Rischio cardiovascolare e terapie reumatologiche: i farmaci immunomodulatori

TORINO, 4-5 *aprile* 2014

Starhotels Majestic, corso Vittorio Emanuele II 54

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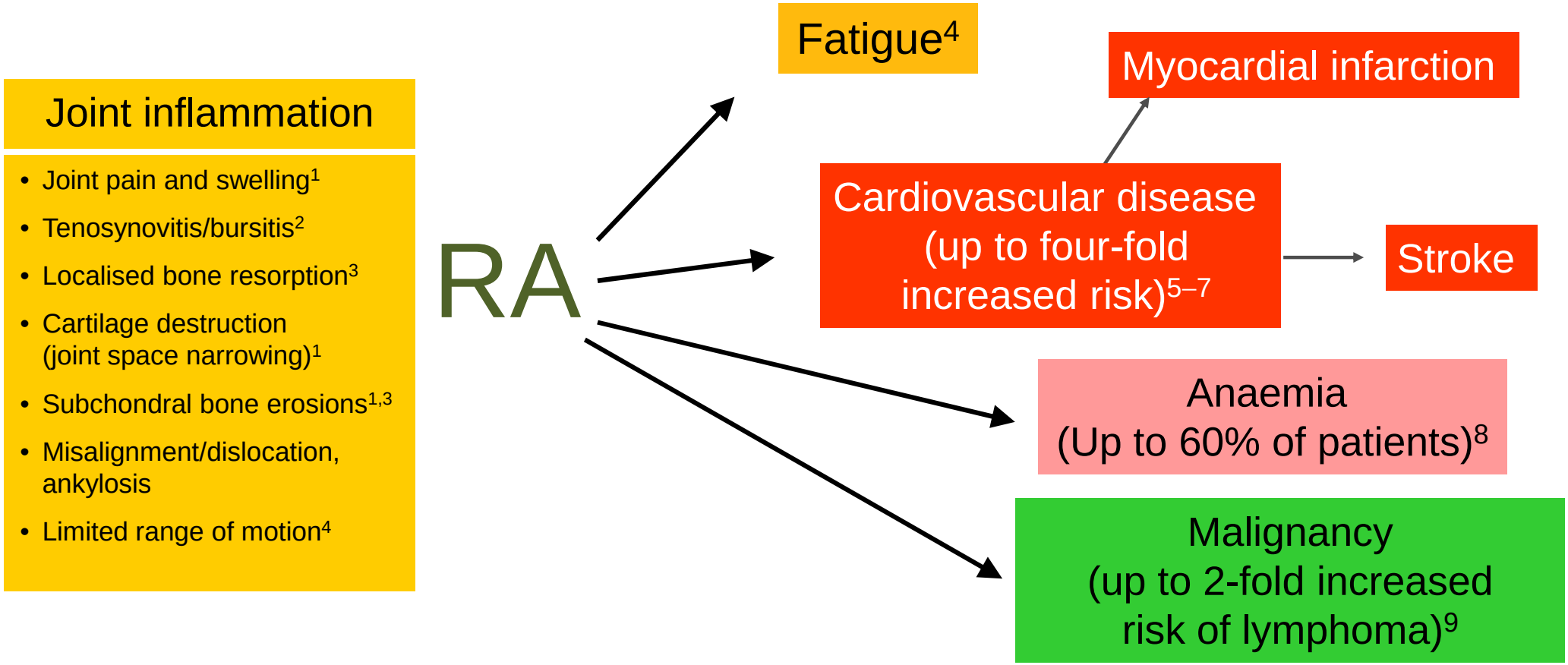
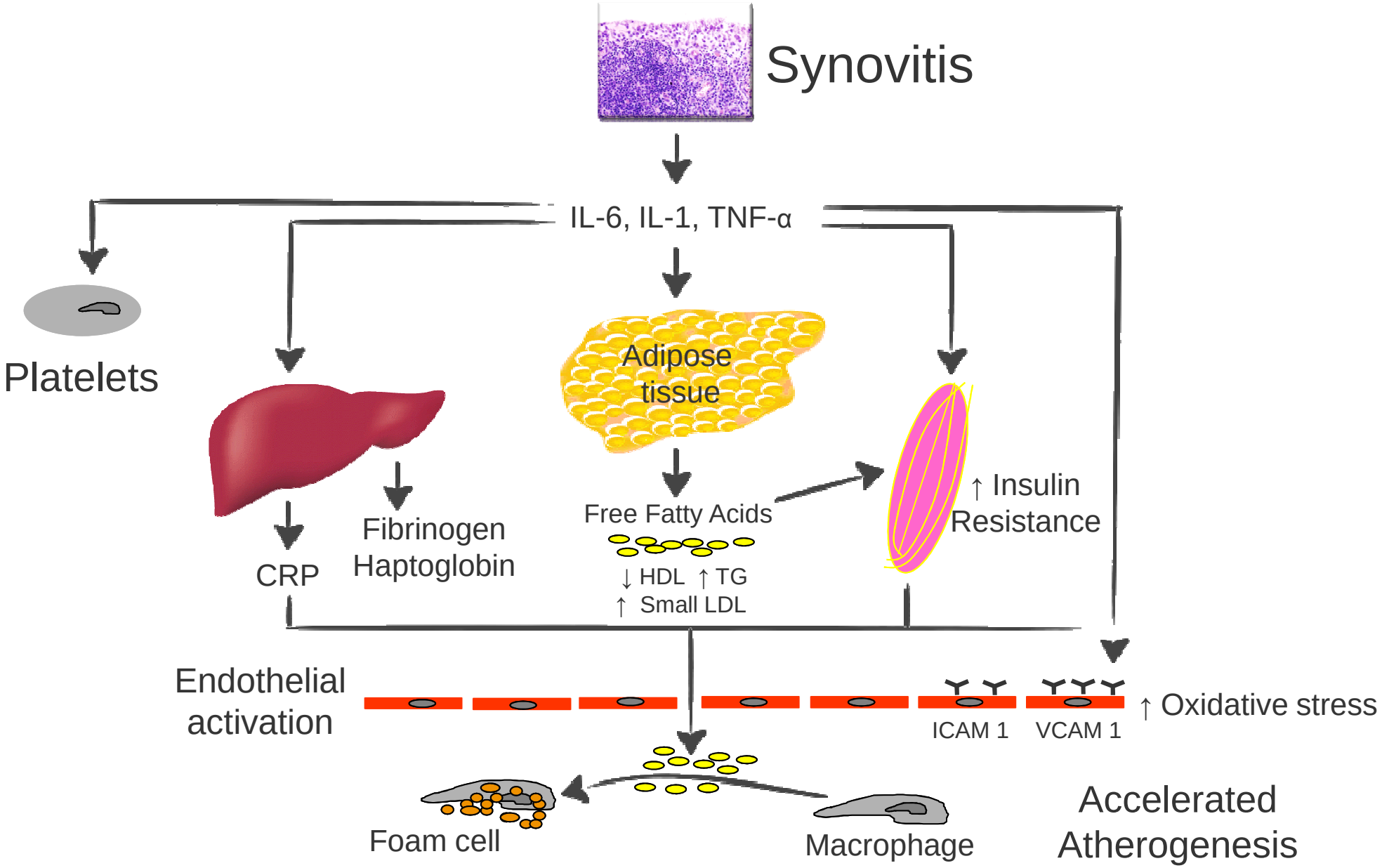
RA is a chronic systemic autoimmune inflammatory arthritis associated with extra-articular manifestations



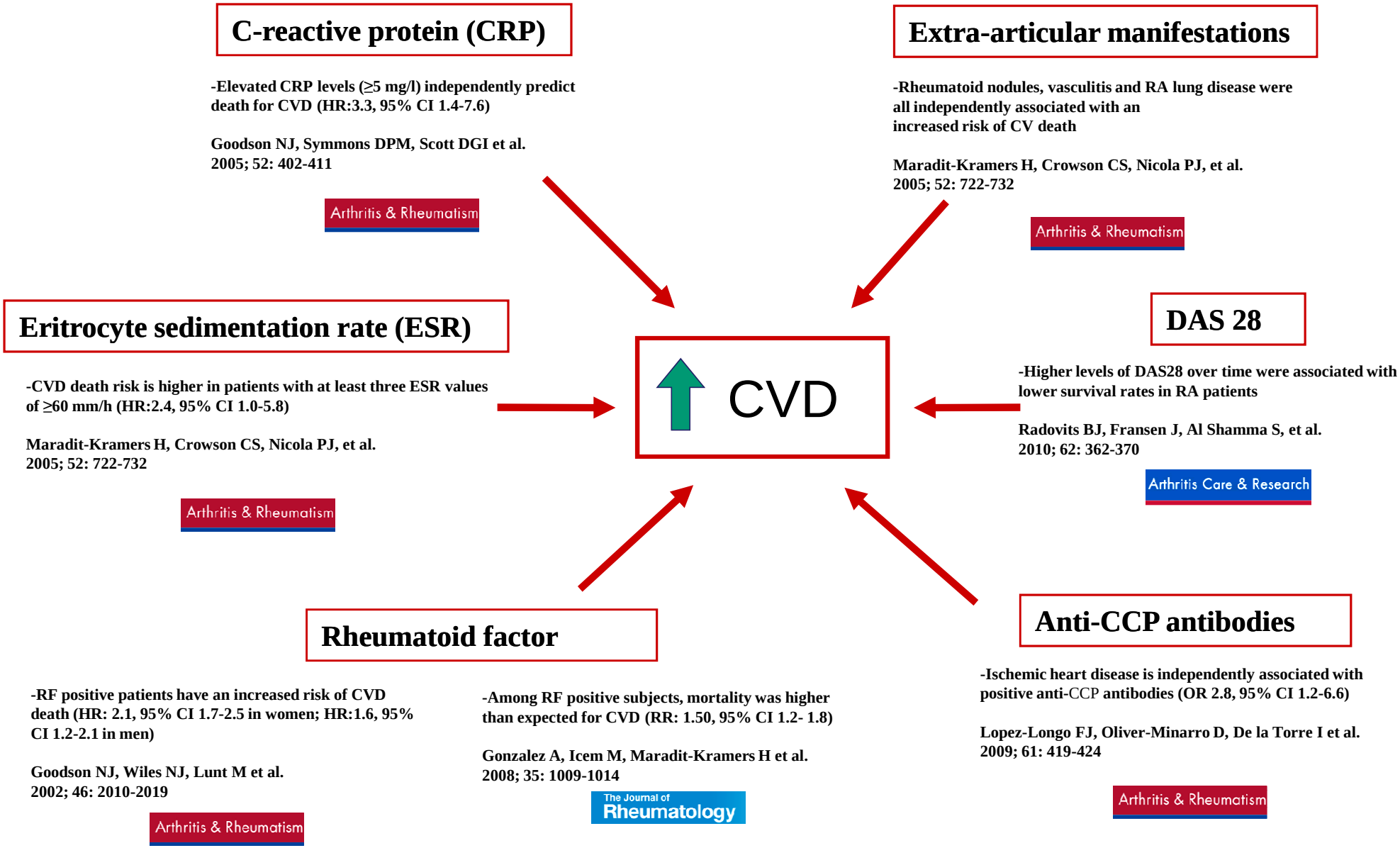
[1]Smolen JS, *et al. Nat Rev Drug Disc* 2003;2:473–488. [2]Grassi W, *et al. Eur J Radiol* 1998;27 (Suppl 1):S18–24.
[3]Firestein G. *Nature* 2003;423:356–361. [4]Smolen JS, *et al. Lancet* 2007;370:1861–1874.
[5]Turesson C, *et al. Ann Rheum Dis* 2004;63:952–955. [6]del Rincón I, *et al. Arthritis Rheum* 2001;44:2737–2745.
[7]Hochberg MC, *et al. Curr Med Res Opin* 2008;24:469–480. [8]Peeters HR, *et al. Ann Rheum Dis*. 1996;55:162–168.
[9]Smitten AL, *et al. Arthritis Res Ther* 2008;10:R45

Mechanisms linking RA and increased vascular risk



Sattar N, et al. Circulation 2003

In RA patients, systemic inflammation and disease activity markers are associated with an increased CV risk

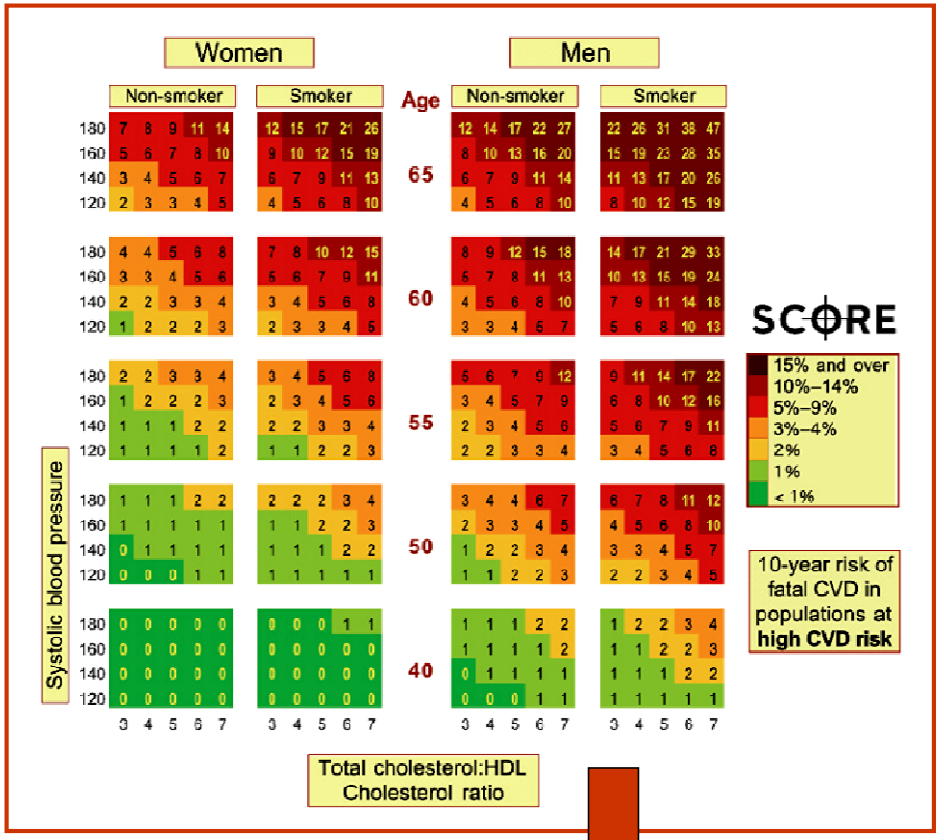


CV risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor

Table 1 The 10 recommendations for cardiovascular (CV) risk management in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

	Recommendations	Level of evidence	Strength of recommendation
1.	RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden	2b–3	B
2.	Adequate control of disease activity is necessary to lower the CV risk	2b–3	B
3.	CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed	3–4	C
4.	Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: – Disease duration of more than 10 years – RF or anti-CCP positivity – Presence of certain extra-articular manifestations	3–4	C
5.	TC/HDL cholesterol ratio should be used when the SCORE model is used	3	C
6.	Intervention should be carried out according to national guidelines	3	C
7.	Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options	2a–3	C-D
8.	The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors	2a–3	C
9.	Corticosteroids: use the lowest dose possible	3	C
10.	Recommend smoking cessation	3	C

ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2 inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.



When RA patient meets 2 of the following 3 criteria:

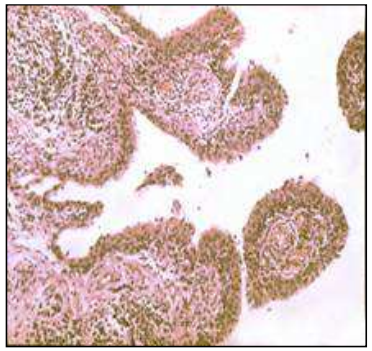
1. Disease duration > 10 years
2. RF or anti-CCP positivity
3. Presence of severe extra-articular ***manifestations***

derived CV risk estimate x 1.5

Peters MJL, Symmons DPM, McCarey D et al. 2010; 69: 325-331

Annals of the RHEUMATIC DISEASES The EULAR Journal

Mechanisms accounting for increased CV risk in RA

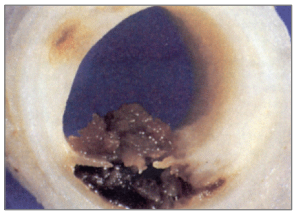


Inflammation

Coronary Heart Disease

Shared risk factors:
Smoking, obesity,
low physical activity

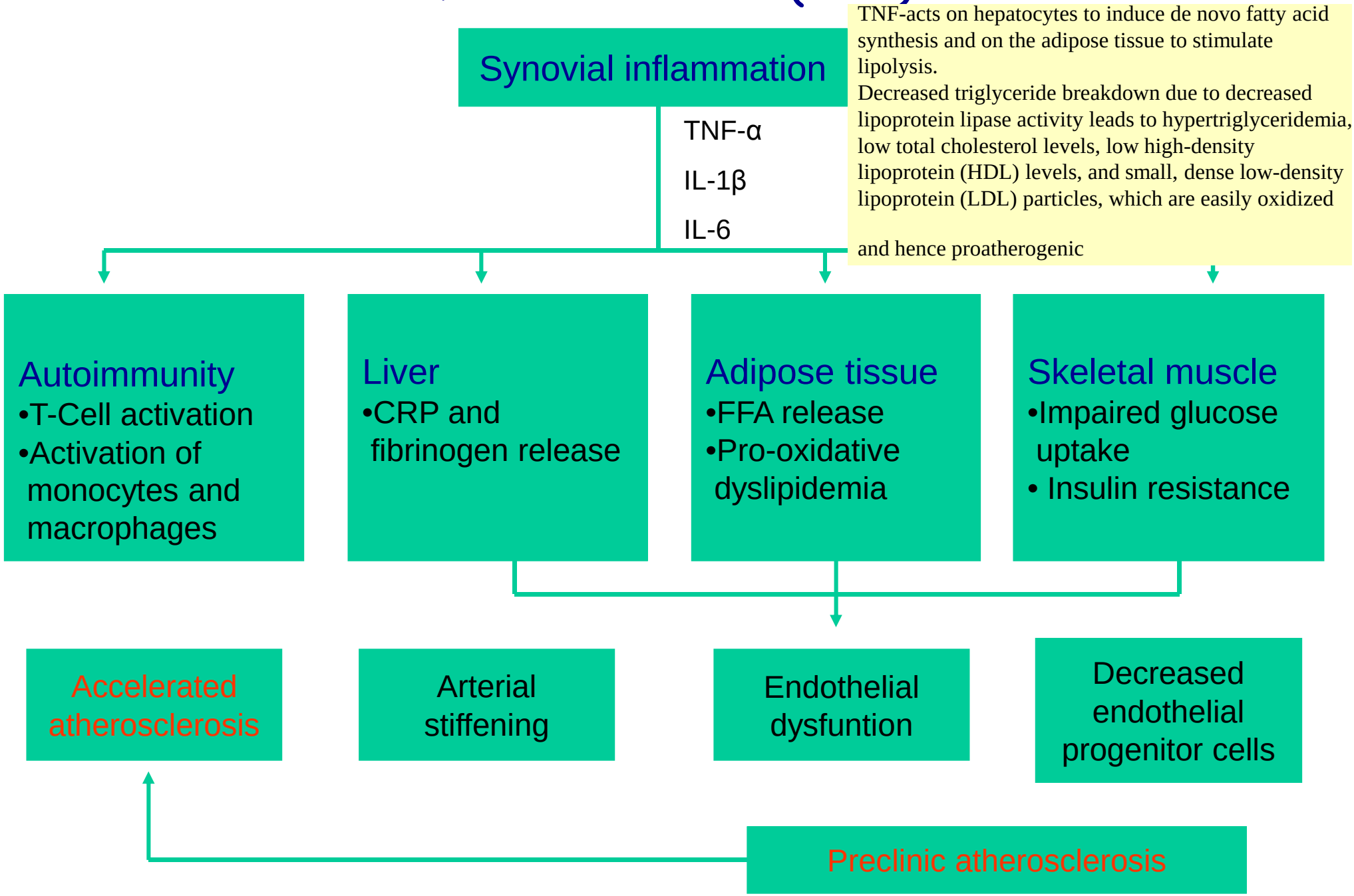
Dyslipidemia
Insulin resistance
Hypercoagulation
Endothelial dysfunction



Vascular disease or risk
is undertreated in RA

Drug therapy
NSAIDs, coxibs, steroids

Diagram of the pathophysiology of atherosclerosis in rheumatoid arthritis (RA)



Saurabb S Dhawan et al, Current Atheroscleris Reports 2008, 10:128-133

Changes in lipid and inflammatory parameters associated with RA and its treatment with biologics

Pre-RA

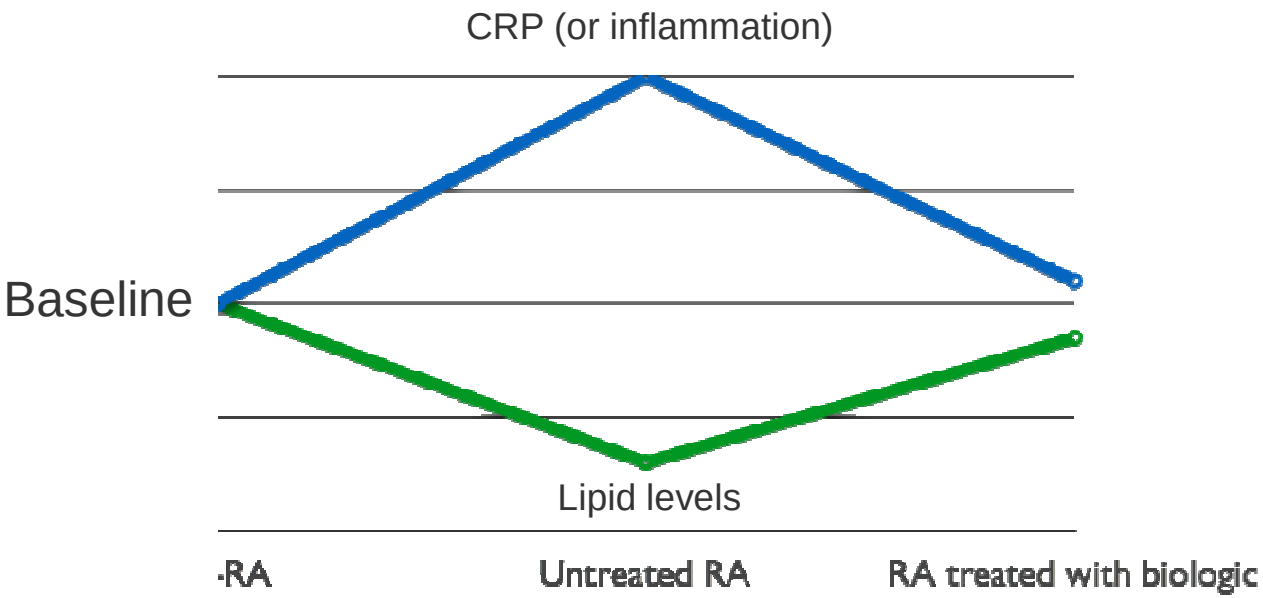
- ↑ Cholesterol
- ↑ Triglycerides
- ↓ HDL-C
- CRP normal

Active untreated RA

- ↓ Cholesterol
- ↓ Triglycerides
- ↓↓ HDL-C
- ↑↑↑ CRP

Treated RA with biologics

- ↑ Cholesterol
- ↑ Triglycerides
- ↑ HDL-C
- ↓↓ CRP

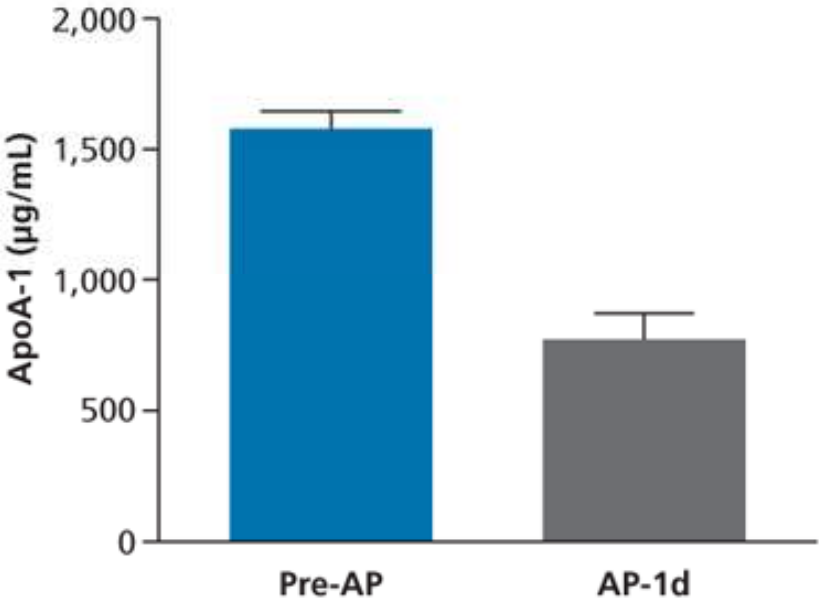


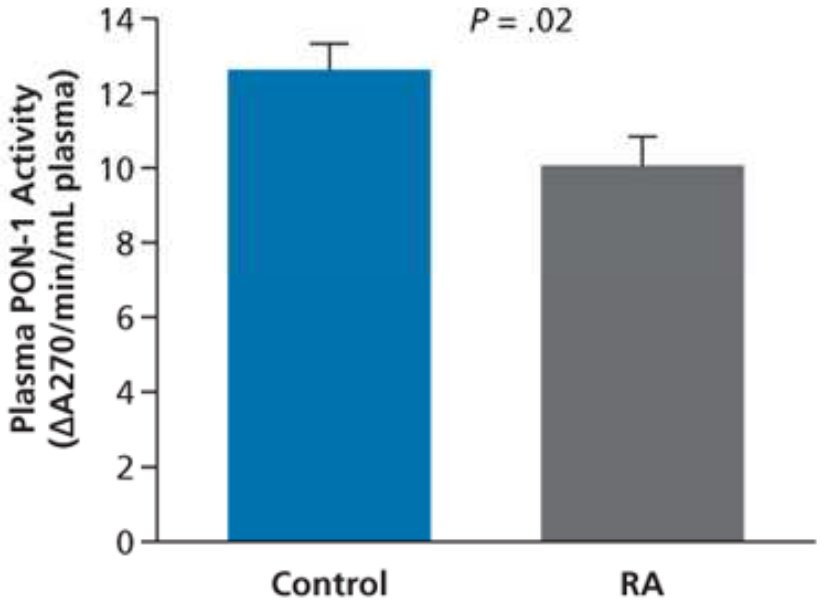
- Lipid levels may be higher before the onset of RA
- However, levels of all lipid particles generally decrease in severe, untreated RA when inflammatory levels are high
- Suppression of inflammation with biologics can, therefore, be anticipated to raise levels of all lipids and current evidence support this paradigm.

