# Artrite reumatoide
# comorbidità e attività di malattia

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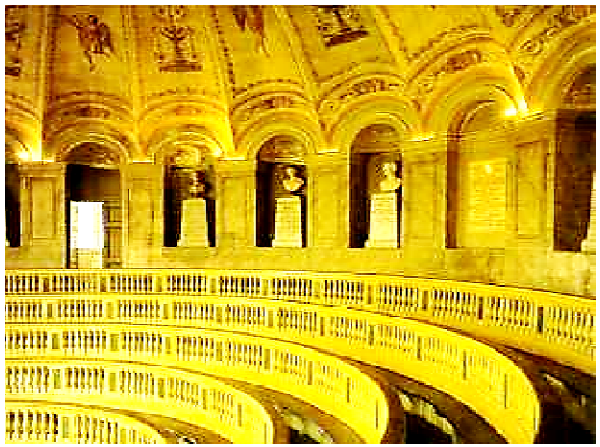
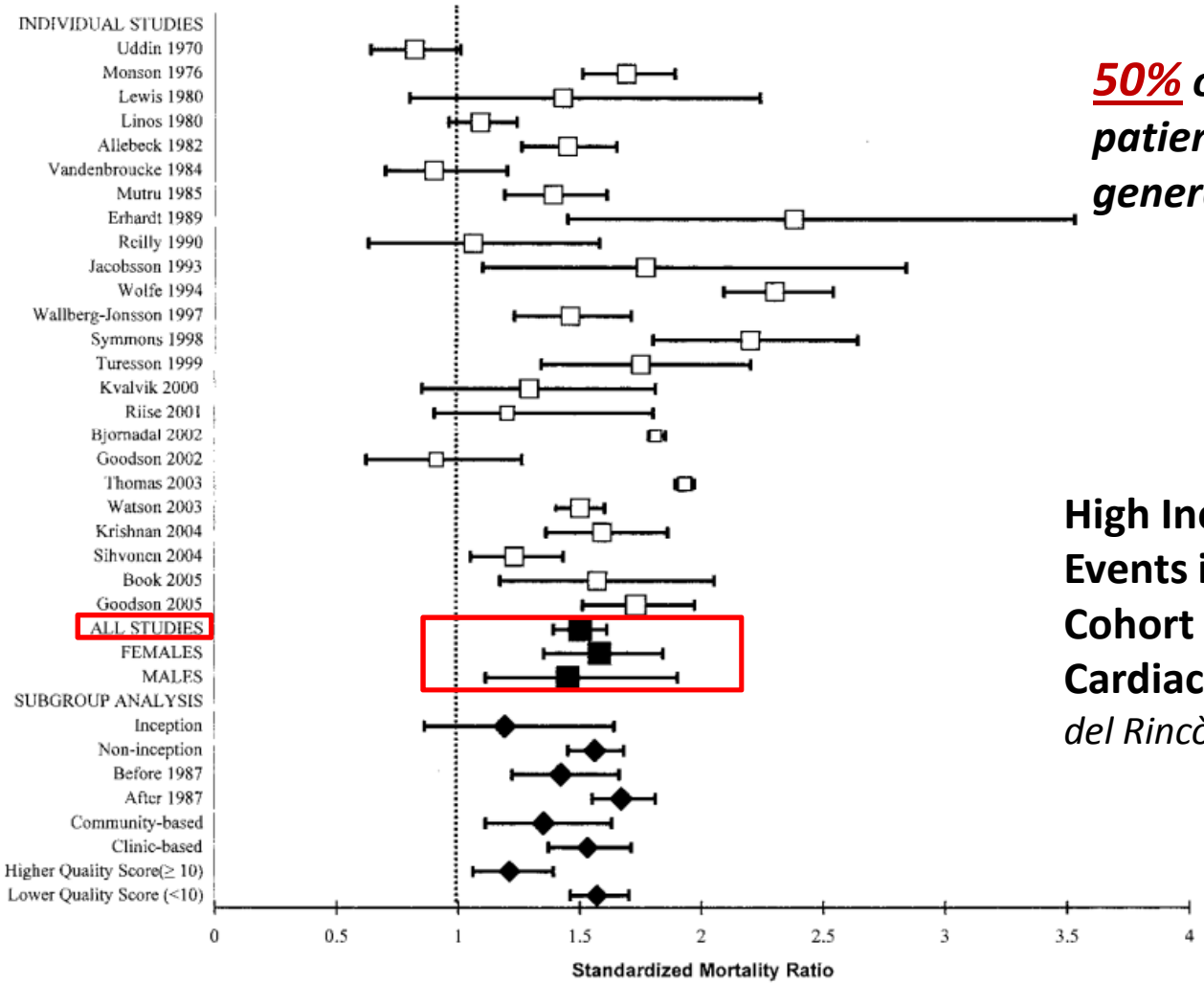


# Cardiovascular disease mortality in patients with rheumatoid arthritis




***50%** of increased risk of CVD in patients with RA compared with general popolation*

**High Incidence of Cardiovascular Events in a Rheumatoid Arthritis Cohort Not Explained by Traditional Cardiac Risk Factors**

*del Rincòn et al, Arthritis Rheum 2001*

*Aviña-Zubieta JA et al. Arthritis Rheum 2008*

# Cardiovascular Risk and Rheumatoid Arthritis

REVIEW

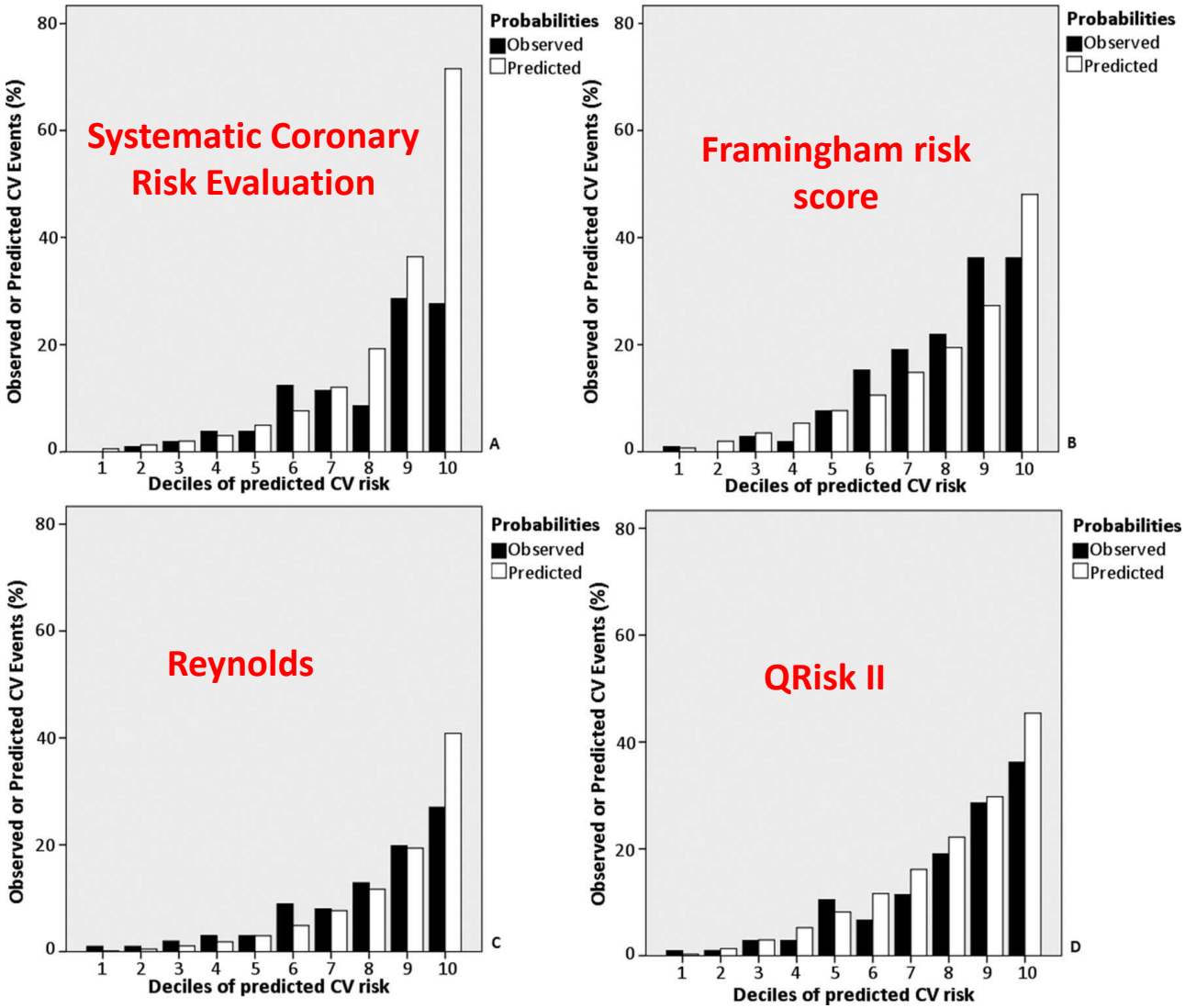
*Circ J* 2009; **73:** 977–985

## Rheumatoid Arthritis
## —— A Model of Systemic Inflammation Driving Atherosclerosis ——

Ivy A. Ku, MD; John B. Imboden, MD*;
Priscilla Y. Hsue, MD; Peter Ganz, MD

Similarities between the inflammatory pathways in atherosclerosis and rheumatoid arthritis (RA) are striking. Chronic systemic inflammation in RA patients leads to cardiovascular (CV) events beyond traditional cardiac risk factors. Clinicians typically focus on treating the joint manifestations of RA while neglecting to eliminate systemic inflammation, which leaves RA patients vulnerable to adverse CV events. In this review we provide an understanding of how systemic inflammation in RA accelerates atherosclerosis. This knowledge should guide therapeutic targets to minimize CV risk in RA, and may lead to insights into the inflammatory mechanisms of atherosclerosis in general. (*Circ J* 2009; **73:** 977–985)

# CV risk prediction algorithms and RA




**Commonly used algorithms provide <u>less accurate predictions of CV risk in the RA population</u>, compared with results reported in the general population**

