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Authors

Singh, Siddharth

Fumery, Mathurin

Singh, Abha

et al.

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Comparative Risk of Cardiovascular Events with Biologic and Synthetic Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis

Siddharth Singh, MD MS[1,2,*], **Mathurin Fumery, MD**[3,*], **Abha G. Singh, MD**[4], **Namrata Singh, MD MS**[5], **Larry J. Prokop, MLS**[6], **Parambir S. Dulai, MD**[1], **William J. Sandborn, MD**[1], **Jeffrey R. Curtis, MD MS MPH**[7]

[1]Division of Gastroenterology, University of California San Diego, La Jolla, California

[2]Division of Biomedical Informatics, University of California San Diego, La Jolla, California

[3]Gastroenterology Unit, Amiens University and Hospital, Université de Picardie Jules Verne, Amiens, France

[4]Division of Rheumatology, Allergy and Immunology, University of California San Diego, La Jolla, California

[5]Division of Rheumatology, Allergy and Immunology, University of Iowa Hospitals and Clinics, Iowa City, Iowa

[6]Department of Library Services, Mayo Clinic, Rochester, Minnesota

[7]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama

Abstract

Objective: We performed a systematic review and meta-analysis to evaluate the comparative effects of tumor necrosis factor-α inhibitors (TNFi), non-TNFi biologic and conventional synthetic

Corresponding author: Siddharth Singh, MD, MS, Assistant Professor of Medicine, Division of Gastroenterology and Division of Biomedical Informatics, University of California San Diego, 9452 Medical Center Dr., ACTRI 1W501, La Jolla, CA 92093, sis040@ucsd.edu, Phone: 858-246-2352, Fax: 858-657-7259.

Author Contribution:

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- Acquisition of data: SS, MF, AGS, LJP
- Analysis and interpretation of data: SS, MF, AGS, NS, PSD, JRC
- Drafting of the manuscript: SS
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*Co-first authors

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disease-modifying anti-rheumatic drugs (csDMARDs) on cardiovascular risk in rheumatoid arthritis (RA).

Methods: Through a systematic search through May 8, 2018, we included 14 observational studies in adults with RA treated with TNFi, non-TNFi biologics, tofacitinib or csDMARDs, reporting the risk of major adverse cardiovascular events (MACE) or stroke. Only studies reporting active comparators were included. We performed random effects meta-analysis and estimated odds ratios (OR) and 95% confidence interval (CI).

Results: As compared to TNFi, tocilizumab was associated with a decreased risk of MACE (OR, 0.59 [0.34-1.00]), whereas csDMARDs were associated with increased risk of MACE (csDMARDs, including methotrexate: OR, 1.45 [1.09-1.93]; without methotrexate: OR, 2.57 [1.32-5.00]), without heterogeneity (I^2=0%); there was no difference in risk of MACE between abatacept and TNFi (OR, 0.89 [0.71-1.11]), or between tocilizumab and abatacept (OR, 0.81 [0.57-1.16]). Based on 11 cohorts (n=135,053 patients), as compared to TNFi, csDMARDs were associated with increased risk of stroke (OR, 1.17 [1.01-1.36]); there was no difference in risk of stroke between different biologics (tocilizumab vs. TNFi: OR, 0.98 [0.59-1.61]; abatacept vs. TNFi: OR, 1.08 [0.86-1.34]; tocilizumab vs. abatacept: OR, 0.73 [0.39-1.38]), without heterogeneity (I^2=0%). No comparative studies on cardiovascular risk with tofacitinib were identified.

Conclusion: Based on meta-analysis, as compared to TNFi, tocilizumab may be associated with reduced risk of MACE, whereas csDMARDs may be associated with increased risk of MACE and stroke.

Keywords

Inflammation; cardiovascular risk; cerebrovascular events; biologics; disease-modifying therapy; arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is associated with increased risk of cardiovascular events and mortality, which is partly attributed to systemic inflammation that promotes premature atherosclerosis.(1) Treatment of RA using disease-modifying anti-rheumatic drugs (DMARDs), including conventional synthetic DMARDs (csDMARDs) as well as biologic agents, has been associated with decreased risk of cardiovascular events; in contrast, corticosteroids and non-steroidal anti-inflammatory drug (NSAIDs) use has been associated with increased risk.(2) This protective association with biologic therapies may be attributed to better disease control resulting in lower systemic inflammatory burden.

However, the comparative effect of different biologic and csDMARDs on cardiovascular risk has not been well studied. Most prior studies and meta-analyses have several inherent limitations: these studies have been non-comparative, evaluating exposure to specific medications vs. no treatment, or comparing exposure to a diverse and heterogeneous group of comparators; combined a variety of outcomes under the umbrella of a pooled cardiovascular event outcome; and have included studies that may not adequately adjust for important confounders including cardiovascular risk factors, RA disease activity and

concomitant medication use.(2–5) This has resulted in high heterogeneity in these analyses. Moreover, these meta-analyses have not evaluated the impact of non-tumor necrosis factor inhibitor (TNFi) biologics such as tocilizumab (interleukin [IL]-6 inhibitor) and abatacept (a selective inhibitor of T-cell co-stimulation), and targeted synthetic DMARDs (like tofacitinib) on cardiovascular risk. Clinical trials of tocilizumab suggest that it may increase low-density lipoprotein cholesterol (LDL);(6) however, the IL-6 pathway is central to atherogenesis, and its inhibition may decrease risk of cardiovascular events.(7, 8)

Hence, we evaluated the comparative effect of csDMARDs, non-TNFi biologic agents, targeted synthetic DMARDs (like tofacitinib), on the risk of major adverse cardiovascular events (MACE) and stroke, as compared to TNFi, in patients with RA. By focusing on comparative studies, using TNFi as a common reference, and evaluating major coronary and cerebrovascular accidents separately, we sought to minimize conceptual heterogeneity across studies to more optimally inform evidence.

METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was conducted following an *a priori* established protocol (available upon request).