Choy E, et al. Ann Rheum Dis 2009

Pro-Atherogenic Alterations of HDL Composition: ApoA-1 and PON-1

- ApoA-1 promotes cholesterol efflux; has both anti-inflammatory and anti-oxidative properties[1]
- ApoA-1 is displaced from HDL by acute-phase proteins, resulting in loss of cardioprotective properties[1]
- PON-1 prevents lipid oxidation of both LDL and HDL[2,3]
- Patients with RA experience significant reduction in PON-1 activity[2,3]





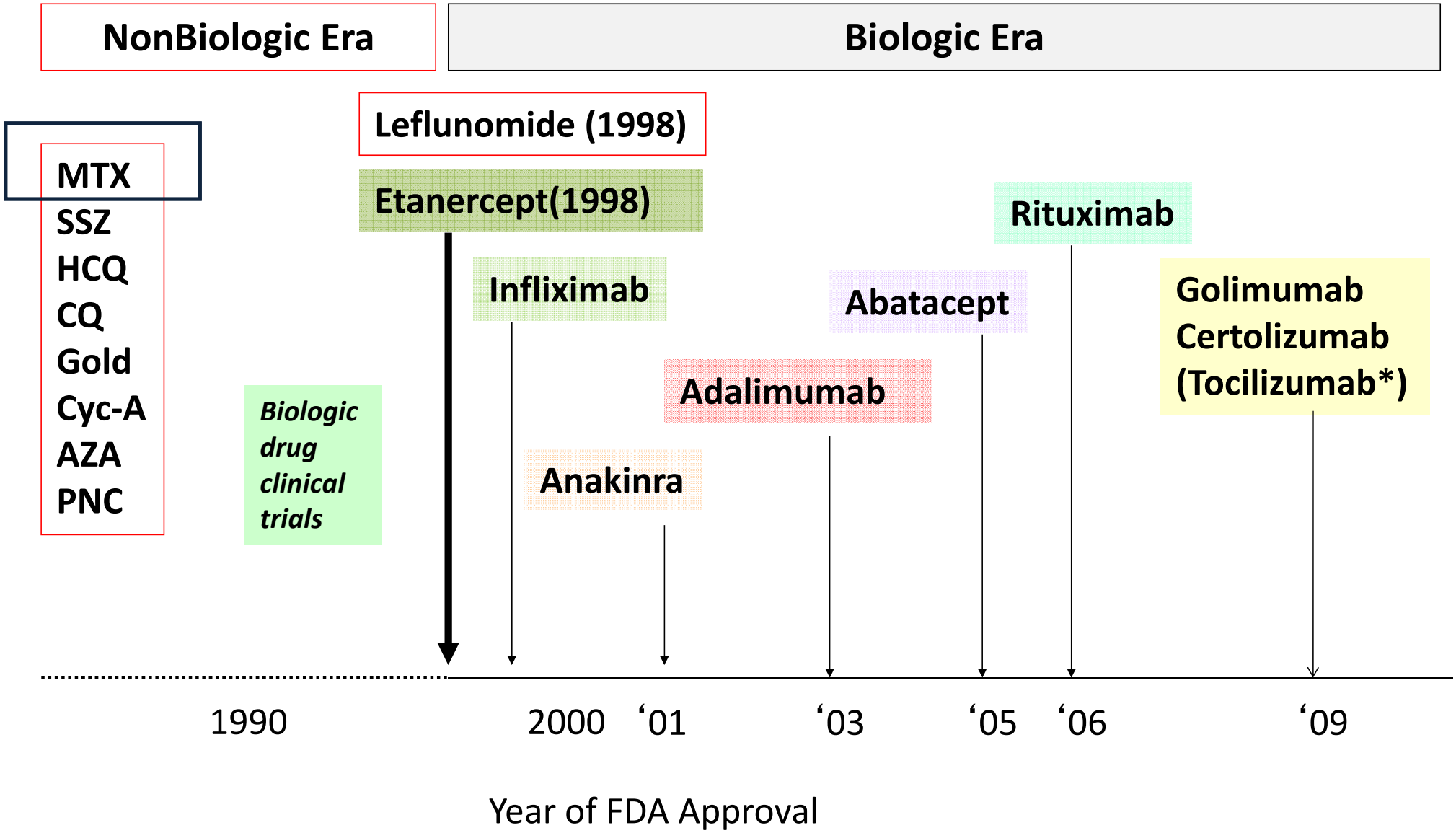
Charles-Shoemann C et al. Ann Rheum Dis 2012; 71:1157-1571

Conventional disease modifying antirheumatic drugs and cardiovascular risk in rheumatoid arthritis

- If inflammation is a key driver of CVD risk in RA, then therapy to reduce disease activity and preferably to achieve remission should help attenuate CVD risk.

- In addition, certain drugs may have additional benefits (and some harm) with regard to cardiovascular safety in RA.

Spectrum of RA Treatment



Research article

Open Access

Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study

Antonio Naranjo[1], Tuulikki Sokka[2], Miguel A Descalzo[3], Jaime Calvo-Alén[4], Kim Hørslev-Petersen[5], Reijo K Luukkainen[6], Bernard Combe[7], Gerd R Burmester[8], Joe Devlin[9], Gianfranco Ferraccioli[10], Alessia Morelli[10], Monique Hoekstra[11], Maria Majdan[12], Stefan Sadkiewicz[13], Miguel Belmonte[14], Ann-Carin Holmqvist[15], Ernest Choy[16], Recep Tunc[17], Aleksander Dimic[18], Martin Bergman[19], Sergio Toloza[20], Theodore Pincus[21] for the QUEST-RA Group

4,363 patients

from 18 sites in 15 countries

78 % female more than 90% Caucasian
mean age 57 years

QUEST – RA project

- The prevalence for lifetime CV events in the entire sample was :
  - 3.2 % for myocardial infarction
  - 1.9 % for stroke
  - 9.3 % for any CV event

Naranjo et al, Arthritis Research & Therapy 2008, 10 : 2-10

QUEST – RA project

The prevalence for CV risk factors was :

- 32 % for hypertension
- 14 % for hyperlipidemia
- 8 % for diabetes
- 43 % for ever-smoking
- 73 % for physical inactivity
- 18 % for obesity

Traditional risk factors except obesity and physical inactivity were significantly associated with CV morbidity

Naranjo et al, Arthritis Research & Therapy 2008, 10 : 2-10

QUEST – RA project

There was an association between any CV event and age and male gender and between extra-articular disease and myocardial infarction

QUEST – RA project

Prolonged exposure to :

- methotrexate (HR 0.85; 95 % CI 0.81 to 0.89)
- leflunomide (HR 0.59; 95 % CI 0.43 to 0.79)
- sulfasalazine (HR 0.92; 95 % CI 0.87 to 0.98)
- glucocorticoids (HR 0.95; 95 % CI 0.92 to 0.98)
- biologic agents (HR 0.42; 95 % CI 0.21 to 0.81)

was associated with significant reduction of the risk of CV morbitity; analyses were adjusted for traditional risk factors and countries

Naranjo et al, Arthritis Research & Therapy 2008, 10 : 2-10

Cardiovascular Risk in Rheumatoid Arthritis: Comparing TNF-a Blockade with Nonbiologic DMARDs

Daniel H. Solomon, MD, MPH,a Jeffrey R. Curtis, et al

Incidence Rates (per 100 Person-years) of Composite Cardiovascular Outcomes and Each Component through 6 Months of Follow-up

Type of Analysis	nbDMARD		TNF-α blocking agent	
First exposure carried forward	Events	Rate	Events	Rate
Composite CV end point	116	3.05 (2.54-3.65)	133	2.52 (2.12-2.98)
Myocardial infarction	38	1.00 (0.72-1.37)	39	0.74 (0.54-1.01)
Stroke	41	1.07 (0.79-1.46)	59	1.12 (0.86-1.44)
Coronary re-vascularization	56	1.47 (1.13-1.91)	55	1.04 (0.80-1.35)
As-treated				
Composite CV endpoint	82	3.07 (2.47-3.81)	103	2.31 (1.90-2.80)
Myocardial infarction	28	1.04 (0.72-1.51)	30	0.67 (0.47-0.96)
Stroke	30	1.12 (0.78-1.60)	49	1.09 (0.83-1.45)
Coronary re-vascularization	36	1.34 (0.97-1.86)	44	0.98 (0.73-1.32)

CV = cardiovascular; nbDMARD = nonbiologic disease-modifying anti-rheumatic drug; TNF = tumor necrosis factor.

Notes: See text for definition of the analysis types. The number of events of each of the component cardiovascular outcomes does not add to the total events in the composite outcome because subjects were censored at their first event in the composite (primary) analysis.

The hazard ratio for cardiovascular events for rheumatoid arthritis patients using TNF-α blocking agent compared with nonbiologic disease-modifying antirheumatic drug was reduced by 20%-29%, depending on the analysis.

The American Journal of Medicine (2013) 126, 730.e9-730.e17

Research article

Open Access

Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study

Vokko P van Halm[1], Michael T Nurmohamed[2], Jos WR Twisk[3], Ben AC Dijkmans[1] and Alexandre E Voskuyl[1]

Arthritis Research & Therapy 2006, **8**:R151 (doi:10.1186/ar2045)

Odds ratios for cardiovascular disease

Groups	Model 1 OR (95 percent CI)	Model 2 OR (95 percent CI)	Model 3 OR (95 percent CI)
Never MTX, SSZ or HCQ (reference)	1.0	1.0	1.0
Only MTX ever	0.16 (0.04–0.66)[a]	0.47 (0.07–3.23)	0.11 (0.02–0.56)[a]
Only SSZ ever	0.42 (0.16–1.10)	0.31 (0.07–1.33)	0.37 (0.14–0.99)[a]
Only HCQ ever	0.55 (0.18–1.67)	0.45 (0.10–2.04)	0.47 (0.15–1.46)
MTX and SSZ ever	0.20 (0.08–0.51)[a]	0.24 (0.07–0.85)[a]	0.16 (0.06–0.42)[a]
MTX and HCQ ever	0.22 (0.04–1.19)	0.54 (0.08–3.66)	0.19 (0.04–1.02)
SSZ and HCQ ever	0.44 (0.14–1.41)	0.34 (0.05–2.16)	0.37 (0.11–1.24)
MTX, SSZ and HCQ ever	0.20 (0.08–0.54)[a]	0.27 (0.07–0.99)[a]	0.16 (0.06–0.43)[a]

Model 1: correcting for age, gender, smoking and rheumatoid arthritis duration. Model 2: identical to 'Model 1' plus correction for hypertension, diabetes and hypercholesterolemia. Model 3: identical to 'Model 1' plus correction for a positive rheumatoid factor test and erosions. [a]Significant. CI, confidence interval; HCQ, hydroxychloroquine; MTX, methotrexate; OR, odds ratio; SSZ, sulfasalazine.

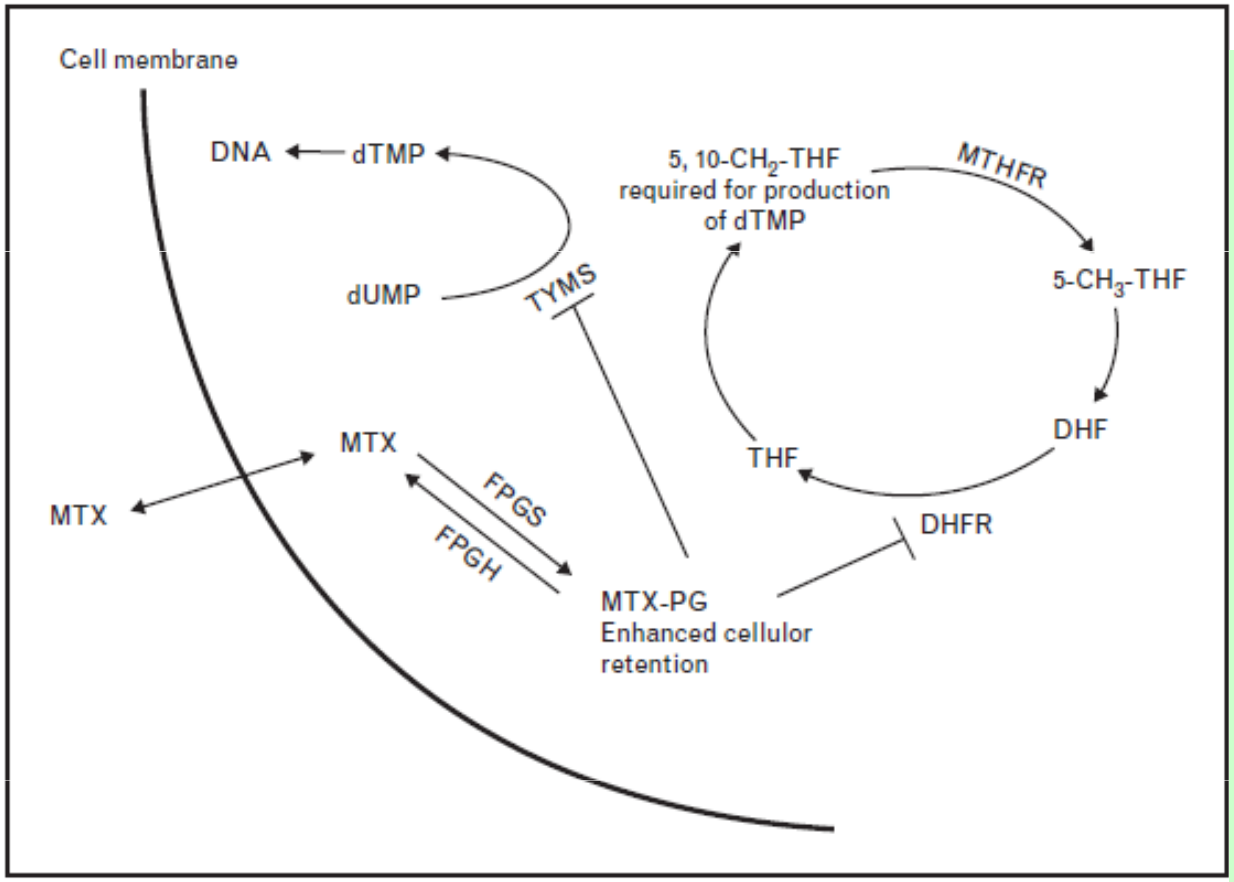
MTX and cardiovascular risk

- Mechanisms of action, CV risk and MTX

Methotrexate and CV risk

	Effect of MTX	Strenght of the effect
CVD		
ALL CAUSE CV	Reduced by MTX	Strong
HEART FAILURE	Reduced by MTX	Strong
ACUTE MI	No conclusive evidence	Moderate
STROKE	Trend toward < incidence	Moderate
CV RISK FACTORS		
METABOLIC SYNDROME	Trend toward < incidence	Moderate
ATHEROSCLEROSIS (cIMT)	No conclusive evidence	Moderate

Mechanism of action of methotrexate



(1) Reduction of cell proliferation,

(2) Increase of apoptosis of T cells,

(3) Increase of endogenous adenosine release,

(4) Alteration of expression of cellular adhesion molecules,

(5) Influence on production of cytokines, humoral responses, and bone formation.

Basic metabolic processes associated with MTX cellular uptake and PG. Progressive glutamic acid moieties are added slowly by the enzyme FPGS and are removed by FPGH. Polyglutamated forms of MTX inhibit several key enzymes in folate metabolism (dihydrofolate reductase and thymidylate synthase) and prevent de-novo purine biosynthesis.

The methylation of dUMP is needed for DNA synthesis to generate dTMP. Enzyme inhibition, folate depletion, and direct or indirect effects on cytokine release signaling pathways all create routes via which MTX could suppress RA.

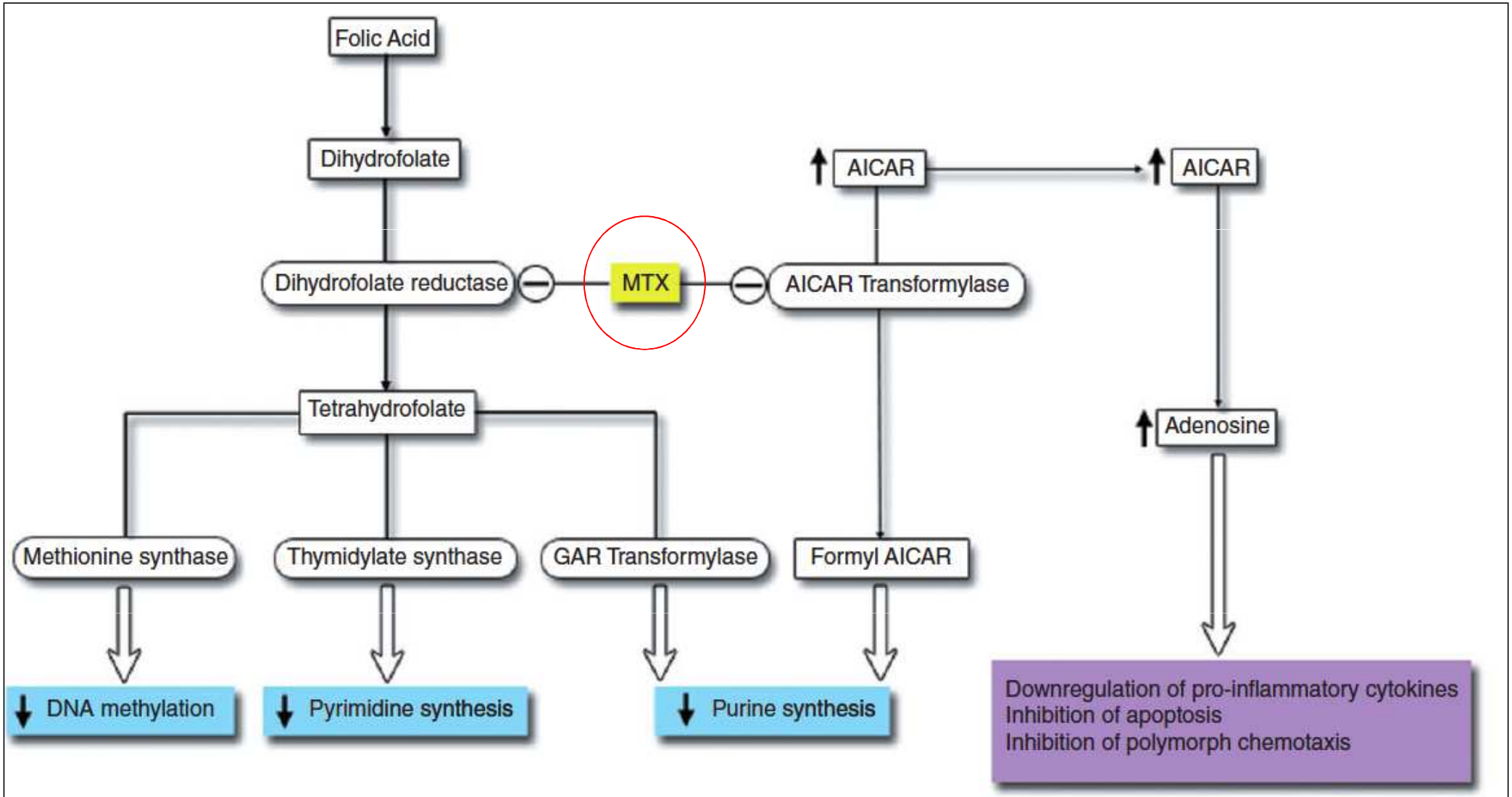
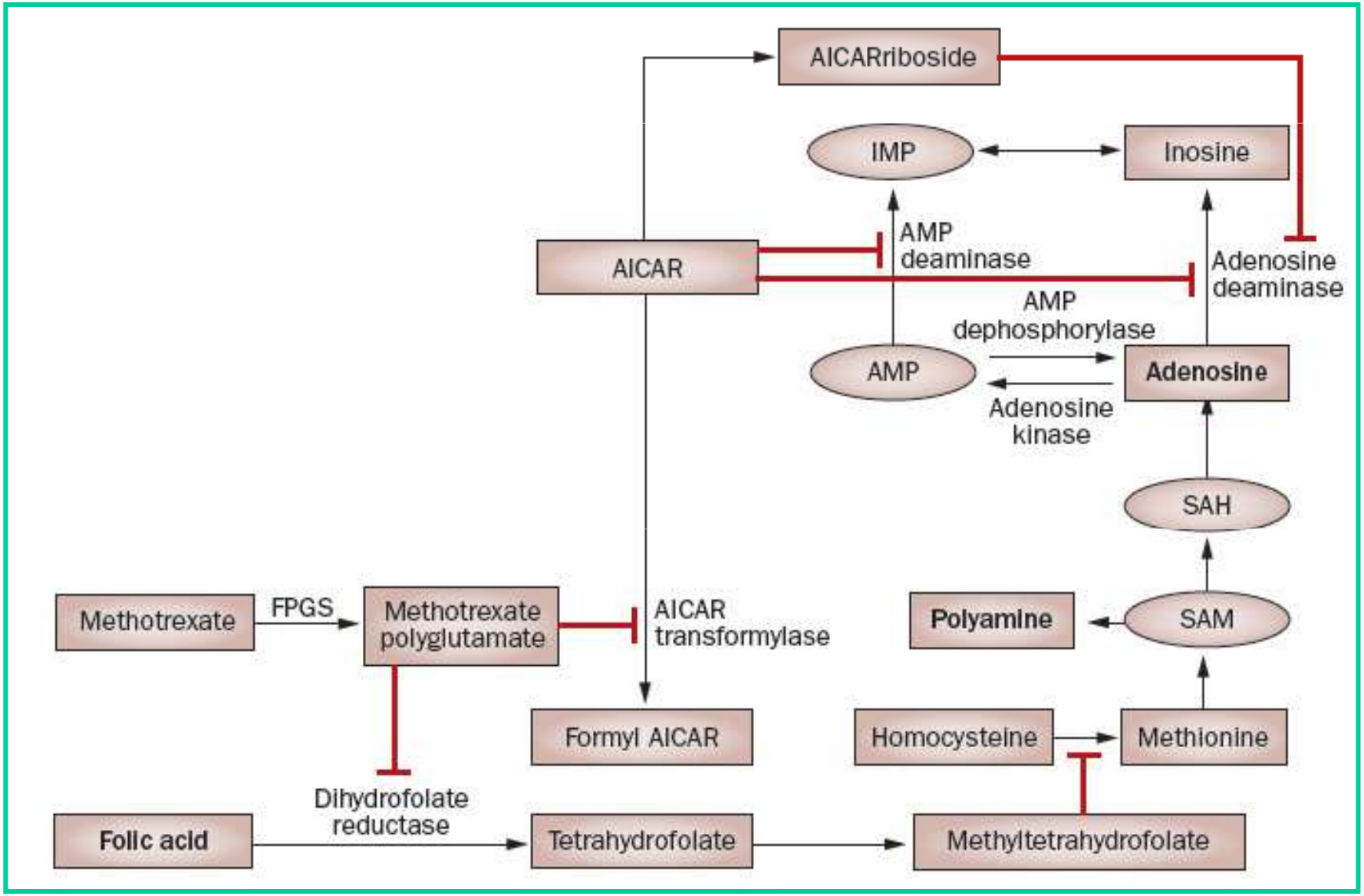