*Arts E E A et al.* Ann Rheum Dis *2013*

Mediators of Inflammation
Volume 2012, Article ID 147354, 8 pages

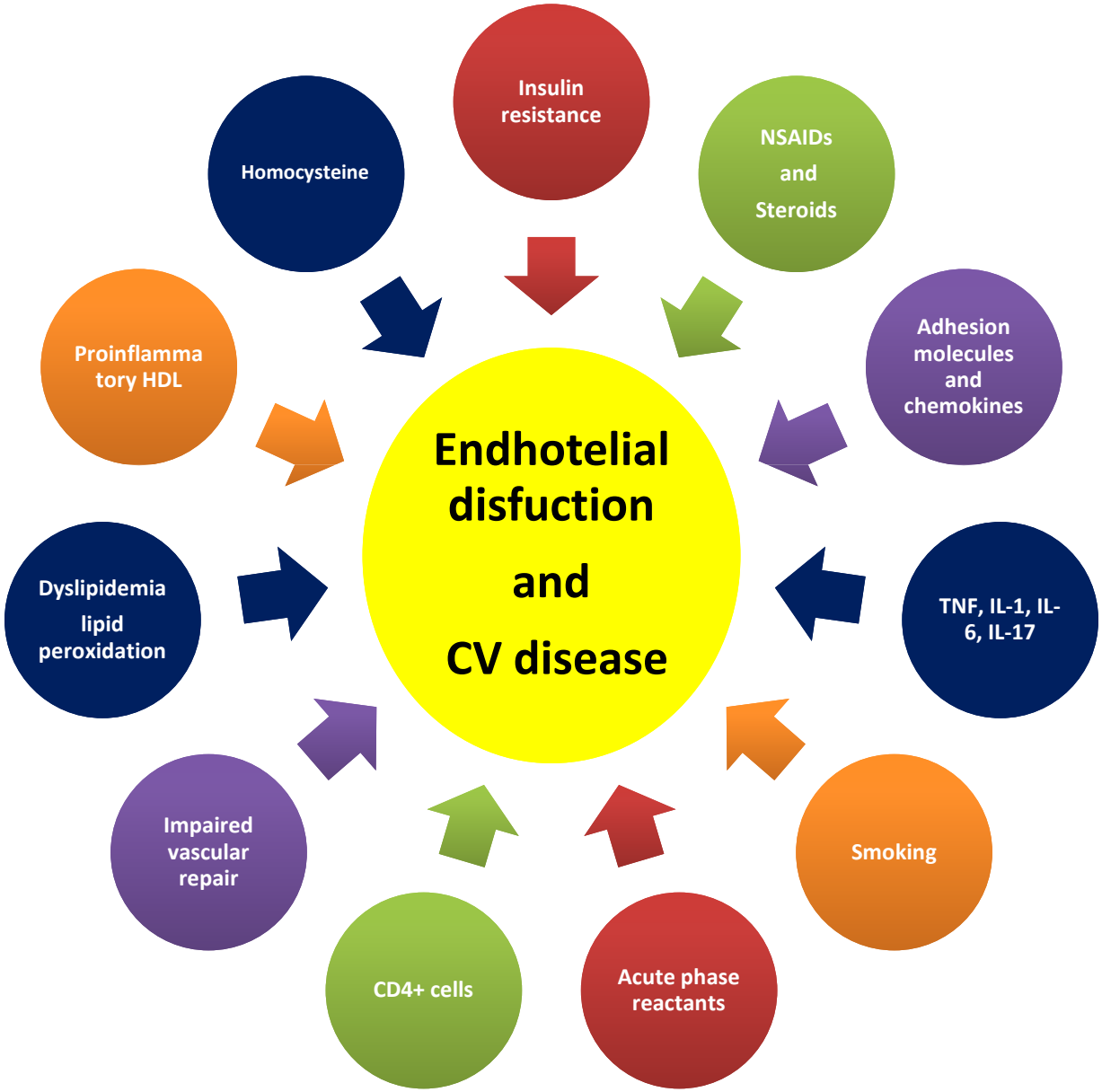
*Review Article*

# Atherosclerosis and Rheumatoid Arthritis: More Than a Simple Association

**Lorenzo Cavagna, Nicola Boffini, Giovanni Cagnotto, Flora Inverardi, Vittorio Grosso, and Roberto Caporali**

In the last decades a large amount of evidence linked rheumatoid arthritis (RA) to atherosclerosis. In fact, RA patients have an increased risk of cardiovascular events that is not fully explained by other classic cardiovascular risk factors. RA and atherosclerosis may share several common pathomechanisms and inflammation undoubtedly plays a primary role. The proinflammatory cytokines such as tumor necrosis factor alpha and interleukin-6, involved in the pathogenesis of RA, are also independently predictive of subsequent cardiovascular disease (CVD). In RA, inflammation alters HDL constituents and the concentration of LDL and HDL, thus facilitating atherosclerosis and CVD events. On the other hand, also the increase of oxidative processes, frequently observed in RA, induces atherosclerosis. Interestingly, some genetic polymorphisms associated with RA occurrence enhance atherosclerosis, however, other polymorphisms associated with RA susceptibility do not increase CVD risk. Several other mechanisms may influence atherosclerotic processes in RA. Moreover, atherosclerosis may be directly mediated also by underlying autoimmune processes, and indirectly by the occurrence of metabolic syndrome and impaired physical activity. Finally, the effects of RA therapies on cardiovascular system in general and on atherosclerosis in particular are really wide and different. However, the starting point of every RA treatment is that disease control, or better remission, is the best way we have for the reduction of CVD occurrence.

# Potential mechanisms



# Citokines and CV risk

Choy E. Rheumatology 2012;51:v3v11
doi:10.1093/rheumatology/kes113

TABLE 1 Actions of cytokines that play major roles in RA pathobiology

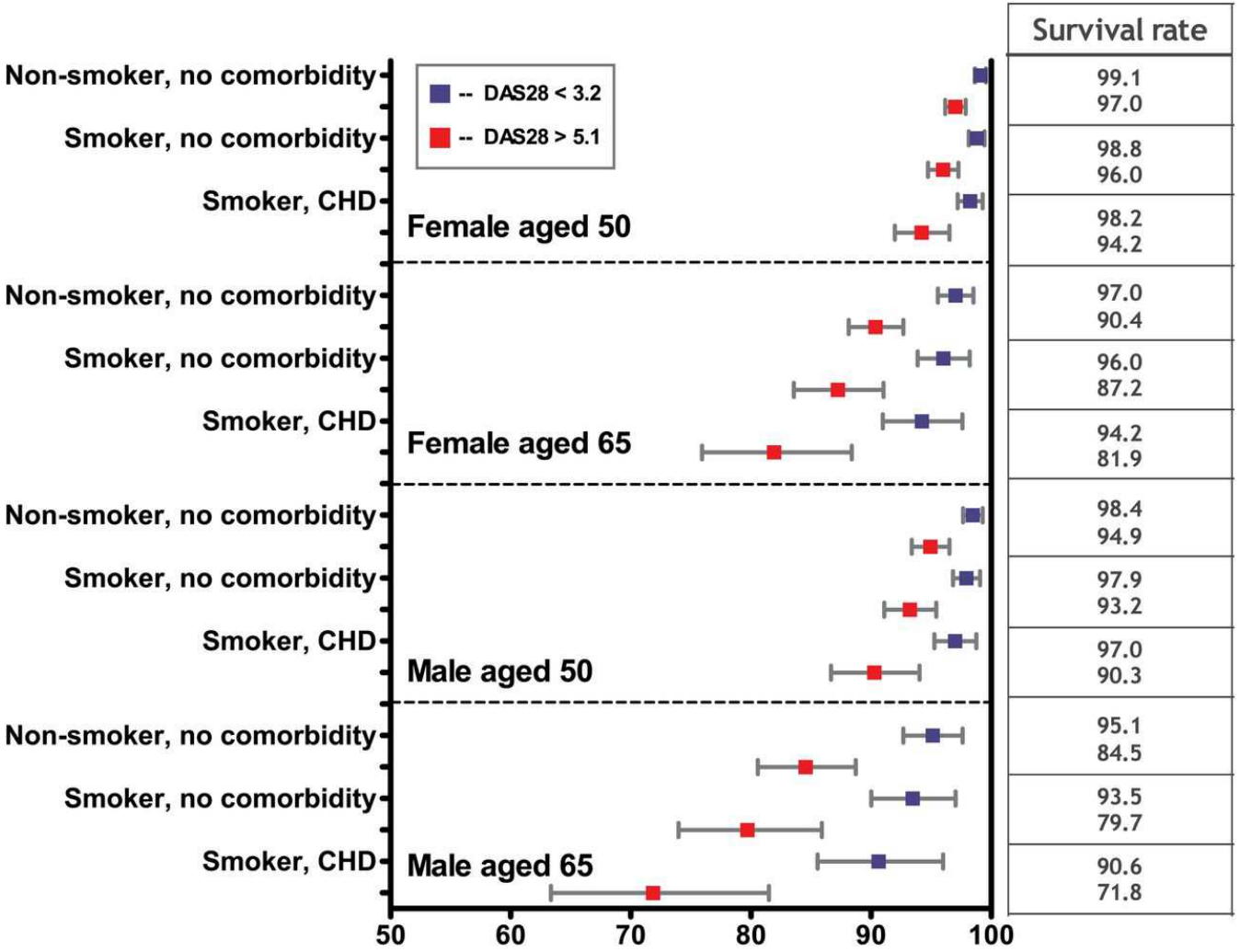
| Cytokine | Role in the disease process |
|---|---|
| TNF-α | Local effects |
| | Increased monocyte activation, cytokine release, PG release [20] |
| | Increased polymorphonuclear leucocyte priming, apoptosis and oxidative burst [20] |
| | T-cell apoptosis, clonal regulation, TCR dysfunction [20] |
| | Increased endothelial cell adhesion molecule expression, cytokine release [20] |
| | Decreased synovial fibroblast proliferation, collagen synthesis [20] |
| | Increased MMP and cytokine release [20] |
| | Systemic effects |
| | Acute-phase protein production [22] |
| | HPA axis dysregulation (fatigue and depression) [24] |
| | CVD promotion [23] |
| IL-6 | Local effects |
| | Osteoclast activation [25, 26] |
| | Neutrophil recruitment [27] |
| | Pannus formation via promotion of VEGF production [28, 29] |
| | B-cell proliferation and antibody production [20] |
| | T-cell proliferation and differentiation [20] |
| | Systemic effects |
| | Acute-phase protein production [22] |
| | Anaemia (via hepcidin production) [30] |
| | CVD promotion [23] |
| | Osteoporosis [31, 32] |
| | HPA axis dysregulation (fatigue and depression) [24] |
| IL-1 | Local effects |
| | Increased synovial fibroblast cytokine, chemokine, MMP and PG release [20] |
| | Increased monocyte cytokine, reactive oxygen intermediate and PG release [20] |
| | Osteoclast activation [20] |
| | Endothelial cell adhesion molecule expression [20] |
| | Systemic effects |
| | Acute-phase protein production [22] |
| | CVD promotion [23] |
| | HPA axis dysregulation (fatigue and depression) [24] |
| IL-17 | Recruitment of monocytes and neutrophils by increasing local chemokine production [33] |
| | Facilitation of T-cell infiltration and activation [33] |
| | Amplification of immune response (e.g. by induction of IL-6 production) [33] |
| | Increased synovial fibroblast cytokine and MMP release [20] |
| | Osteoclastogenesis [20] and cartilage damage [35] |
| | Synergistic activity with IL-1β, TNF-α and IFN-γ [33, 34] |
| VEGF | Angiogenesis, contributing to pannus formation [28] |