Selection Criteria

We screened observational cohort (or nested case-control) studies that met the following inclusion criteria: (1) patients with RA, (2) treated with TNFi, non-TNFi biologics, targeted synthetic DMARDs (tofacitinib) or csDMARDs and (3) reporting risk of MACE (non-fatal myocardial infarction, need for coronary revascularization, and cardiovascular death, without or without angina, incident congestive heart failure [CHF], peripheral artery disease or abdominal aortic aneurysm) and/or acute cerebrovascular events (stroke/TIA). From these, only studies that reported comparative risk estimates with different medications were included, i.e., comparator group included patients treated with either csDMARDs, TNFi, or non-TNFi biologics. If studies reported results from multiple databases in same study, each database was treated as an independent cohort if feasible.

The following studies were excluded: (1) non-comparative studies (in which cardiovascular risk was reported in patients exposed vs. not exposed to medication of interest or to no treatment), (2) studies reporting only cardiovascular death outcome or only reporting on CHF or angina, and (3) studies performed in patients with other, non-RA, autoimmune diseases. Randomized controlled trials of different therapies specifically designed to study cardiovascular safety were discussed qualitatively.

Data Sources, Search Strategy and Study Selection

The search strategy was designed and conducted by an experienced medical librarian with input from study investigators, utilizing various databases from inception to May 8, 2018. Details of the search strategy are shown in the online supplement.

Data Abstraction and Risk of Bias Assessment

After study selection, two authors independently abstracted data on study and patient characteristics, exposure variables, outcomes, confounding variables and statistical analyses, using a standardized data abstraction form. Discrepancies between investigators for data abstraction and risk of bias assessment were resolved through carefully re-review of articles together, and if unresolved, in consultation with the senior investigator. The following data were collected from each study: (a) study characteristics: primary author, time period of study including period of recruitment and follow-up/year of publication, country of origin, study design (cohort vs. nested case-control; prospective vs. retrospective; new-user vs. prevalent user design; administrative claims databases vs. clinical registries), study duration (timing of outcome assessment), factors pertinent to risk of bias assessment; (b) patient characteristics: approach to identifying patients with RA, age, sex, smoking status, cardiovascular risk factors (diabetes, hypertension, hyperlipidemia), prior MACE or stroke/TIA, concomitant medications (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], statins); (c) exposure characteristics: classification of medication exposures (TNFi, non-TNFi biologics including abatacept, tocilizumab, rituximab, targeted synthetic DMARDs like tofacitinib and csDMARDs), whether patients could be included only once vs. multiple times with different exposures, timing of occurrence of event in relation to exposure ('on-treatment' [event occurs during active therapy with exposure], 'as-treated' [event occurring either on-treatment or within 1-3 month period after drug discontinuation] or 'ever-exposed' [event occurring any time after initiation of therapy, regardless of whether patient is on- or off-therapy at time of event), how medication exposures, outcome and covariates were ascertained; (d) outcomes studied: type and definition of outcomes, incident events; (e) potential confounding variables accounted for in analysis including RA disease activity (objectively or via surrogates), disease duration, cardiovascular risk factors including prior cardiovascular event, and use of RA- and cardiovascular medications; and (f) statistical approach: unadjusted and adjusted hazard ratio (HR), relative risk (RR) or odds ratio (OR) and 95% confidence intervals (CI), incidence rate of events in each exposure group, and methods to control for bias including use of propensity score methods and inclusion of time-varying covariates.

Risk of bias was assessed by 2 investigators independently, using the Quality In Prognosis Studies tool, which evaluates validity and bias in studies of prognostic factors across six domains: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting.(9)

Outcomes Assessed

The primary outcomes of interest were comparative risk of (1) MACE and (2) stroke/TIA in patients exposed to csDMARDs and non-TNFi biologics, using TNFi as reference medication (for ease of comparability). For the primary analysis, non-TNFi biologics were considered individually, including abatacept, tocilizumab and rituximab; similarly, csDMARDs including and excluding methotrexate were analyzed separately.

In order to evaluate stability of the association between different medications exposures and cardiovascular outcomes, and to examine potential sources of heterogeneity, we performed

several *a priori* subgroup analyses based on: adjustment for RA disease severity (studies adjusted for RA disease activity based on objective markers including disease activity indices or C-reactive protein vs. based on surrogate measures for disease severity/activity such as number of intra-articular procedures or orthopaedic surgeries vs. no adjustment), prior cardiovascular disease (only incident cardiovascular events vs. prior cardiovascular disease included); study design (nested case-control vs. cohort; retrospective vs. prospective; claims analysis vs. registry studies); geographic location (USA vs. outside USA); and analysis approach (propensity score-matched or -adjusted analysis vs. only multivariable analysis). We also performed meta-regression to assess whether effect estimates varied depending on the prevalence of diabetes, concomitant corticosteroids and concomitant NSAID use. For all subgroup analyses, grouped medication exposure categories were considered (non-TNFi biologics, csDMARDs and TNFi biologics). When different studies used the same databases but over different time periods with partial overlap, sensitivity analysis was performed after excluding overlapping cohorts.

Statistical Analysis

We used the random-effects model described by DerSimonian and Laird to calculate summary OR and 95% confidence intervals (CI).(10) Maximally adjusted OR, where reported in studies, was used for analysis to account for confounding variables. When studies used different effect estimates including hazard ratios, the summary estimate was considered equivalent to OR in our quantitative synthesis; when event rate is low as noted in this synthesis, hazard ratios approach ORs. To estimate what proportion of total variation across studies was due to heterogeneity rather than chance, an I^2 statistic was calculated.(11) An I^2 value of <30%, 30%−60%, 60%−75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively. Between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics (as described above). In this analysis, a p-value for differences between subgroups of <0.10 was considered statistically significant. Publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's regression test.(12) All analyses were performed using Comprehensive Meta-Analysis version 2.0 (Englewood, New Jersey).

RESULTS

From 9,488 unique studies identified using our search strategy, full text of 129 studies were reviewed in detail, and eventually 14 studies were included in the analysis.(13–26) Figure 1 shows the study selection flowsheet. Of these 14 studies, nine utilized administrative claims databases (using Medicare, Truven MarketScan, IMS PharMetrics, national Veterans' Administration, an Italian administrative health database from Lombardy, and a collaborative multi-database study including Medicaid Analytic Extract linked to Medicare, Tennessee Medicaid, two US states' Medicare, Kaiser Permanente); one utilized a large healthcare system (Geisinger health system), and four studies were based on large biologic registries (British Society for Rheumatology Biologics Register [BSRBR], Rheumatoid Arthritis: Observation of Biologic Therapy [RABBIT], Consortium of Rheumatology

Researchers of North America [CORRONA]). Articles excluded after full-text review (n=115) along with reasons for exclusion are listed in the online supplement.

