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# The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis

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## ABSTRACT

The objective of this systematic literature review was to determine the association between cardiovascular events (CVEs) and antirheumatic drugs in rheumatoid arthritis (RA) and psoriatic arthritis (PsA)/psoriasis (Pso).

Systematic searches were performed of MEDLINE, EMBASE and Cochrane databases (1960 to December 2012) and proceedings from major relevant congresses (2010–2012) for controlled studies and randomised trials reporting confirmed CVEs in patients with RA or PsA/Pso treated with antirheumatic drugs. Random-effects meta-analyses were performed on extracted data.

Out of 2630 references screened, 34 studies were included: 28 in RA and 6 in PsA/Pso. In RA, a reduced risk of all CVEs was reported with tumour necrosis factor inhibitors (relative risk (RR), 0.70; 95% CI 0.54 to 0.90; p=0.005) and methotrexate (RR, 0.72; 95% CI 0.57 to 0.91; p=0.007). Non-steroidal anti-inflammatory drugs (NSAIDs) increased the risk of all CVEs (RR, 1.18; 95% CI 1.01 to 1.38; p=0.04), which may have been specifically related to the effects of rofecoxib. Corticosteroids increased the risk of all CVEs (RR, 1.47; 95% CI 1.34 to 1.60; p<0.001). In PsA/Pso, systemic therapy decreased the risk of all CVEs (RR, 0.75; 95% CI 0.63 to 0.91; p=0.003).

In RA, tumour necrosis factor inhibitors and methotrexate are associated with a decreased risk of all CVEs while corticosteroids and NSAIDs are associated with an increased risk. Targeting inflammation with tumour necrosis factor inhibitors or methotrexate may have positive cardiovascular effects in RA. In PsA/Pso, limited evidence suggests that systemic therapies are associated with a decrease in all CVE risk.

## INTRODUCTION

Patients with rheumatoid arthritis (RA) have increased risk of cardiovascular morbidity and mortality.[1 2] Although less evidence has been published so far,[3 4] this increased risk is also suspected in patients with psoriasis (Pso), with or without psoriatic arthritis (PsA). Irrespective of classical cardiovascular risk factors, the systemic inflammation characteristic of RA and Pso/PsA plays a pivotal role in increasing cardiovascular risk by accelerating atherosclerosis.[5] Vascular inflammation and the related elevated cardiovascular risk may affect all patients with RA, beginning in the early stage of disease (perhaps even preceding clinical onset)[6] and worsening with additional classical cardiovascular risk factors.

Many anti-inflammatory strategies have emerged as potential therapeutic approaches for atherosclerosis.[7] Likewise, treatment of the underlying inflammatory process could contribute to improved cardiovascular outcomes in patients with RA and Pso/PsA.[8] This is reflected in one of the current European League Against Rheumatism recommendations in RA,[9 10] which advises achieving remission or low disease activity as early as possible, not only for better structural and functional outcomes, but also to reduce cardiovascular risk. However, it is still open to discussion as to whether targeting systemic inflammation itself with disease-modifying antirheumatic drugs (DMARDs) reduces the occurrence of cardiovascular events (CVEs) in patients with RA or Pso/PsA.

The purpose of this systematic literature review and meta-analysis was to explore the association between the use of biologics (including tumour necrosis factor (TNF) inhibitors), non-biological DMARDs (including methotrexate), corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and CVEs in patients with RA or Pso/PsA.

## METHODS

A systematic literature review and meta-analysis were performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.[11]

### Data sources and searches

A systematic literature search of MEDLINE (via PubMed), EMBASE and the Cochrane Library databases (1960 to December 2012) was performed to identify observational studies and randomised controlled trials that reported CVEs in adults with RA or Pso/PsA treated with biologics (including TNF inhibitors), non-biological DMARDs (including methotrexate), NSAIDs and corticosteroids (see online supplementary eMethods). Searches were restricted to English language. We also searched the

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proceedings of the American College of Rheumatology, European League Against Rheumatism, American Academy of Dermatology and European Academy of Dermatology and Venereology annual meetings (2010–2012) and hand-searched reference lists for relevant additional studies.

### Study selection

Studies were included if they were observational studies or randomised controlled trials that reported relevant confirmed CVEs (including all CVEs, myocardial infarction, heart failure, stroke and/or major adverse cardiac events); included patients with RA or Pso/PsA treated with biologics, non-biological DMARDs, corticosteroids or NSAIDs (or phototherapy for Pso/PsA); and included a suitable control group (another treatment, such as a TNF inhibitor compared with methotrexate, or non-use of the investigative treatment, such as use of a TNF inhibitor compared with non-use of a TNF inhibitor). Studies were excluded if they only reported data on cardiovascular risk factors (eg, diabetes mellitus), intermediate endpoints (eg, lipid levels) or surrogate markers of atherosclerosis (eg, arterial intimae media thickness); reported data on <400 patients; had a follow-up duration <1 year (to ensure that impact of the assessed treatment was most likely to be a true effect and not due to chance in a short duration of observation); included a patient population with a mean age of 80 years or older (to allow homogeneous cross-study populations, as the majority of studies included populations with a mean age of approximately 60 years); or did not have sufficient data to convert to relative risk (RR). Two studies that specifically included veteran patients with RA[12 13] were excluded because 90% of the study population comprised men, which is not representative of the classical gender stratification in RA.

One author (CR) screened all titles and abstracts for potential inclusion. Two authors (CR and BH) then independently screened the full text of the selected studies for inclusion in the systematic review and meta-analysis according to the predetermined criteria. Disagreements were resolved by consensus.

### Data extraction and quality assessment

Two investigators (CR and BH) independently extracted the following data for each study using a predefined data collection form: study design; data sources; sample size; age of the subjects; underlying disease (RA or Pso/PsA); duration of follow-up; treatments under investigation; cardiovascular outcomes of interest; number of outcomes and models of adjustment (age and gender, cardiovascular risk factors, history of cardiovascular disease, RA disease activity, and use of TNF inhibitors, methotrexate, corticosteroids or NSAIDs). HRs, ORs, RRs, rate ratios or mean effect sizes for each drug and comparator, together with their associated 95% CIs, were recorded for each endpoint. When only incident outcomes were reported, the numbers of events in the compared groups were extracted. We contacted authors for missing data when necessary. If studies reported data on several drugs and/or on several cardiovascular endpoints, each value was included in the analysis, so one reference could contribute several different data values to the final meta-analysis. When several models of adjustment were reported, the most adjusted estimates were used in the analysis. Selected studies were assessed for quality using the Newcastle-Ottawa Scale, designed to assess the quality of non-randomised studies such as cohort and case–control studies.[14] Briefly, this scale allocates points for appropriateness of participant selection (0–4 points), comparability (0–2 points) and exposure or outcome (0–3 points).

### Data synthesis and statistical analysis

Extracted data were combined for meta-analysis using Review Manager (RevMan) software (Cochrane Collaboration). When only incident outcomes were reported, RRs were computed. If patient-years of follow-up were available, rate ratios were calculated and used in analysis. The resulting adjusted or unadjusted RRs, HRs and rate ratios were considered equivalent measures of effect size and entered into RevMan. ORs were transformed to RRs.[15 16] These measures were generically referred to as risk ratios. For all outcomes, random-effects meta-analyses were conducted. This assumes that different studies were estimating different intervention effects and partly explains the heterogeneity between studies. Forest plots were constructed to summarise the risk ratio estimates and their 95% CIs. These figures present measures of heterogeneity across studies (Cochrane Q statistic, noted as $\chi^2$ and the $I^2$ statistic) and a test for overall effect (Z). Funnel plots and Egger's regression test were also produced to help detect potential publication bias.

### Primary and secondary outcomes

The primary outcome was the association between treatment and all CVEs. The secondary outcomes were the association between treatment and myocardial infarction, heart failure, stroke or major adverse cardiac events.

## RESULTS

### Study selection

We identified 2630 unique references through searching databases, conference proceedings and reference lists (figure 1). Of these, 2526 were excluded as they were not relevant to our topic or related to cardiovascular risk factors or surrogate markers of atherosclerosis. Of the 104 remaining references, 66 were selected for full-text review. Finally, 34 references met the selection criteria for meta-analysis (see online supplementary table S1): 28 in RA (total of 236 525 subjects; 5410 CVEs)[17–44] and 6 in Pso/PsA (220 209 subjects; 2701 CVEs).[12 45–49]

### Cardiovascular outcomes in RA: results of meta-analyses

In RA, TNF inhibitors were significantly associated with a reduction in the risk of all CVEs (RR, 0.70; 95% CI 0.54 to 0.90; p=0.005), as well as in myocardial infarctions, strokes and major adverse cardiac events (figure 2A). No significant effect on heart failure was observed (figure 2A). A beneficial association between methotrexate and reduction in the risk of all CVEs (RR, 0.72; 95% CI 0.57 to 0.91; p=0.007) and myocardial infarction was also found (figure 2B). However, in contrast with TNF inhibitors, methotrexate was not associated with a significant decrease in the risk of strokes and major adverse cardiac events, although trends towards decreasing risk of heart failure were found (figure 2B). This may be due to the low number of events included in the meta-analysis, which did not provide sufficient statistical power to observe a differential effect.