Figure 1 Schematic diagram of mechanism of action of methotrexate. The anti-proliferative actions of methotrexate (MTX) are mediated via the inhibition of folate-dependent pathways. The anti-inflammatory actions are thought to be due to the upregulation of adenosine resultant from the increase in the level of aminoimidazole-carboxamide-ribonucleoside (AICAR). GAR, glycinamide ribonucleotide.

OPINION

Methotrexate—how does it really work?

Chan, E. S. L. & Cronstein, B. N. *Nat. Rev. Rheumatol.* **6**, 175–178 (2010); doi:10.1038/nrrheum.2010.5



British Journal of Rheumatology 1997;**36:**1196–1204

DISEASE-MODIFYING DRUGS
SERIES EDITOR: T. PULLAR

THE RATIONAL USE OF METHOTREXATE IN RHEUMATOID ARTHRITIS AND OTHER RHEUMATIC DISEASES

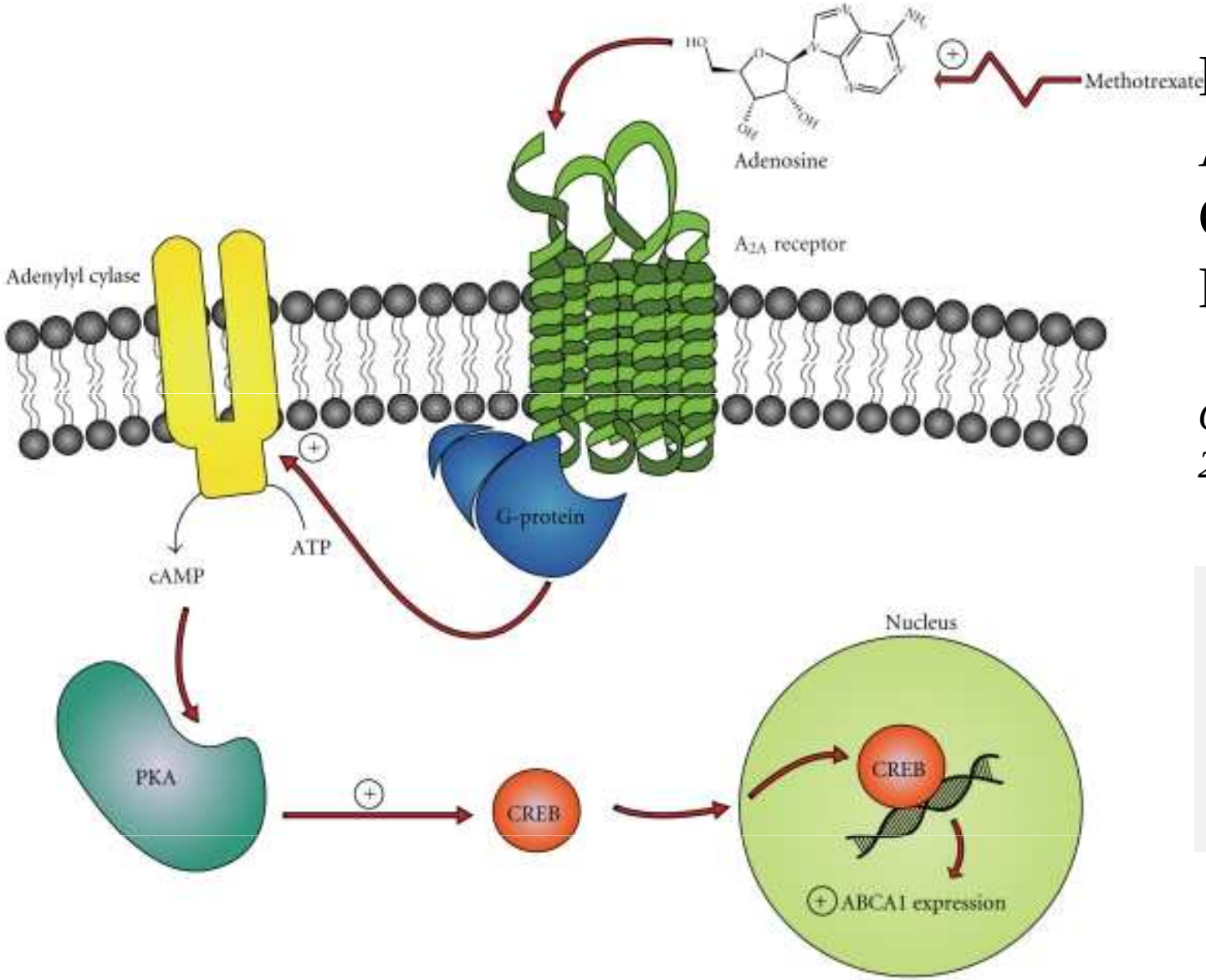
D. E. FURST

Virginia Mason Research Center, 1100 Ninth Avenue, PO Box 900 (R1-RC), Seattle, WA 98111, USA

Other potential mechanisms

- include normalization of low interleukin-2 (IL-2) through an effect on polyamine synthesis,
- reduced IgM-rheumatoid factor (RF) production,
- decreased IL-1 production, secretion or binding,
- decreased IL-6 activity

Methotrexate in Atherogenesis and Cholesterol Metabolism



Coomes E et al. Cholesterol. 2011; 2011: 503028

effects on the expression of proteins involved in cholesterol homeostasis. These proteins, ATP-binding cassette transporter (ABC) A1 and cholesterol 27-hydroxylase, facilitate cellular cholesterol efflux and defend against cholesterol overload. Methotrexate upregulates expression of cholesterol 27-hydroxylase and ABCA1 via adenosine release,

Regulation of adenosine triphosphate binding cassette transporter A1 (ABCA1) expression by adenosine. Methotrexate via numerous steps (jagged arrow) results in increased levels of adenosine. Adenosine activates the G-protein coupled receptor, A_{2A}, inducing an increase in adenylyl cyclase activity. The subsequent rise in cyclic adenosine monophosphate (cAMP) activates protein kinase A (PKA) which phosphorylates the cAMP response element-binding protein (CREB). CREB then translocates into the nucleus where it upregulates ABCA1 gene expression

Atheroprotective Effects of Methotrexate on Reverse Cholesterol Transport Proteins and Foam Cell Transformation in THP-1 Human Monocytes/Macrophages

Allison B. Reiss, M.D.[1], Steven E. Carsons, M.D.[1], Kamran Anwar, Ph.D.[1], Soumya Rao, M.D.[1], Sari D. Edelman, D.O.[1], Hongwei Zhang, M.D.[1], Patricia Fernandez, Ph.D.[2], Bruce N. Cronstein, M.D.[2], and Edwin S.L. Chan M.D.[2]

MTX provides protection from atherosclerotic cardiovascular disease (ASCVD) by increasing expression of anti-atherogenic molecules (cholesterol 27-hydroxylase and ATP binding cassette transporter A1 (ABCA1) involved in cholesterol efflux, likely via a pathway involving adenosine release.

MTX protects against cardiovascular mortality in RA patients is through facilitation of cholesterol outflow from cells of the artery wall.

Arthritis Rheum. 2008 December; 58(12): 3675–3683.

Adenosine and MTX

- **Ability to alter the expression of adhesion molecules**, such as l-selectin and the β2 integrins.

- **Neutrophil adhesion** to endothelial cells can be enhanced by activation of certain adenosine receptor subtypes and inhibited by other types, providing just one example of the opposing functions of adenosine receptors.

- Neutrophils activated by tumor necrosis factor (tnF) release vascular endothelial growth factor and are induced to transmigrate across the endothelium. **this propensity to increase vascular permeability in the presence of an inflammatory milieu is also inhibited by adenosine.**

- **Activated neutrophils also release 5'-adenosine mono phosphate which, when dephosphorylated to adenosine, directly enhances endothelial barrier function.**

Hyperhomocysteinemia

- L’omocisteina è elevata nei pazienti affetti da AR.

Roubenoff R et al. Arthritis Rheum 1997; 40: 718-22

- L’omocisteina è significativamente aumentata nei pazienti con AR e comorbidità cardiovascolare

Cisternas M et al J Rheumatol 2002; 29: 1619-22

- L’utilizzo a lungo termine del methotrexate e della sulfasalazina determina un incremento dell’omocisteina

Haagsma CJ et al Ann Rheum Dis 1999; 58: 79-84

- La supplementazione di folati previene l’innalzamento dei livelli di omocisteina con l’uso di MTX

Van Ede Rheumatology 2002; 41: 658-65

Abnormal homocysteine metabolism in rheumatoid arthritis

Fasting levels of tHcy were 33% higher in the RA patients than in the control subjects (mean +/- SD 11.7 +/- 1.5 nmoles/ml versus 8.8 +/- 1.1 nmoles/ml; $P < 0.01$).

Four hours after Met challenge, the increase in plasma tHcy levels (delta tHcy) was higher in the RA patients (20.9 +/- 10.4 nmoles/ml) than in the control subjects (15.5 +/- 1.6 nmoles/ml) ($P < 0.02$).

In a subgroup analysis, the delta tHcy in patients taking methotrexate (12.9 +/- 2.2 nmoles/ml) did not differ from that in the control group, while the delta tHcy in patients not taking methotrexate (25.3 +/- 1.7 nmoles/ml) was significantly higher ($P < 0.0001$).

Roubenoff R, et al. Abnormal homocysteine metabolism in rheumatoid arthritis. Arthritis Rheum. 1997 Apr;40(4):718-22.

Homocysteine and antiphospholipid antibodies in rheumatoid arthritis patients: Relationships with thrombotic events

Twenty-five RA patients and 5 controls reported a history of thrombotic events. Eleven and 5 of RA patients were found to have been previous ly affected by venous or arterial thrombosis, respectively.

Plasma levels of homocysteine in aPL antibody positive patients with thrombosis were found to be significantly higher than in aPL antibody positive RA patients without thrombosis ($p < 0.001$).

When RA patients with thromboses were analyzed, a significant increase of plasma homocysteine levels was found in aPL antibody-positive RA patients versus aPL antibody negative RA patients ($p < 0.04$) and versus related controls ($p < 0.003$).

Clinical and Experimental Rheumatology 2001; 19: 561-564.

The role of homocysteine as a significant risk factor for white matter lesions in Japanese women with rheumatoid arthritis

Futoshi Anan[a,*], Takayuki Masaki[b], Hiroshi Tatsukawa[c], Shuji Nagano[c], Motohiro Oribe[d], Nobuoki Eshima[e], Tetsunori Saikawa[f], Hironobu Yoshimatsu[b]

Clinical characteristics of studied patients (N = 65)

	WML negative	WML positive	*P* value
Age (y)	60 ± 7	61 ± 6	NS
n	40	25	NS
Body mass index (kg/m^2)	23.2 ± 2.1	23.6 ± 2.6	NS
Duration of RA (y)	7.1 ± 5.4	10.6 ± 7.4	.0316
Hypertension (%)	38	40	NS
Dyslipidemia (%)	33	36	NS
Diabetes mellitus (%)	23	28	NS
Drug use (%)			
NSAID	72	76	NS
DMARD	56	60	NS
Methotrexate	51	52	NS
Steroid	85	88	NS
Systolic blood pressure (mm Hg)	130 ± 11	133 ± 8	NS
Diastolic blood pressure (mm Hg)	75 ± 7	76 ± 9	NS
Heart rate (beats/min)	67 ± 7	68 ± 8	NS
Total cholesterol (mg/dL)	190 ± 34	202 ± 39	NS
Triglyceride (mg/dL)	128 ± 30	146 ± 36	.0309
HDL-C (mg/dL)	47 ± 7	42 ± 8	.0086
LDL-C (mg/dL)	118 ± 35	131 ± 30	NS
FPG (mg/dL)	111 ± 16	119 ± 13	.0393
Creatinine (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	NS
CRP (mg/dL)	1.09 ± 1.46	1.16 ± 1.33	NS
ESR (mm/h)	19.6 ± 6.3	22.9 ± 9.3	NS
Homocysteine (μmol/L)	11.8 ± 4.2	21.0 ± 6.9	<.0001

Data are means ± SD. NSAID indicates nonsteroidal anti-inflammatory drug; DMARD, disease-modifying antirheumatic drug; NS, not significant.

Multivariate logistic analysis revealed that WML was independently predicted by the tHcy (odds ratio, 1.35; 95% confidence interval, 1.12-1.63; P b .0001).

Our findings indicate that the presence of WML was associated with the tHcy in Japanese patients with rheumatoid arthritis.

ARTHRITIS & RHEUMATISM
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Changes in Lipoproteins Associated With Methotrexate or Combination Therapy in Early Rheumatoid Arthritis

Results From the Treatment of Early Rheumatoid Arthritis Trial

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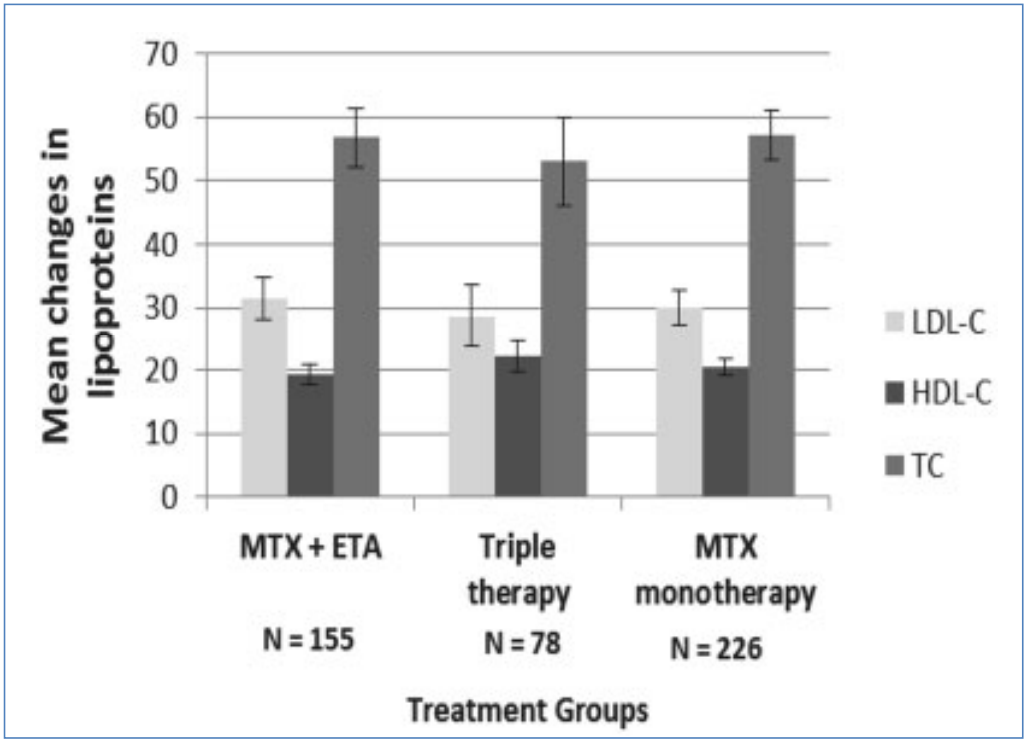
Objective. **To study changes in lipid profiles at 24 weeks among patients with early rheumatoid arthritis (RA) participating in the Treatment of Early RA (TEAR) trial and randomized to receive methotrexate (MTX) plus etanercept, triple therapy (MTX plus sulfasalazine plus hydroxychloroquine), or aggressively titrated MTX monotherapy.**

Methods. **This TEAR substudy included 459 participants with biologic specimens. Serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured at 0 and 24 weeks.**

Treatment with MTX increases lipid levels

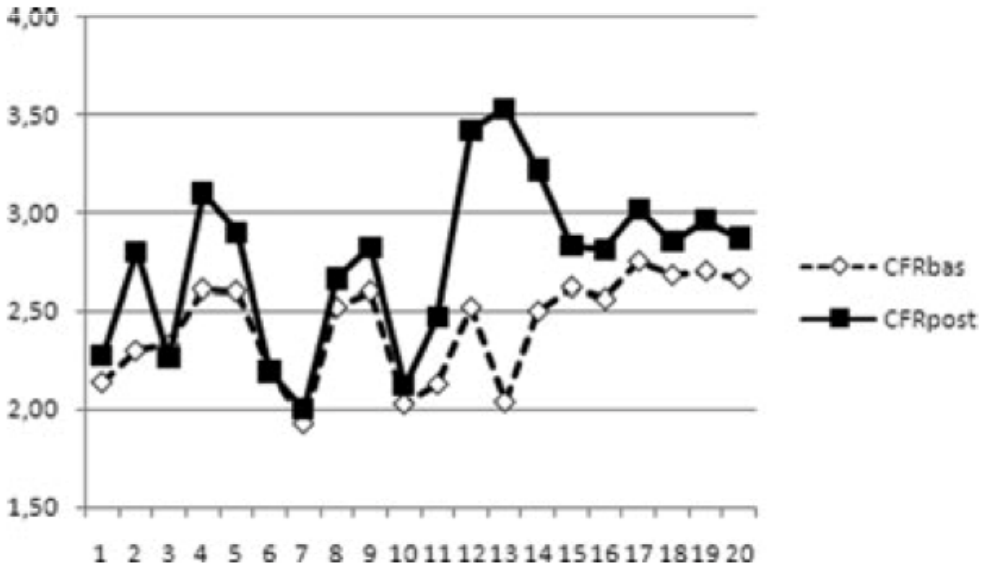
- In patients with early RA, lipid levels were significantly increased after MTX treatment for 24 weeks ($P < 0.001$ vs baseline)
- However, ratio of TC:HDL-C (atherogenic index) decreased in all treatment arms
- Decrease in atherogenic index could imply CV-protective effect of MTX



Navarro-Millan I et al. Arthritis Rheum 2013; 6:1430-1438

Effects of synthetic and biologic DMARDs on Endothelial Function in Patients with Early RA (n=10 MTX, 10 ADA)

CFR (2D-echo derived coronary flow reserve)
pre- and post-treatment with MTX or ADA



	Baseline	Post-treatment (18 months)	P-value
Diastolic blood pressure (mmHg)	80.8 ± 9.4	74.3 ± 6.75	0,025
DAS 28	5.86 ± 0.64	2.01 ± 0.74	0,0001
CRF	2.4 ± 0.2	2.7 ± 0.5	0,01
ADMA (µmoles/L)	0.65 ± 0.07	0.7 ± 0.17	NS
IMT (mm)	0.68 ± 0.10	0.66 ± 0.15	NS

DMARDs are able to improve coronary microcirculation without a direct effect on IMT* and ADMA**, clinical markers of atherosclerosis

*IMT=common carotid intima-media thickness
**ADMA=plasma asymmetric dimethylarginine

Turiel M, et al. Am J Med 2002

MTX and cardiovascular risk

- Chronic heart failure and MTX

ARTHRITIS & RHEUMATISM
Vol. 52, No. 2, February 2005, pp 412–420
DOI 10.1002/art.20855
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The Risk of Congestive Heart Failure in Rheumatoid Arthritis

A Population-Based Study Over 46 Years

Paulo J. Nicola, Hilal Maradit-Kremers, Véronique L. Roger, Steven J. Jacobsen, Cynthia S. Crowson, Karla V. Ballman, and Sherine E. Gabriel

Table 1. Framingham Heart Study criteria for the diagnosis of congestive heart failure*

Major criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S3 gallop
Increased venous pressure ≥16 cm of water
Circulation time ≥25 seconds
Hepatojugular reflux
Minor criteria
Ankle edema
Night cough
Dyspnea upon exertion
Hepatomegaly
Pleural effusion
Vital capacity decreased by one-third from the maximum
Tachycardia rate ≥120 beats/minute
Major or minor criteria
Weight loss ≥4.5 kg in 5 days in response to treatment

* Congestive heart failure is present if 2 major criteria or 1 major and 2 minor criteria are met. Adapted with permission of the American College of Cardiology Foundation, © 1993 (ref. 24).

The prevalence of CHF ranges from 2.4% to 5.5% in the general population older than 65 years of age, and the presence of CHF confers a 4–18-fold increased risk of dying of CV-related causes .