Table 1 shows the study-level characteristics of included studies. All included studies adjusted for age, sex and key cardiovascular risk factors (diabetes, hypertension, hyperlipidemia) and prior history of cardiovascular disease; eight adjusted for smoking status. Five studies adjusted for RA disease activity objectively based on clinical disease activity indices or serum C-reactive protein, and seven adjusted for surrogates of RA disease activity (intra-articular procedures, orthopaedic surgeries). Twelve studies adjusted for concomitant RA-related medications, and twelve adjusted for use of cardiovascular medications including statins. Claims-based studies relied on validated international classification of diseases, version 9 (ICD-9) algorithms to identify patients with RA, generally including two outpatient codes or single inpatient ICD-9 code for RA, in combination with use of RA-related medications (eTable 1). Likewise, most administrative claims studies relied on validated claims-based diagnostic criteria for identification of patients with MACE and stroke/TIA during inpatient hospitalization; only two studies allowed outpatient diagnosis of coronary artery disease or cerebrovascular accidents (eTable 1). All registry-based studies verified physician-reported cardiovascular events, through an adjudication process reviewing medical records, using standardized criteria. All studies except one attributed outcomes to exposure only if they occured ‘on-treatment’ or within a short period of drug discontinuation. Overall, most included studies were at low risk of bias (eTable 2). Due to the limited number of studies for each comparison (<10), formal evaluation of publication bias was not performed, consistent with Cochrane recommendations.(27)

Table 2 shows key patient characteristics across studies. Across non-Medicare studies, mean age of participants ranged from 51 to 64y, whereas mean age of participants in Medicare studies ranged from 72 to 81y. Approximately 6-31% patients across studies were diabetic, except in one study where diabetics and non-diabetics were analysed separately. Across studies, median 34% (interquartile range, 30-60) were concomitantly on corticosteroids, and median 50% (interquartile range, 45-56) were concomitantly receiving NSAIDs.

Comparative Risk of Major Adverse Cardiovascular Events

Eleven studies (13 cohorts) estimated comparative risk of MACE with different interventions.(14–20, 22, 24–26) Four studies (seven cohorts) compared risk of MACE with non-TNFi biologics vs. TNFi (n=103,051 patients),(15, 16, 18, 24) and six studies (six cohorts) compared MACE risk with csDMARDs vs. TNFi (n=71,115 patients).(14, 19, 20, 22, 25, 26) No comparative studies on cardiovascular risk of tofacitinib were identified.

Non-TNFi biologics vs. TNFi: Exposure to tocilizumab (OR, 0.59 [0.34-1.00]; I^2=0%), but not to abatacept (OR, 0.89 [0.71-1.11]; I^2=44%), was associated with a lower risk of MACE as compared to TNFi (Figure 2A). After exclusion of Medicare cohorts in studies by Kim *et al.*(16) and Kang *et al*,(15) with cohorts partially overlapping with Zhang *et al*,(24) the observed associations were not statistically significant (tocilizumab vs. TNFi: OR, 0.56 [0.29-1.08]; abatacept vs. TNFi: OR, 0.98 [0.86-1.13]). Results were stable on subgroup analysis based on whether studies adjusted for RA disease activity, whether studies used

propensity-score adjusted methods, and by geographic location (Table 3). In contrast, the protective association between non-TNFi biologics vs. TNFi for modifying the risk of MACE was only observed in a subset of studies that included patients with prior coronary artery disease (six studies; OR, 0.73 [0.57-0.93]), but not in patients without history of coronary artery disease (one study; OR, 0.99 [0.85-1.15]). On meta-regression, prevalence of concomitant NSAID use (p=0.70), corticosteroid use (p=0.15) or diabetes (p=0.09) did not significantly alter effect estimates. There was no difference in the risk of MACE between tocilizumab vs. abatacept (4 cohorts; OR, 0.81 [0.57-1.16], I^2=4%).(17, 24) In a single study comparing the risk of MACE with rituximab vs. abatacept, no difference was observed (HR, 0.94 [0.75-1.17]).(24) csDMARDs vs. TNFi: Exposure to csDMARDs was associated with an increased risk of MACE, as compared to treatment with TNFi (OR, 1.58 [1.16-2.15], I^2=16%) (Figure 2B); these effects were seen in cohorts where methotrexate was included as csDMARD (OR, 1.45 [1.09-1.93]), or where it was excluded (OR, 2.57 [1.32-5.00]). Results were robust across subgroups (Table 3). On meta-regression, prevalence of concomitant NSAID use (p=0.16), corticosteroid use (p=0.77) or diabetes (p=0.82) did not significantly alter effect estimates. There was insufficient information to evaluate comparative risk of MACE between TNFi and csDMARDs, stratified by different dose of prednisone exposure.

Comparative Risk of Stroke/Transient Ischemic Attacks

Eight studies (11 cohorts) analysed comparative risk of stroke/TIA with different interventions (vs. TNFi as reference). Three studies (six cohorts) compared risk of stroke/TIA with non-TNFi biologics vs. TNFi (n=55,858 patients),(15, 16, 18) and five studies (five cohorts) compared stroke/TIA risk with csDMARDs vs. TNFi (n=79,195 patients).(13, 20, 21, 25, 26) No comparative studies on risk of stroke/TIA in patients treated with rituximab or tofacitinib were identified.

