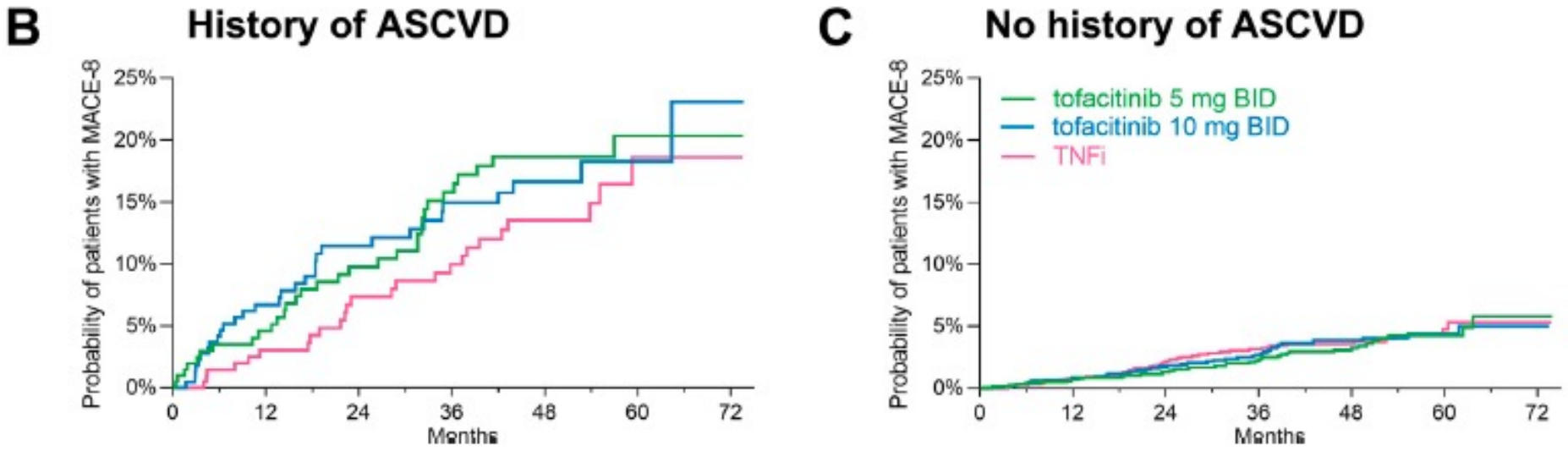
Post Hoq Analysis of Oral Surveillence

Tofacitinib vs anti-TNF



Increased risk in patients with history of CVD
Increased risk in patients ≥ 65 years

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Post Hoq Analysis of Oral Surveillence

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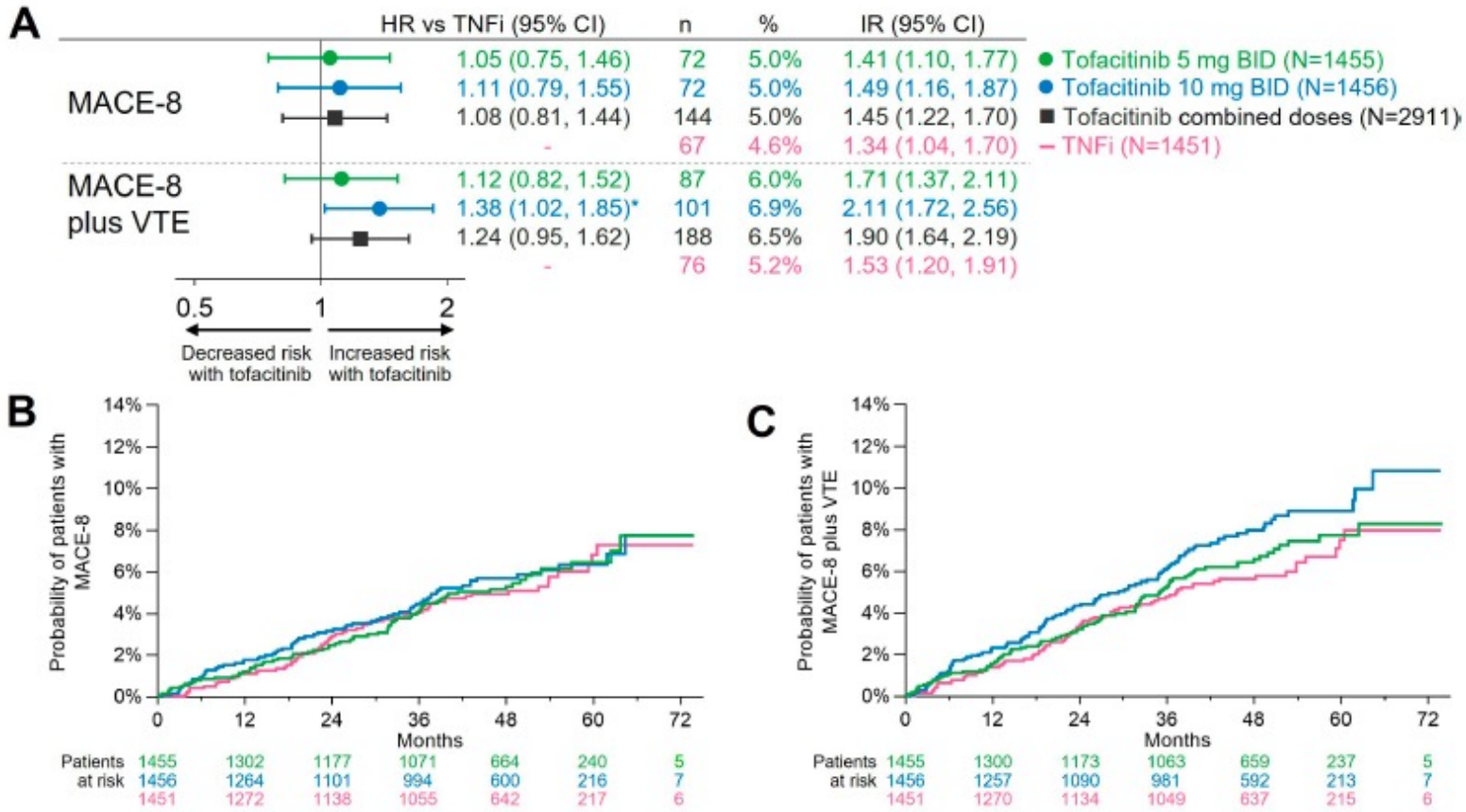

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