NSAIDs increased the risk of all CVEs (RR, 1.18; 95% CI 1.01 to 1.38; p=0.04) and strokes. This effect appears mostly driven by cyclooxygenase-2 (COX-2) inhibitors (RR, 1.36; 95% CI 1.10 to 1.67; p=0.004) rather than non-selective NSAIDs (RR, 1.08; 95% CI 0.94 to 1.24; p=0.28) (figure 2C). Of note, some studies assessing rofecoxib, which has already been withdrawn from the market, have been included. Hence, we



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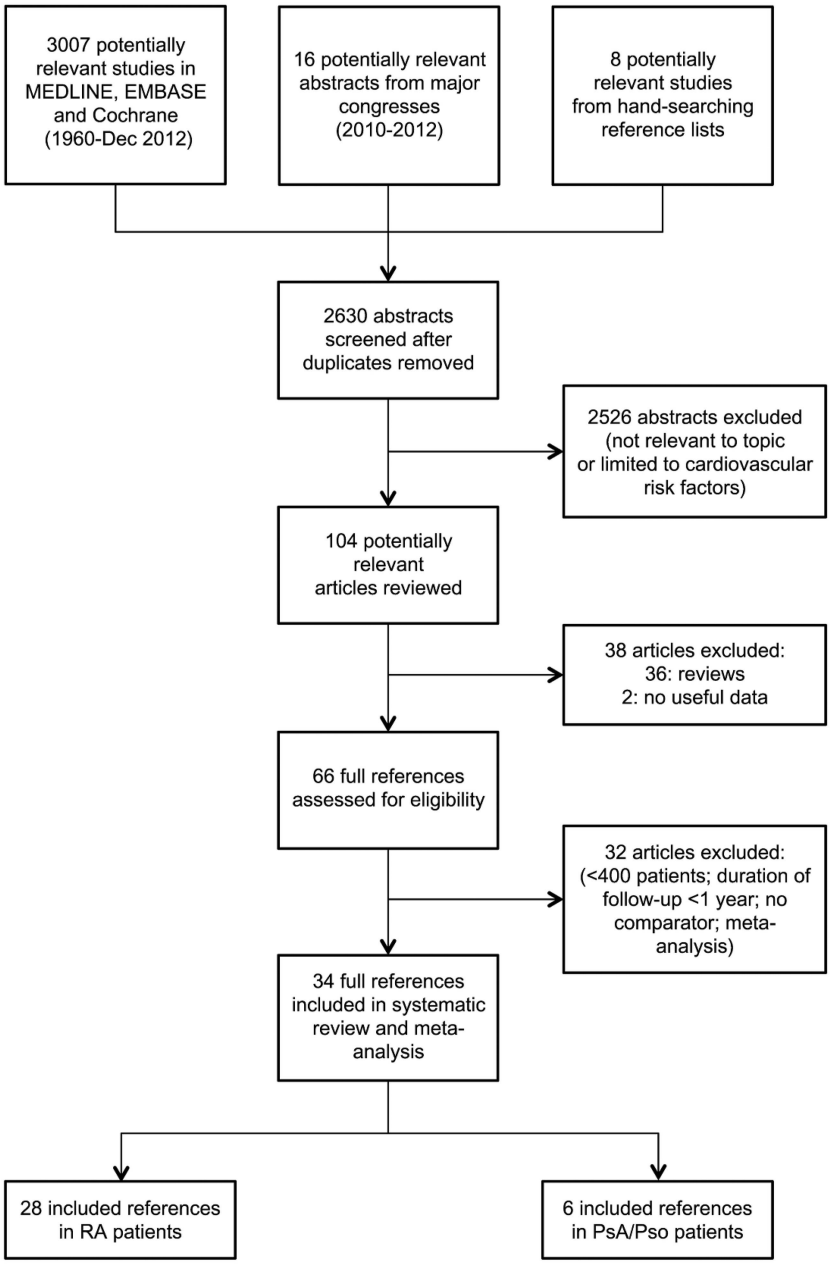


**Figure 1** Search and selection of studies for systematic review and meta-analysis. PsA, psoriatic arthritis; Pso, psoriasis; RA, rheumatoid arthritis.

performed separate meta-analyses for rofecoxib and celecoxib. While rofecoxib increased the risk of all CVEs (RR, 1.58; 95% CI 1.24 to 2.00; p<0.001), celecoxib did not (RR, 1.03; 95% CI 0.80 to 1.32; p=0.81) (see online supplementary figure S1). Additionally, NSAIDs did not demonstrate any significant effect on risk of myocardial infarction, heart failure or major adverse cardiac events (figure 2C); however, with few studies included, these findings should be interpreted with caution.

Corticosteroids were associated with an increased risk of all CVEs (RR, 1.47; 95% CI 1.34 to 1.60; p<0.001), as well as risk of myocardial infarction, stroke, heart failure and major adverse cardiac events (figure 2D).

In the meta-analyses evaluating TNF inhibitors or methotrexate, some heterogeneity was found between studies for all endpoints (except stroke). Heterogeneity was only observed for the all CVE endpoint in the meta-analyses evaluating all NSAIDs or COX-2 inhibitors. Of note, no significant heterogeneity was found for the all CVE endpoint in the meta-analyses evaluating non-selective NSAIDs and corticosteroids or for any specific endpoint in the meta-analyses evaluating NSAIDs and corticosteroids. Analysis for publication bias was performed using funnel plots for all CVE endpoints (figure 3). Although subjective, visual inspection did not suggest publication bias for this outcome. Egger's asymmetry coefficient, known to be low powered, did detect potential bias in the meta-analysis of corticosteroid use (p=0.02, figure 3) and COX-2 inhibitor use (p<0.01; see online supplementary figure S2).

### Cardiovascular outcomes in Pso/PsA: results of meta-analyses

Only six studies met our selection criteria in patients with Pso and/or PsA; therefore, we only had sufficient data to evaluate the effect of systemic therapy compared with no systemic therapy or topical treatment on risk of all CVEs. Systemic therapy was associated with a significant decrease in risk of all CVEs in Pso/PsA (RR, 0.75; 95% CI 0.63 to 0.91;



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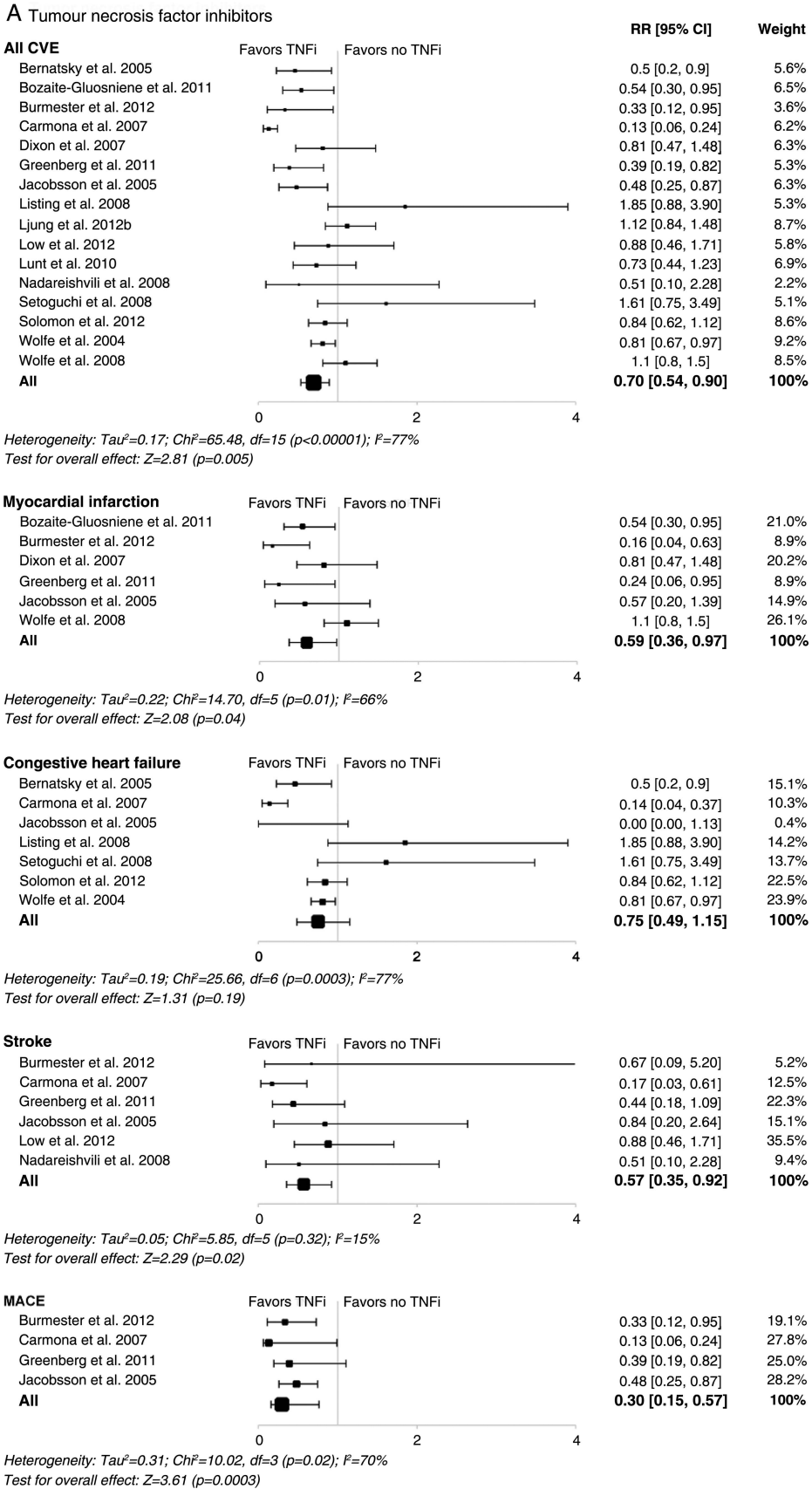


**Figure 2** Meta-analyses of all cardiovascular events and individual cardiovascular events in patients with rheumatoid arthritis treated with (A) tumour necrosis factor inhibitors; (B) methotrexate; (C) non-steroidal anti-inflammatory drugs; or (D) corticosteroids in controlled studies. Size of data markers indicates relative weight of the study (from random-effects analysis). COX-2, cyclooxygenase-2; CVE, cardiovascular event; MACE, major adverse cardiac event; MTX, methotrexate; RR, relative risk; TNFi, tumour necrosis factor inhibitor.

p=0.003) (see online supplementary figure S3). No significant heterogeneity was observed (see online supplementary figure S4).