Non-TNFi biologics vs. TNFi: On meta-analysis, as compared to TNFi, there was no significant association between exposure to tocilizumab (OR, 0.98 (0.59-1.61); I^2=0%), or abatacept (OR, 1.08 [0.86-1.34]; I^2=0%) and risk of stroke/TIA (Figure 3A). Results were stable on multiple subgroup analyses (eTable 3). On meta-regression, prevalence of concomitant NSAID use (p=0.98), corticosteroid use (p=0.86) or diabetes (p=0.51) did not significantly alter effect estimate. There was no difference in the risk of stroke/TIA between tocilizumab vs. abatacept-treated patients (3 cohorts; OR, 0.73 (0.39-1.38), I^2=0%). No comparative studies on risk of stroke/TIA in patients treated with rituximab or tofacitinib were identified.

csDMARDs vs. TNFi: Exposure to csDMARDs was associated with an increased risk of stroke/TIA, as compared to treatment with TNFi (OR, 1.19 [1.03-1.38], I^2=0%) (Figure 3B); these effects were seen in cohorts where methotrexate was included as csDMARD (four studies; OR, 1.17 [1.01-1.36]), but was not statistically significant in the one study where methotrexate was excluded (OR, 2.27 [0.92-5.59]). Results were stable across subgroup analyses (eTable 3). On meta-regression, prevalence of concomitant NSAID use (p=0.61), corticosteroid use (p=0.82) or diabetes (p=0.85) did not significantly alter effect estimate.

DISCUSSION

In this systematic review and meta-analysis of 14 cohort studies on the comparative risk of cardiovascular events within csDMARDs, TNFi and non-TNFi biologics, in patients with RA, we made several key observations. First, tocilizumab, may be associated with lower risk of MACE as compared to TNFi. Risk of MACE with abatacept was similar to that observed with TNFi. Second, there was no difference in risk of stroke/TIA in TNFi- and tocilizumab- and abatacept-treated patients with RA. Third, TNFi had lower risk of MACE and stroke/TIA as compared to csDMARDs. These results were stable across multiple subgroup analyses, including adjustment for RA disease activity, cardiovascular risk factors, as well as studies that used propensity score-matched or -adjusted analysis. Prevalence of concomitant NSAID and corticosteroid use, and prevalence of diabetes in included cohorts, did not significantly impact summary estimates.

Several randomized clinical trials have demonstrated increase in LDL cholesterol levels in tocilizumab-treated patients with RA.(6) This has raised concerns whether tocilizumab may be associated with increased cardiovascular risk. However, our findings of a potentially protective association between tocilizumab use and risk of MACE are reassuring at the very least, suggesting the risk is no higher, and may be lower, than that associated with TNFi in patients with RA. IL-6 has been consistently associated with increased risk of atherosclerosis, with each standard deviation increase in log IL-6 leading to a 25% higher risk of future cardiovascular events.(8) IL-6 signalling has also been associated with plaque initiation and destabilization, microvascular flow dysfunction and adverse outcomes in the setting of acute ischemia.(7) Tocilizumab, by blocking the IL-6 receptor, may conceivably decrease risk of cardiovascular events. Alternatively, this potentially lower risk of cardiovascular events in tocilizumab-treated patients vs. patients treated with TNFi in observational studies, may be a result of unmeasured confounders, particularly confounding by indication. With increase in LDL cholesterol, providers and patients may be inherently hesitant to prescribe this medication over TNFi or other biologics in a subset of patients with RA at higher risk of cardiovascular events. However, comparisons between the baseline characteristics of tocilizumab vs. TNFi-treated patients in the included studies did not provide much empiric evidence that this channelling was occurring. More specifically, the prevalence of cardiovascular related risk factors was generally comparable in the tocilizumab- vs. TNFi-treated patients. Arguing against this explanation is results from a recently completed head-to-head ENTRACTE trial of 3080 patients with RA followed up to 4.9 years, designed to compare cardiovascular safety of tocilizumab and etanercept. In that randomized trial, the investigators observed no significant difference in risk of MACE between tocilizimab vs. etanercept (HR, 1.05 [0.77-1.43]).(28)

In our meta-analysis, we did not find any significant difference in risk of MACE with abatacept as compared to TNFi or to tocilizumab. In a prior study using Medicare data, Zhang and colleagues had observed a modestly lower risk of acute MI, but not a composite MACE endpoint, with abatacept as compared to TNFi.(24) It is probable that by decreasing systemic inflammation associated with RA, all effective biologic therapies may be expected to decrease cardiovascular risk in rheumatoid arthritis and other immune-mediated inflammatory diseases. In a Swedish cohort study based on 6592 person-year follow-up of

TNFi-treated patients. Ljung and colleagues observed that risk of acute coronary syndrome was 60% lower in patients with good clinical response to TNFi as compared to non-responders, and the risk in responders was comparable to the general population.(29)

No significant differences were found between different TNFi and non-TNFi-biologics and risk of stroke. The reason for this is unclear. It may be related to differences in pathophysiology of acute cardiac events vs. ischemic cerebrovascular events, wherein chronic inflammation related to immune-mediated diseases may be a stronger risk factor for the former, rather than the latter.

Our findings on comparative risk of MACE and stroke with TNFi vs. csDMARDs build upon previous meta-analyses on the topic. Prior meta-analyses have demonstrated that both TNFi and methotrexate are associated with decreased risk of cardiovascular events, whereas exposure to NSAIDs and corticosteroids is associated with increased risk of cardiovascular events in patients with RA.(2–5) However, these analyses have not compared cardiovascular risk with TNFi vs. csDMARDs. By limiting analyses to studies using an active comparator design, we observed that exposure to TNFi is associated with lower risk of MACE and stroke/TIA, as compared to csDMARDs (including methotrexate). This may be related to superior control of inflammation, and lower ongoing exposure to NSAIDs and corticosteroids, with biologic DMARDs.

The strengths of this systematic review include: (a) direct comparative assessment of cardiovascular risk with TNFi, non-TNFi biologics, tofacitinib and csDMARDs; (b) minimal heterogeneity across all analyses, through well-defined inclusion and exclusion criteria, carefully excluding studies where the exposure was compared to a diverse and heterogeneous group of comparators and a wide variety of outcomes were combined under an umbrella of cardiovascular events, and (c) multiple subgroup analyses and meta-regression confirmed the stability of findings, including those that adjusted for cardiovascular risk factors, RA disease activity and concomitant medication use.