# Cardiovascular risk factors : Smoking

- Strongest known environmental factor for RA
- Decreasing prevalence of smoking in general population
- Prevalence of smoking in RA
  - OR: 1.56 (1.35 – 1.80)

Boyer JF et al Joint Bone Spine, 2011

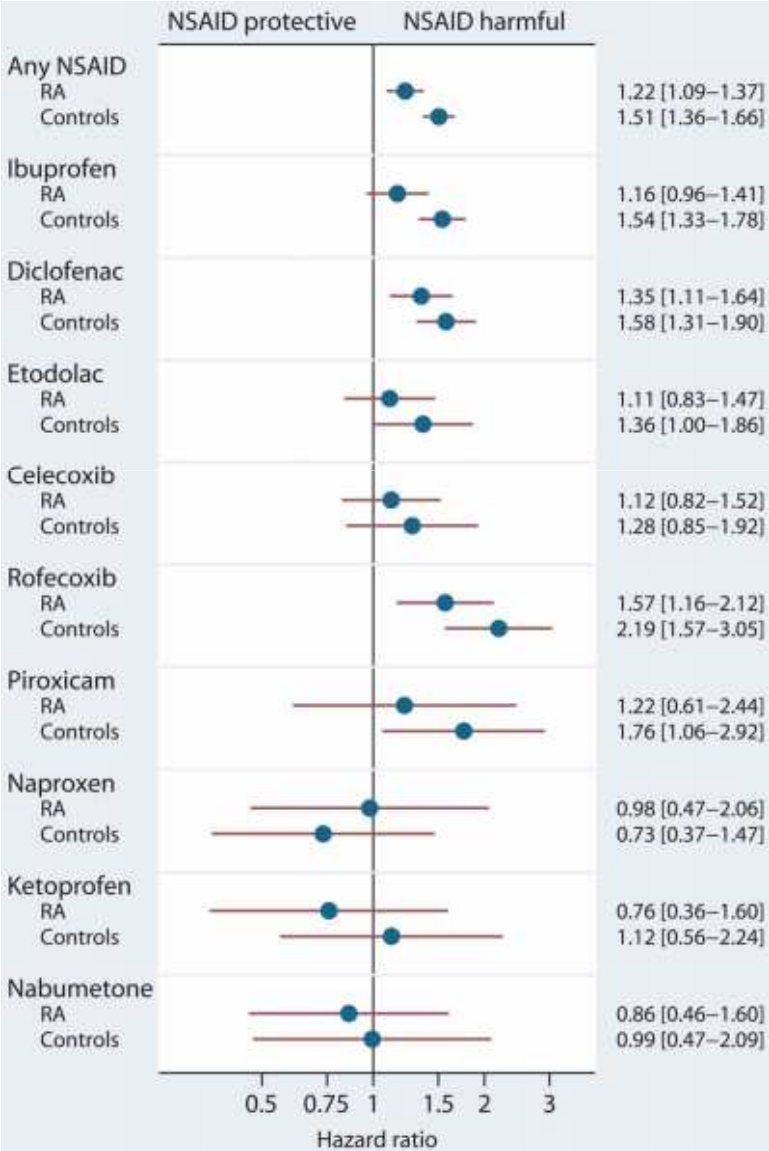
**Five-year survival rates (in %) for patients with highly active disease (DAS28 scores >5.1 at ≥80% of the observation time (18% of patients) and low disease activity (DAS28 scores <3.2 for ≥80% of the observation time (9% of patients) CHD: coronary heart disease.**

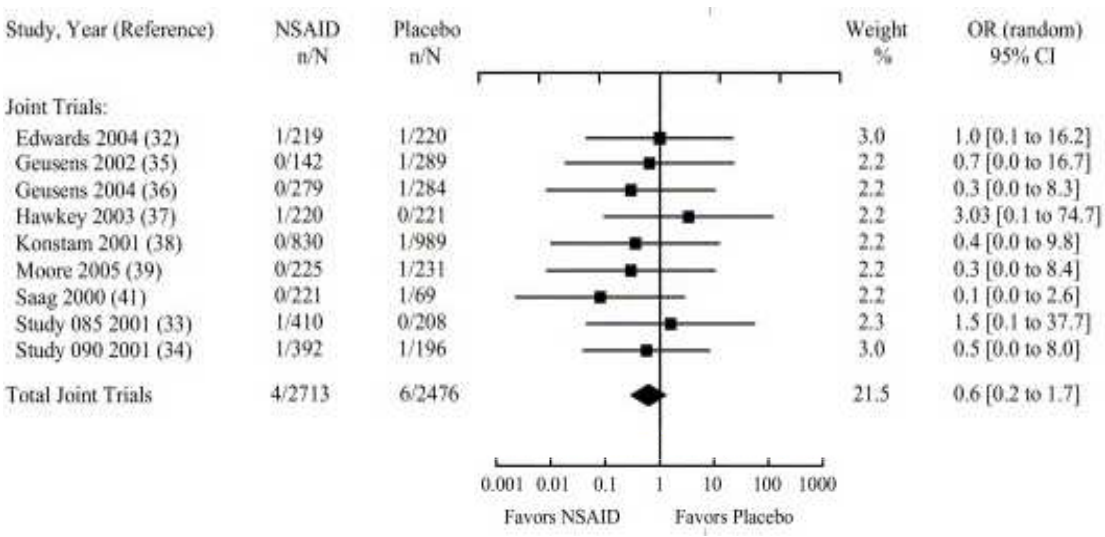



Listing J et al. Ann Rheum Dis -2013-

ARD

# NSAIDs in rheumatoid arthritis




*Salpeter SR et al. Am J Med. 2006*

**The cardiovascular risk associated with NSAIDs use in RA patients was significantly lower than in non-RA individuals.**

*Lindhardsen J et al. Ann Rheum Dis. 2013*

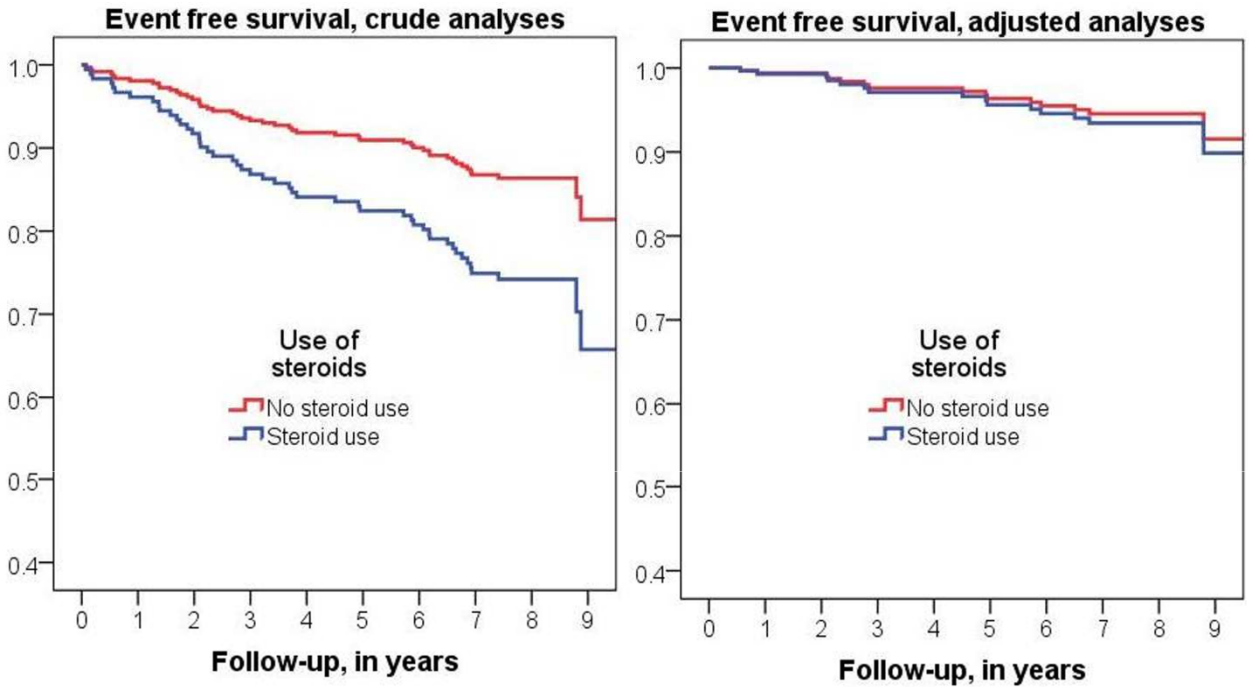
# Glucocorticoids and survival in RA

Table 4 Adjusted HRs ; Adjustments were made for all parameters shown in the table

| | Unadjusted HR | | Adjusted HR: 6 (rituximab 12) months risk window approach | | | Adjusted HR: Ever exposed approach | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | p Value | HR | 95% CI | p Value | Deaths | PYRS |
| Prednisone most recent 12 months: 0 mg/d | Ref. | | Ref. | | | Ref. | | | 88 | 9036 |
| 1–5 mg/d | 1.33 | 1.00 to 1.76 | 1.05 | 0.80 to 1.38 | 0.71 | 1.04 | 0.79 to 1.37 | 0.77 | 177 | 13 615 |
| >5–10 mg/d | 2.22 | 1.65 to 2.98 | 1.46 | 1.09 to 1.95 | 0.013 | 1.41 | 1.06 to 1.89 | 0.021 | 140 | 7086 |
| >10–15 mg/d | 3.95 | 2.61 to 5.98 | 2.00 | 1.29 to 3.11 | 0.0033 | 2.01 | 1.30 to 3.11 | 0.0030 | 37 | 1170 |
| >15 mg/d | 6.68 | 4.06 to 11.0 | 3.59 | 2.11 to 6.13 | <0.0001 | 3.43 | 2.01 to 5.86 | <0.0001 | 21 | 448 |
| FFbH* in % of full function per 10% improvement | 0.76 | 0.73 to 0.79 | 0.88 | 0.84 to 0.93 | <0.0001 | 0.89 | 0.85 to 0.93 | <0.0001 | | 31 378 |