## DISCUSSION

To our knowledge, this is the first systematic literature review and meta-analysis of published controlled studies assessing the



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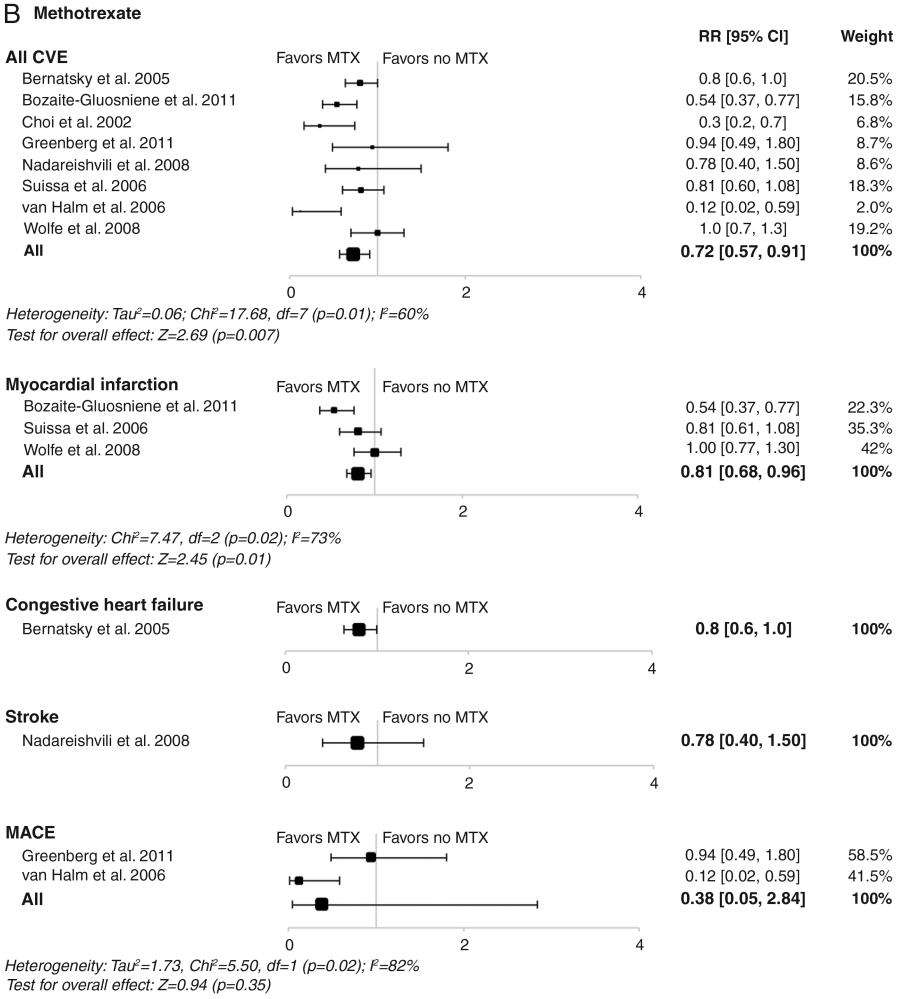
**Figure 2** Continued




association between CVEs and use of TNF inhibitors, methotrexate, NSAIDs or corticosteroids in patients with RA or Pso/PsA.

In patients with RA, treatment with TNF inhibitors or methotrexate was associated with a 30% and 28% reduction in the risk of CVEs, respectively, while use of NSAIDs or corticosteroids was associated with 18% and 47% increase in risk of all CVEs, respectively. Moreover, while TNF inhibitors and methotrexate were also found to be associated with a reduction in risk of some specific cardiovascular endpoints, corticosteroids were associated with an increase in risk of all specific outcomes. In patients with Pso/PsA, data suggest that biologics and other DMARDs may be associated with a decreased risk of CVEs, but we acknowledge that evidence is less conclusive than in RA and that further studies are needed.

Compared with the general population, patients with RA have an increased risk of cardiovascular disease or events[50] and reduced survival.[2] Systemic inflammation is the cornerstone of both RA and atherosclerosis. However, whether effective DMARD-based therapy can ameliorate this increased risk in RA or Pso/PsA is still under debate. Considering these immunomodulatory strategies in atherosclerosis may also provide new perspective in managing cardiovascular disease in the general population. Indeed, in the (non-RA) primary cardiovascular disease prevention Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin randomised controlled trial, the absolute risk of first major adverse cardiac events increased with increasing high-sensitivity C-reactive protein (CRP) levels, a measure of systemic inflammation.[51 52] This study clearly showed an association between inflammation and cardiovascular risk in otherwise 'healthy' individuals. In RA, elevated baseline CRP has been associated with cardiovascular death, persisting after adjustment for classical cardiovascular risk factors, supporting a relevant link between systemic inflammation and risk of cardiovascular disease.[5] Hence, by controlling the systemic inflammation, TNF inhibitors and methotrexate may decrease cardiovascular risk. Our present findings in RA support this hypothesis.

Several previous publications have also suggested that TNF inhibitors have a beneficial impact on cardiovascular risk.[53 54] As suggested in a systematic literature review,[55] another meta-analysis reported that TNF inhibitors in RA may reduce the risk of all CVEs (pooled adjusted RR, 0.46; 95% CI 0.28 to 0.77), myocardial infarction (pooled adjusted RR, 0.81; 95% CI 0.68 to 0.96) and cerebrovascular accident (pooled adjusted RR, 0.69; 95% CI 0.53 to 0.89).[15] Our analyses included more studies than those previously reported and our results are consistent with these prior findings. Interestingly, we found no association between TNF inhibitors and risk of heart failure in RA. In the general population with heart failure, TNF-α levels are increased[56] and associated with severity of clinical signs and symptoms.[57] Experimental heart failure models have suggested that TNF inhibitors may improve ventricular dysfunction[58]; however, a large clinical trial assessing etanercept in the treatment of congestive heart failure showed no benefit[59] while another one found that high-dose infliximab worsened heart failure in patients with moderate-to-severe chronic heart failure.[60] Consequently, the presence of severe heart failure



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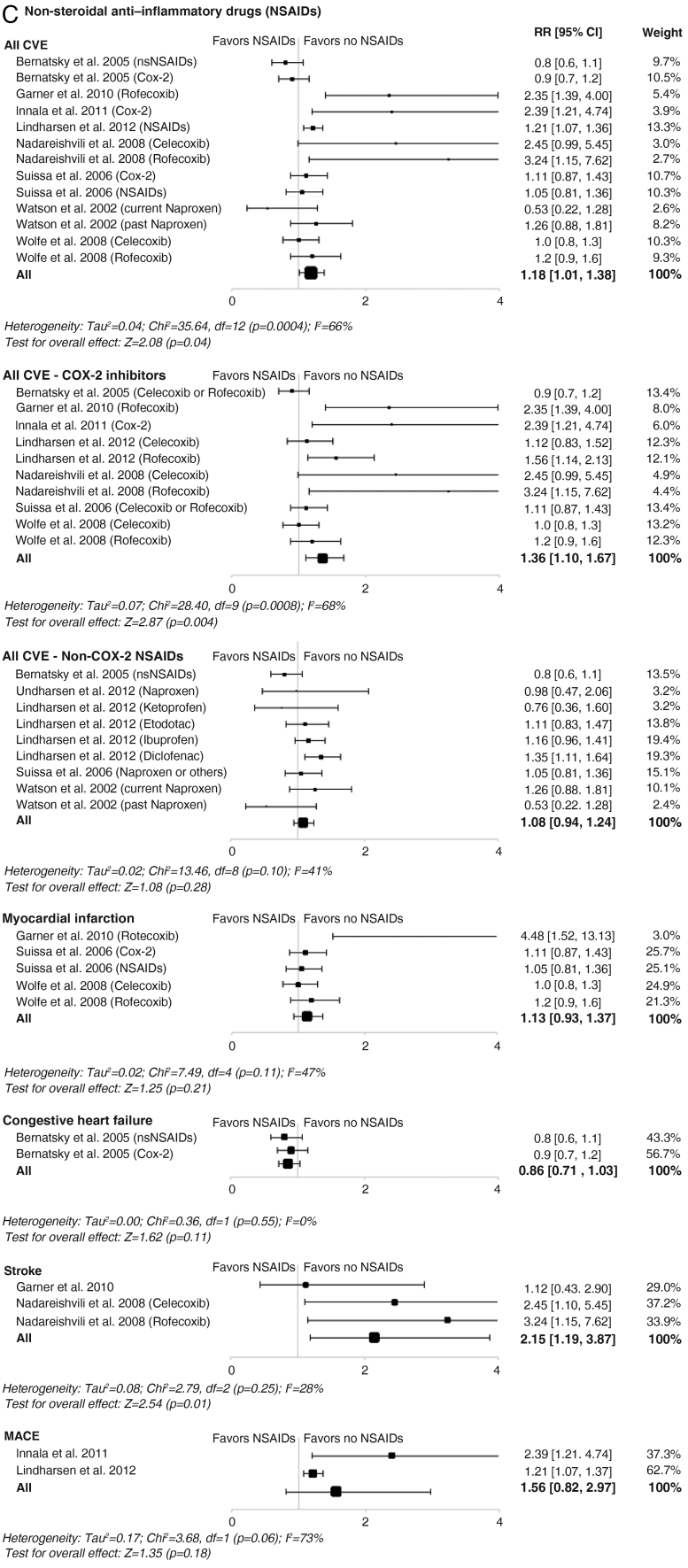
**Figure 2** Continued