There are several limitations in our study. First, the meta-analysis included only observational studies. As noted above, only a single randomized trial, ENTRACTE, has designed to compare cardiovascular safety of tocilizumab and etanercept.(28) Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for several covariates, it is not possible to eliminate the potential of residual confounding, especially with regard to factors that go into prescribing specific medications to patients through factors not easily captured via claims or registry-based analyses. Moreover, depending on geographic location and health insurance coverage, there are intrinsic barriers for access to different types of DMARDs that may potentially bias findings due to sequence of medication use. While this may limit interpretation of comparison between different biologics, it is unlikely to have impacted our findings regarding comparison of TNFi vs. csDMARDs. TNFi (and other biologics) are generally prescribed to patients with severe disease who have failed csDMARDs; these patients may intrinsically be at higher risk of cardiovascular events on the basis of a greater burden of systemic inflammation, yet we observed a lower risk of events with TNFi vs. csDMARDs. It is possible that in studies conducted in the United

States, in the absence of universal healthcare coverage, patients receiving TNFi may have higher socioeconomic status and better access to preventive health services than patients receiving csDMARDs; in this scenario, healthy user bias may potentially decrease risk of cardiovascular events in TNFi-treated patients. Second, there were subtle differences in the definition of exposures and outcomes. Though we restricted definition of MACE, studies were heterogeneous in terms of inclusion of patients with unstable or stable angina, CHF, etc. However, as noted above, there was minimal heterogeneity in our analysis, and results were stable on multiple subgroup analyses. Yet, there were other differences between studies that we could not adequately account for, such as duration of RA, concomitant medications, including dose of corticosteroids and use of NSAIDs. Third, we were unable to rule out the presence of a publication bias. With such a limited number of studies, statistical testing for publication bias assessment is not recommended. We tried to minimize the potential for this by carefully examining published abstracts, as well as reviewing clinical trial websites.

In conclusion, based on a meta-analysis, there does not appear to be a significant difference in the risk of MACE and stroke between non-TNFi and TNFi biologics in patients with RA. TNFi, and potentially by extension other non-TNFi biologics, are associated with a lower risk of cardiovascular events and stroke as compared to csDMARDs. This may be related to more effective control of systemic inflammation that may be the primary driver of premature atherosclerosis in patients with RA. Future clinical trials and prospective studies, particularly comparing different non-TNFi biologics and targeted synthetic DMARDs (for example, janus kinase inhibitors) are warranted to inform the comparative cardiovascular safety of different therapies in patients with RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovation

1. We performed a systematic review and meta-analysis of 14 cohort studies directly comparing risks of major adverse cardiovascular events (MACE) and stroke with different biologic and synthetic DMARDs in patients with rheumatoid arthritis
2. Tocilizumab may be associated with a lower risk of MACE as compared to tumor necrosis factor inhibitors (TNFi), whereas risk of MACE seems to be comparable for abatacept and TNFi
3. There is no significant difference in risk of stroke between different non-TNFi and TNFi
4. TNFi is associated with a significantly lower risk of MACE and stroke as compared to synthetic DMARDs