Listing J et al. Ann Rheum Dis doi:10.1136/annrheumdis-2013-204021

# Glucocorticoid and CV risk

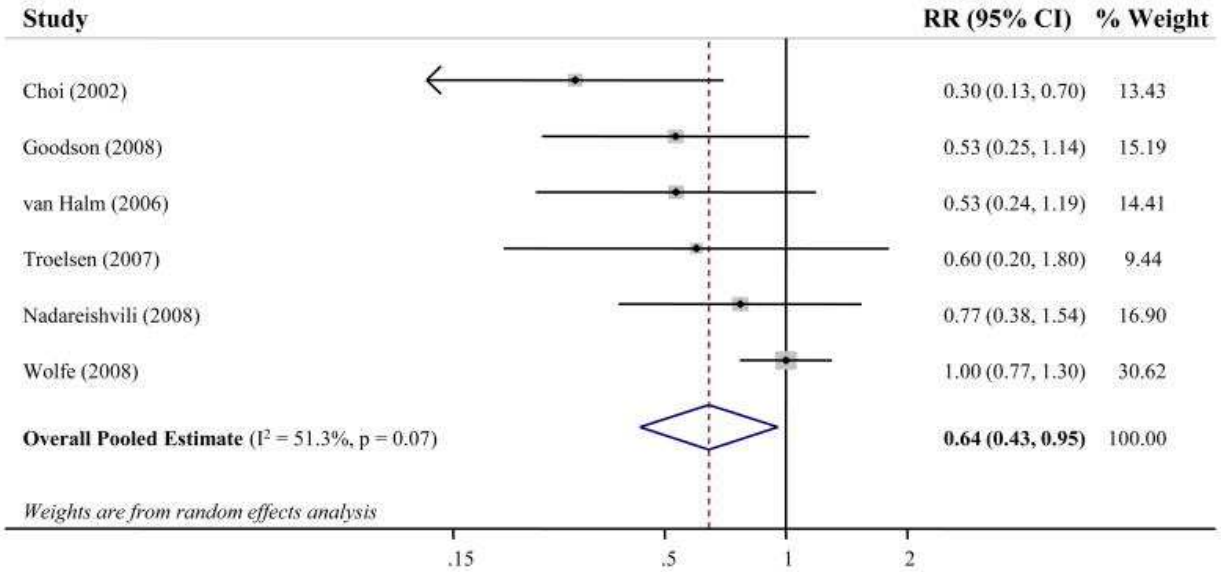



*Glucocortioid use is a risk factor for CV events in RA, but that this association is* ***strongly confounded by disease activity and disability****.*

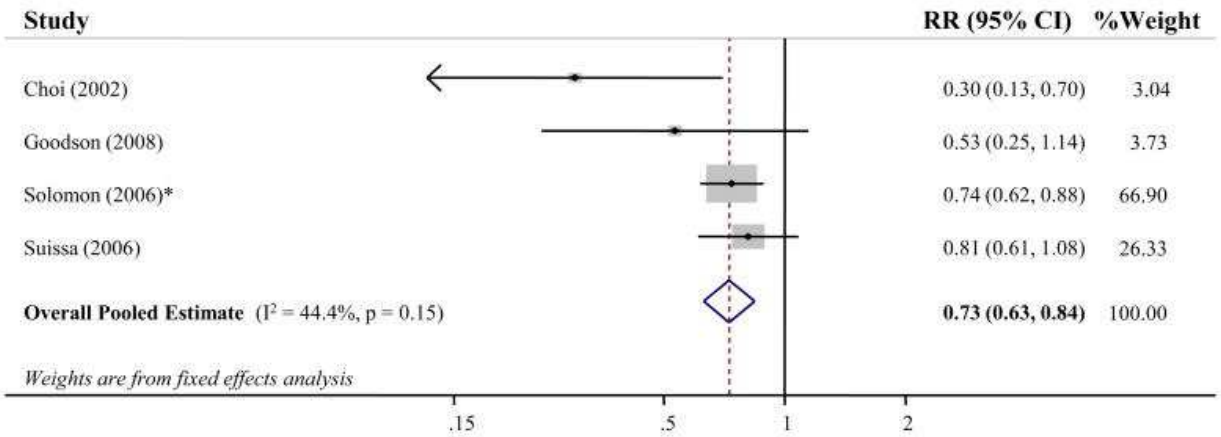
*Subgroup-analysis for patients who were not on concomittant NSAIDs did not reveal essentially different results.*

*van Sijl AM et al. PLoS One. 2014*

# Methotrexate and CV risk




**Methotrexate use and CVD among studies that adjusted for underlying disease severity**




**Methotrexate use and CVD among studies that adjusted for use of other drugs for underlying disease**

*Micha R et al.* Am J Cardiol. *2012*

# Biologic agents and survival in RA

Table 4 Adjusted HRs ; Adjustments were made for all parameters shown in the table

| | Unadjusted HR | | Adjusted HR: 6 (rituximab 12) months risk window approach | | | Adjusted HR: Ever exposed approach | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | p Value | HR | 95% CI | p Value | Deaths | PYRS |
| Methotrexate | Ref. | | Ref. | | | Ref. | | | 96†/78‡ | 7012†/6469‡ |
| Other synth. DMARDs | 2.53 | 1.95 to 3.28 | 1.14 | 0.86 to 1.51 | 0.36 | 0.98 | 0.60 to 1.59 | 0.92 | 126†/31‡ | 3513†/1581‡ |
| TNFα inhibitors | 0.77 | 0.61 to 0.98 | 0.64 | 0.50 to 0.81 | 0.0007 | NA | | | 182† | 16 843† |
| Rituximab | 1.01 | 0.70 to 1.46 | 0.57 | 0.39 to 0.84 | 0.0062 | NA | | | 36† | 2599† |
| TNFα inhibitors or rituximab | NA | | NA | | | 0.77 | 0.60 to 0.97 | 0.0312 | 330‡ | 22 370‡ |
| Other biologics | 1.02 | 0.68 to 1.52 | 0.64 | 0.42 to 0.99 | 0.043 | 0.91 | 0.66 to 1.25 | 0.54 | 25†/51‡ | 1654†/2806‡ |
| DAS28>4.1 for > 6 (12) months after discon- tinuation of a biologic without start of a new one | NA | | NA | | | 2.08 | 1.59 to 2.72 | <0.0001 | 86‡ | 1812‡ |

Listing J et al. Ann Rheum Dis doi:10.1136/annrheumdis-2013-204021

# TNF inhibitors and CV risk

Table 1 Studies Evaluating the Effect of TNF-α Antagonists on Arterial Stiffness in RA Patients

| Study(yr) | Study Design | Outcome Measures | Result |
|---|---|---|---|
| Van Doornum et al. (2005) (22) | Either Etancept/Adalimumab/ Infliximab for 6 wk in 14 RA patients | 1. Augmentation index (AIx) | 1. AIx did not change during the study period ($P = 0.504$) |
| Mäki-Petäjä et al. (2005) (14) | Administration of etanercept for 12 wk in 9 RA patients compared to a nontreatment control group | 1. Aortic PWV<br>2. Augmentation index<br>3. Brachial PWV | 1. Aortic PWV reduced significantly at weeks 0.4 and 12 ($P = 0.0003$) and comparable to control subjects at 12 wk<br>2. Augmentation index did not change significantly over the study period ($P = 0.6$)<br>3. Brachial PWV did not change significantly over the study period ($P = 0.8$) |
| Cypiene et al. (2007) (23) | Retrospective study in 15 RA patients taking infliximab compared to nontreatment group | 1. Brachial PWV<br>2. Augmentation index | 1. Brachial PWV reduced significantly post infliximab therapy ($P = 0.004$) compared to controls<br>2. Augmentation index unchanged post infliximab therapy when compared to controls |
| Komai et al. (2007) (24) | Administration of infliximab for 6 wk in 15 Japanese RA patients | 1. Aortic PWV | 1. Aortic PWV remain unchanged at weeks 2 and 6 of the study period |
| Wong et al. (2008) (25) | Administration of infliximab for 56 wk in 26 RA patients[a] | 1. Aortic PWV<br>2. Augmentation index | 1. Aortic PWV reduced significantly over the 56 wk ($P = 0.004$)<br>2. Augmentation index unchanged post infliximab therapy ($P = 0.265$) |
| Galarraga et al. (2009) (26) | Etanercept administered to 26 RA patients for 4 mo compared to control group of 21 RA patients taking methotrexate | 1. Augmentation index corrected for 75 bpm (AIx@75) | 1. AIx@75 significantly improved arterial stiffness at 2 and 4 mo ($P = 0.025$) in etanercept group but not in methotrexate group ($P = 0.971$) |
| Angel et al. (2009) (27) | Either etanercept/ adalimumab/infliximab administered for 3 mo in 60 arthritic patients[b] compared to a nontreatment control group | 1. Aortic PWV<br>2. Augmentation index | 1. Aortic PWV reduced significantly after 3 mo in all patients including RA patients ($P = 0.002$ and 0.05, respectively) compared to controls<br>2. Augmentation index did not change significantly over the study period in all patients ($P = 0.53$) compared to controls |
| Pieringer et al. (2010) (31) | Infliximab administered to 30 patients(17 RA, 13 AS) for 6 wk compared to a nontreatment control group | 1. Augmentation index corrected for 75 bpm (AIx@75) | 3. AIx@75 significantly increased over the study period in all patients ($P = 0.03$) and RA subgroup ($P = 0.01$) |

AS, ; PWV, pulse wave velocity; RA, rheumatoid arthritis.
[a]Refer to Results/Discussion for full methodology.
[b]Group contained ankylosing spondylitis and psoriatic arthritis patients as well.