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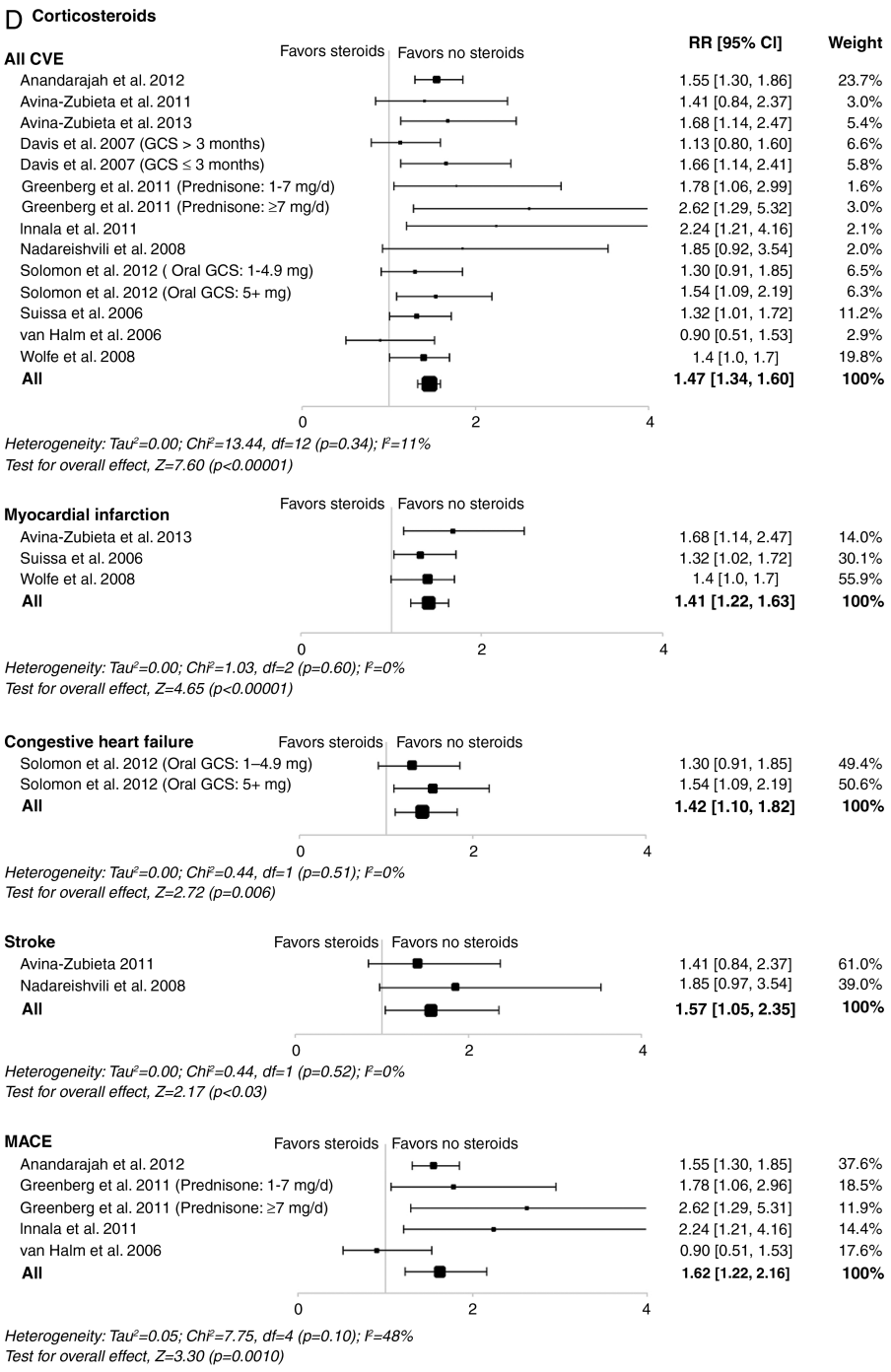


remains a contraindication to the use of TNF inhibitors in patients with RA. This may account for our results, given that the selected studies probably included patients with RA without pre-existing heart failure, consistent with a bias by indication. However, one recent study comparing 8656 new users of non-biological DMARDs with 11 587 new users of TNF inhibitors showed that TNF inhibitors were not associated with an increased risk of hospital admissions due to heart failure.[37] Further specifically designed trials assessing cardiovascular outcomes are needed to evaluate the use of TNF inhibitors in patients with RA, including those with heart failure.

In RA, methotrexate has recently been associated with a 70% reduction in mortality[61] and may also be associated with a reduced risk of cardiovascular disease.[62] Consistent with our results, methotrexate has been associated with a 21% lower risk of total cardiovascular disease and an 18% lower risk of myocardial infarction in patients with chronic inflammatory diseases including RA.[63] Corticosteroids and NSAIDs are generally considered to have deleterious effects, although little evidence-based data are available in patients with RA. Both non-selective NSAIDs and COX-2 inhibitors have been demonstrated to increase cardiovascular risk[64–66]; however, few studies have evaluated the impact of corticosteroids and NSAIDs on CVEs specifically in RA.[17–22 36 44] Our meta-analysis in patients with RA revealed that COX-2 inhibitors were associated with an increased risk of all CVEs and strokes, mainly because of rofecoxib, which is now withdrawn from the market. Conversely, non-selective NSAIDs and celecoxib were not associated with increased risk of CVEs. The practical consequence of this finding may be to weigh the benefit–risk ratio of using NSAIDs



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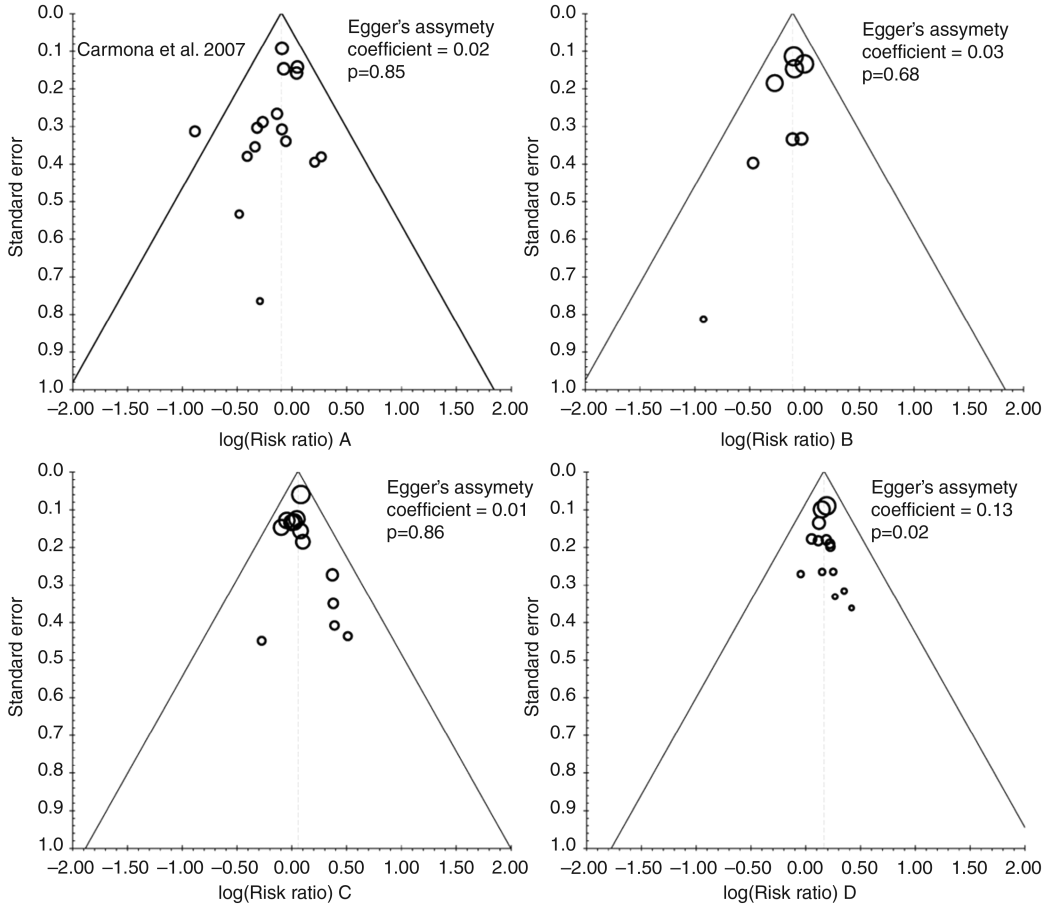


**Figure 3** Funnel plots for the meta-analysis of occurrence of cardiovascular events associated with treatment with (A) tumour necrosis factor inhibitors, (B) methotrexate, (C) non-steroidal anti-inflammatory drugs and (D) corticosteroids. The importance (weight) of each study is proportional to the marker size.

in patients with RA with higher cardiovascular risk, while not avoiding them at all costs.

The potential harmful cardiovascular effects of corticosteroids are well-known but not strongly evidence based.[65] To our knowledge, our meta-analysis is the first to report a deleterious association between corticosteroids and all CVEs, myocardial infarction, heart failure, stroke and major adverse cardiac events in the RA population. Corticosteroids may modulate the risk of cardiovascular disease in patients with RA in two competing directions: by increasing the risk due to deleterious effects on lipids, glucose tolerance, weight gain and hypertension,[67] but conversely potentially decreasing the risk by exerting anti-inflammatory and antiproliferative effects on vascular wall. Additionally, corticosteroids may result in two independent effects over time: an immediate effect of current exposure and a long-term cumulative effect of past exposure.[22 68] Notably, corticosteroid use has recently been associated with a dose-dependent increased mortality in RA.[69]

In PsA/Pso, less evidence on risk of CVEs has been published. However, the results of our meta-analysis are consistent with recent reviews,[70 71] underlining the need for adequately powered trials to assess the cardiovascular effects of systemic therapy including TNF inhibitors in patients with PsA/Pso.

Interpreting the evidence from observational studies requires caution as these can generate more bias than randomised controlled trials. Hence, only an association between medication use and CVEs can be determined. However, we were unable to find any adequately powered randomised controlled trial assessing the impact of RA therapy on risk of CVEs. Furthermore, the duration of follow-up of most randomised controlled trials in patients with RA or PsA/Pso may not be long enough to investigate the effects of such treatments on CVE rates. Finally, our results are consistent with two large meta-analyses evaluating methotrexate and TNF inhibitors in RA.[15 63]

Despite the mounting published evidence of an increased cardiovascular risk in patients with RA, few studies have investigated DMARD-based therapeutic strategies to reduce this risk. Therefore, a low number of studies assessing the impact of methotrexate on specific cardiovascular endpoints were included in our analysis. Additionally, lack of sufficient data did not allow for subgroup analyses of dose effect for methotrexate and corticosteroids in RA, or of the influence of psoriasis severity on the impact of systemic therapy on CVE rates in patients with PsA/Pso. No study evaluating the impact of non-TNF inhibitor biologics was found, although several studies evaluating the vascular impact of rituximab (NCT00844714) and tocilizumab (NCT00844714 and NCT01752335) are ongoing in RA.

Another limitation in this analysis is the differences in the cardiovascular definitions and comparators across studies. To mitigate this, we used selection criteria that would provide as homogeneous as possible study populations to provide clinically relevant results.

## CONCLUSION

Our meta-analysis provides important insights into the effect of antirheumatic drugs on CVEs in RA by suggesting that TNF inhibitors and methotrexate decrease the risk of such events while NSAIDs and corticosteroids increase the risk in RA. In



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PsA/Pso, limited evidence suggests that systemic therapies are associated with a decrease in the risk of all CVEs. While current evidence implies deleterious cardiovascular effects of corticosteroids and COX-2 inhibitors in RA, suppressing diverse mediators of inflammation with methotrexate and TNF inhibitors may have positive cardiovascular effects. Large, prospective, adequately controlled and powered studies are needed to explore the effects of such drugs on cardiovascular morbidity and mortality in the RA and PsA/Pso populations.