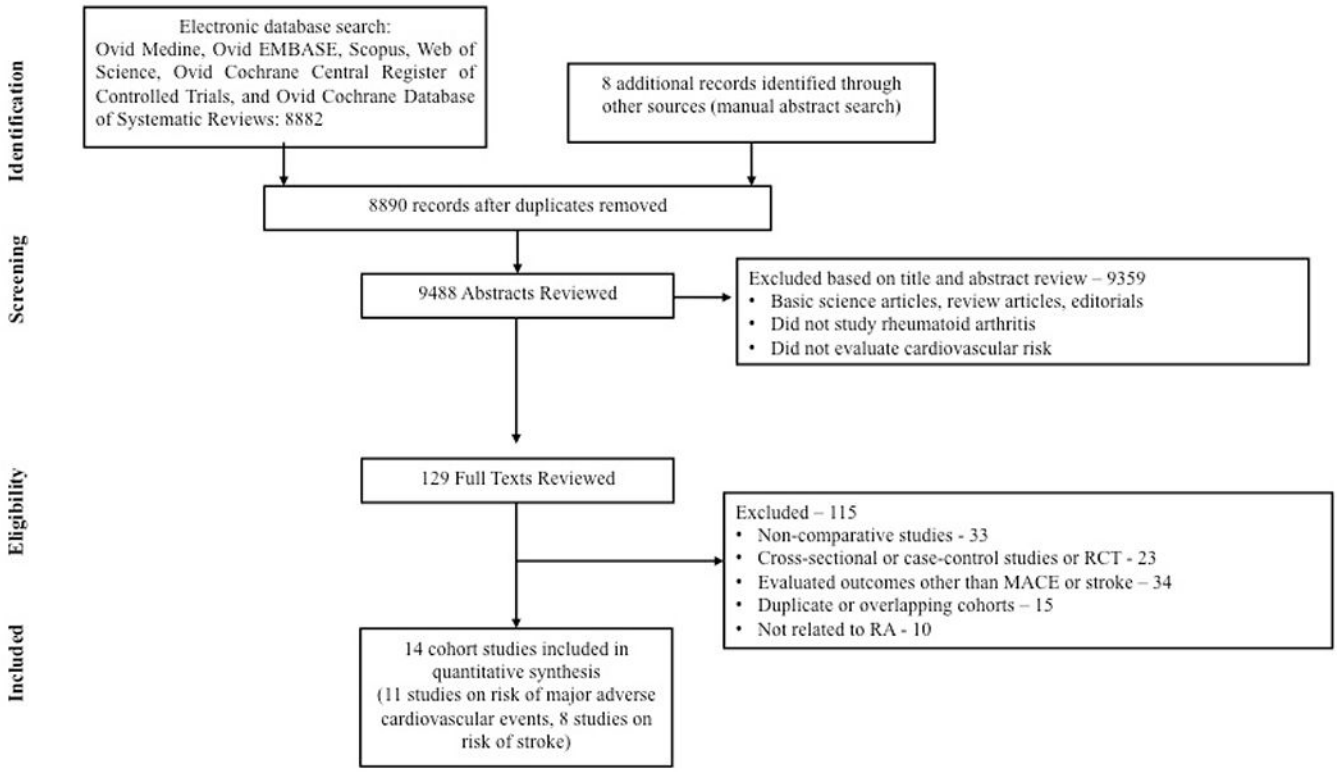

Figure 1.
Study selection flowsheet

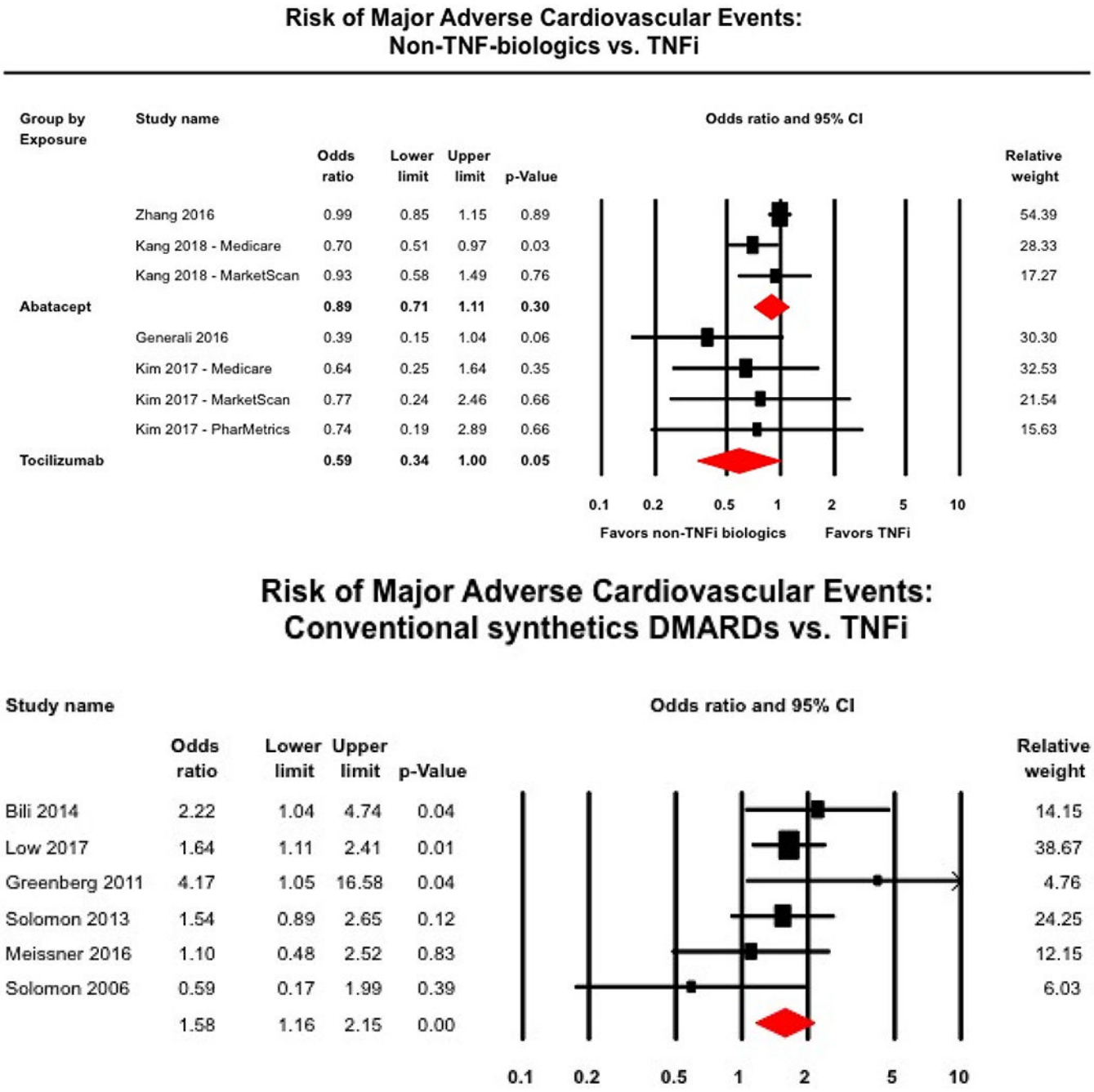

Figure 2.

Forest Plots – Comparison of risk of major adverse cardiovascular events in patients treated with (A) non-TNFi biologics vs. TNFi (I^2=0% for abatacept vs. TNFi, and 44% for tocilizumab vs. TNFi), and (B) csDMARDs vs. TNFi (I^2=16%)