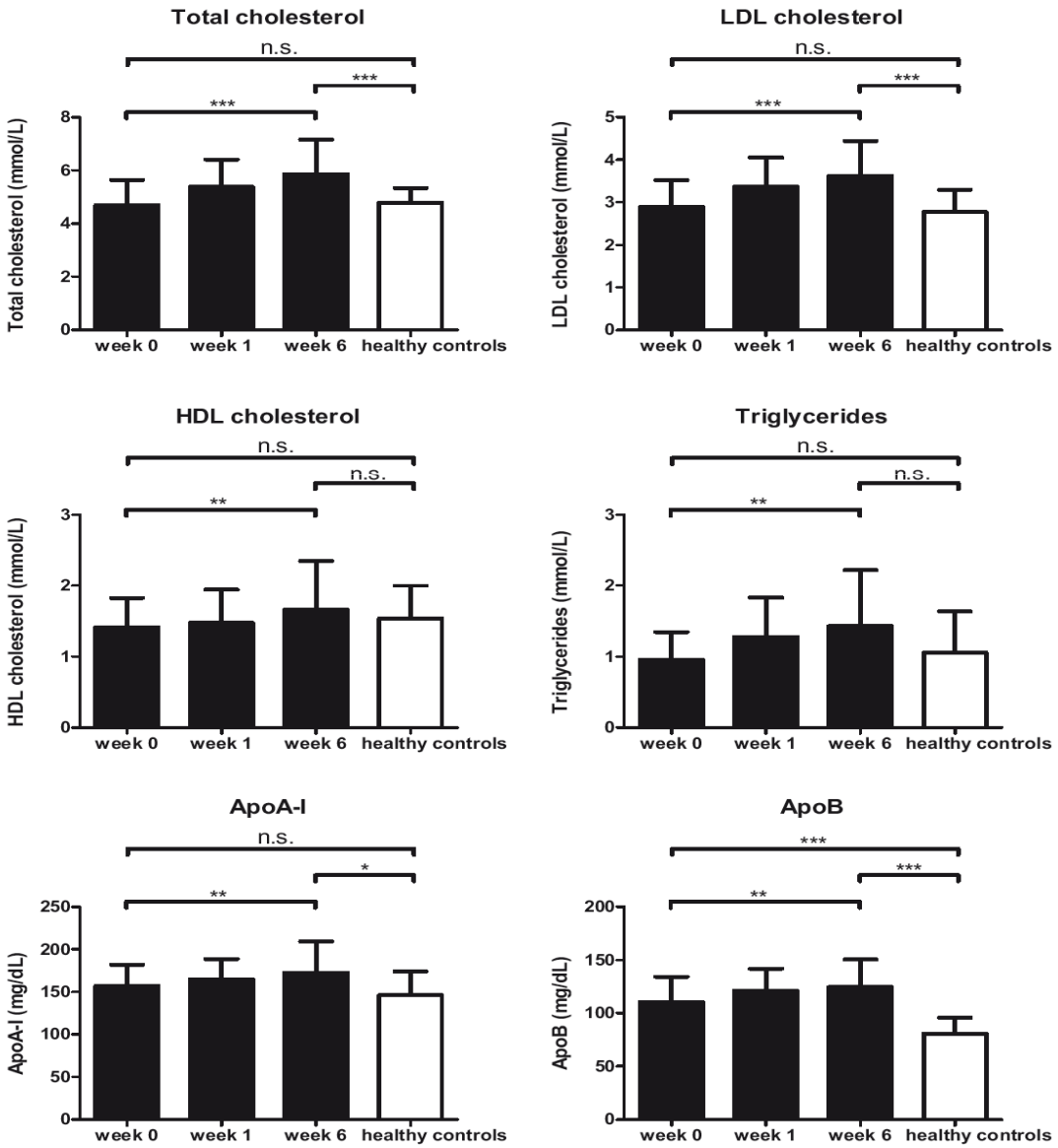
## The Effect of Tumor Necrosis Factor-α Antagonists on Arterial Stiffness in Rheumatoid Arthritis: A Literature Review

Rajdip Dulai, BSc (Hons),* Mark Perry, PhD,*
Richard Twycross-Lewis, PhD,* Dylan Morrissey, PhD,*
Fabiola Atzeni, MD, PhD,† and Stephen Greenwald, PhD‡

**The balance of evidence suggests that TNF-antagonists <u>may have a beneficial effect on arterial stiffness and therefore cardiovascular risk</u>.**

# lipid changes by tocilizumab in rheumatoid arthritis

A.C. Strang et al. / Atherosclerosis 229 (2013) 174–181



# Tocilizumab and CV risk

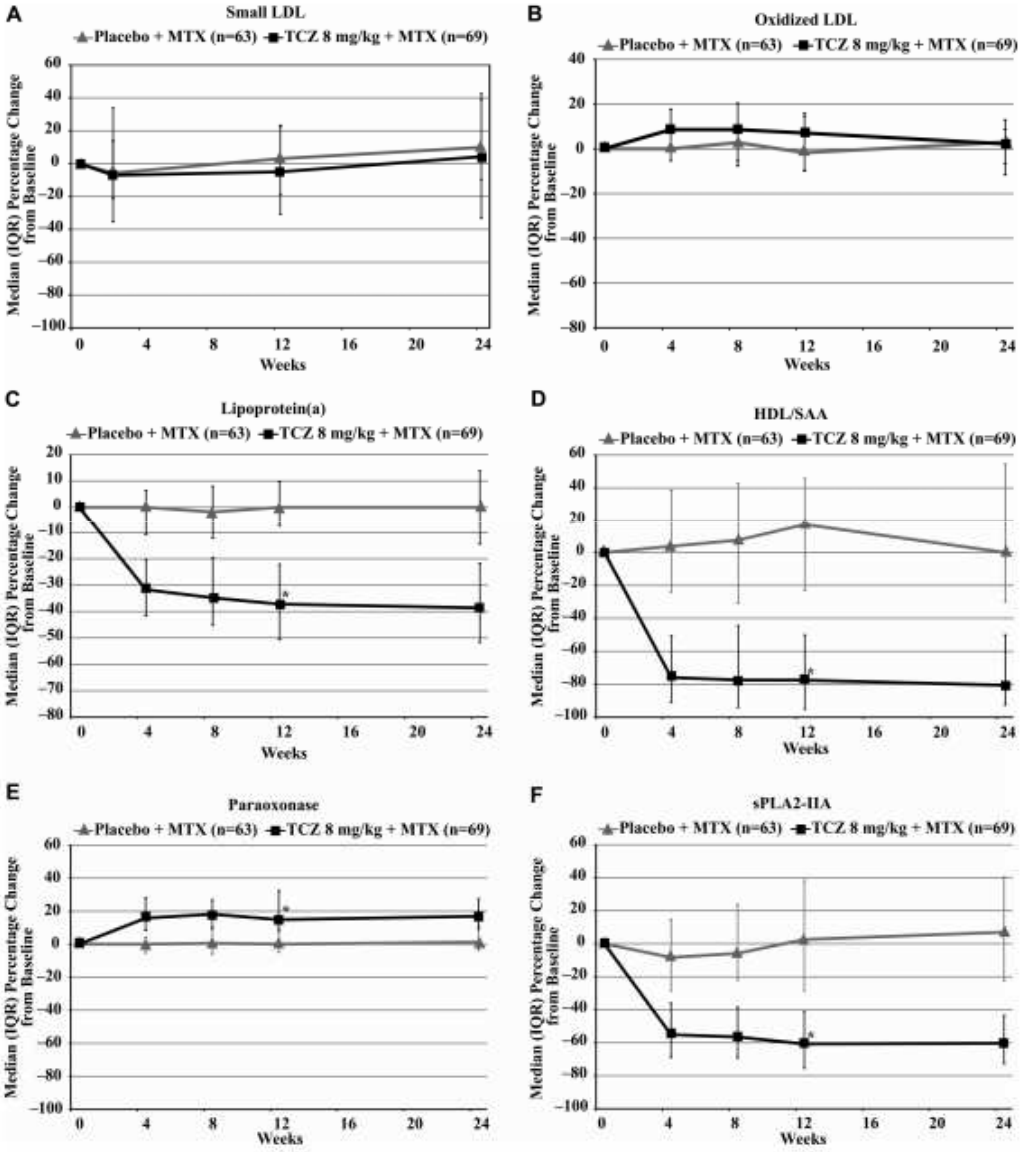



Figure 2 (A–F) Effects on lipoproteins (TCZ vs placebo). HDL, high-density lipoprotein; LDL, low-density lipoprotein; MTX, methotrexate; SAA, serum amyloid A; sPLA2-IIA, secretory phospholipase A2-IIA; TCZ, tocilizumab. *p<0.0001 (TCZ vs placebo).

**TCZ** induced elevations in LDL-C but altered HDL particles towards an anti-inflammatory composition and **favourably modified most, but not all, measured vascular risk surrogates**

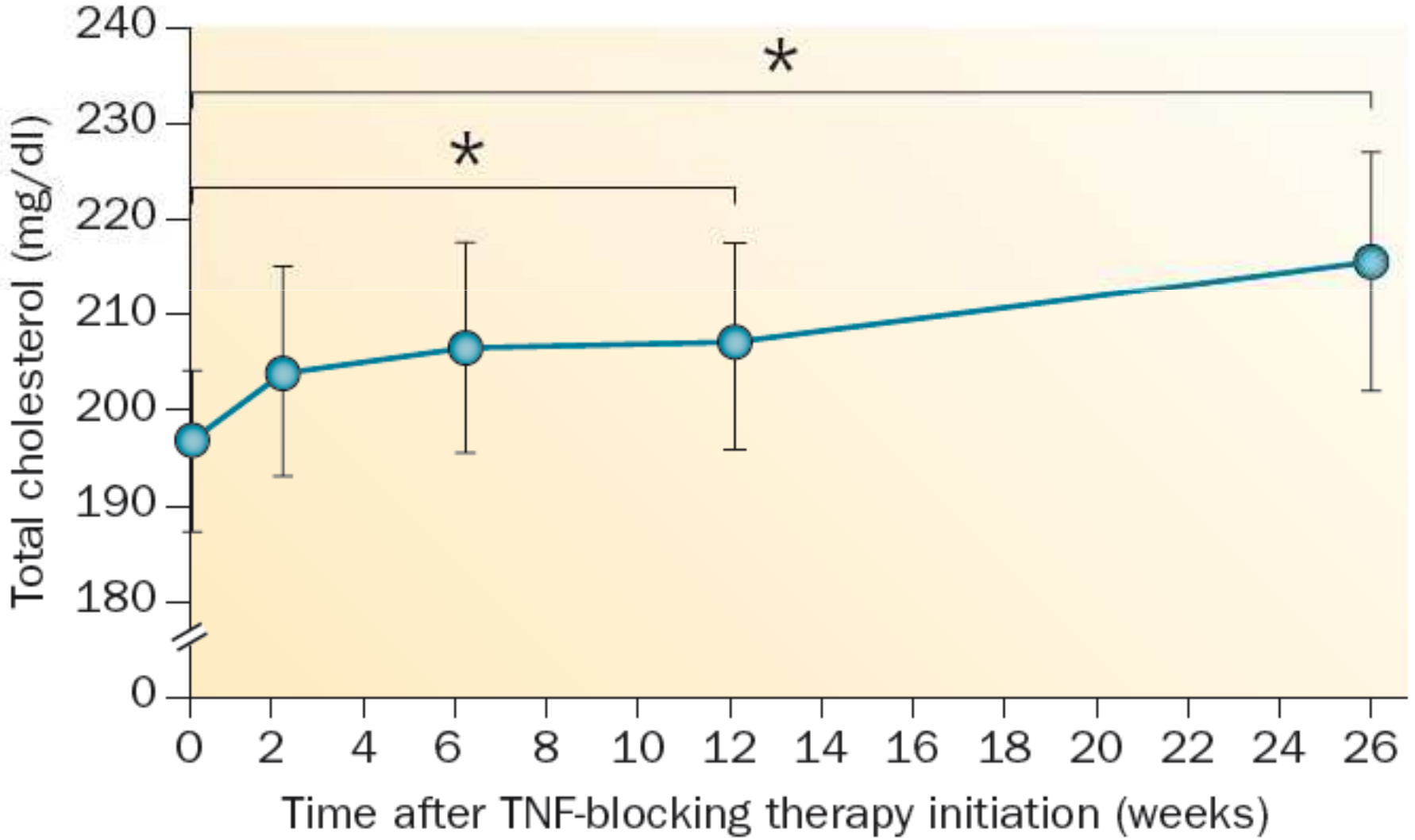
The net effect of such changes for cardiovascular risk requires further studies