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# Systemic treatments for inflammatory disease may protect against cardiovascular risks such as stroke

Some medicines used to treat inflammatory diseases such as rheumatoid arthritis, psoriasis or psoriatic arthritis might help to protect patients against cardiovascular problems such as heart attacks or stroke.

## INTRODUCTION

Rheumatoid arthritis, psoriasis and psoriatic arthritis are chronic inflammatory conditions. Rheumatoid arthritis and psoriatic arthritis affect the joints, and psoriasis affects the skin. All three diseases can cause pain and disability. It is known that patients with rheumatoid arthritis, psoriasis or psoriatic arthritis are more likely to have cardiovascular problems such as heart attacks, heart failure or stroke. This is because these diseases have an inflammatory effect on other systems in the body, as well as the joints and the skin.

## WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to see whether there was a link between the medicines that some patients take for rheumatoid arthritis, psoriasis or psoriatic arthritis and the likelihood of having cardiovascular problems. They looked at four different types of systemic medicines used in these diseases. A systemic medicine is one that may have an effect anywhere in the body, as well as in the place where the disease is active – for example, in the joints.

## HOW WAS THE REVIEW CONDUCTED?

A systematic review aims to identify all the published evidence on a particular topic and draw it together into one summary. This paper was also a meta-analysis, which means that statistical analyses have been performed on the results in order to be sure that the conclusions being drawn are meaningful.

The authors searched for trials and studies that reported cardiovascular problems in patients taking a group of medicines called TNF inhibitors, as well as those taking methotrexate, corticosteroids or non-steroidal anti-inflammatory drugs (also known as NSAIDs). The search gave a long list of 2630 articles. Of these 34 had the correct type of information and were included in the review.

## WHAT DO THE RESULTS SAY?

The review found that in patients with rheumatoid arthritis TNF inhibitor medicines or methotrexate reduce the chance of suffering from cardiovascular problems by around one-third. For patients taking TNF inhibitors there were reductions in the numbers of heart attacks and strokes that would normally be expected, although no difference was seen for heart failure. Methotrexate was not associated with a significant reduction in the risk of having a stroke, but there was a trend towards fewer instances of heart failure. The review also found that corticosteroids and non-steroidal anti-inflammatory drugs increased the chance of having a cardiovascular problem, especially a stroke.

In patients with psoriasis or psoriatic arthritis the evidence was more limited as only six studies in these patients were included, so it was harder to draw conclusions. But the findings suggest that some of the medicines used to treat the symptoms of psoriasis/psoriatic arthritis might also reduce the chance of patients experiencing cardiovascular problems.

## ARE THESE FINDINGS NEW?

Yes – this is the first time anyone has performed a systematic review and meta-analysis to look at the association between certain medicines and cardiovascular risks in patients with rheumatoid arthritis, psoriasis or psoriatic arthritis. But there have been two previous systematic reviews[1 2] and two separate meta-analyses[3 4] that asked similar questions. These four reviews also found that TNF inhibitors and methotrexate may reduce the number of cardiovascular problems in patients with rheumatoid arthritis, but they did not look at corticosteroids or non-steroidal anti-inflammatory drugs, or at the effects in patients with psoriasis or psoriatic arthritis.

## HOW RELIABLE ARE THE FINDINGS?

There were some limitations in the review. The search included only articles written in English, and only one reviewer screened all the initial search results, so it is possible that some articles were excluded that would not have been by other people. The review also included only observational studies, not randomised clinical trials. These different types of studies have different rules for which patients are included and how they are treated and followed up. In general, randomised clinical trials are very strict because they are testing a certain question or medicine in a very precise way. A randomised clinical trial assigns patients by chance to separate groups.

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Using chance in this way means that the groups will be similar and will allow the variable or treatment under investigation to be compared objectively. Observational studies follow a set of normal patients and draw conclusions from them, but these patients have not been assigned to their treatments by chance, and not all groups will be similar. This means that the authors of this review can suggest that there might be an association between the medicines and the cardiovascular problems recorded, but because the studies were not randomised clinical trials they cannot say for sure that the medicines have caused the effect. Also, there are differences in some of the definitions and variables between some of the studies, which could mean that it is difficult to exactly compare the results.

There were only six studies included for psoriasis and psoriatic arthritis, which means the results for these diseases are less reliable than the ones for rheumatoid arthritis because the sample is smaller. This can affect how reliable we can say the statistics are for this group.

Some of the studies included looked at the effects of a medicine called rofecoxib – a non-steroidal anti-inflammatory drug which is no longer available for safety reasons. This may have affected the results for this group of medicines. But overall the authors are confident that this is a reliable review of the current knowledge that is available.

## WHAT DOES THIS MEAN FOR ME?

The authors say that using medicines that target inflammation in rheumatoid arthritis, psoriasis and psoriatic arthritis might also have a positive effect on the cardiovascular problems commonly found in these patients. In particular, TNF inhibitors and methotrexate may offer protection against heart attacks, heart failure and stroke in addition to their disease-modifying effects on the joint disease. Patients who are taking corticosteroids or non-steroidal anti-inflammatory drugs for their rheumatoid arthritis should be monitored closely by their doctor for signs of cardiovascular problems. The results of this study might mean that doctors will weigh the risks of prescribing corticosteroids or non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis against the benefit in terms of less joint inflammation, less pain and better function. Some doctors may consider prescribing TNF inhibitors or methotrexate instead of corticosteroids or non-steroidal anti-inflammatory drugs, although TNF inhibitors are usually only recommended in people who have already tried other treatments, or who aren't able to take other treatments. More studies will be needed to confirm these findings and for recommendations to be made to doctors.

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4 Micha R, *et al*. *Am J Cardiol* 2011;108:1362–70.

**The Effects of Tumor Necrosis Factor Inhibitors, Methotrexate, Non-steroidal Anti-inflammatory Drugs and Corticosteroids on Cardiovascular Events in Rheumatoid Arthritis, Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-Analysis.**

## SUPPLEMENTARY METHODS

Three themes were created using keywords and synonyms in titles and abstracts and using medical subject headings. These themes were "rheumatoid arthritis, psoriasis, psoriatic arthritis", "tumor necrosis factor-alpha inhibitors, disease-modifying anti-rheumatic drugs, methotrexate, corticosteroids, non-steroidal anti-inflammatory drugs, phototherapy" and "cardiovascular events, myocardial infarction, heart failure, strokes, major adverse cardiac events" (see MEDLINE and EMBASE strategies below for the complete list of search terms). These three themes were combined using the Boolean operator "AND" to identify studies reporting on cardiovascular events occurring in RA and in Pso/PsA patients treated with TNF inhibitors, methotrexate, non-biological DMARDs, NSAIDs and corticosteroids.

### MEDLINE strategy

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1 exp Arthritis, Psoriatic/ or psoriatic arthritis.mp. (5100)

2 psoriasis.mp. or Psoriasis/ (31437)

3 rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/ (113438)

4 1 or 2 or 3 (144090)

5 exp Tumor Necrosis Factors/ai [Antagonists & Inhibitors] (10341)

6 exp Receptors, Tumor Necrosis Factor/tu [Therapeutic Use] (2739)

7 infliximab.mp. (7800)

8 etanercept.mp. (3681)

9 alefacept.mp. (411)

10 adalimumab.mp. (2839)

11 certolizumab.mp. (372)

12 golimumab.mp. (209)

13 abatacept.mp. (2254)

14 tocilizumab.mp. (605)

15 rituximab.mp. (9965)

16 anakinra.mp. (680)

17 ustekinumab.mp. (274)

18 exp *Antirheumatic Agents/ (162197)

19 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (187185)

20 exp Methotrexate/ (30447)

21 leflunomide.mp. (1676)

22 exp Hydroxychloroquine/ (1772)

23 exp Sulfasalazine/ (3514)

24 exp Azathioprine/ (12771)

25 exp Cyclosporine/ (25246)

26 exp Cyclophosphamide/ (45276)

27 d-penicillamine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4258)

28 exp prednisone/ or exp prednisolone/ (73629)

29 exp etretinate/ or oral retinoids.mp. or exp acitretin/ (2170)

30 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (168106)

31 exp Anti-Inflammatory Agents, Non-Steroidal/ (147544)

32 aspirin like agents.mp. (3)

33 exp Naproxen/ (3194)

34 exp Ibuprofen/ (6273)

35 dexibuprofen.mp. (50)

36 dexketoprofen.mp. (103)

37 Flurbiprofen/ (1555)

38 exp Ketoprofen/ (2110)

39 aceclofenac.mp. (234)

40 exp Diclofenac/ (5556)

41 lornoxicam.mp. (252)

42 meloxicam.mp. (1248)

43 exp Piroxicam/ (2403)

44 tenoxicam.mp. (532)

45 exp Indomethacin/ (27977)

46 exp Sulindac/ (1204)

47 exp Tolmetin/ (1287)

48 exp Phenylbutazone/ (7291)

49 nabumeton.mp. (10)

50 exp Cyclooxygenase 2 Inhibitors/ or exp Cyclooxygenase Inhibitors/ (101648)

51 celecoxib.mp. (4406)

52 etoricoxib.mp. (471)

53 parecoxib.mp. (337)

54 rofecoxib.mp. (2504)

55 valdecoxib.mp. (464)

56 lumiracoxib.mp. (214)

57 exp Salicylic Acid/ (12957)

58 exp Aspirin/ (36708)

59 exp Diflunisal/ (424)

60 coxibs.mp. (680)

61 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (153788)

62 exp Phototherapy/ or exp photochemotherapy/ (25839)

63 cardiovascular risk.mp. (35723)

64 cardiovascular events.mp. (15894)

65 mace.mp. (2343)

66 cardiovascular death.mp. or Death, Sudden, Cardiac/ (12710)

67 exp Cardiovascular Diseases/ (1773930)

68 exp Heart Function Tests/ (436573)

69 exp Heart Failure/ (79987)

70 exp Heart Diseases/ (841789)

71 exp Atrial Fibrillation/ (30667)

72 exp Heart Valve Diseases/ (86311)

73 exp Ventricular Dysfunction/ (23497)

74 exp Venous Thromboembolism/ (3418)

75 exp Coronary Artery Disease/ (33029)

76 exp Myocardial Infarction/ (139655)

77 exp Myocardial Ischemia/ (338734)

78 exp Acute Coronary Syndrome/ (5799)

79 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 (1926146)

80 risk.mp. or exp Risk Assessment/ or exp Risk/ or exp Risk Factors/ (1429977)