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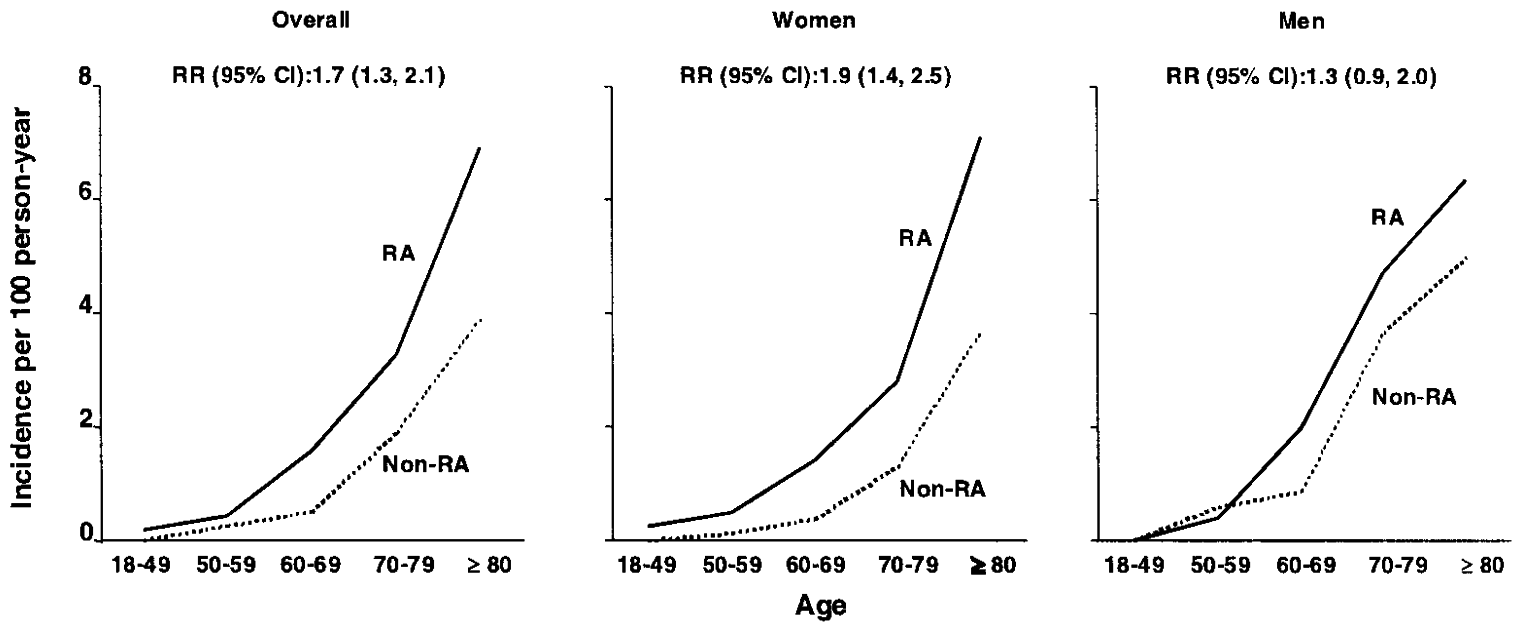
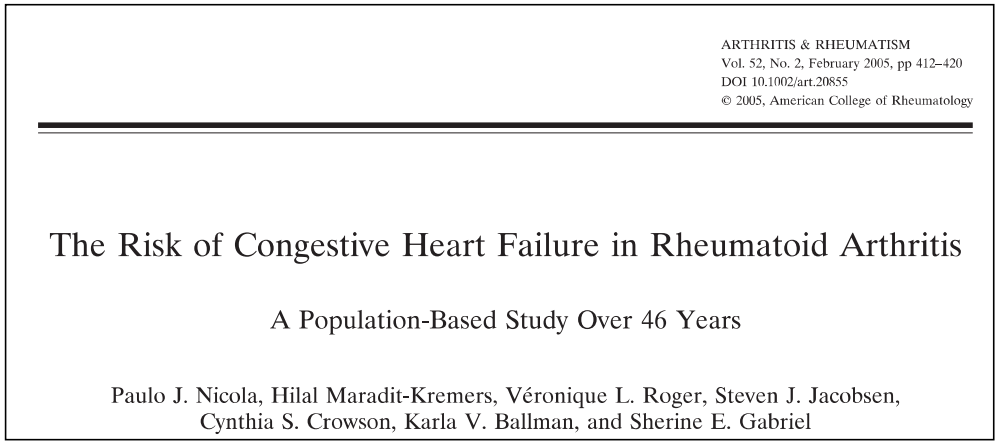


Number of events / number at risk

Non-RA	0/179	5/282	13/366	42/351	55/219	0/136	2/207	7/264	22/253	43/172	0/43	3/75	6/102	20/98	12/47
RA	3/186	8/272	35/334	58/306	61/153	3/144	6/198	23/237	37/221	46/115	0/42	2/74	12/97	21/85	15/38

Figure 1. Comparison of the incidence of congestive heart failure, according to age and sex, among 575 patients with rheumatoid arthritis (RA) and 583 non-RA subjects. RR = rate ratio; 95% CI = 95% confidence interval.



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- After 30 years of followup, **the cumulative incidence of CHF was 34.0% in patients with RA and 25.2% in non-RA subjects** (P< 0.001).

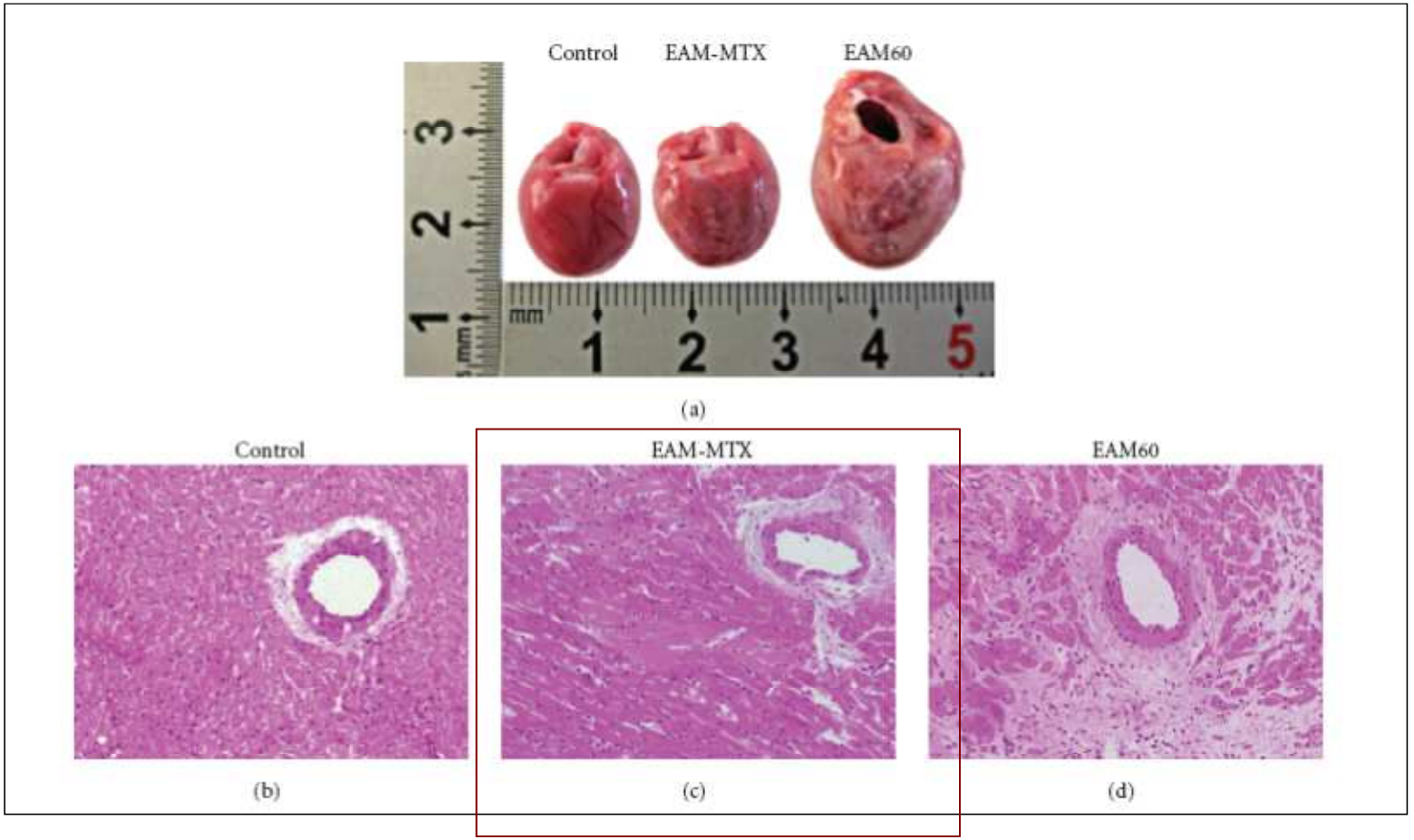
- **RA conferred a significant excess risk of CHF (hazard ratio [HR] 1.87, 95% CI 1.47–2.39)** after adjusting for demographics, ischemic heart disease, and CV risk factors.

- The risk was higher among patients with RA who were **rheumatoid factor (RF) positive** (HR 2.59, 95% CI 1.95–3.43) than among those who were RF negative (HR 1.28, 95% CI 0.93–1.78).

Effects of Methotrexate on Plasma Cytokines and Cardiac Remodeling and Function in Postmyocarditis Rats

Zhengang Zhang, Pei Zhao et al

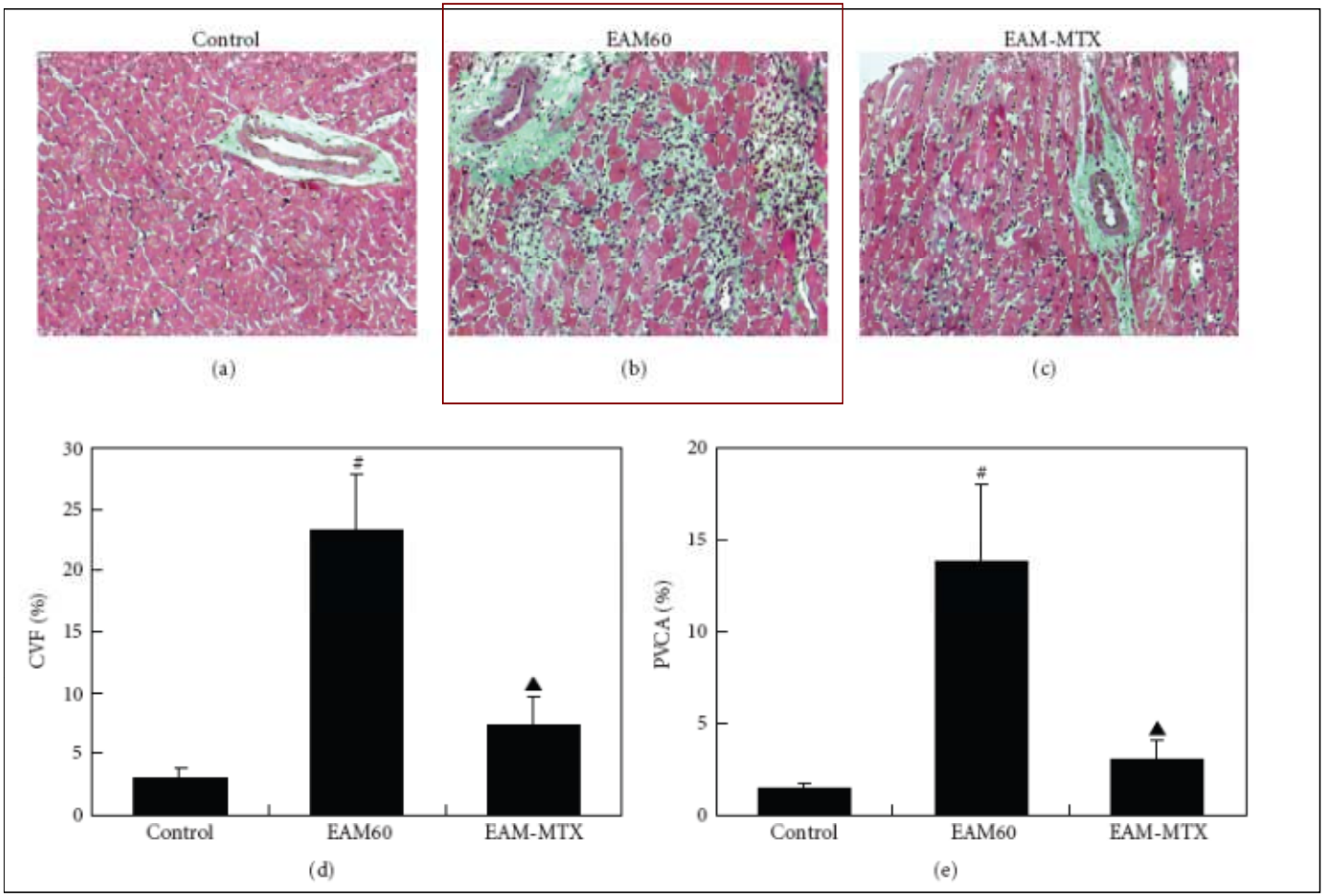
Macroscopic and microscopic assessment of the hearts.
(a)Representative gross appearance of the heart from each group of rats.
(b)Representative photomicrographs of the ventricular sections (HE staining; ×200).
In hearts from the control group, myocytes is well organized. In EAM60 group, the cardiac myocytes exhibited extensive necrosis, degeneration, and disorder. MTX treatment led to a significant decrease in the size of these lesions.



Mediators of Inflammation Volume 2009, Article ID 389720

Effects of Methotrexate on Plasma Cytokines and Cardiac Remodeling and Function in Postmyocarditis Rats

Zhengang Zhang, Pei Zhao et al



Masson′s trichrome staining. Representative photomicrographs of the ventricular sections from the three groups of rats are shown (×200). Green staining represents the collagen fibers (a)–(c).Myocardial collagen volume fraction (CVF; (d)) and perivascular collagen area (PVCA; (e)) were calculated in the control, EAM60 and EAM-MTX groups, respectively. All results are represented as mean ± SD ($n = 10$).

*$P < .05$, #$P < .01$ versus control group; ▲$P < .01$ versus EAM60 group.

Mediators of Inflammation Volume 2009, Article ID 389720

Methotrexate e rilevanza clinica del rischio cardiovascolare

MTX, myocardial infarction and heart failure in RA

- Four studies, one cross-sectional and three case–control,related MTX use to the risk of myocardial infarction (MI)
- One study (quantitative clinical assessment of patients with rheumatoid arthritis), a large multi-national study (n = 4363), demonstrated an 18% reduction in the risk of MI in patients treated for 1 year with MTX.

Naranjo A, Sokka T, Descalzo MA et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.

- The other studies showed a non-statistically significant trend towards a reduction in the risk of MI with current or ever use of MTX

Radovits BJ, Popa-Diaconu DA, Popa C et al. Disease activity as a risk factor for myocardial infarction in rheumatoid arthritis. Ann Rheum Dis 2009;68:1271–6.

Suissa S, Bernatsky S, Hudson M. Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55:531–6.

Edwards CJ. Myocardial infarction in rheumatoid arthritis.The effects of DMARDs and prednisolone [Abstract]. Arthritis Rheum 2008;56(Suppl. 9):688.

MTX and stroke in RA

- Two studies, one cross-sectional and one case–control, considered MTX and the risk of stroke.
- One large multi-national study demonstrated an 11% reduction in the risk of stroke with ever use of MTX. In this study, the analysis was adjusted for features of RA [disease activity score (DAS)-28 and HAQ].

Naranjo A, Sokka T, Descalzo MA et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10:R30.

- The second study, a large (n = 33 191) unpublished study including patients with RA from a primary care database in the UK, demonstrated a trend towards an increased risk of stroke in ever users of MTX

Endean A. The risk of stroke in patients with rheumatoid arthritis compared to the general population [Abstract]. Arthritis Rheum 2007;56(Suppl. 9):S293.

RHEUMATOLOGY

Rheumatology 2010;49:295–307
doi:10.1093/rheumatology/kep366
Advance Access publication 17 November 2009

Original article

The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review

Sarah L. Westlake[1], Alexandra N. Colebatch[2], Janis Baird[3], Patrick Kiely[4], Mark Quinn[5], Ernest Choy[6], Andrew J. K. Ostor[7] and Christopher J. Edwards[2]

- MTX and lipids in RA

No change in lipid profile

- MTX and hypertension in RA

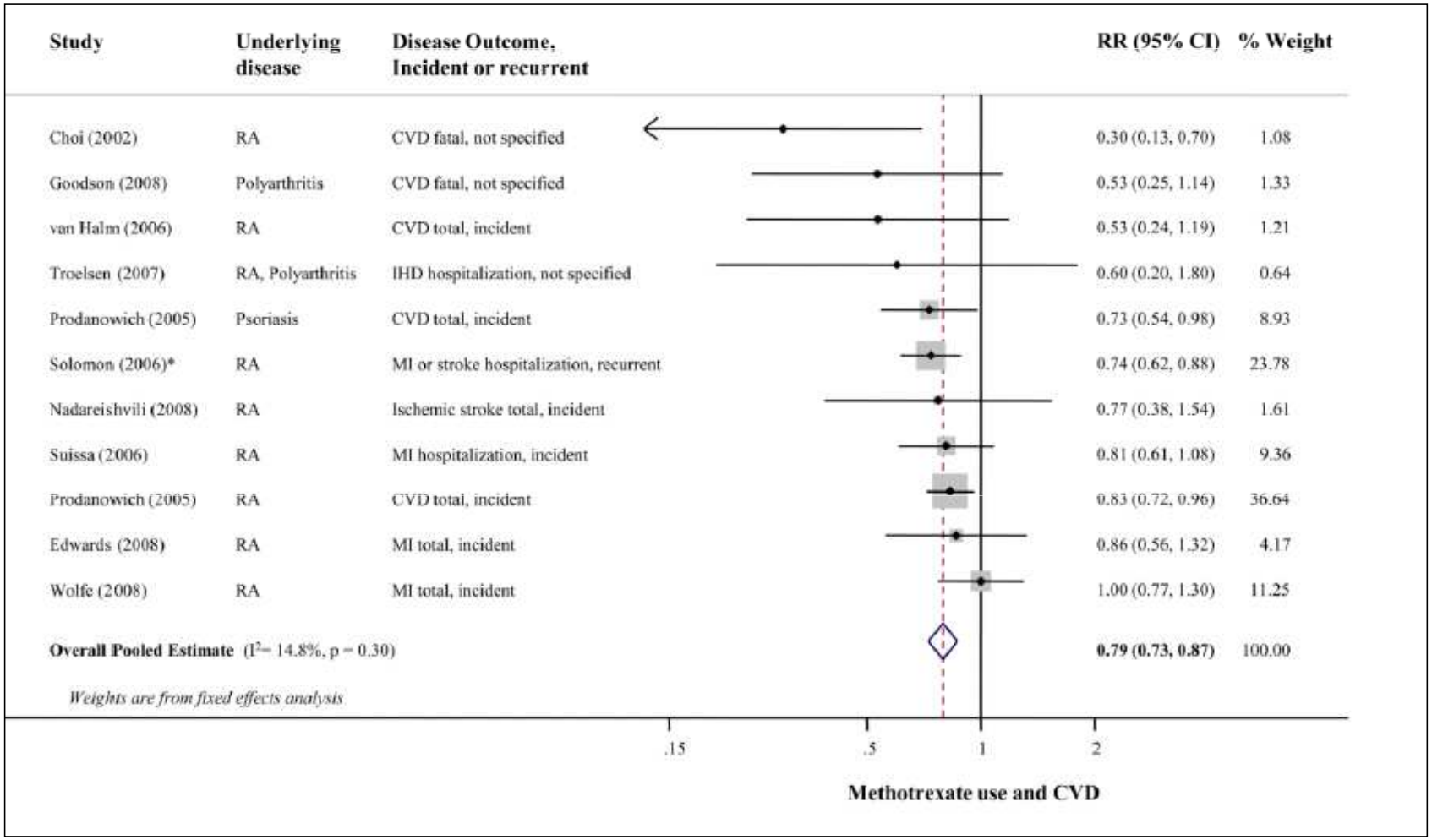
no difference in the current use of MTX between RA hypertensive and normotensive patients

- MTX and insulin resistance in RA

No change in insulin resistance was seen after 3 months treatment with MTX

Systematic Review and Meta-analysis of Methotrexate Use and Risk of Cardiovascular Disease

Renata Micha, RD PhD[a], Fumiaki Imamura, PhD[a], Moritz Wyler von Ballmoos, MD PhD[b], Daniel H. Solomon, MD[c], Miguel A. Hernán, MD DrPH[a,e], Paul M Ridker, MD[d], and Dariush Mozaffarian, MD DrPH[a,d]



Am J Cardiol . 2011 November 1; 108(9): 1362–1370.