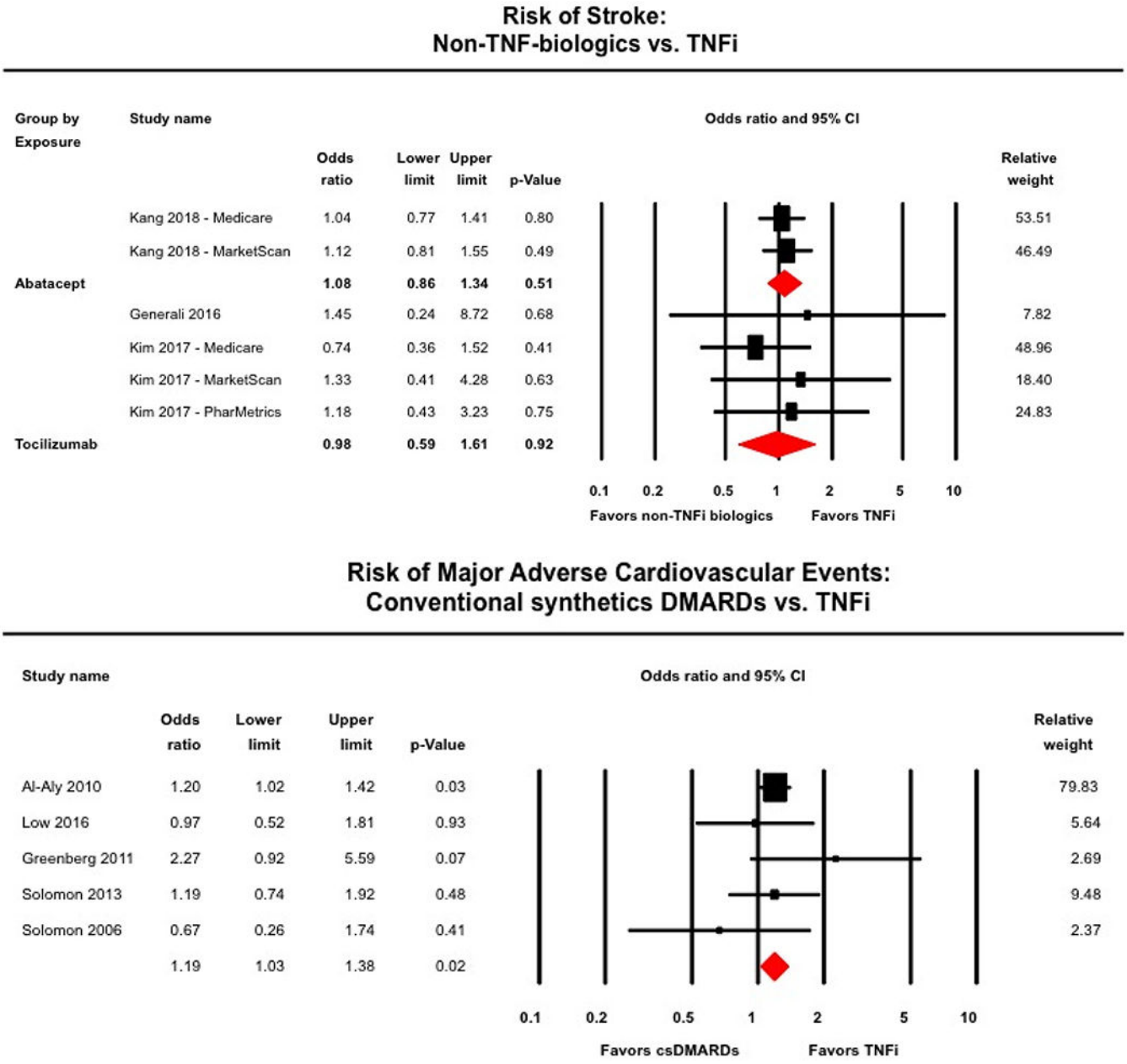

Figure 3.

Forest Plots – Comparison of risk of stroke/TIA in patients treated with (A) non-TNFi biologics vs. TNFi (I^2=0% for abatacept vs. TNFi, and 0% for tocilizumab vs. TNFi), and (B) csDMARDs vs. TNFi (I^2=0%)

Table 1.

Characteristics of studies included in the analysis

First author, Year, ref.	Location; setting; # patients	Study design	Time period, follow-up	Outcomes; # of events	Medications		Analytical approach	Variables adjusted for
					Exposure, #	Comparator, #		
Al-Aly, 2010(21)	USA; national VA; 20,811	Retrospective cohort; new-user design in prevalent RA; multiple unidirectional exposures per patient	1998-2005; median 3.4y (IQR, 2.0-5.3), 75,329 p-y	CV event (composite of acute MI, stable or unstable angina, coronary artery disease, CHF, PAD, CVA), based on ICD-9 codes (N=9,121); 'On treatment' events	TNFi (n=3796, 9563 p-y); IR=23 per 100p-y	nbDMARDs (1-10), anakinra (n=19899, 65766 p-y); IR=18 per 100p-y	Cox-proportional hazard, with time-dependent exposure and covariates	1,2,4-8,10
Bili, 2014(22)	PA, USA; Geisinger health system; 2,101	Retrospective cohort; new-user design in incident RA; multiple unidirectional exposures per patient	2001-11; median 3.4y (IQR, 1.5-6.2)	Incident CV event (composite of CAD [MI, unstable angina, coronary revascularization], stroke/TIA, abdominal aortic aneurysm, PAD), based on ICD-9 codes (N= 82); 'As-treated' events	(E1) TNFi (n=1022, 2349 p-y), IR=1.1 per 100p-y; (E2) MTX (n=1698, 3193 p-y), IR=1.0 per 100p-y	nbDMARDs (2-5,11) (n=1131, 1627 p-y); IR=1.5 per 100p-y	Propensity score matched, cox proportional hazard, with medications as time-dependent covariates	1-6,9,11-14
Desai, 2014(23)	USA; 2 databases - MarketScan and Medicare; 10,316	Nested case-control of early RA; new-user design, with cases having CV event, age- and sex-matched with 12 CV event free- controls obtained through incidence density sampling	2007-10; at least 3 months, NR	Incident CV event (composite of acute MI, stable and unstable angina, CHF, chronic heart disease, stroke/TIA), based on ICD-9 codes (N= 279 cases vs. 3348 controls); 'As-treated' events	Ascertained within 90 days prior to CV event (or corresponding date in controls); 2 current exposures		Incident rate ratios, and multivariable logistic regression	1,2,4-8,10,13,14
					Current TNFi <90d prior to CV event (with or without nbDMARDs) (n=409)	Current nbDMARDs alone (1-11) (n=2582)		
Low, 2017(14)	UK; BSRBR-RA linked to Myocardial Ischaemia National Audit Project (MINAP); 14,258	Prospective linked cohort; new-user design in prevalent RA; single exposure per patient	2001-09, with follow-up through April 2010; median 3.5-4.1y, 65,973 p-y	Incident MI, reported to BSRBR-RA or MINAP, verified by American Heart Association/ European Society of Cardiology criteria for MI (N=252); 'As-treated' events	TNFi (n=11,200 55,636 p-y); IR=0.35 per 100p-y	nbDMARDs (including 1, others NR), (n=3058, 10,337 p-y); IR=0.56 per 100p-y	Propensity score adjusted, cox proportional hazard analysis	1-5,7-11,13,14
Low, 2016(13)	UK; BSRBR-RA; 14,913	Prospective cohort; new-user design in prevalent RA; single exposure per patient	2001-09, with follow-up through April 2010; median 3.9-5.6y, 73,199 p-y	Incident stroke, reported to BSRBR-RA, verified by World Health Organization criteria for stroke by two physicians (N=222); 'As-treated' events	TNFi (n=11,642 61,226 p-y); IR=1.73 per 100p-y	nbDMARDs (1-11), (n=3271, 11,973 p-y); IR=1.75 per 100p-y	Propensity score adjusted, cox proportional hazard analysis	1-5,7-11,13,14
Greenberg, 2011(20)	USA; CORRONA; 10,156	Prospective cohort; prevalent user design in prevalent RA; multiple exposures per patient	2001-06; median 1.9y, 17,233 p-y	CV event (composite of MI, stroke/TIA, CV-related death) reported by physicians (N=88); 'As-treated' events	(E1) TNFi (n=4684, 7837 p-y), IR=0.29 per 100p-y; (E2) MTX (n=4969, 7132 p-y), IR=0.67 per 100p-y	nbDMARDs (2-11) (n=1785, 2264 p-y); IR=0.75 per 100p-y	Cox proportional hazard analysis	1-7,9,13,14
Solomon, 2013(26)	USA; SABER including 4 databases: Medicaid Analytic Extract linked to Medicare, Tennessee Medicaid, two US states Medicare,	Retrospective cohort; new-user design in prevalent RA being treated with MTX; single unidirectional exposure per patient	1998-2007; 6-12 months	CV event (MI, stroke or coronary revascularization), based on ICD-9 codes	TNFi (n=11,587), IR=2.31 per 100p-y	nbDMARDs (2-4) (n=8656), IR=3.07 per 100p-y	Propensity score adjusted, cox proportional hazard analysis	1-8,10,13,14