81 79 and 80 (320879)

82 exp Atherosclerosis/ (18488)

83 exp Hyperlipidemias/ (53509)

84 exp Carotid Intima-Media Thickness/ (447)

85 exp Vascular Stiffness/ (435)

86 arterial compliance.mp. (1586)

87 vascular compliance.mp. (585)

88 pulse wave velocity.mp. or exp Blood Flow Velocity/ (52167)

89 flow mediated vasodilatation.mp. (281)

90 exp Blood Pressure/ (238677)

91 exp Diastole/de, ph [Drug Effects, Physiology] (4787)

92 exp Systole/de, ph [Drug Effects, Physiology] (4904)

93 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 (353104)

94 exp Stroke/ (74872)

95 exp Insulin Resistance/ or exp Obesity/ or exp Metabolic Syndrome X/ or exp Diabetes Mellitus, Type 2/ (219394)

96 exp Dyslipidemias/ (60192)

97 aptc.mp. (21)

98 94 or 95 or 96 or 97 (343338)

99 81 or 93 or 98 (861465)

100 19 or 30 or 61 or 62 (392863)

101 4 and 100 (31815)

102 99 and 101 (701)

**EMBASE strategy**

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1 exp *psoriatic arthritis/ (4458)

2 exp *psoriasis/ (31411)

3 exp *rheumatoid arthritis/ (94948)

4 1 or 2 or 3 (128708)

5 exp tumor necrosis factor inhibitor/ (2671)

6 exp tumor necrosis factor receptor/ (9433)

7 exp infliximab/ (23609)

8 exp etanercept/ (15062)

9 exp alefacept/ (1443)

10 exp adalimumab/ (10811)

11 exp certolizumab pegol/ (1981)

12 exp golimumab/ (1145)

13 exp abatacept/ (2993)

14 exp tocilizumab/ (1538)

15 exp rituximab/ (29973)

16 exp anakinra/ or exp recombinant interleukin 1 receptor blocking agent/ (3643)

17 exp ustekinumab/ (983)

18 exp *antirheumatic agent/ (139030)

19 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (194731)

20 exp methotrexate/ (119493)

21 exp leflunomide/ (6518)

22 exp hydroxychloroquine/ (12432)

23 Sulfasalazine.mp. or exp salazosulfapyridine/ (18514)

24 exp azathioprine/ (67472)

25 exp cyclosporin/ (59480)

26 exp cyclophosphamide/ (156302)

27 exp penicillamine/ (17156)

28 exp prednisone/ or exp prednisolone/ (204949)

29 exp etretinate/ or exp etretin/ or oral retinoids.mp. (7520)

30 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (442046)

31 exp nonsteroid antiinflammatory agent/ (408214)

32 aspirin like agents.mp. (4)

33 exp naproxen/ (20275)

34 exp ibuprofen/ (33667)

35 exp dexibuprofen/ (159)

36 exp dexketoprofen/ (301)

37 exp flurbiprofen/ (6228)

38 exp ketoprofen/ (9998)

39 exp aceclofenac/ (913)

40 exp diclofenac/ (26580)

41 exp lornoxicam/ (613)

42 exp meloxicam/ (3764)

43 exp piroxicam/ (9714)

44 exp tenoxicam/ (1750)

45 exp indometacin/ (69603)

46 exp sulindac/ (5953)

47 exp tolmetin/ (2580)

48 exp phenylbutazone/ (15231)

49 exp nabumetone/ (1739)

50 exp cyclooxygenase 2 inhibitor/ or Cyclooxygenase Inhibitors.mp. (36826)

51 exp celecoxib/ (14269)

52 exp etoricoxib/ (1790)

53 exp parecoxib/ (1257)

54 exp rofecoxib/ (9310)

55 exp valdecoxib/ (2245)

56 exp lumiracoxib/ (905)

57 exp salicylic acid/ (16731)

58 exp acetylsalicylic acid/ (147218)

59 exp diflunisal/ (2299)

60 coxibs.mp. (1052)

61 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (411638)

62 exp phototherapy/ or exp photochemotherapy/ (47577)

63 exp cardiovascular risk/ or exp coronary risk/ or exp cardiometabolic risk/ (106405)

64 cardiovascular events.mp. (23216)

65 mace.mp. (5545)

66 exp heart death/ or cardiovascular death.mp. (16882)

67 exp cardiovascular disease/ (2743085)

68 exp heart function test/ (24208)

69 exp heart failure/ (256711)

70 exp heart disease/ (1223961)

71 exp heart atrium fibrillation/ (64749)

72 exp valvular heart disease/ (106153)

73 ventricular dysfunction.mp. (16299)

74 exp venous thromboembolism/ (83292)

75 exp coronary artery disease/ (203950)

76 exp heart infarction/ (248189)

77 exp heart muscle ischemia/ (69941)

78 exp acute coronary syndrome/ (20524)

79 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 (2771936)

80 exp risk/ or exp risk factor/ or exp risk assessment/ or exp attributable risk/ (1256450)

81 79 and 80 (402770)

82 exp atherosclerosis/ (140183)

83 exp hyperlipidemia/ or exp dyslipidemia/ (123860)

84 exp arterial wall thickness/ or arterial stiffness/ (11260)

85 exp artery compliance/ or exp blood vessel compliance/ (6167)

86 pulse wave velocity.mp. or exp pulse wave/ (10756)

87 exp blood flow velocity/ (33989)

88 flow mediated vasodilatation.mp. (434)

89 exp blood pressure/ (362556)

90 exp diastole/ or exp systole/ (20052)

91 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 (635855)

92 exp cerebrovascular accident/ (44628)

93 exp metabolic syndrome X/ or exp obesity/ (245863)

94 exp diabetes mellitus/ or exp insulin resistance/ (560809)

95 aptc.mp. (29)

96 92 or 93 or 94 or 95 (764174)

97 81 or 91 or 96 (1510710)

98 19 or 30 or 61 or 62 (941301)

99 4 and 98 (44598)

100 97 and 99 (2598)