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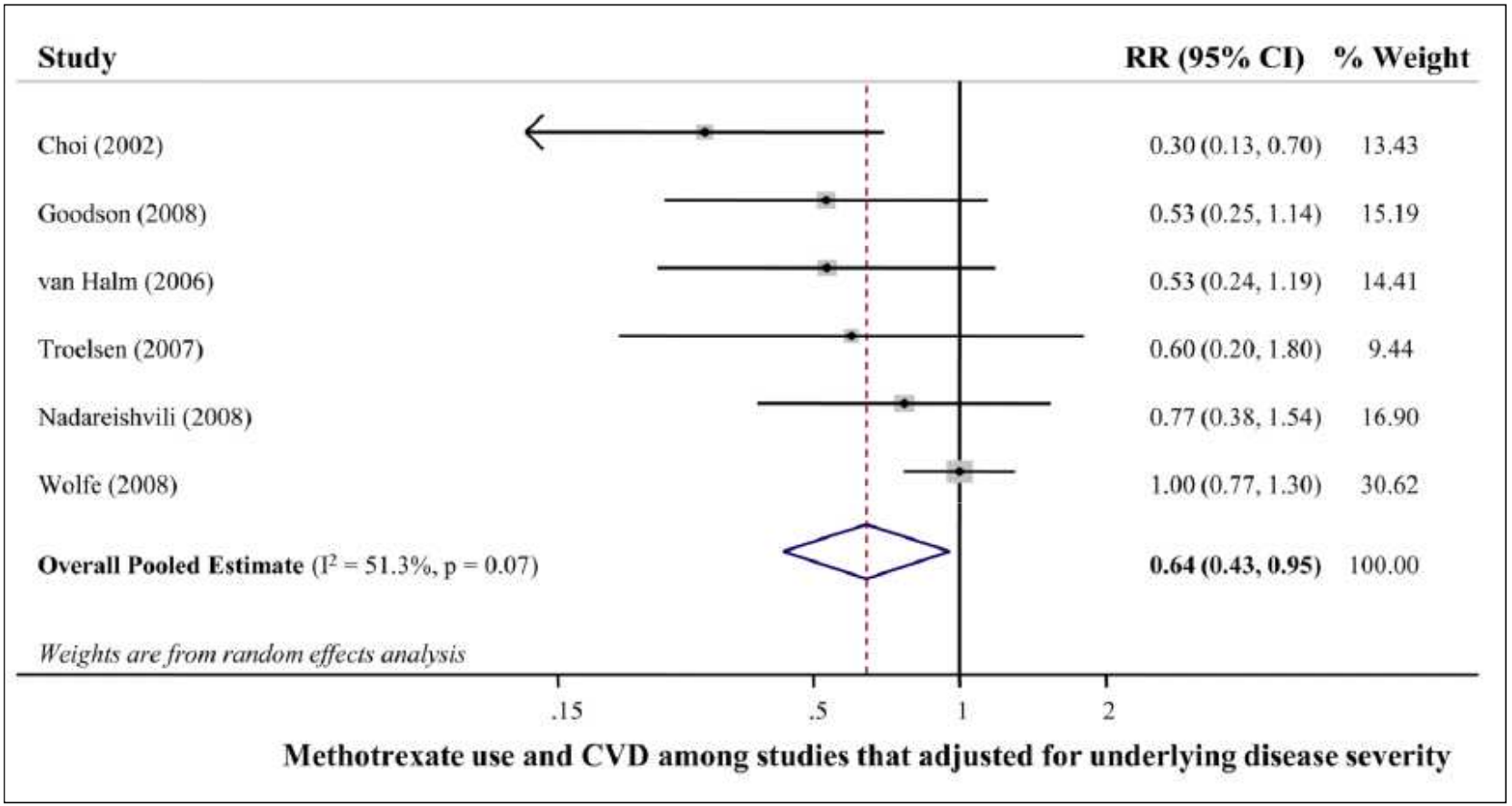
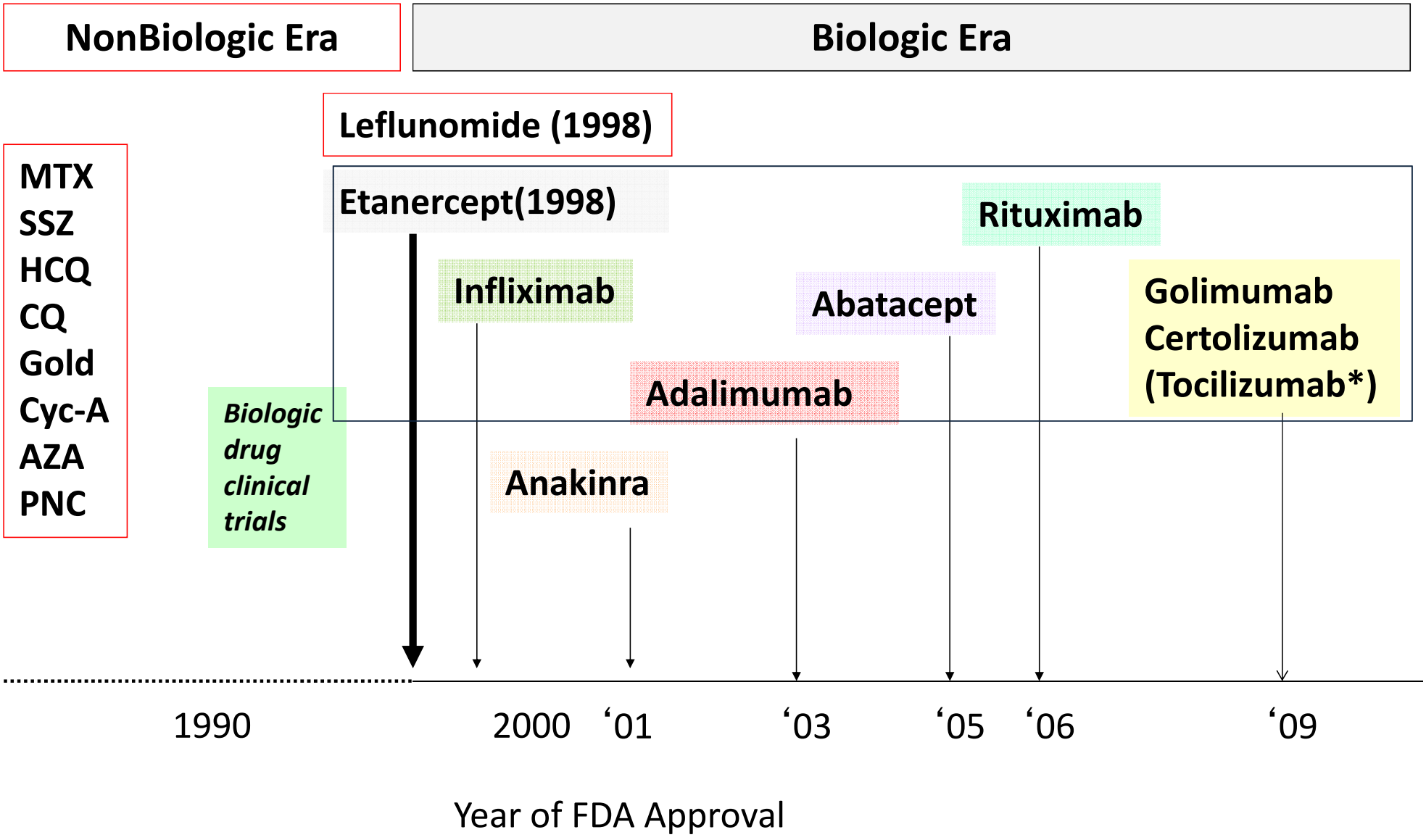


Am J Cardiol . 2011 November 1; 108(9): 1362–1370.

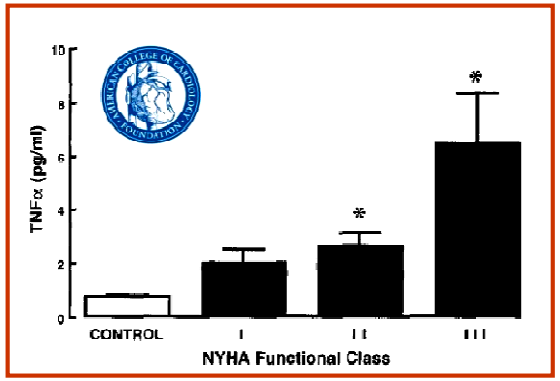
RA and cardiovascular risk

- CV risk and biotechnological agents

Spectrum of RA Treatment



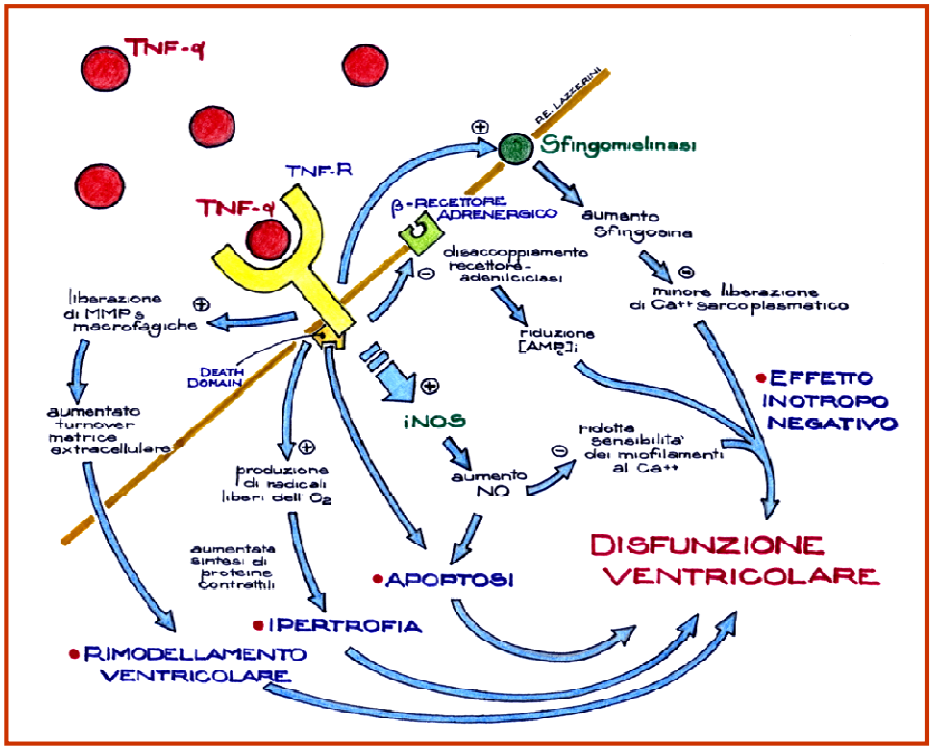
TNF-α and heart failure

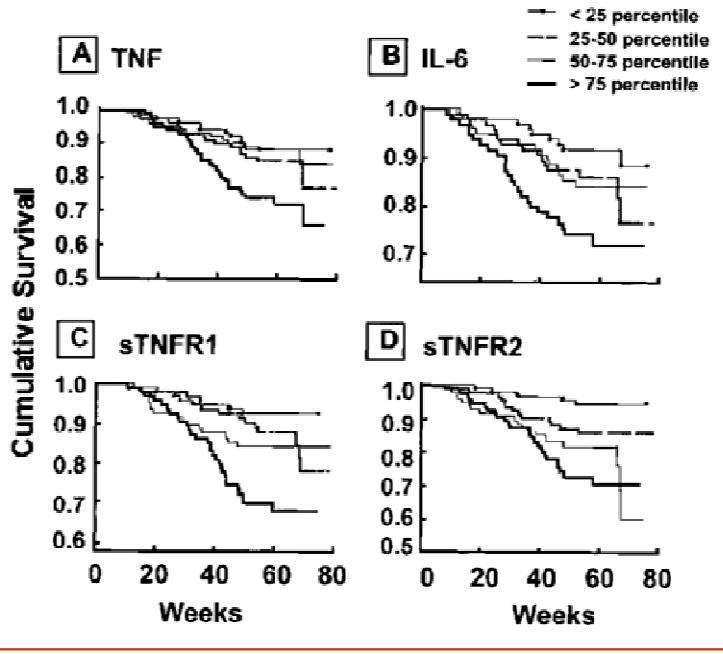


Torre-Amione G, Kapadia S, Benedict C, et al. 1996;27:1201-1206

JACC

In patients with HF, circulating levels of TNFa increase as their functional class deteriorates





In patients with advanced HF, increasing circulating levels of TNF□ and TNF□ receptors are independently associated with increased mortality.

Vesnarinone trial (VEST); n=1200

American Heart Association
Learn and Live

Deswal A, Petersen NJ, Feldman AM et al. 2001;103:2055

Circulation

Based on: Gullestad L, Ueland T, Vinge LE, et al. 2012;122:23-35

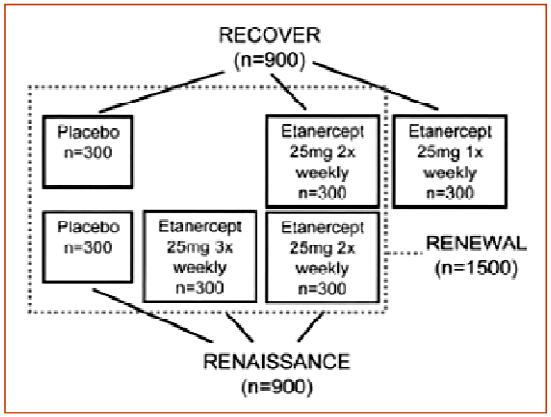
CARDIOLOGY
International Journal of Cardiovascular Medicine, Surgery, Pathology and Pharmacology

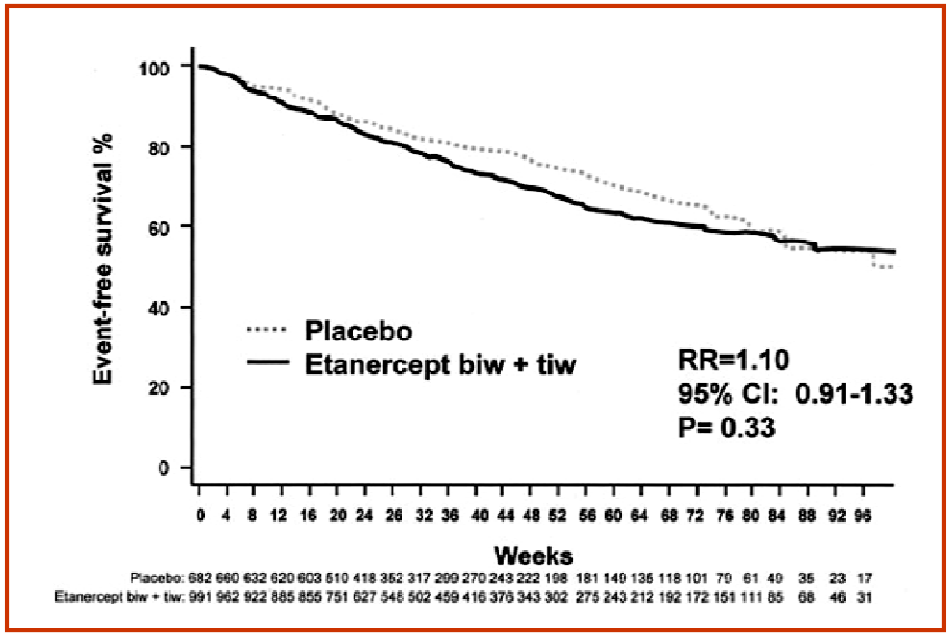
Anti-TNF-α drugs and heart failure

RENEWAL trial

In patients with mild-to-severe HF (NYHA class II to IV and LVEF ≤30%), 24 week treatment with etanercept had not effect on the death or HF hospitalization

Randomized, double blind, placebo controlled, multicenter clinical trial; n=1500



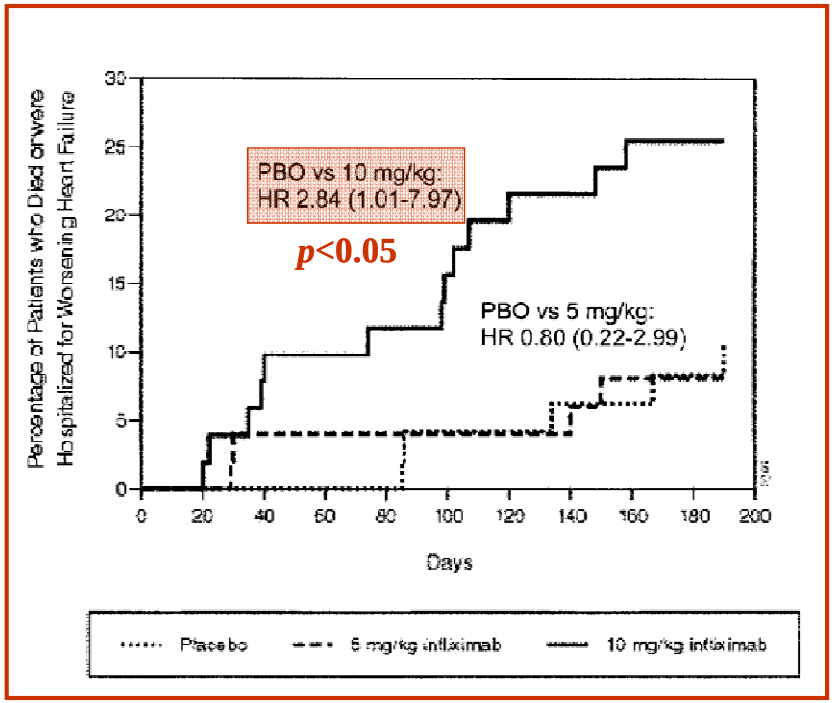


American Heart Association Learn and Live

Mann DL, McMurray JJV, Packer M, et al. 2004;109:1594

Circulation

ATTACH trial



In patients with moderate-to-severe HF (NYHA class III or IV and LVEF ≤35%), 28 week treatment with infliximab did not improve and high doses (10 mg/kg) increased the risk of death or hospitalization for HF (about 3 times)

Randomized, double blind, placebo controlled, pilot trial; n=150

American Heart Association Learn and Live

Chung ES, Packer M, Hung Lo K, et al. 2003;107:3133

Circulation

Anti-TNF-α drugs and heart failure

FDA* → **47 cases**
of new or worsening CHF in patients receiving anti-TNFa drugs for RA/Crohn's disease

- **New onset CHF** *n=38*
  - **Etanercept** *n=26*
  - **Infliximab** *n=12*

  in 19 cases (50%)
  no identificable risk factors
- **CHF exacerbation** *n=9*

Anti-TNF□-inhibitors and CHF: RECOMMENDATIONS

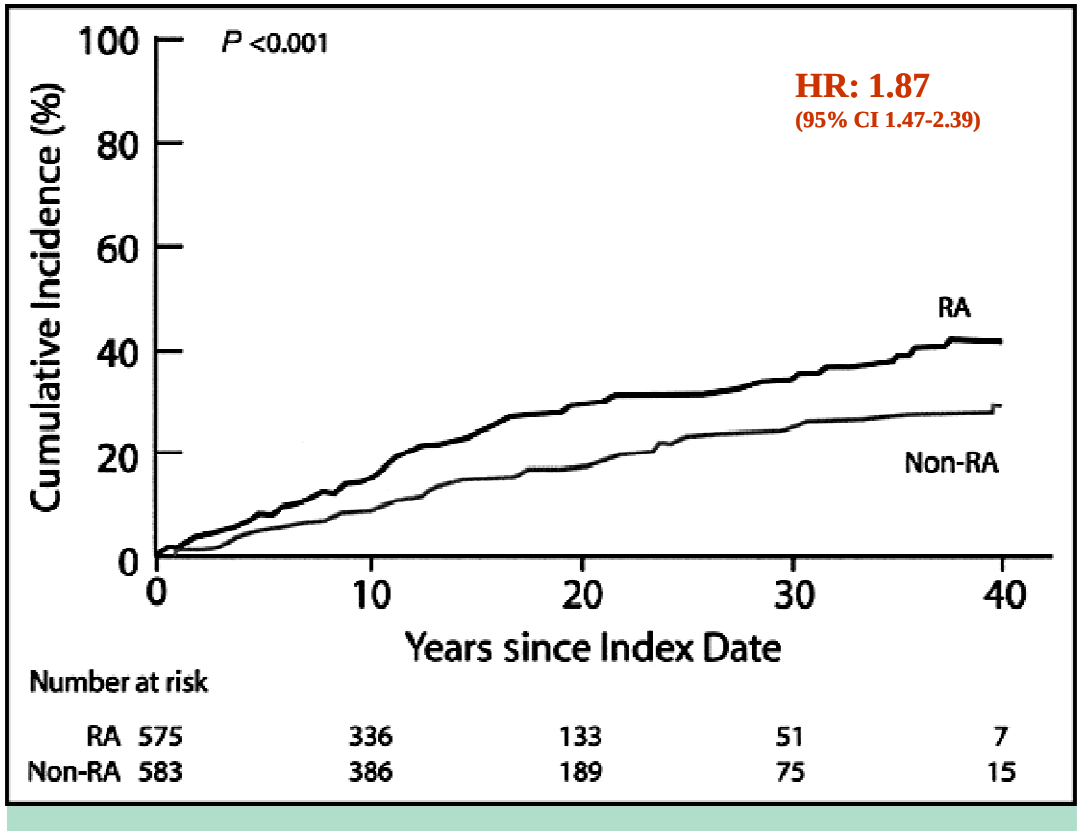
1. To avoid in patients with NYHA class III-IV

2. To monitor closely for symptoms in patients with NYHA class I-II

* **FDA MedWatch passive surveillaince program**

RA patients are at increased risk of heart failure (HF)

Rochester Epidemiology Project



Nicola PJ, Maradit-Kramers H, Roger VL, et al. 2005; 52: 412-420

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Education • Treatment • Research
Arthritis & Rheumatism

RA and heart failure risk

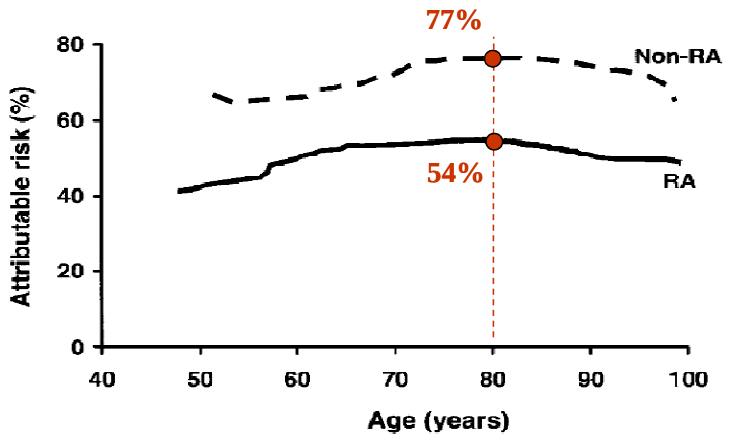


Figure 2. Risk of HF attributable to all CV risk factors, IHD, and alcohol abuse as a function of age in 575 RA subjects and 583 non-RA subjects.

The excess of risk of HF among RA patients is not explained by an increased frequency or effect of traditional CV risk factors (family history, hypertension, dyslipidemia, obesity, diabetes mellitus, smoking) and IHD: at age 80 years 77% of the HF among non-RA subjects was attributable to these factors vs only 54% among RA patients (p<0.01)

Maradit-Kramers H, Crowson CS, Nicola PJ, Maradit-Kramers H, et al.
2005; 52: 3039-3044 Arthritis & Rheumatism

In RA patients, the risk to develop HF was associated with systemic inflammation (*ESR*) and disease activity markers (*RF positivity, extra-articular manifestations*).
On the contrary, DMARDs use (particularly MTX) was associated with a 50% risk reduction of HF

Myasoedova E, Crowson CS, Nicola PJ, et al.
2011; 38: 1601-1606 The Journal of Rheumatology

Table 2. RA characteristics and their associations with the risk of heart failure (HF) in 795 incident RA patients. Values are given as number (%) if not indicated otherwise.

Characteristics	Value	Hazard Ratio ** (95% CI), Adjusted for Age, Sex, and Calendar Year of RA Incidence
RF-positive	527 (66)	**1.6 (1.0, 2.5)**
ESR at RA incidence, mm/h, mean ± SD	24.2 ± 19.9	**1.6 (1.2, 2.0)†**
≥ 3 ESR ≥ 60 mm/h	99 (12)	**2.1 (1.2, 3.5)**
Large-joint swelling	624 (78)	1.1 (0.7, 1.8)
Joint erosions/destructive changes	424 (53)	1.1 (0.8, 1.7)
Joint surgery		
Arthroplasty	134 (17)	1.5 (0.9, 2.5)
Synovectomy	86 (11)	1.1 (0.6, 2.2)
Rheumatoid nodules	266 (33)	1.1 (0.7, 1.7)
Severe ExRA*	87 (11)	**3.1 (1.9, 5.1)**
History of rheumatic fever	22 (3)	1.0 (0.4, 2.7)

* Malmö criteria[32]. ** Significant ($p < 0.05$) hazard ratios are shown in bold type. † Per 30 mm/h increase. RA: rheumatoid arthritis; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; ExRA: extraarticular manifestations of RA.