*McInnes I A et al. Ann Rheum Dis 2013*

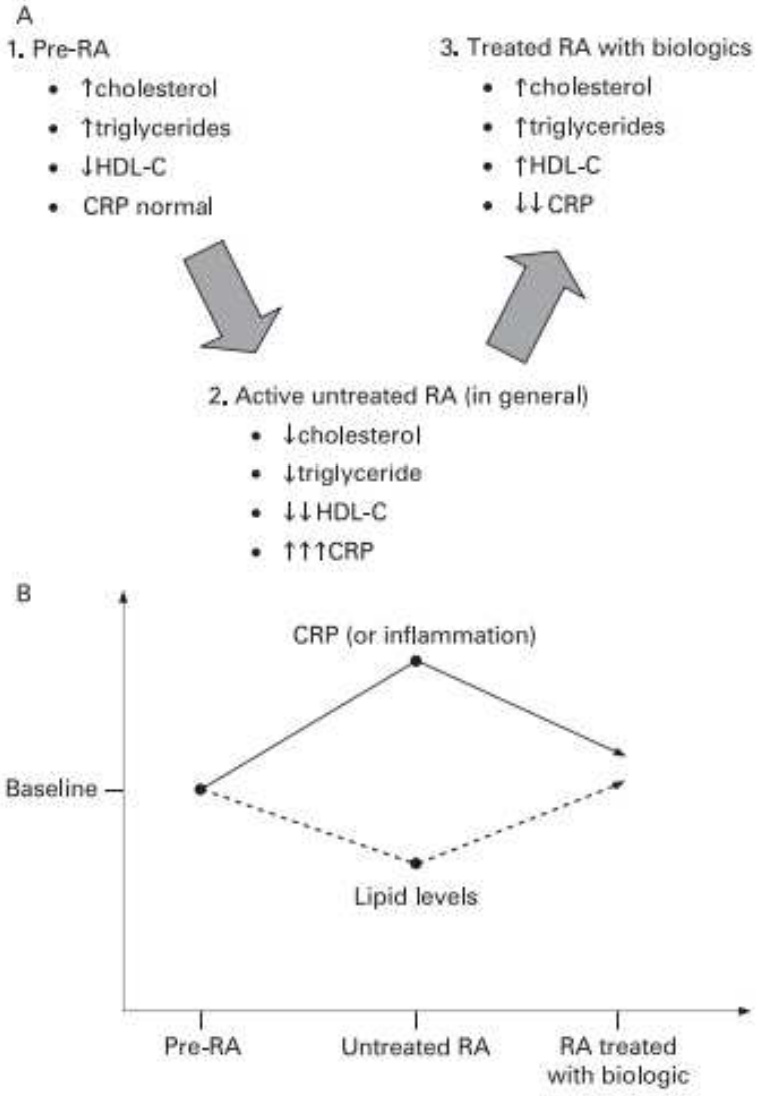
# Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm

*Iamie Robertson, Mike J. Peters, Iain B. McInnes and Naveed Sattar*

Nat Rev Rheumatol 2013



# TNF inhibitors effects on CRP and lipids




**<u>Levels of all lipid particles generally decrease in severe, untreated RA</u> when inflammatory levels are high**

**<u>Suppression of inflammation with biologics</u> can, therefore, be anticipated to <u>raise levels of all lipids</u>**

**Therefore, changes in lipid profiles, particularly increases in cholesterol and triglycerides that occur with treatments for severe inflammation, <u>may not represent increased cardiovascular risk</u> as in the usual understanding of lipid-level elevations in individuals without significant inflammation.**

*Choy E et al.* Ann Rheum Dis. 2009

# Dyslipidemia and RA activity

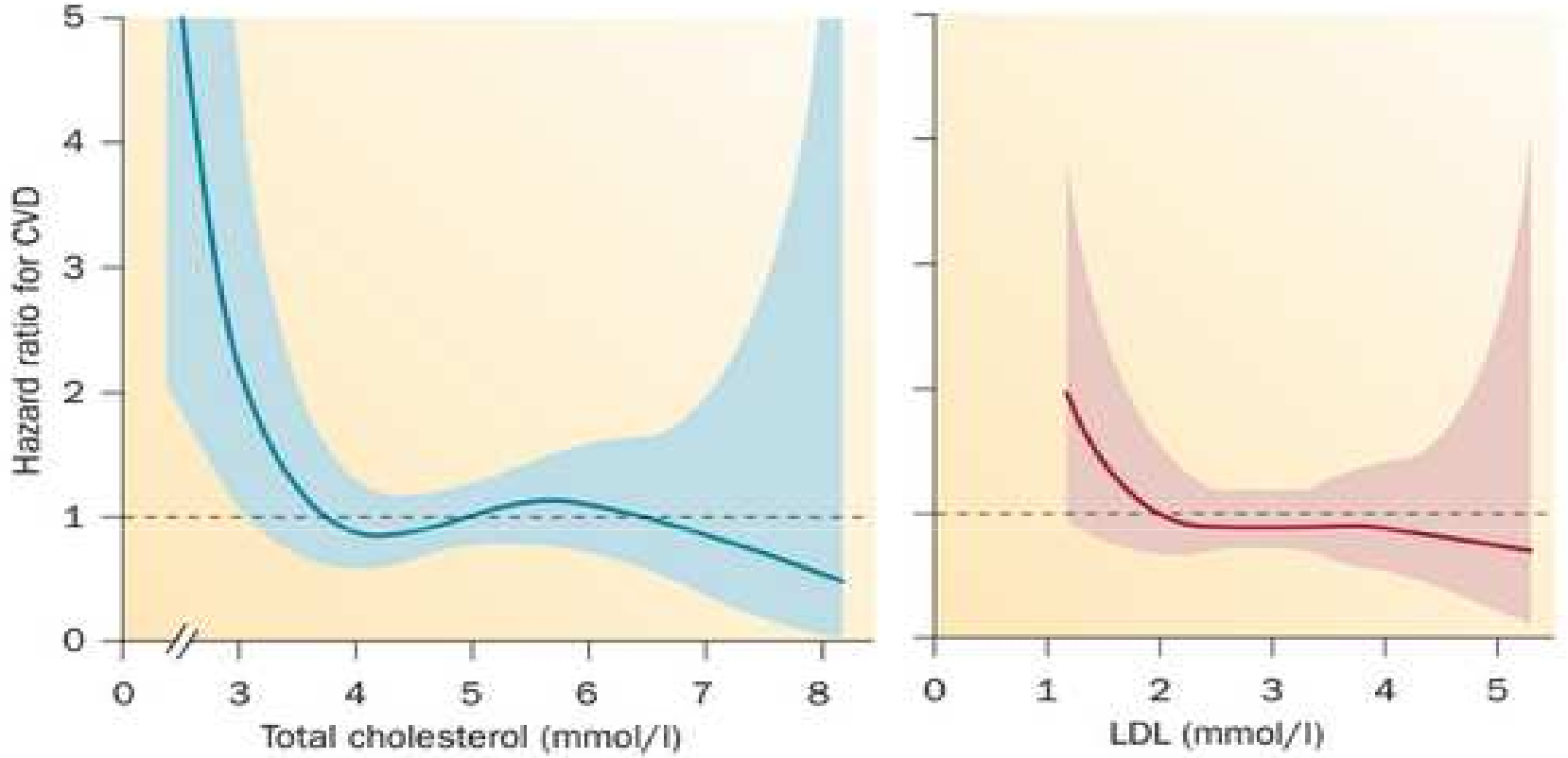



**Figure 2** | Hazard ratios for CVD in RA according to serum levels of total cholesterol and LDL. Shaded areas indicate 95% confidence intervals. CVD risk in relation to total cholesterol and LDL levels could potentially be represented by a U-shaped curve (considering the wide confidence intervals) in patients with RA. This pattern reflects the 'lipid paradox' in RA, a disease associated with increased CVD risk in patients with active disease despite reduced serum cholesterol levels compared with the general population. Abbreviations: CVD, cardiovascular disease;