**Supplementary Table 1. Characteristics of studies included in systematic review and meta-analyses.**

| Study | Design | Treatment(s) | Comparator(s) | Measure | Outcomes | Subjects (N) | Outcomes (n) | Mean age (years) | Model adjustments[a] | Quality Assessment Scale[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rheumatoid arthritis** | | | | | | | | | | |
| Anandarajah et al. 2012 | CS<br>*CORONA* | CST | No CST | HR | MACE | 25,700 | NA | NA | 1,2,4,5,6 | 1-2-1 |
| Avina-Zubieta et al. 2011 | CS<br>*Population-based RA cohort (British Columbia)* | CST | No CST | HR | CVA and MI | 7051 | 178 | 58 | 1,2,3,5,6 | 4-2-2 |
| Avina-Zubieta et al. 2013 | CS<br>*Population-based RA cohort (British Columbia)* | CST | No CST | HR | MI | 8384 | 298 | 58 | 1,2,3,5,6 | 4-2-2 |
| Bernatsky et al. 2005 | NCC<br>*North American insurance claims databases (Protocare and PharMetrics)* | TNFi<br>DMARDs<br>MTX<br>Non-selective NSAIDs<br>COX-2 inhibitors | No DMARDs | Rate ratios | HF hospitalization | 41,885 | 570 | 67 | 1,2,3,5,6 | 4-2-2 |
| Bili et al. 2011 | CS | HCQ > 36 months | HCQ non-users | HR | CAD, REVPr | 1881 | 166 | NA | 1,2,4,5,6 | 4-2-2 |
| Bozaite-Gluosniene et al. 2011 | CS | MTX<br>TNFi | No MTX<br>No TNFi | HR | CAD, REVPr | 1829 | NA | 58 | 1,2,4,5,6 | 4-2-2 |
| Burmester et al. 2012 | RCTs<br>*ARMADA, DE019, PREMIER, and OPTIMA* | TNFi + MTX | MTX | HR | MACE<br>nfMI<br>nfSTK | 2447 | 15<br>9<br>4 | 53 | 1,2,3 | 4-2-2 |
| Carmona et al. 2007 | CS<br>*BIOBADASE, EMECAR* | TNFi | No TNFi | Rate ratios | IHD, HF, STK<br>HF<br>STK | 1578 | 86<br>33<br>17 | 60 | 7 | 3-0-2 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Choi et al. 2002 | CS<br>*Wichita Arthritis Center* | MTX | No MTX | HR | fCVD | 1240 | 84 | 57 | 1,2,4,5 | 4-2-3 |
| Davis et al. 2007 | CS<br>*Adult RA patients residing in Rochester, Minnesota* | CST (exposure >3 months)<br>CST (exposure ≤3 months) | No CST exposure | HR | MI, HF, fCVD | 603 | 232 | 58 | 1,2,4,5 | 4-2-2 |
| Dixon et al. 2007 | CS<br>*British Society for Rheumatology Biologics Register (BSRBR)* | TNFi | DMARDs | Ratio ratios | MI | 10,829 | 80 | 57 | 1,2,3,4 | 4-2-2 |
| Garner et al. 2010 | RCT<br>*VIGOR* | Rofecoxib | Naproxen | RR[c] | CVE<br>nfMI<br>STK | 8076 | 64<br>22<br>17 | 58 | 7 | 4-0-2 |
| Greenberg et al. 2011 | CS<br>*CORONA RA registry* | TNFi | Non-MTX nbDMARDs | HR | MACE<br>nfMI<br>nfSTK/TIA | 9783 | 88<br>26<br>45 | 58 | 1,2,3,4,6 | 4-2-2 |
| | | MTX | Non-MTX nbDMARDs | | MACE | | 88 | | | |
| | | Prednisone (1–7 mg/d)<br>Prednisone (≥7 mg/d) | No prednisone | | MACE<br><br>MACE | | 88<br><br>88 | | | |
| Innala et al. 2011 | CS<br>*Swedish Rheumatoid Arthritis Registry* | DMARDs within 3 months<br>Corticosteroids<br><br>COX-2 inhibitors | No DMARDs within 3 months<br>No Corticosteroids<br>No COX-2 inhibitors | HR | MI, CABG, STK/TIA | 442 | 48 | 55 | 1,2,4,5,6 | 4-2-3 |
| Jacobsson et al. 2005 | CS<br>*South Swedish Arthritis Treatment Group (SSATG) and a register of all* | TNFi | No TNFi | Rate ratios | CVD<br>HF<br>MI<br>STK | 983 | 98<br>12<br>39<br>19 | 58 | 1<br><br>7 | 3-0-2 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *known patients with RA in Malmö* | | | | | | | | | |
| Lindharsen et al. 2013 | CC | Any NSAID<br>Ibuprofen<br>Diclofenac<br>Etodolac<br>Celecoxib<br>Rofecoxib<br>Ketoprofen<br>Naproxen | No NSAIDs | HR | MI, STK, fCVD | 17,320 | NA | 59 | 7 | 2-0-2 |
| Listing et al. 2008 | CS<br>*German Biologics Register RABBIT* | TNFi | nbDMARDs | HR | HF | 4248 | 25 | 55 | 1,2,3,4,6 | 4-2-2 |
| Ljung et al.2012 (EULAR) | CS<br>*Swedish Biologics Register* | Any TNFi exposure | No TNFi exposure | HR | ACS | 9869 | 85 | 59 | 1,2,4 | 4-2-2 |
| Low et al.2012 (ACR) | CS<br>*BSRBR-RA* | TNFi | nbDMARDs | HR | Ischemic CVA | 14,913 | 130 | 57 | 1,2,3,4,5,6 | 4-2-2 |
| Lunt et al. 2010 | CS<br>*BSRBR-RA* | TNFi | nbDMARDs | HR | Cardiovascular death | 16,196 | 322 | 58 | 1,3,4 | 4-1-2 |
| Nadareishvili et al. 2008 | NCC<br>*National Data Bank for Rheumatic Diseases (NDB)* | TNFi<br>MTX<br>Rofecoxib<br>Celecoxib<br>Prednisone | No TNFi<br>No MTX<br>No rofecoxib<br>No celecoxib<br>No prednisone | RR[c] | STK | 832 | 41 | 69 | 3,4 | 4-0-1 |
| Setoguchi et al. 2008 | CS<br>*Medicare and drug benefit programs in 2 states (1994–2004)* | TNFi | MTX | HR | HF hospitalization | 3761 | NA | 74 | 1,2,3,4,5,6 | 4-2-2 |
| Solomon et al. 2012 | CS<br>*Four different US healthcare programs* | TNFi<br>Oral CST | nbDMARDs<br>No oral CST | HR | HF hospitalization | 20,243 | 195 | 56 | 1,2,3,4,5,6 | 4-2-2 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Suissa et al. 2006 | NCC *PharMetrics Patient-Centric Outcomes Database, a North American insurance claims database* | Current DMARDs<br>MTX<br>Leflunomide<br>Biologic agents<br>Other DMARDs<br>Current NSAIDs<br>Naproxen<br>Others<br>Current COX-2 inhibitors<br>Colecoxib<br>Rofecoxib<br>Current CST | No current DMARDs | Rate ratios | MI | 5580 | 558 | 54 | 1,2,3,5,6 | 4-2-2 |
| van Halm et al. 2006 | CC *Jan van Breemen Institute, Amsterdam, the Netherlands* | Only MTX ever | Never MTX, SSZ or HCQ | RR[c] | CVD | 613 | 72 | 63 | 1,2,4 | 4-2-2 |
| | | Prednisone ever | No prednisone | | | | | | | |
| Watson et al. 2002 | CC *General Practice Research Database (GPRD)- Britain* | Naproxen (current use)<br>Naproxen (past use) | No naproxen | HR | MI, SCD, STK | 3094 | 809 | NA | 1,2,3,5,6 | 4-2-2 |
| Wolfe et al. 2004 | CS *National Data Bank for Rheumatic Diseases, US* | TNFi | No TNFi | RR[c] | HF | 13,171 | 461 | 61 | 7 | 4-0-2 |
| Wolfe et al. 2008 | NCC | TNFi<br>MTX<br>Rofecoxib<br>Celecoxib<br>Prednisone | No TNFi<br>No MTX<br>No rofecoxib<br>No celecoxib<br>No prednisone | RR[c] | MI | 3974 | 198 | NZ | 2,3,4 | 4-2-2 |
| **Psoriatic arthritis and psoriasis** | | | | | | | | | | |
| Abuabara et al. 2011 | CS *Medical and pharmacy administrative* | Traditional systemics<br>Biologics | No traditional systemics<br>No biologics | HR | MI | 17,520 | 157 | 44 | 1,2 | 4-2-2 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *claims data from the UnitedHealth* | | | | | | | | | |
| Ahlehoff et al. 2012 | CS *Danish nationwide prospectively recorded registries* | Biologics MTX | Therapies other than biologics and MTX | HR | fCVD, MI, STK | 2400 | 54 | 51 | 1,2,3,5,6 | 4-2-2 |
| Chen et al. 2012 | CS *National Health Insurance Research Database* | MTX monotherapy | Other non-biological antipsoriatic drugs | HR | Hospitalization for new-onset IHD | 12,049 | 400 | 45 | 1,2 | 4-2-2 |
| Lan et al. 2012 | NCC *Population based RA using the Taiwanese National Health Insurance database* | MTX only Retinoid only | No MTX and no retinoid | HR | CVD | 171,780 | NA | NA | 7 | 4-0-2 |
| Prodonovich et al. 2005 | CS *Veterans Integrated Service Network (VISN)* | MTX | No MTX | RR[c] | Vascular diseases | 7615 | 1869 | 63 | 1,2,3,4 | 4-2-4 |
| Wu et al. 2012 | CS *Kaiser Permanente Southern California (KPSC)* | TNFi Oral agents/ phototherapy | Topical agents | HR | MI | 8845 | 221 | 53 | 1,2,3 | 4-2-2 |

Abbreviations: ACS=Acute coronary syndrome; CABG=Coronary artery bypass grafting, CAD=Coronary artery disease, CC=Case-control study, CeVD=Cerebrovascular disease, COX-2=Cyclooxygenase-2; CS=Cohort study, CST=Corticosteroids,

CVD=Cardiovascular disease (fCVD=Fatal cardiovascular disease), DMARDs= Disease-modifying anti-rheumatic drugs, HCQ=Hydroxychloroquine, HF=Heart failure, HR=Hazard ratio, IHD=Ischemic heart disease, MACE=Major adverse cardiac event; MI=Myocardial infarction (nfMI=non-fatal myocardial infarction), MTX=Methotrexate, NA=Not available; nbDMARDs=non-biologic disease-modifying anti-rheumatic drugs, NCC=Nested case-control study, NSAIDs=Nonsteroidal anti-inflammatory drugs, OR=Odds ratio, RCT=Randomized control trial, REVPr=Revascularization procedure, RR=Relative risk; SCD=Sudden coronary death, SSZ=Sulfasalazine, STK=Stroke (nfSKT=non-fatal stroke), TIA=Transient ischemic attack, TNFi=Tumor necrosis factor inhibitor.

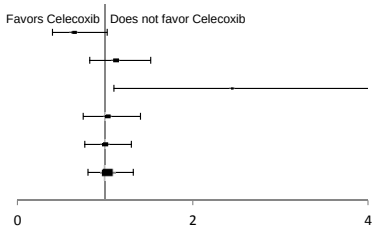
a. RR estimate adjusted for 1=Age and gender, 2=Cardiovascular risk factor(s), 3=History of CVD, 4=RA activity, 5=TNFi or DMARDs use, 6=Steroids or NSAIDs use, 7=Unadjusted and/or computed from available data.

b. Newcastle-Ottawa quality assessment scale.

c. Adjusted odds ratio converted to RR using the method of Zhang et al.[1]

1 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

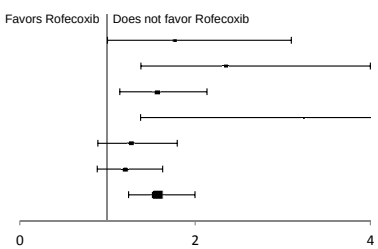
**(A) Celecoxib**




| | RR [95% CI] | Weight |
|---|---|---|
| **All CVE** | | |
| Bernatsky et al. 2005 | 0.64 [0.40, 1.02] | 16.3% |
| Lindharsen et al. 2012 | 1.12 [0.83, 1.52] | 24.6% |
| Nadareishvili et al. 2008 | 2.45 [1.10, 5.45] | 7.7% |
| Suissa et al. 2006 | 1.03 [0.75, 1.40] | 24.1% |
| Wolfe et al. 2008 | 1.00 [0.77, 1.30] | 27.3% |
| All | 1.03 [0.80, 1.32] | 100.0% |

*Heterogeneity: Tau² = 0.04; Chi² = 8.78, df = 4 (p = .07); I² = 54%*
*Test for overall effect: Z = 0.24 (p = .81)*