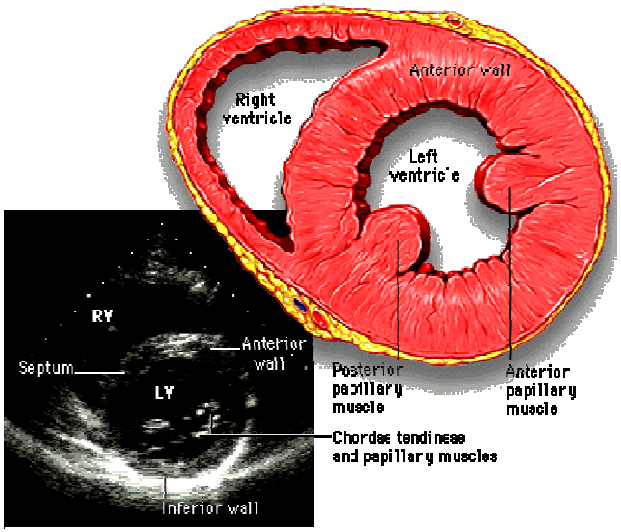
Subclinical cardiac damage in RA

Increased LV mass

RA is associated with increased LV mass and the prevalence of LV hypertrophy is higher in RA patients than controls (18 vs 6.7%).
LV mass in indipendently associated with disease duration

Rudominer RL, Roman MJ, Deveraux RB, et al.
2009; 60: 22-29

Arthritis & Rheumatism

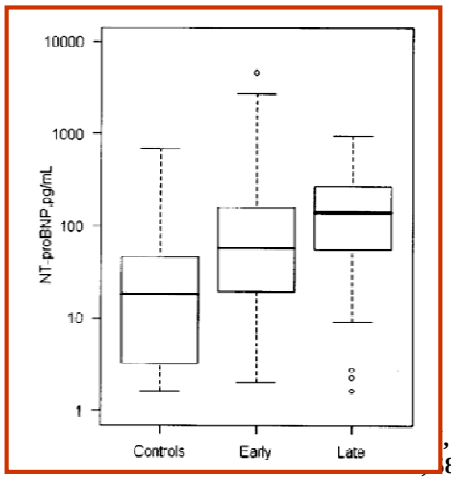


Diastolic dysfunction

RA patients hve an higher prevalence of diastolic dysfunction (31 vs 26%) than non-RA subjects.
Diastolic dysfunction in RA is independently associated with IL-6 levels and disease duration

Liang KP, Myasoedova E, Crowson CS, et al.
2010; 69: 1665-1670

Annals of the RHEUMATIC DISEASES The EULAR Journal



NT-proBNP elevation

RA patients without HF have high NT-proBNP levels than controls.
In multivariate analysis, *BNP levels are associated with disease activity (DAS 28), TNF□, IL-6 and CRP concentrations*

, Chung CP, Oeser A, et al.
8: 2662-2669

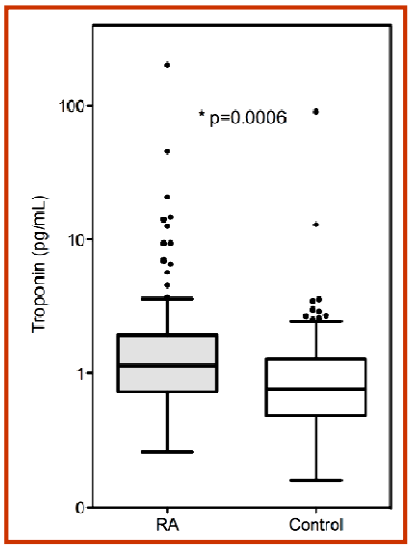
Arthritis & Rheumatism

Increased Troponin I levels

High-sensitivity cardiac troponin-I is elevated in patients with RA

Bradham WS, Bian A, Oeser A, et al.
2012; 7: e38930

PLoS one



Subclinical cardiac damage in RA and anti-TNF-α drugs

Increase of LVEF

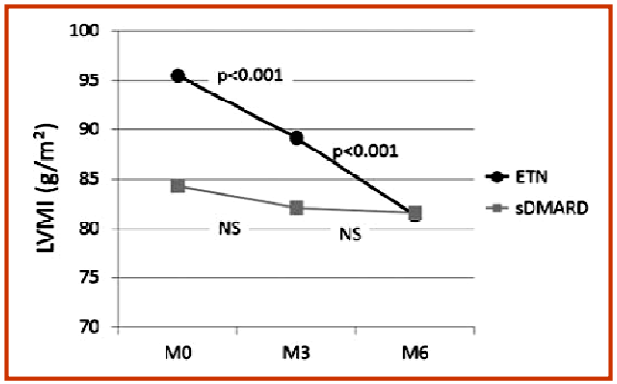
	Before Treatment	After 12 Months	p
ESR, mm/h*	39.7 ± 6.4	25.2 ± 4.6	< 0.001
CRP, mg/l*	34.3 ± 7.3	15.0 ± 4.8	< 0.001
Platelets, g/l*	350.1 ± 22.8	236.8 ± 14.1	< 0.05
Right ventricle, mm*	20.8 ± 2.1	23.0 ± 2.8	< 0.001
LVEF, %†	55.0/58.5/64.0	60.0/63.0/65.0	< 0.05
Left ventricle mass, g*	193.7 ± 44.0	182.3 ± 35.4	< 0.05
V_e*	0.88 ± 0.17	0.90 ± 0.32	0.21
V_a*	0.78 ± 0.19	0.83 ± 0.28	0.82
IL-6, pg/ml†	7.22 (58.46/104.85)	1.18 (3.46/16.05)	< 0.001
Endothelin, fmol/ml†	0.29 (1.26/4.34)	0.24 (0.43/3.28)	< 0.01
NT-proBNP, fmol/ml†	23.04 (43.06/62.72)	12.8 (14.78/30.22)	< 0.01

Twelve month treatment with infliximab significantly incresed LV ejection fraction in RA patients. *Concomitantly, DAS 28, as well as IL-6, NT-proBNP and ET-1 levels significantly decreased.*

Owczarek A, Rakoczy J et al.
1-706

The Journal of Rheumatology

Normalization of LV mass



Medium term (3-6 months) treatment with etaanercept significantly decreased LV mass in RA patients. *Such an effect was stricly correlated with the reduction of the disease activity (DAS 28) induced by the drug.*

Immediato Daien C, Fesler P, du Cailar G, et al.
2012 (article in press)

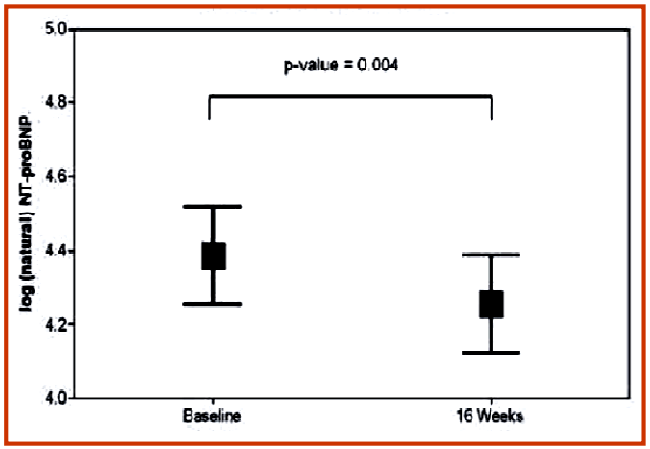
Annals of the RHEUMATIC DISEASES The EULAR Journal

Reduction of NT-proBNP levels

Circulating levels of NT-proBNP decreased after 16 weeks of adalimumab administration in patients with active RA.
Changes in NT-proBNP levels were associated with changes in ESR

Peters MJL, Welsh P, McInnes I, et al.
2010; 69: 1281-1285

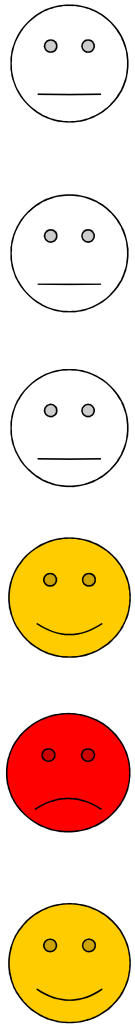
Annals of the RHEUMATIC DISEASES The EULAR Journal



Anti-TNF-α drugs and heart failure risk in RA

Study	Study type	Number of subjects	Exposure—TNF antagonist use	CVD outcome	Analysis	Confounding factors adjusted for	Size of effect	Conclusion (risk of bias)
[36]	Cohort	2757 cases treated with TNF (mean age 53.7 years, 78.1% female, mean disease duration 9 years) and 1491 controls treated with DMARDs (mean age 56.1 years, 76.9% female, mean disease duration 6 years) from German cohorts.	TNF use (etanercept, infliximab and adalimumab) within the last 6 months.	Heart failure, acute heart failure, congestive heart failure or ventricular failure diagnosed by a rheumatologist.	Cox proportional hazards model with time-dependent covariates applied to calculate the HR.	Age, sex, BMI and comorbid conditions, disease duration, RF, functional capacity, rheumatoid nodules, erosive disease and propensity score.	Adjusted HR 1.66 (95% CI 0.67, 4.1), $P=0.28$.	Compared with patients treated with DMARDs recent use of TNF antagonists was not associated with an altered risk of HF Low.
[37]	Cohort	Cases $n=1138$. 330 infliximab, mean age 40 years, 70% female; 808 etanercept, mean age 38 years, 75% female. Controls $n=983$. TNF unexposed, on MTX. Mean age 39 years, 75% female. No disease duration given.	Use of infliximab or etanercept within the last 9 months.	Inpatient or outpatient diagnosis of HF by ICD-9 code.	Cumulative incidence ratios (CIRs) to compare the relative risk	None. The number of cases was too small to do multivariate analysis.	Etanercept CIR 5.0 (95% CI 1.3, 12.6), RR 4.9 and infliximab CIR 3.0 (95% CI 0.1, 16.8), RR 3.0. Number needed to harm 294.	The incidence of HF in patients <50 years is low. There is a non-significant increased risk of HF in patients treated with etanercept and infliximab compared with MTX. Medium.
[38]	Cohort	USA Veterans affairs. Cases (TNF) $n=103$. Mean age 59 years, 8% female. Controls $n=100$, (TNF unexposed). Mean age 68 years, 7% female. No disease duration given.	Treated with at least one dose of infliximab, etanercept or adalimumab.	New or worsening heart failure by ICD-9 code.	Pearson chi square analysis and Fisher's exact test to determine differences between the groups in CHF, CHF exacerbation and mortality.	None.	No difference in HF admissions between cases and controls ($P=0.940$).	Compared with TNF naïve patients there was no increased risk of HF in patients treated with TNF antagonists. Medium.
[39]	Cohort	USA database. Cases $n=5032$ (TNF). Mean age 60 years, 78% female, mean disease duration 14 years. Controls $n=7339$ (no TNF). Mean age 61.5 years, 76% female, mean disease duration 15 years.	Current use of infliximab or etanercept.	Incident or prevalent HF.	Adjusted rates of heart failure between cases and controls.	Propensity score, HAQ, global severity, pain, prednisolone use, age, age squared and sex.	All HF the adjusted frequency in cases 2.6 *vs* 3.9% in controls ($P=0.03$). Incident HF in both cases and controls 0.2% ($P=0.68$).	Current treatment with etanercept or infliximab is associated with a decreased risk of HF compared with non-current use. Medium.
[40]	Cohort	Cases, $n=1002$ (TNF). Mean age 72–73 years, 78–79% female. Controls (MTX), $n=4591$. Mean age 74–77 years, 74–79% female. No disease duration given.	Current use of etanercept of infliximab compared with current use of MTX. Median duration of use 1.2 years, 55%, >2 years.	Hospitalization with HF.	Cox proportional hazards regression to determine the HR, with adjustment for the multiple confounders and the propensity score.	Demographic variables, risk factors for CVD, previous heart failure hospitalizations, factors associated with severity of RA (oral steroids, NSAIDs and other DMARDs) and other major comorbid conditions.	HR with TNF use 1.70 (95% CI 1.07, 2.69).	In elderly patients current treatment with etanercept or infliximab is associated with a significantly increased risk of HF compared with current treatment with MTX. Medium.
[41]	Case–control	520 cases and 5200 controls from and insurance database. Mean age of cases 67 years, and controls 65 years. 67% of cases were female and 75% of controls. No disease duration given.	Current use of infliximab or etanercept compared with non-current use of a DMARD.	First occurrence of congestive heart failure requiring hospitalization defined by ICD-9 code.	Conditional logistic regression to estimate the RR of hospitalization for CHF with use of infliximab or etanercept.	Age, gender, duration of time in the cohort, comorbidity, NSAIDs, COX-2 inhibitors and other DMARDs.	RR 0.5 (95% CI 0.2, 0.9).	Compared with no current DMARD use, current use of infliximab or etanercept (but not MTX, LEF or other DMARDs) is associated with a significantly decreased risk of CHF Medium.

CHF: chronic heart failure.



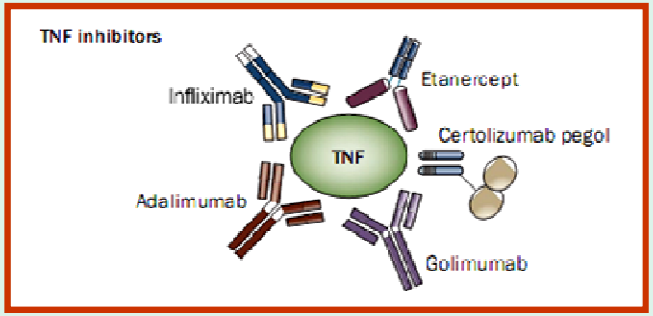
Westlake SL, Colebatch AN, Baird J, et al. 2011; 50: 518-531

RHEUMATOLOGY

Anti-TNF-α drugs and heart failure risk in RA

1. Reassuringly, TNF□ antagonist treatment does not appear associated with an increased risk of heart failure.

However, the results of the avilable studies are conflicting and therefore no definite conclusion can be drawn (promotion or prevention of HF?), particularly when comparing TNF□ antagonist users with DMARD users



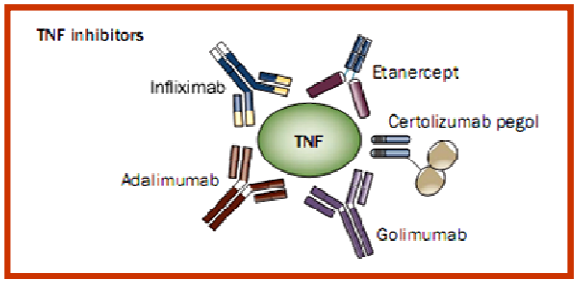
2. Compared with non-DMARD users there may be a decreased risk of heart failure in TNF□ antagonist users

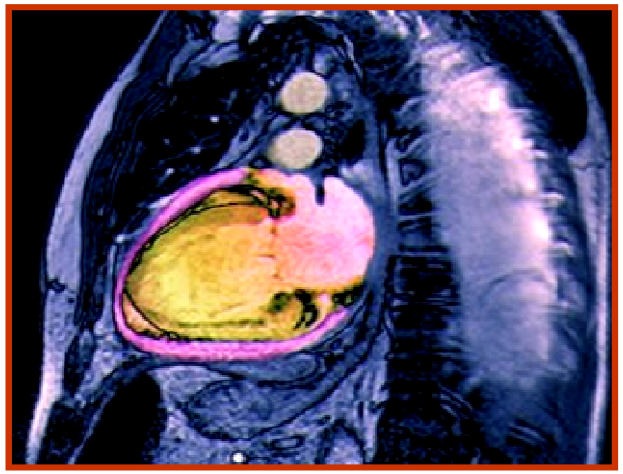
3. In elderly patients, the use of TNF□ antagonists may be associated with an increased risk of heart failure

Westlake SL, Colebatch AN, Baird J, et al. 2011; 50: 518-531

RHEUMATOLOGY

Biologic drugs and heart failure





ANSWERS

1. Should be all the candidate patients instrumentally screened for heart failure ?

No, they should not.
Basal echocardiography should be only performed in:
a. patients with NYHA class I or II CHF
b. patients with a pre-existing cardiac disase
c. elderly patients

2. What about patients with heart failure in II/III NYHA class ?

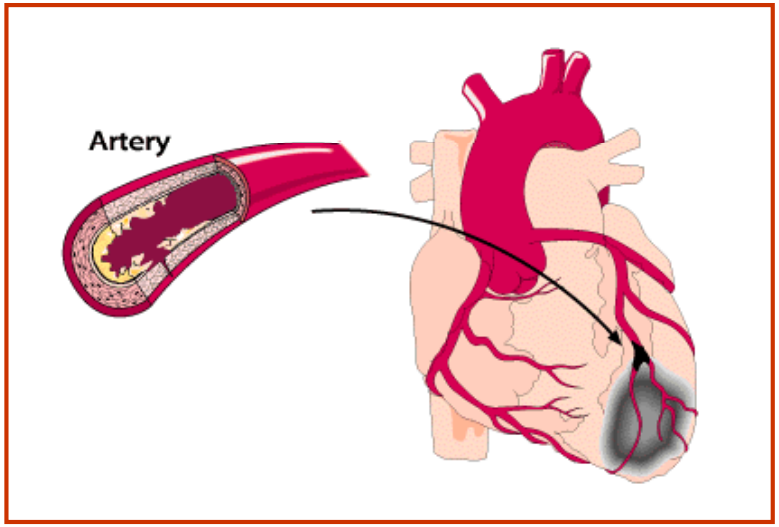
In these patients is absolutely necessary to optimize CHF treatment to improve the functional class. When the patient will reach class II or lesser, therapy with biologic drugs can be started although under strict clinical monitoring

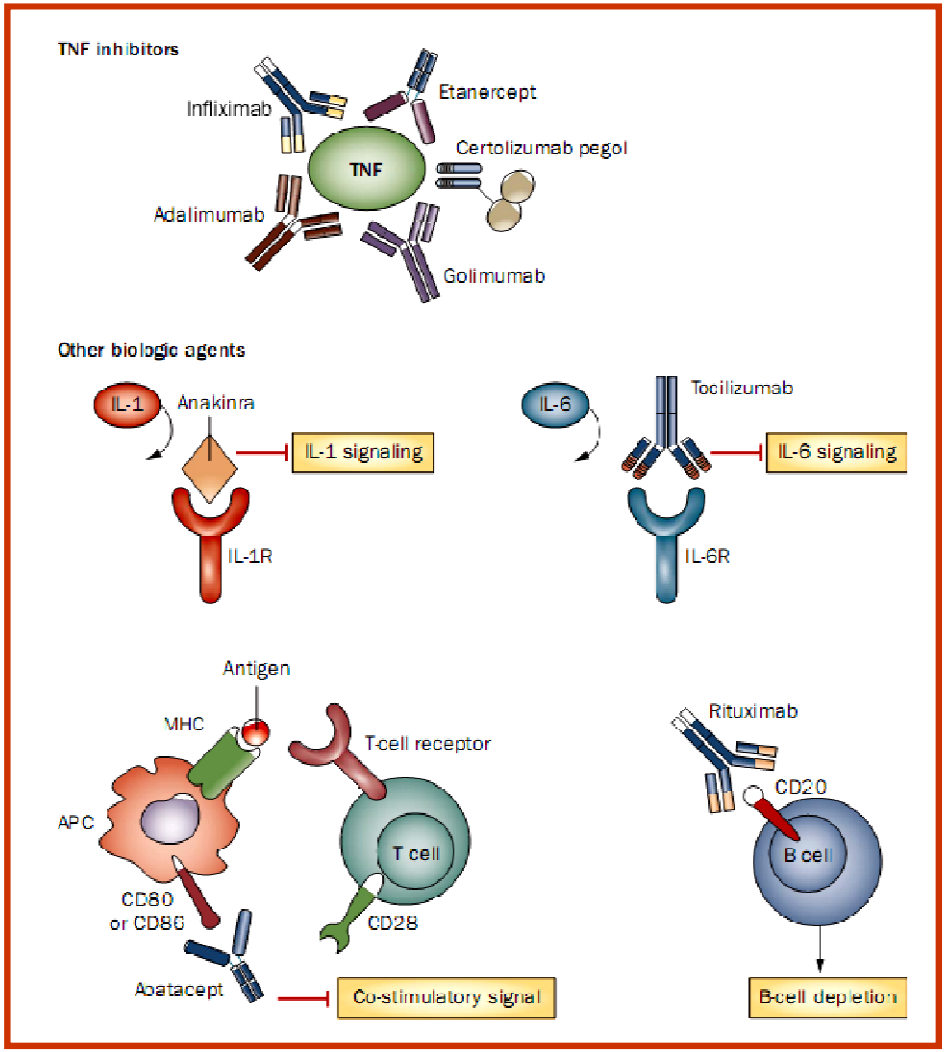
Biologic drugs and ischemic heart disease

QUESTIONS

1. ***Should be all the candidate patients instrumentally screened for ischemic heart disease?***

2. ***How should we menage patients with myocardial infarction, pre-existing or occurring during treatment with biologic drugs?***





Woodrick RS and Ruderman EM.
2011; 7: 639-652
nature REVIEWS RHEUMATOLOGY

Circulating levels of TNF receptors are highly predictive of CV mortality in RA patients

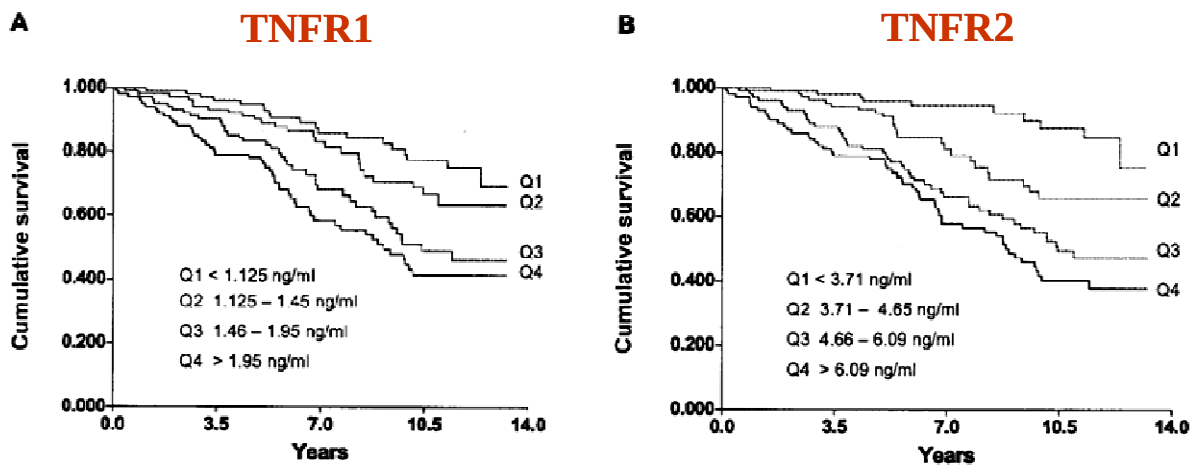


Figure 1. Kaplan-Meier survival curves for patients with rheumatoid arthritis in relation to circulating levels of soluble tumor necrosis factor receptor I (sTNFRI) (**A**) and sTNFRII (**B**). For these analyses, levels of TNF receptors were arbitrarily divided into quartiles (Q1–Q4). For quartiles of both sTNFRI and sTNFRII levels, P for trend < 0.0001 by log rank test.

Table 3. Mortality risk associated with sTNFRI and sTNFRII levels in patients with RA*

	sTNFRI	sTNFRII
All causes		
Men	1.70 (1.20–2.41)	1.18 (1.05–1.32)
Women	1.33 (0.99–1.79)	1.14 (1.02–1.28)
Cardiovascular causes		
Men	2.13 (1.40–3.24)	1.35 (1.18–1.55)
Women	1.50 (0.99–2.30)	1.11 (0.97–1.35)

* Values are the hazard ratio (95% confidence interval), representing the risk of mortality per 1-ng/ml increase in sTNFRI or sTNFRII.