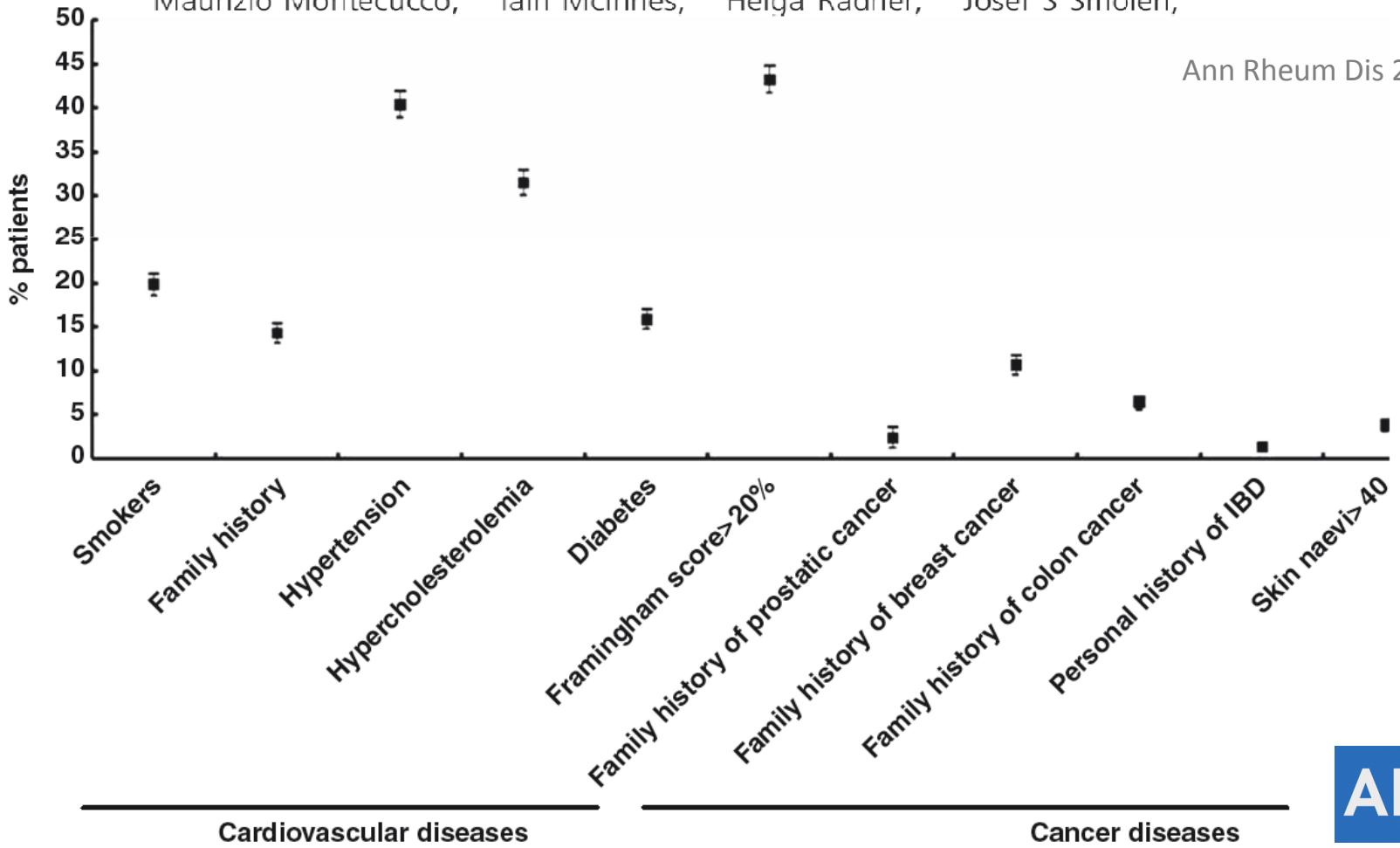
*Robertson J L et al. Nature Rev Rheum 2013*

EXTENDED REPORT

# Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA)

Maxime Dougados,[1,2] Martin Soubrier,[3] Anna Antunez,[4] Peter Balint,[5] Alejandro Balsa,[6] Maya H Buch,[7,8] Gustavo Casado,[9] Jacqueline Detert,[10] Bassel El-zorkany,[11] Paul Emery,[7,8] Najia Hajjaj-Hassouni,[12] Masayoshi Harigai,[13] Shue-Fen Luo,[14] Reka Kurucz,[5] Gabriel Maciel,[15] Emilio Martin Mola,[16] Carlo Maurizio Montecucco,[17] Iain McInnes,[18] Helga Radner,[19] Josef S Smolen,[19]

Ann Rheum Dis 2013




ARD

# Atorvastatin and CV risk in RA

## Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial

| | Atorvastatin (n=58) | Placebo (n=58) | p |
|---|---|---|---|
| **Primary outcome measure** | | | |
| Disease activity score | −0·50 (−0·75 to −0·25) | 0·03 (−0·23 to 0·28) | 0·004 |
| **Secondary outcome measures** | | | |
| Erythrocyte sedimentation rate (mm/h) | −5·03 (−8·4 to −1·67) | 1·91 (−1·61 to 5·44) | 0·005 |
| C-reactive protein (log mg/L) | −0·46 (−0·64 to −0·28) | 0·12 (−0·09 to 0·34) | <0·0001 ★ |
| Clinical measures | | | |
| Tender joint count | −1·21 (−3·28 to 0·86) | 0·38 (−1·16 to 1·92) | 0·22 |
| Early morning stiffness (log) | −0·47 (−0·82 to −0·12) | −0·13 (−0·47 to 0·22) | 0·17 |
| Visual analogue score | −5·07 (−10·5 to 0·36) | 1·97 (−3·15 to 7·08) | 0·06 |
| Swollen joint count | −2·69 (−3·81 to −1·57) | −0·53 (−1·59 to 0·52) | 0·0058 |
| Patient global assessment | −4·14 (−7·80 to −0·48) | 0·15 (−4·25 to 4·56) | 0·14 |
| Health assessment questionnaire | 0·02 (−0·12 to 0·16) | 0·04 (−0·04 to 0·13) | 0·75 |
| Lipids | | | |
| Cholesterol (mmol/L) | −1·48 (−1·73 to −1·23) | −0·01 (−0·14 to 0·12) | <0·0001 |
| Triglyceride (mmol/L) | −0·24 (−0·34 to −0·14) | 0·07 (−0·04 to 0·18) | <0·0001 ★ |
| LDL-cholesterol (mmol/L) | −1·40 (−1·63 to −1·17) | −0·07 (−0·23 to 0·10) | <0·0001 |
| HDL-cholesterol (mmol/L) | 0·03 (−0·03 to 0·09) | −0·04 (−0·10 to 0·02) | 0·097 |
| Other risk markers | | | |
| Fibrinogen (g/L) | −0·38 (−0·69 to −0·07) | 0·00 (0·19 to −0·20) | 0·041 |
| Plasma viscosity (mPa/s) | −0·05 (−0·06 to −0·03) | −0·00 (−0·02 to 0·01) | 0·0004 |
| Von Willebrand factor (IU/dL) | −8·5 (−20·6 to 3·58) | −4·53 (−16·7 to 7·6) | 0·64 |
| Intercellular adhesion molecule 1 (ng/mL) | −22·6 (−41·6 to −3·7) | 2·37 (−18·2 to 22·9) | 0·076 |
| Interleukin 6 (pg/mL) | −6·6 (−13·2 to 0·01) | 3·84 (−2·85 to 10·5) | 0·028 |

Table 3: **Differences after 6 months of treatment**

| | Methotrexate status at baseline | | | | Difference | p |
|---|---|---|---|---|---|---|
| | Not taking (n=29) | p | Taking (n=29) | p | | |
| ★ DAS28 | −0·40 (−0·74 to −0·06) | 0·02 | −0·59 (−0·97 to −0·21) | 0·004 | 0·19 (−0·31 to 0·69) | 0·46 |
| Erythrocyte sedimentation rate (mm/h) | −4·17 (−6·88 to −1·47) | 0·004 | −5·90 (−12·28 to 0·49) | 0·069 | 1·72 (−5·06 to 8·51) | 0·61 |
| C-reactive protein (log mg/L) | −0·40 (−0·67 to −0·13) | 0·006 | −0·52 (−0·77 to −0·27) | 0·0002 | 0·12 (−0·24 to 0·49) | 0·51 |

Table 4: **Changes in key study variables in the atorvastatin group according to baseline methotrexate status**

*McCarey D W et al.* Lancet. *2004*

# Cardiovascular risk factors : diabetes

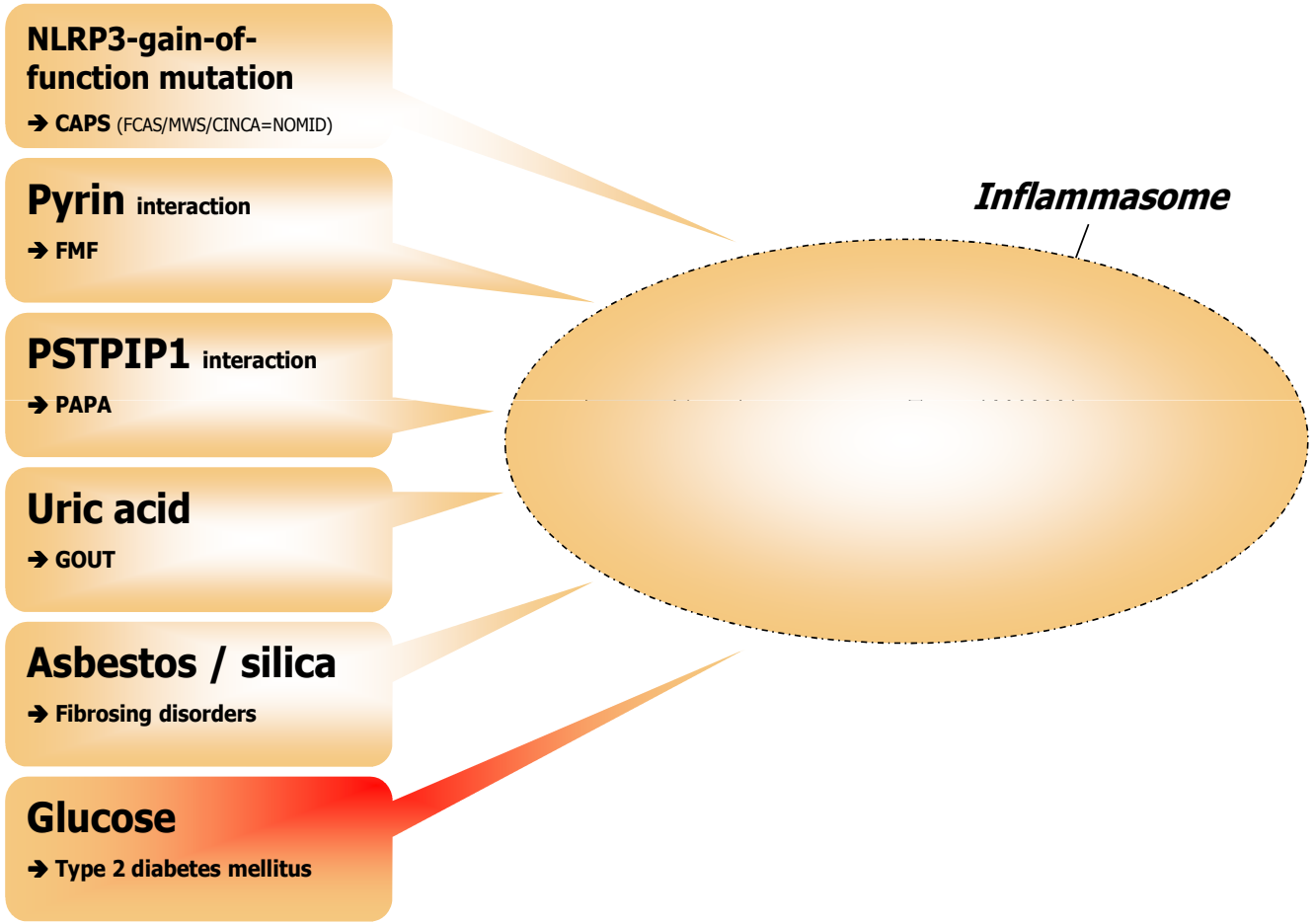
- Increased prevalence : 5/7 studies

- Meta analysis
  - OR : 1.74 (1.22 – 2.50)