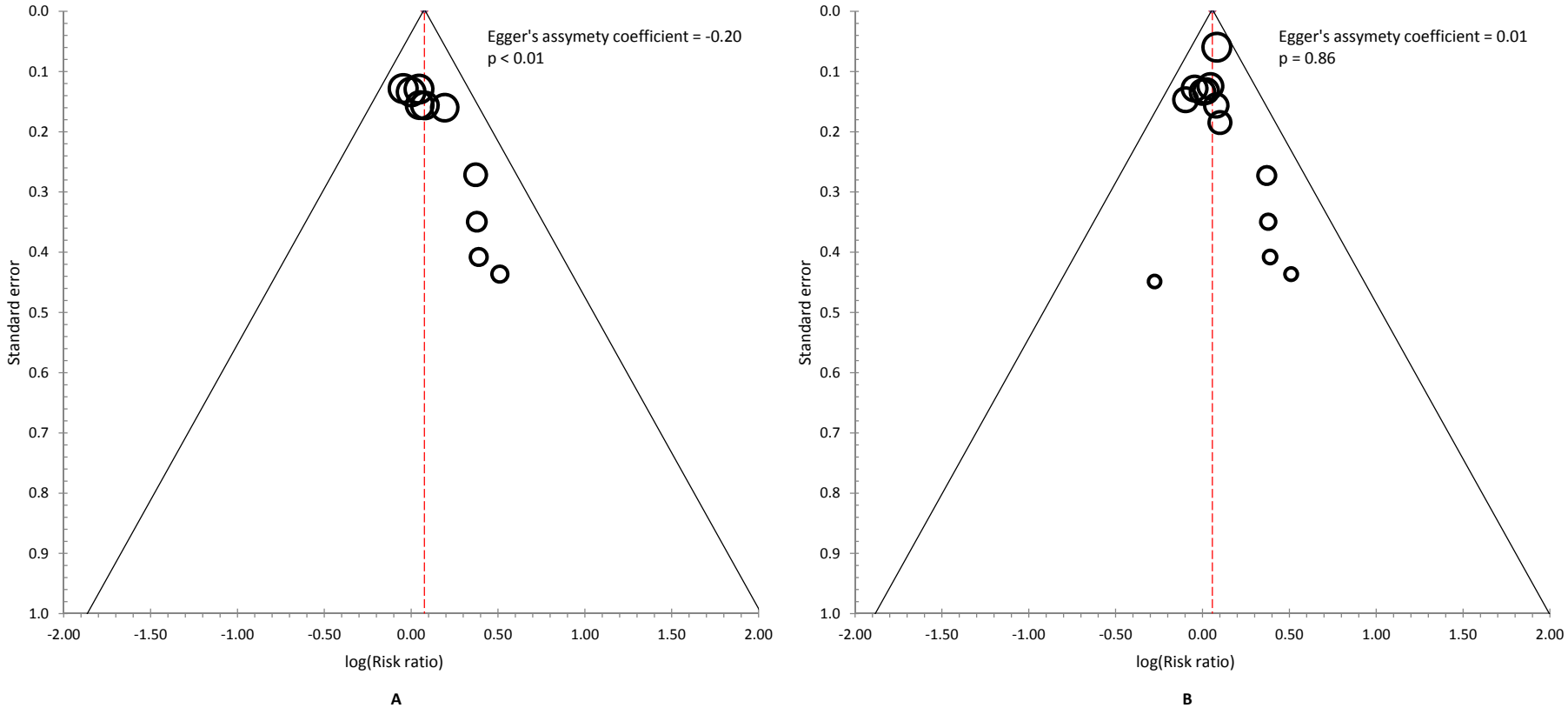
**(B) Rofecoxib**




| | RR [95% CI] | Weight |
|---|---|---|
| **All CVE** | | |
| Bernatsky et al. 2005 | 1.76 [1.00, 3.10] | 12.2% |
| Garner et al. 2010 | 2.35 [1.38, 4.00] | 13.2% |
| Lindharsen et al. 2012 | 1.56 [1.14, 2.13] | 23.3% |
| Nadareishvili et al. 2008 | 3.24 [1.38, 7.62] | 6.5% |
| Suissa et al. 2006 | 1.26 [0.89, 1.80] | 21.1% |
| Wolfe et al. 2008 | 1.20 [0.88, 1.63] | 23.7% |
| **All** | 1.58 [1.24, 2.00] | **100%** |

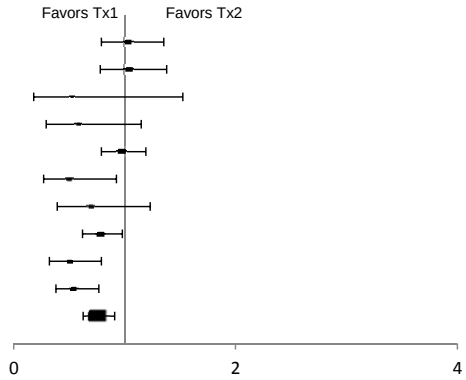
*Heterogeneity: Tau² = 0.04; Chi² = 9.17, df = 5 (p = .10); I² = 45%*
*Test for overall effect: Z = 3.74 (p < .001)*

Supplementary Figure 1. Meta-analyses of all cardiovascular events in rheumatoid arthritis patients treated with (A) celecoxib and (B) rofecoxib in controlled studies. Size of data markers indicates relative weight of the study (from random-effects analysis). CI = confidence interval; CVE = cardiovascular events; RR = relative risk.



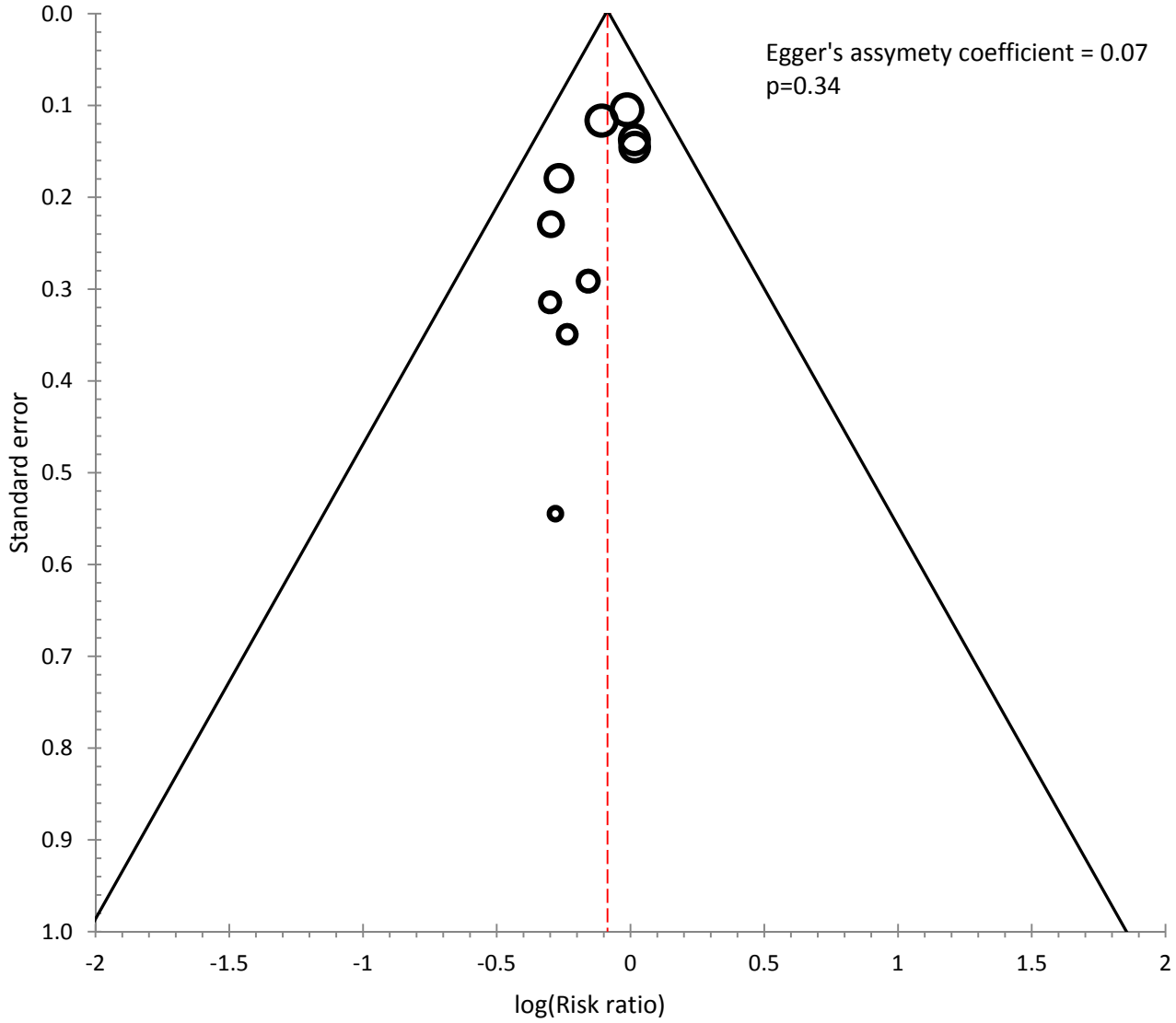

Supplementary Figure 2. Funnel-plots for the meta-analysis of occurrence of cardiovascular event (any) associated with treatment with (A) COX-2 non-steroidal anti-inflammatory drugs and (B) non COX-2 non-steroidal anti-inflammatory drugs in rheumatoid arthritis. In these graphs, the importance (weight) of each study is proportional to the marker size.

| Study | Compared trreatments (Tx1 vs. Tx2) | Endpoint | RR [95% CI] | Weight |
|---|---|---|---|---|
| Abuabara et al. 2011 | Traditional systemics vs. no traditional systemics | MI | 1.03 [0.79, 1.35] | 13.9% |
| Abuabara et al. 2011 | Biologics vs. no biologics | MI | 1.04 [0.78, 1.38] | 13.4% |
| Ahlehoff et al. 2012 | Biologics vs. therapies other than biologics or MTX | Fatal CVD, MI or stroke | 0.52 [0.18, 1.52] | 2.7% |
| Ahlehoff et al. 2012 | MTX vs. therapies other than biologics or MTX | Fatal CVD, MI or stroke | 0.58 [0.29, 1.15] | 5.4% |
| Chen et al. 2012 | MTX vs. other nonbiologic antipsoriatic drugs | Hospitalization for new-onset IHD | 0.97 [0.79, 1.19] | 15.8% |
| Lan et al. 2012 | MTX only vs. no MTX and no retinoid | CVE | 0.50 [0.27, 0.93] | 6.3% |
| Lan et al. 2012 | Retinoid only vs. no MTX and no retinoid | CVE | 0.70 [0.39, 1.23] | 6.9% |
| Prodanowich et al. 2005 | MTX vs. no MTX | Vascular diseases | 0.78 [0.62, 0.98] | 15.1% |
| Wu et al. 2012 | TNFi vs. topical agents | MI | 0.50 [0.32, 0.79] | 9.2% |
| Wu et al. 2012 | Oral agents/phototherapy vs. topical agents | MI | 0.54 [0.38, 0.77] | 11.5% |
| **All** | | | **0.75 [0.63, 0.91]** | **100.0%** |




*Heterogeneity: Tau² = 0.05; Chi² = 22.60, df = 9 (P = 0.007); I² = 60%*
*Test for overall effect: Z = 2.95 (P = 0.003)*

Supplementary Figure 3. Meta-analyses of all cardiovascular events in psoriasis and/or psoriatic arthritis patients treated with systemic therapy in controlled studies. Size of data markers indicates relative weight of the study (from random-effects analysis). CI = confidence interval; CVE = cardiovascular events; IHD = ischemic heart disease; MI = myocardial infarction; RR = relative risk.




Supplementary Figure 4. Funnel plots for the meta-analysis of occurrence of cardiovascular events associated with systemic treatment of psoriasis and/or psoriatic arthritis. In these graphs, the importance (weight) of each study is proportional to the marker size.