Mattey DL, Glossop JR, Nixon NB, et al. 2007; 56: 3940-3948

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Arthritis & Rheumatism

IL-6 (174G/C) polimorphism increases both IL-6 circulating levels and prevalence of CVD in RA patients

Table 3
Prevalence of cardiovascular disease components in all, overweight/obese and ever smokers, RA patients

IL6-174 SNP	All			BMI > 25			C/P smokers		
	GG	GC/CC	P	GG	GC/CC	P	GG	GC/CC	P
Angina	12 (8.9)	38 (15.3)	0.074	7 (7.1)	30 (18.8)	0.009	4 (5.5)	26 (19.4)	0.007
MI	7 (5.2)	19 (7.7)	0.357	5 (5.1)	12 (7.5)	0.439	3 (4.1)	11 (8.2)	0.387
HF	5 (3.7)	5 (2)	0.322	4 (4)	4 (2.5)	0.486	1 (1.4)	4 (3)	0.470
CVA	3 (2.2)	13 (5.2)	0.158	3 (3)	7 (4.4)	0.585	2 (2.7)	7 (5.2)	0.402
PVD	3 (2.2)	10 (4)	0.556	1 (1)	7 (4.4)	0.160	3 (4.1)	6 (4.5)	1
CV death	2 (1.5)	6 (2.4)	0.718	1 (1)	4 (2.5)	0.397	0 (0)	3 (2.2)	0.554
Total CVD	23 (17)	65 (26.2)	0.041	16 (16.2)	47 (29.4)	0.016	10 (13.7)	39 (29.1)	0.013

IL6: interleukin 6, SNP: single nucleotide polymorphism, BMI: body mass index, C/P: current or past, MI: myocardial infarction, HF: heart failure, CVA: cerebrovascular accident (stroke, transient ischaemic attack), PVD: peripheral vascular disease, CV: cardiovascular, and CVD: cardiovascular disease.

RA patients, n=383

Table 4
Adjusted OR for cardiovascular disease in RA patients

	OR (95%CI)	P-value
Use of daily medium dose (≥7.5 mg) prednisolone	2.22 (1.12–4.38)	0.022
Male sex	2.05 (1.10–3.80)	0.024
IL6-174 C-allele vs GG homozygotes	1.92 (1.03–3.58)	0.041
Health assessment questionnaire[a]	1.52 (1.09–2.12)	0.022
Age (years)[a]	1.06 (1.03–1.10)	<0.001
Hypertension	1.14 (0.56–2.32)	0.727
Type 2 diabetes mellitus	1.95 (0.88–4.34)	0.102
Past smokers[b]	0.76 (0.34–1.71)	0.510
Current smokers[b]	0.61 (0.26–1.41)	0.243
Body mass index (kg/m^2)[a]	1.01 (0.96–1.08)	0.645

OR: odds ratio, IL6: interleukin 6.
[a] Per unit increase.
[b] Compared to non-smokers.

RA patients, n=135	GG	GC/CC
Serum IL-6 levels (pg/ml)	14.0* (3.2-38.8)	4.5 (2.2-16.5)

*p=0.028

Table 5
Odds ratio for cardiovascular disease when comparing -174 C-allele carriers to GG homozygotes in RA patients

	All	
	OR (95%CI)	P
Crude	1.73 (1.02–2.94)	0.043
Age, sex	1.80 (1.03–3.15)	0.038
Model 1	1.92 (1.03–3.58)	0.041

Model 1: age, sex, hypertension, type 2 DM, smoking status, BMI, HAQ and use of medium dose prednisolone.

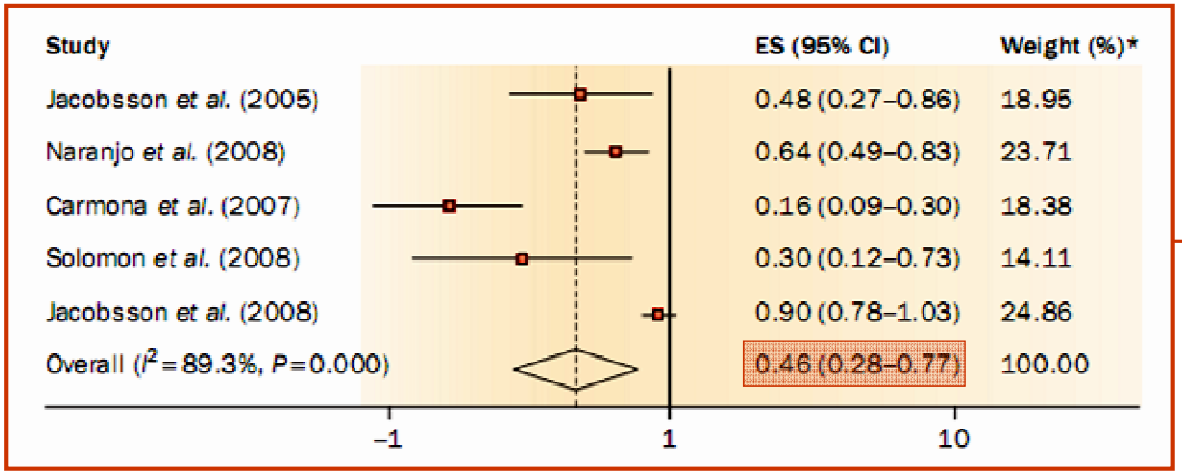
Panoulas VF, Stavropoulos-Kalinoglou A, Metsios GS, et al. 2009; 204: 178-183

ATHEROSCLEROSIS

Anti-TNF drugs reduce the risk of CV events in RA patients

All CV events

Adjusted relative risk of CV events in RA patients treated with anti-TNF agents vs. non-biologic DMARDs in published observational cohort studies: a meta-anlysis



myocardial infarction
RR 0.81, 95% CI 0.68-0.96

cerebrovascular accident
RR 0.69, 95% CI 0.53-0.89

American College of Rheumatology

Barnabe C, Martin BJ, Ghali WA. 2011; 63: 522-529

Arthritis Care & Research

Data from a multi-center US observational RA registry of 10,156 patients (CORRONA study) comparing the rates of CV events among patients with RA prescribed anti-TNF agents (incidence rate 2.93 per 1000 patients-years) versus nonbiologic drugs excluding MTX (7.51 per 1000 patients years)

Greenberg JD, Kremer JM, Curtis JR, et al. 2011; 70: 576-582

Annals of the Rheumatic Diseases

Table 1 | Cardiovascular risks of TNF antagonists versus nonbiologic DMARDs*

Endpoint	Number of events	Hazard ratio	95% CI
Composite endpoint (including cardiovascular deaths)	82‡	0.39	0.19–0.82
Composite endpoint (excluding cardiovascular deaths)	66	0.35	0.16–0.74
Nonfatal myocardial infarction	25	0.24	0.06–0.95
Nonfatal TIA or stroke	41	0.44	0.18–1.09

In RA patients who respond to anti-TNF-α therapy the incidence of MI is markedly lower than nonresponders

Table 3. Incidence rates of verified first MI in nonresponders and responders to anti-TNFα treatment*

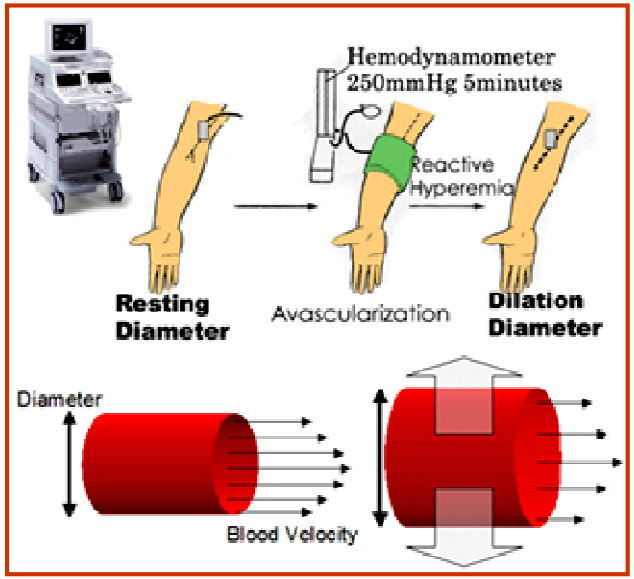
	Nonresponders (n = 1,638)	Responders (n = 5,877)
Person-years	1,815	9,886
No. of reported MIs	17	35
Rate of MIs per 1,000 person-years (95% CI)	9.4 (5.5–15.0)	3.5 (2.5–4.9)
Incidence rate ratio	Referent	0.38 (0.21–0.67)
Incidence rate ratio, adjusted for age and sex	Referent	0.38 (0.22–0.68)
Incidence rate ratio, multivariate analysis†	Referent	0.36 (0.19–0.69)
Incidence rate ratio by sex, multivariate analysis†		
Male patients	Referent	0.31 (0.12–0.81)
Female patients	Referent	0.46 (0.20–1.06)

* 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Adjusted for age, sex, disease severity, body mass index, social deprivation, smoking history, comorbidity, and baseline drug use.

Dixon WG, Watson KD, Lunt M, et al. 2007; 56: 2905-2912

Anti-TNF-α treatment ameliorates surrogate markers of CV disease in RA patients

Flow-mediated dilation (FMD)

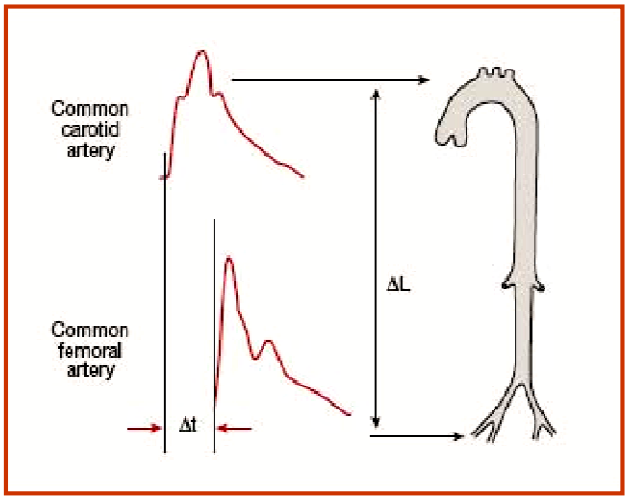


Endothelial dysfunction

Study Reference	TNF-inhibitor	Patients	Follow-up	Results
[65]	IFX	11	12 weeks	Improvement: 3.2% to 4.1% (p=0.018)
[64]	IFX	7	28 days	Improvement: 2.8% to 9.4% (p=0.02) 2 days post-infusion, return to pre-treatment levels 28 days after IFX infusion 2.8% to 4.0%
[66]	IFX	10	6 weeks	Improvement: 3.7% to 17.5% (p=0.001), return to pre-treatment levels at following IFX infusion
[67]	IFX	9	36 weeks	Improvement: 8.6% change as compared with baseline, significant improvement when compared with patients on DMARDS (p=0.009)
[70]	ADA	7	12 weeks	Improvement: 5.8% to 10.1% (p<0.05)
[60]	IFX	8	6 weeks	Improvement: 36.0% to 43.7% (p<0.05)
[68]	IFX	10	14 weeks	Improvement: 7.71% to 12.63% (p=0.005) FMD returned to pre-treatment just before each IFX infusion
[63]	IFX or ADA	12	18 months	Improvement: 7% to 11.1% (p=0.026)
[69]	ETA	11	12 weeks	Improvement: 5.2% to 7.9% (p=0.04)
[62]	IFX or ETA	25	12 weeks	Improvement: IFX 13.1% to 18.8% (p<0.01), ETA 11.8% to 16.7% (p<0.01) at day. Thereafter, FMD returned to baseline levels
[61]	ADA	8	12 weeks	Improvement: 7.0% to 13.2% (p<0.05 at all time points).

ADA, adalimumab; ETA, etanercept; IFX, infliximab

Pulse wave velocity (PWV)



Arterial stiffness

Study Reference	TNF-inhibitor	Patients	Follow-up	Results
[36]	ETA	9	12 weeks	Improvement: 8.82 m/s to 7.68 m/s (p<0.001)
[60]	IFX	15	6 weeks	No change
[59]	IFX, ADA or ETA	17	3 months	Improvement: 7.45m/s to 6.95 m/s (p=0.002)
[58]	IFX	26	56 weeks	Improvement (p<0.01)
[61]	ADA	8	24 weeks	6.8% non-significant improvement: 5.86 m/s to 5.46 m/s

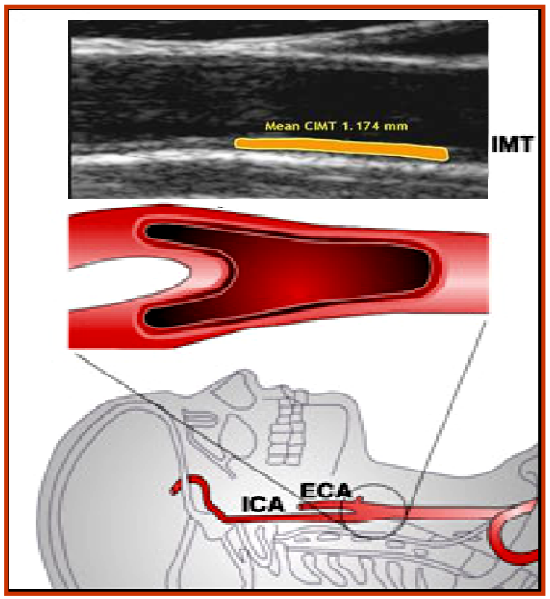
ADA, adalimumab; ETA, etanercept; IFX, infliximab

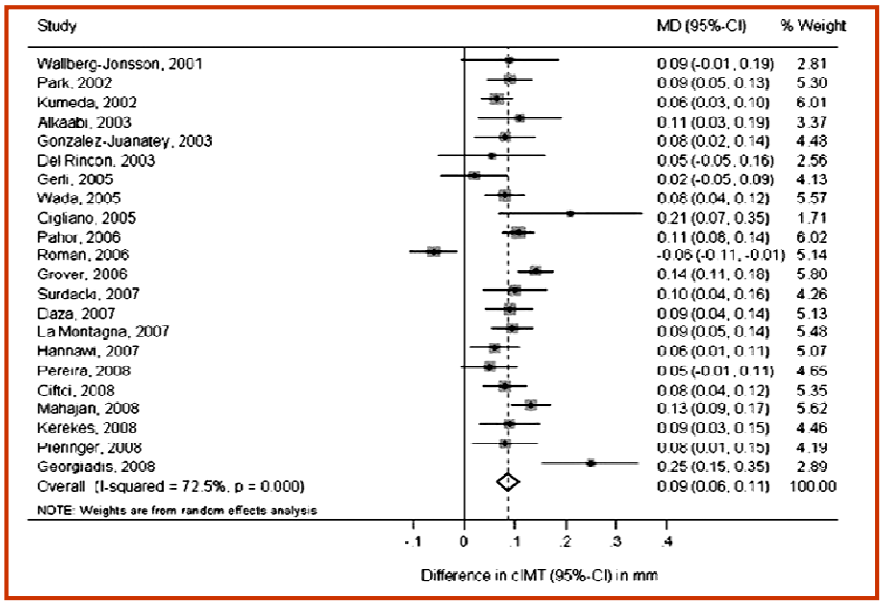
Peters MJL, van Sijl AM, Voskuyl AE, et al. 2012; 18: 1502-1511

CURRENT PHARMACEUTICAL DESIGN

Anti-TNF-α treatment ameliorates surrogate markers of CV disease in RA patients

Carotid intima-media thickness (cIMT)





Van Sijl AM, Peters MJ, Knol DK, et al. 2011; 40: 389-397

SEMINARS IN ARTHRITIS & RHEUMATISM

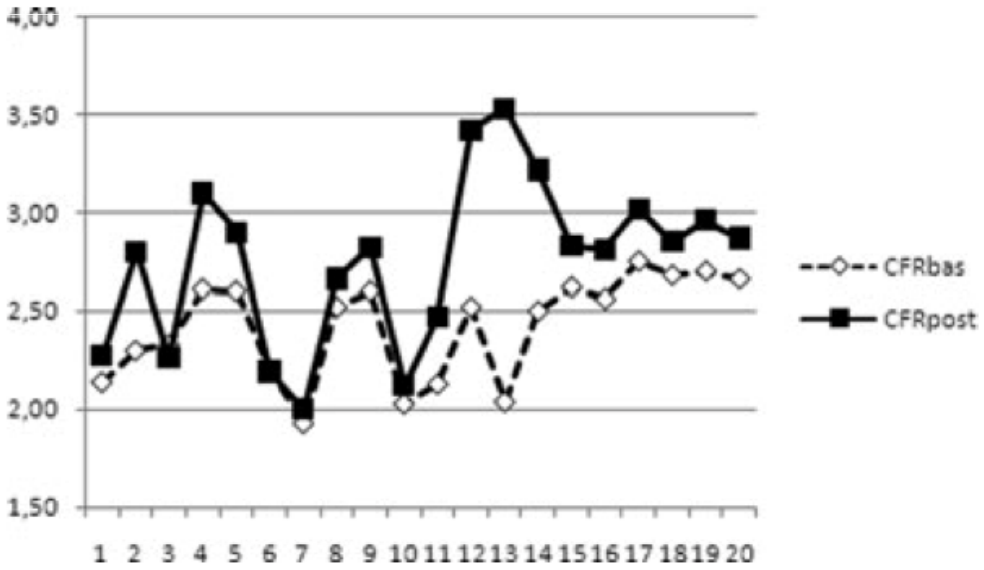
Author, year	TNFa-inhibitor	Patients	Follow-up	Results
Del Porto, 2007	IFX/ETN	30	3 m	Significant reduction
Wong, 2009	IFX	26	56 w	No difference
Sidiropulos, 2009	IFX/ADA	12	18 m	No difference
Di Micco, 2009	IFX	7	12 m	Significant increment
Turiel, 2009	ADA	10	18 m	No significant reduction
Mazzoccoli, 2010	IFX/ADA	25	12 w	No difference
Kerekes, 2011	ADA	8	24 w	Significant reduction

Modificato da: Peters MJL, van Sijl AM, Voskuyl AE, et al. 2012; 18: 1502-1511

CURRENT PHARMACEUTICAL DESIGN

Effects of synthetic and biologic DMARDs on Endothelial Function in Patients with Early RA (n=10 MTX, 10 ADA)

CFR (2D-echo derived coronary flow reserve)
pre- and post-treatment with MTX or ADA



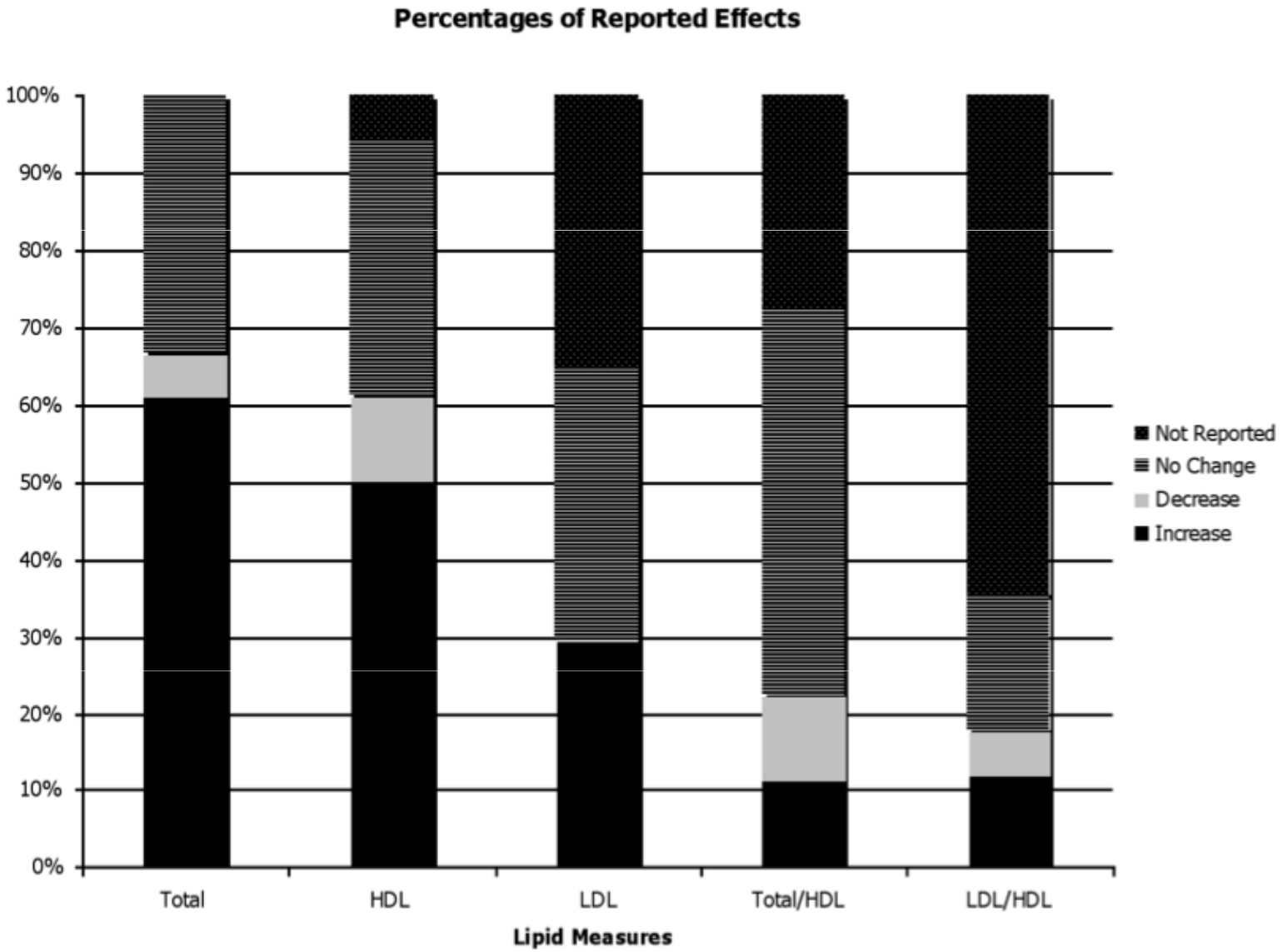
	Baseline	Post-treatment (18 months)	P-value
Diastolic blood pressure (mmHg)	80.8 ± 9.4	74.3 ± 6.75	0,025
DAS 28	5.86 ± 0.64	2.01 ± 0.74	0,0001
CRF	2.4 ± 0.2	2.7 ± 0.5	0,01
ADMA (µmoles/L)	0.65 ± 0.07	0.7 ± 0.17	NS
IMT (mm)	0.68 ± 0.10	0.66 ± 0.15	NS

DMARDs are able to improve coronary microcirculation without a direct effect on IMT* and ADMA**, clinical markers of atherosclerosis

*IMT=common carotid intima-media thickness
**ADMA=plasma asymmetric dimethylarginine