Liao K et al, Rheumatology, 2013

Boyer JF et al Joint Bone Spine, 2011

# Inflammasome and diabetes



# Inflammasome and diabetes



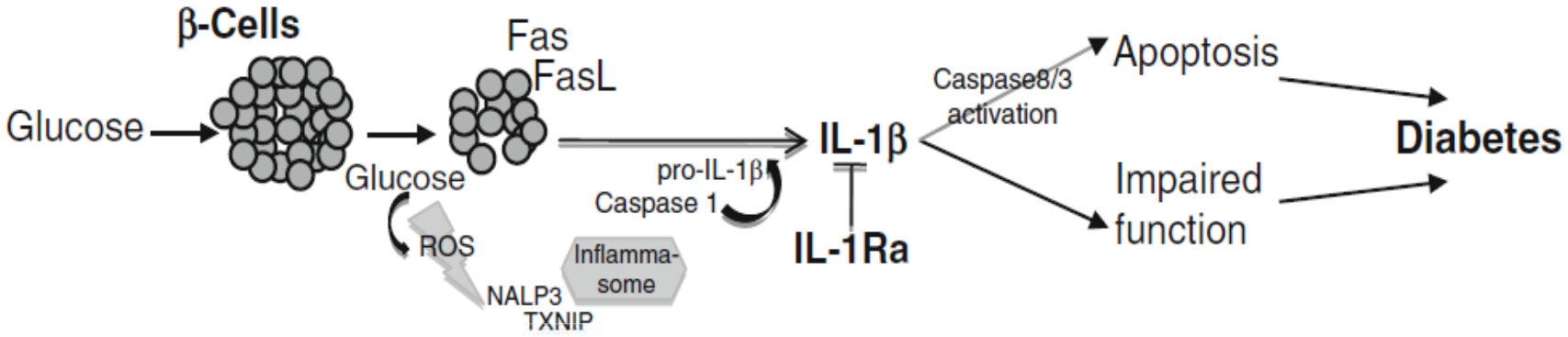
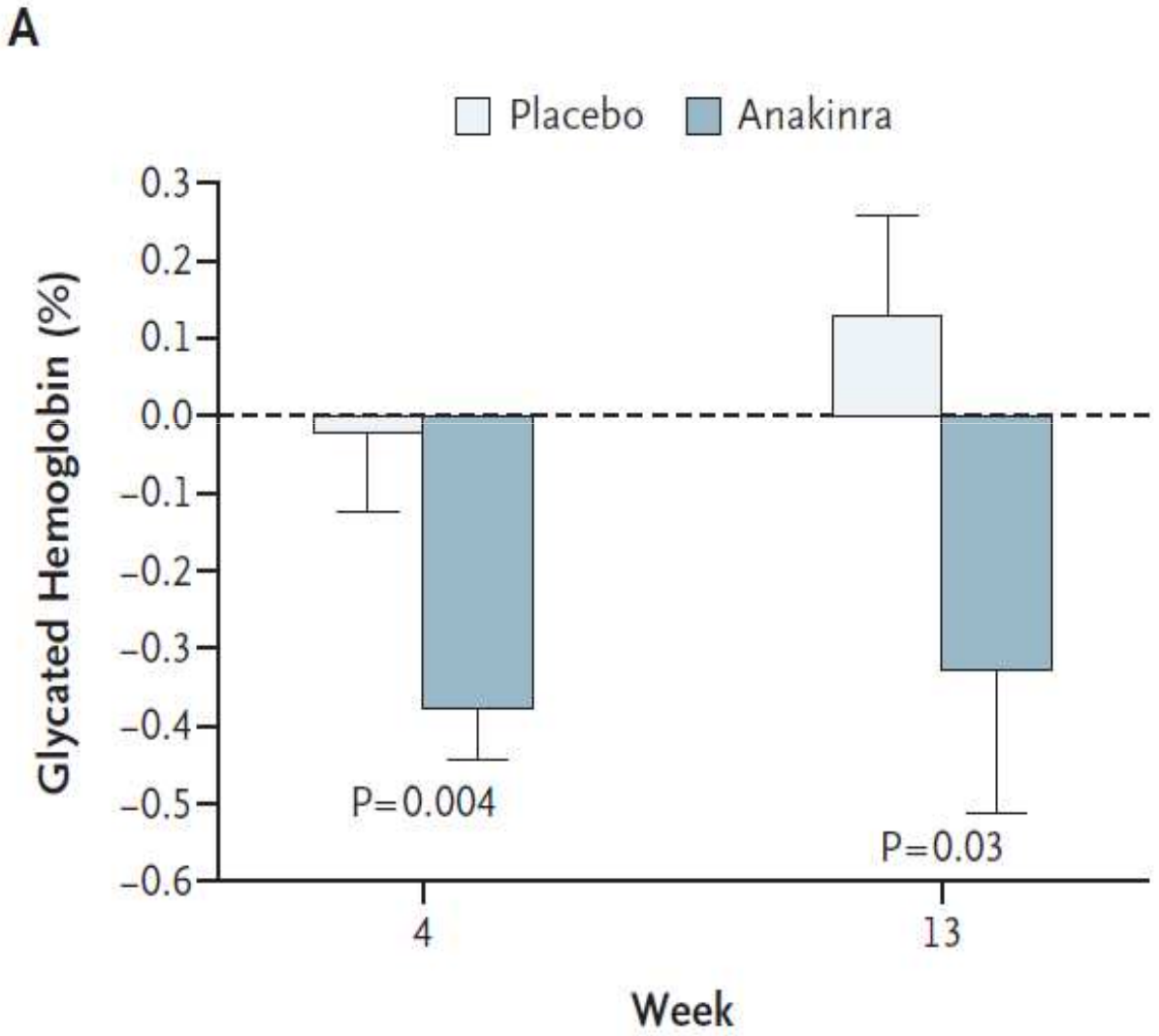



**Fig. 3** Dual role of glucose on β-cell turnover. Stimulation of β-cells with glucose induces insulin secretion and β-cell proliferation. In contrast, chronic glucose exposure leads to upregulation of the Fas receptor and ligation with FasL to caspase activation, apoptosis, and impaired function, which contributes to β-cell failure in diabetes. Under such conditions, IL-1β is produced and secreted by the β-cell. This is mediated through ROS-induced induction of the NALP3 inflammasome, which activates Caspase-1 and maturation of active IL-1β from pro-IL-1β. Preincubation of the islets with the naturally occurring IL-1 antagonist interleukin-1 receptor antagonist (IL-1Ra) inhibits glucose-induced apoptosis and improves β-cell function and could therefore be a valuable tool for diabetes therapy

Dinarello CA. Annu Rev Immunol. 2009

# Inflammasome and diabetes



# Inhibition of IL-6 and CV risk

**Table 2.** Metabolic parameters of the study population.

| | 0 month | 1 month | 3 month |
|---|---|---|---|
| TG (mg/dl) | 141.9±15.1 | 170.8±26.2 | 169.6±27.0 |
| LDL (mg/dl) | 122.5±11.2 | 122.7±10.7 | 133.1±12.0 |
| HDL (mg/dl) | 53.6±6.5 | 61.0±5.0 | 63.0±5.1 |
| Lp(a) (mg/dl) | 34.5±12.8 | 24.3±7.6[(a)] | 19.9±6.3[(b)] |
| Glucose (mg/dl) | 90.5±4.5 | 82.7±2.1 | 87.5±2.7 |
| HbA1c (%) | 5.4±1.5 | 5.3±0.1 | 5.2±0.1 |

TG = triglycerides, LDL = LDL-cholesterol, HDL = HDL-cholesterol, HbA1c = glycosylated haemoglobin A1c levels.
[(a)] = $p<0.05$ compared to 0 month,
[(b)] = $p<0.05$ compared to 0 month. Means ± SEM.
doi:10.1371/journal.pone.0014328.t002

***Conclusions/Significance:*** Inhibition of IL-6 signalling improves insulin sensitivity in humans with immunological disease suggesting that elevated IL-6 levels in type 2 diabetic subjects might be causally involved in the pathogenesis of insulin resistance. Furthermore, our data indicate that inhibition of IL-6 signalling decreases Lp (a) serum levels, which might reduce the cardiovascular risk of human subjects.

*Schultz O et al.* PloS One. 2010

# EULAR recommendations

| Recommendations | Level of evidence | Strength of recommendation |
|---|---|---|
| **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 |
| Adequate **control of disease activity** is necessary to lower the CV risk | 2b–3 | B |
| **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 |
| **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: | 3–4 | C |
| **Disease duration of more than 10 years** | | |
| **RF or anti-CCP positivity** | | |
| **Presence of certain extra-articular manifestations** | | |
| **TC/HDL cholesterol ratio** should be used when the SCORE model is used | 3 | C |
| Intervention should be carried out according to national guidelines | 3 | C |
| **Statins, ACE inhibitors and/or AT-II blockers** are preferred treatment options | 2a–3 | C-D |
| 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 |
| **Corticosteroids: use the lowest dose possible** | 3 | C |
| Recommend **smoking cessation** | 3 | C |

*Micha R et al.* Am J Cardiol*. 2012*

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