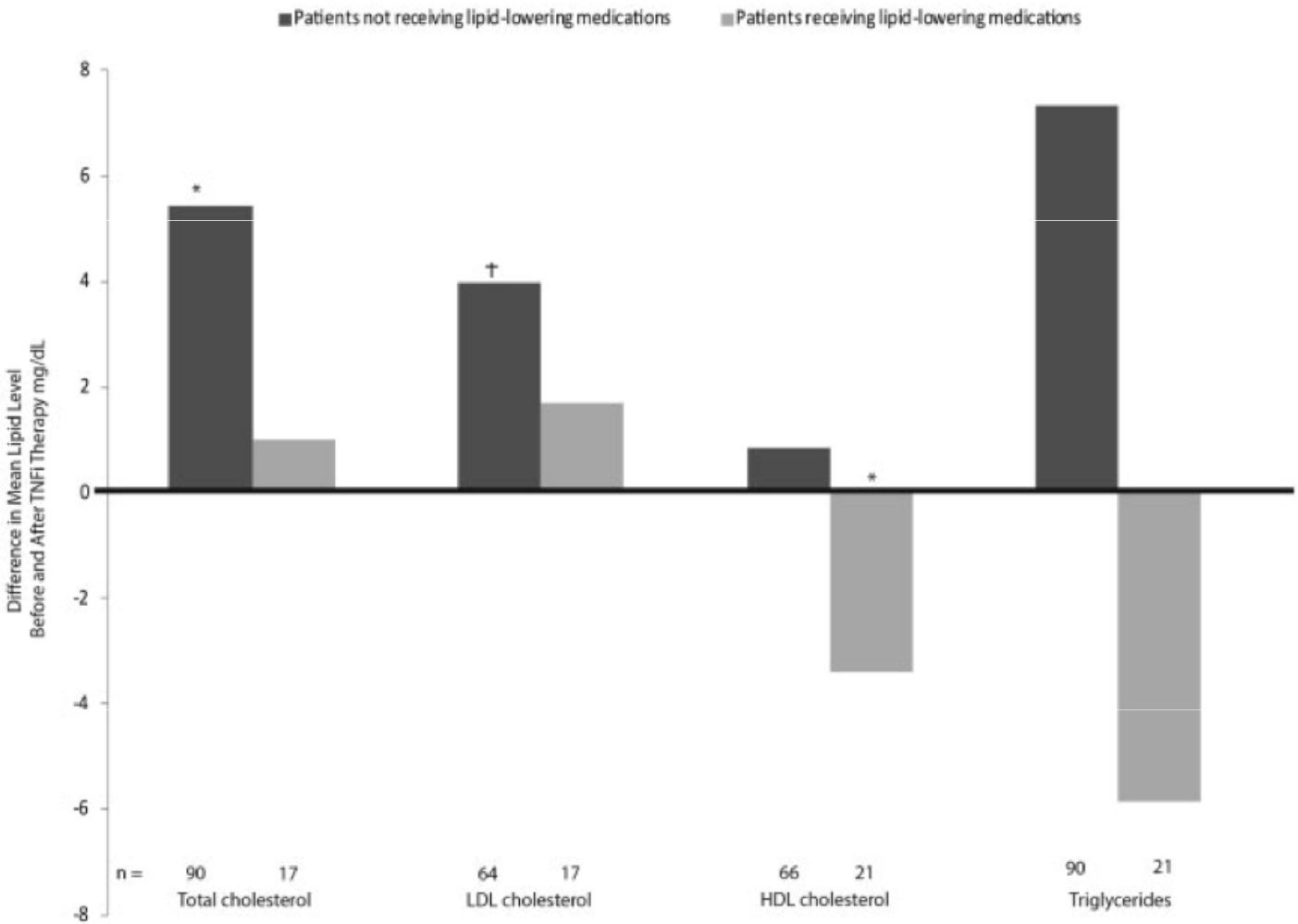
Turiel M, et al. Am J Med 2002

Increased lipid levels but unchanged atherogenic index in RA patients treated with biologic agents



Schimmel EK, et al. Clin Exp Rheumatol 2009

Changes in lipid levels after TNF blockers initiation in patients with RA

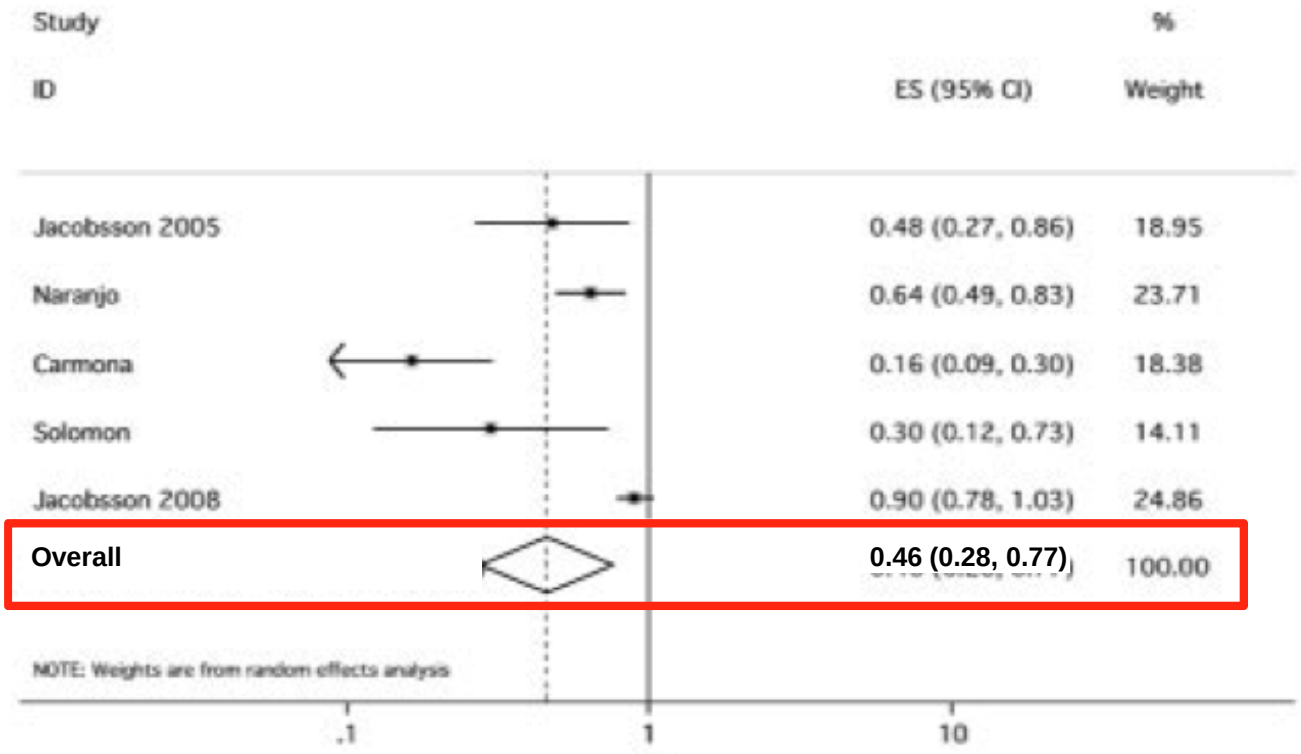


TNF inhibitor therapy modestly increased all lipid parameters

Curtis JR, et al. Arthtiris Res Care 2012

Systematic Review and Meta-Analysis: Anti–TNF and Cardiovascular Events in RA

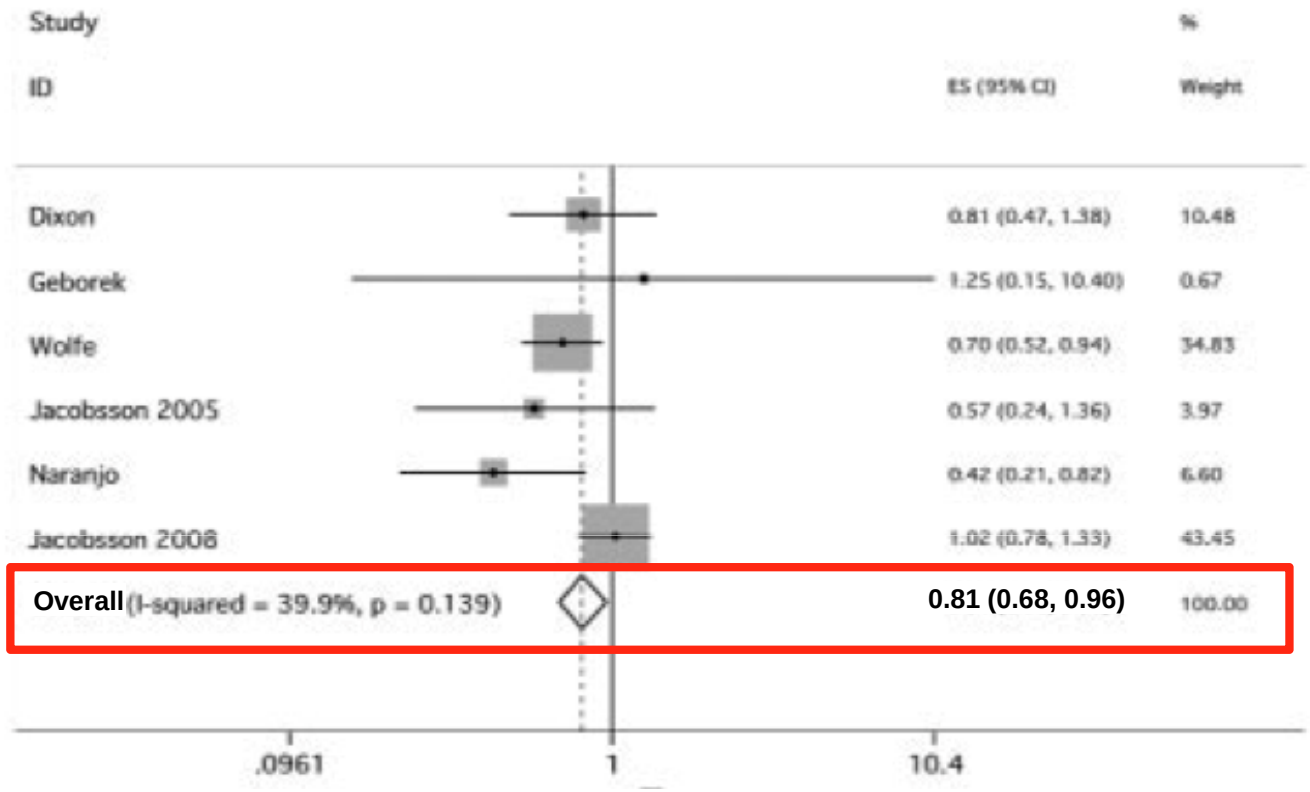
All cardiovascular events vs MTX



Barnabe C, et al. Arthritis Res Care 2011

Systematic Review and Meta-Analysis: Anti–TNF and Cardiovascular Events in RA

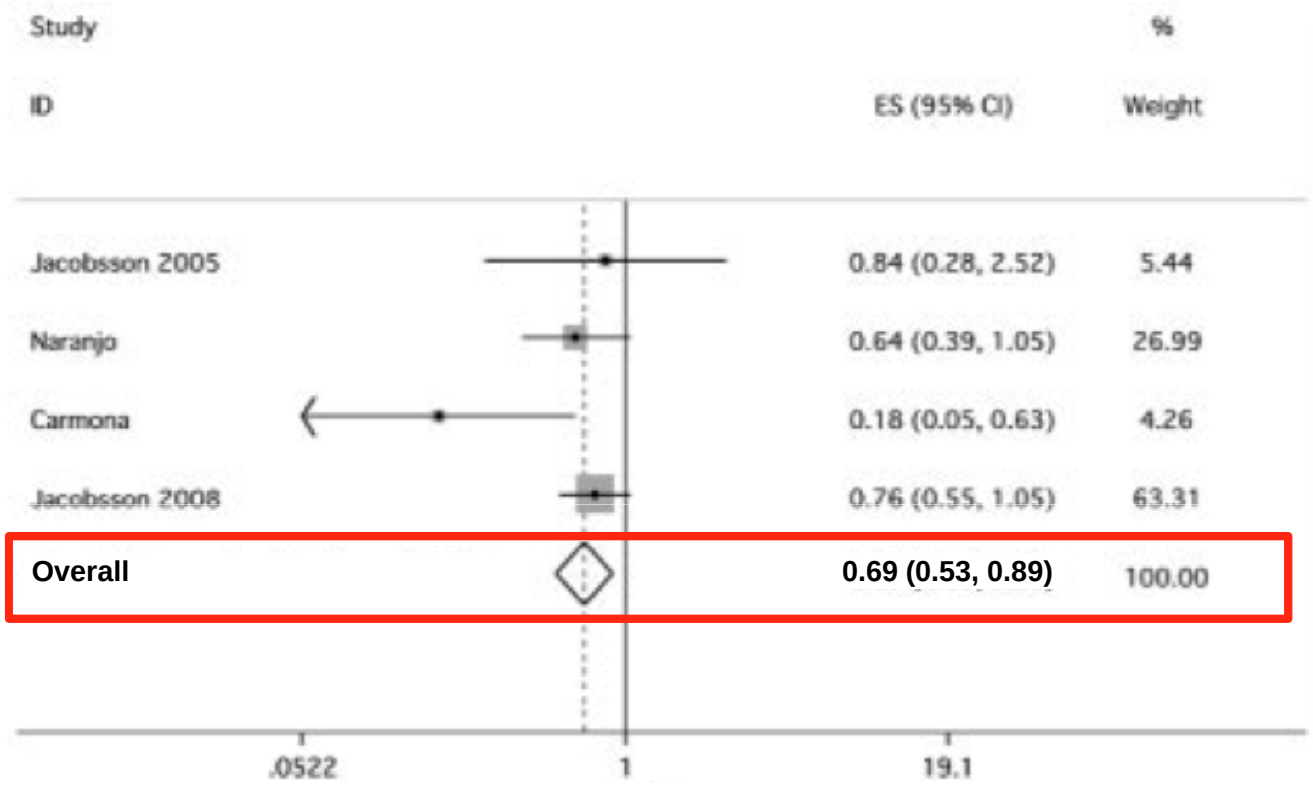
Myocardial infarction vs MTX



Barnabe C, et al. Arthritis Res Care 2011

Systematic Review and Meta-Analysis: Anti–TNF and Cardiovascular Events in RA

Cerebrovascular accident vs MTX



Barnabe C, et al. Arthritis Res Care 2011

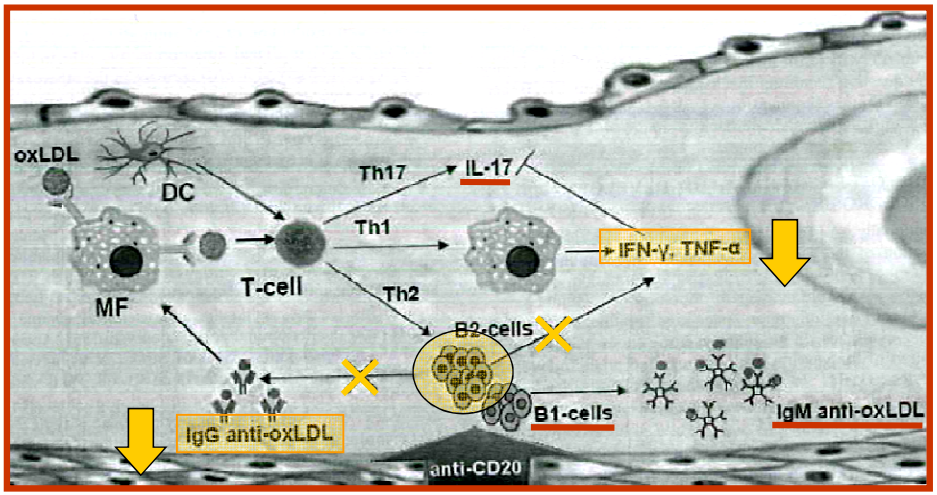
Rituximab and CV risk in RA patients

RTX

disease activity reduction

predominant pro-atherogenic B2 cell depletion

CV risk ?



Endothelial dysfunction

Refs.	P	Main Results	Conclusion
[66]	5 female RA P received 2 infusions of 1000 mg RTX	RTX treatment associated with ↑FMD on 30%, 22%, and 81% in weeks 2, 6, and 16, respectively. RTX therapy resulted in 3-11% ↓TC, 14-35% ↑HDL-C. RTX had little effect on cIMT.	RTX exerted early and sustained favorable effects on ED, as well as plasma HDL-C levels.
[67]	6 RA P (5 w; 55–79 y) refractory to TNFα blockers received 2 infusions of 1000 mg RTX	↑FMD% was observed in all patients in week 2 (7 %) and in month 6 (7.66%) vs before the first infusion (3%).↑FMD% was associated with a significant ↓CRP and DAS 28.	An active effect of rituximab on endothelial function in RA P refractory to TNFα blockers.

P-patients, ↓: lower (decreased); ↑: higher (increased); RA-rheumatoid arthritis, y-years, FMD-flow-mediated dilatation, TC-total cholesterol, HDL-C – high density lipoprotein cholesterol, cIMT – carotid intima-media thickness, CRP-C-reactive protein, TNFα – tumor necrosis factor-α,RTX-rituximab, ED – endothelial dysfunction

Peters MJL, van Sijl AM, Voskuyl AE, et al. 2012; 18: 1502-1511

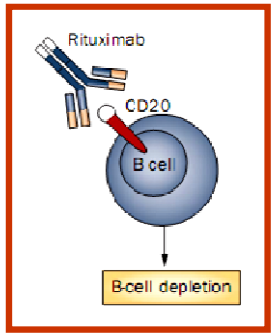
CURRENT PHARMACEUTICAL DESIGN

Arterial stiffness

Characteristics	Rituximab therapy (*n* = 33) Baseline	6 months	12 months	*P*-value[a]
AIx, %	30.4 (8.2)	28.6 (7.6)	29.4 (6.7)	0.216
PWV, m/s	8.1 (3.1)	8.1 (2.8)	8.0 (2.7)	0.924

Mathieau S, Pereira B, Dubost JJ et al. 2012; 51: 1107-1111

RHEUMATOLOGY



Rituximab and CV risk in RA patients

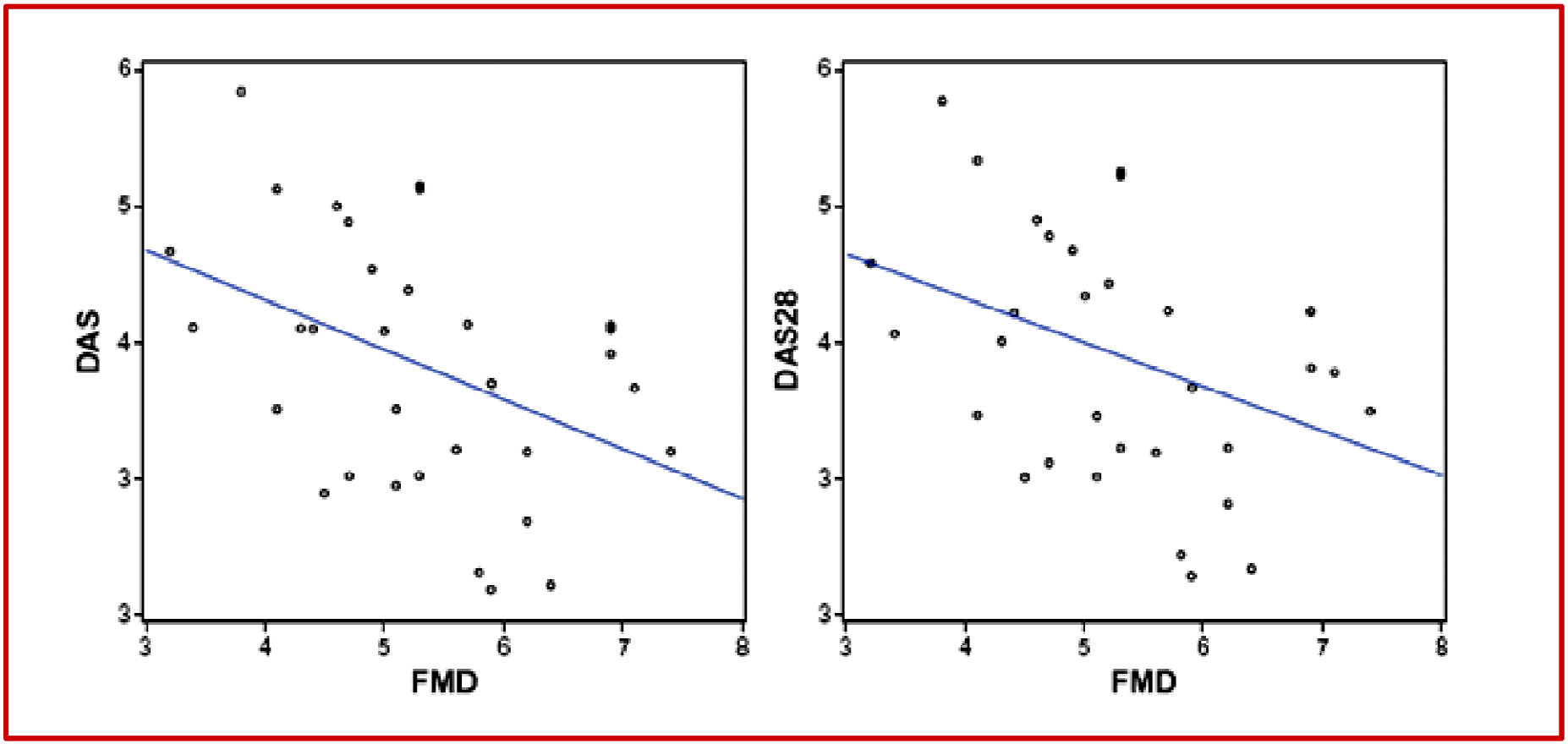


Figure 1 Correlations between FMD% and disease activity scores DAS-DAS28.
Abbreviations: FMD, flow-mediated vasodilatation; FMD%, percent change in FMD; DAS, disease activity score; DAS28, 28-joint disease activity score.

Benucci M, Saviola G, Manfredi M, Sarzi Puttini PC, Atzeni F 2013; 7: 69-75

Biologics: Targets and Therapy

Integrated safety in tocilizumab clinical trials (12293 PY): cardiovascular events

	TCZ (n=2644)	Control (n=1555)
Myocardial infarction	0.29/100 PY	0.49/100 PY
Stroke	0.16/100 PY	0.24/100 PY

Genovese M, et al. J Rheumatol 2013

Lipid and Inflammatory Biomarker Profiles in Patients Receiving Tocilizumab for RA: Analysis of Five Phase 3 Clinical Trials

Mean change [± SD] from baseline to week 24	Tocilizumab in combination with other drugs		Tocilizumab alone	
	TCZ 8mg/kg + DMARD (n=1582)	Placebo + DMARD (n=1170)	TCZ 8mg/kg + placebo (n=288)	Methotrexate (n=284)
Total cholesterol (g/L)	0.30 [±0.35]	0.04 [±0.26]	0.37 [±0.40]	0.07 [±0.35]
LDL-cholesterol (g/L)	0.20 [±0,30]	0.02 [±0.22]	0.26 [±0.34]	0.05 [±0.28]
HDL-cholesterol (g/L)	0.05 [±0.12]	0.01 [±0,10]	0.04 [±0.12]	0.03 [±0.11]
Triglycerides (g/L)	0.28 [±0.77]	0.02 [±0.49]	0.39 [±0.90]	-0.04 [±0.46]
Apolipoprotein A1 (g/L)	0.20 [±0.27]	0.00 [±0.26]	0.20 [±0.30]	0.10 [±0.26]
Apolipoprotein B (g/L)	0.10 [±0.26]	0.00 [±0.19]	0.20 [±0.28]	0.00 [±0.23]
CRP (mg/L)	-23 [±29]	-4 [±25]	-27 [±34]	-19 [±33]
SAA (ng/ml)	-58,479 [±84,929]	-7,017 [±71,535]	-67,857 [±90,304]	-47,623 [±87,819]
Lipoprotein A (mg/L)	-124 [±181]	-1 [±114]	-135 [±172]	-51 [±97]

The serum cholesterol and triglyceride levels increased noticeably within the first 6 treatment weeks and remained stable thereafter

Genovese M, et al. Arthtiris Rheum 2008 (Abstract)

DOES TREATMENT OF RHEUMATOID ARTHRITIS MODULATE CARDIOVASCULAR RISK?

- Clinicians should maintain a high level of suspicion for CVD and its risk factors in RA.
- Until treatment trials have been completed, regular screening for traditional CVD risk factors, education of patients and primary care providers and aggressive management of each risk factor is prudent.
- Treating to target with an aggressive DMARD strategy may also lead to reduced CVD risk. However, this is still an unproven hypothesis.