First author, Year, ref.	Location; setting; # patients	Study design	Time period, follow-up	Outcomes; # of events	Medications		Analytical approach	Variables adjusted for
					Exposure, #	Comparator, #		
	Kaiser Permanente; 22,907							
Meissner, 2016(19)	Germany; RABBIT biologics register for RA; 11,285	Nested case-control of prevalent RA with failure of at least one nbDMARD; new-user design, with cases having CV event, age-, sex-, CV comorbidity and year of enrollment matched with CV event free-controls	2001-13; at least 6 months, NR	MI, based on chart review by local site investigators with central verification (including subset with on-site validation) (N=112 cases vs. 112 controls); 'As-treated' patients	(E1) TNFi (n=105); (E2) non-TNF bDMARDs (n=44)	(C) nbDMARDs (1-11) (n=56)	Multivariable logistic regression	1-7,9,14
Generali, 2018(18)	Lombardy, Italy; administrative health databases; 1752	Retrospective cohort; new-user design in prevalent RA being treated with ETN or TCZ; single unidirectional exposure per patient	2010-13; median NR, 2838 p-y	CV event (composite of acute MI, unstable angina, coronary artery disease, CHF, PAD, CVA), based on ICD-9 codes (N=58); 'As-treated' events	ETN (n=1086, 1835 p-y), IR=1.96 per 100p-y; 57.4% concomitantly on MTX	TCZ (n=666, 1003 p-y), IR=2.19 per 100p-y; 54.8% concomitantly on MTX	Cox proportional hazard analysis	1,2,4-7,11,13
Zhang, 2016(24)	USA; Medicare; 47,193	Retrospective cohort; new-user design in prevalent RA being initiated on biologic therapy; multiple exposures per patient	2006-12; mean 1.2±1.2y,75,834 p-y	Incident CV event (composite of MI, percutaneous coronary intervention, CABG), based on ICD-9 code algorithms (N=967); 'As-treated' events	(E1) TNFi (ADA, IFX, ETN, CZP, GLM) (n=37,942), IR range, 0.76-1.44 per 100p-y (E2) TCZ (n=3332), IR 0.81 per 100p-y (E3) RIT (n=7475), IR 1.34 per 100p-y	ABA (n=13,608), IR 1.37 per 100p-y	Cox proportional hazard analysis, stratified by number of prior biologic exposures	1-8,13,14
Solomon, 2006(25)	USA; Medicare of Pennsylvania; 10,408	Nested case-control of prevalent RA; new-user design, with cases having CV event, age-, sex-, CV comorbidity and year of enrollment matched with CV event free-controls	1998-2004; at least 12 months, NR	CV event (composite of MI and stroke in hospitalized patients), based on ICD-9 code algorithms (N=946 cases vs. 9460 controls), 'As-treated' patients	Biologics (TNFi, Anakinra) (n=494)	MTX monotherapy (n=1180)	Multivariable logistic regression	1,2,4-8,13,14
Kim, 2017(16)	USA; 3 databases – Medicare, PharMetrics, MarketScan; 28,028	Retrospective cohort; new-user design in prevalent RA being initiated on 2nd-line biologic therapy; single exposure per patient	Medicare (2010-13), PharMetrics (2011-14), MarketScan (2011-15); NR, 22,406 p-y	CV event (composite of MI and stroke in hospitalized patients), based on ICD-9 code algorithms (N=125), 'As-treated' patients	TNFi (n=18,810, 15,145 p-y), IR 0.59 per 100 p-y	TCZ (n=9218, 6901 p-y), IR 0.52 per 100 p-y	Propensity score matched, cox proportional hazard analysis	1,2,4-8,10,13,14
Kim, 2018(17)	USA; 3 databases – Medicare, PharMetrics, MarketScan; 20,922	Retrospective cohort; new-user design in prevalent RA being initiated on 2nd-line biologic therapy; single exposure per patient	Medicare (2010-13), PharMetrics (2011-14), MarketScan (2011-15); NR, 16,280 p-y	CV event (composite of MI and stroke in hospitalized patients), based on ICD-9 code algorithms (N=144), 'As-treated' patients	ABA (n=14,685, 11,684 p-y), IR 0.96 per 100 p-y	TCZ (n=6237, 4596 p-y), IR 0.70 per 100 p-y	Propensity score matched, cox proportional hazard analysis	1,2,4-8,10,13,14
Kang, 2018(15)	USA; 2 databases – Medicare, MarketScan; 26,078	Retrospective cohort; new-user design in prevalent RA; multiple exposures per patient	Medicare (2008-13), MarketScan (2006-15); NR	CV event (composite of MI, coronary revascularization, stroke/TIA), based on ICD-9 codes (N=632), 'As-treated' patients	ABA (n=13,039), IR 2.38 per 100 p-y (Medicare), 1.38 per 100 p-y (MarketScan)	TNFi (13,039), IR, 2.97 per 100 p-y (Medicare), 1.45 per 100 p-y (MarketScan)	Propensity score matched, cox proportional hazard analysis	1-8,13,14

[Abbreviations: ABA=Abatacept; ADA=Adalimumab; BSRBR-RA= British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; CABG=Coronary artery bypass graft; CORRONA=Consortium of Rheumatology Researchers of North America; CV=cardiovascular; CVA=cerebrovascular accident including stroke and transient ischemic attack; CHF=congestive heart failure; CZP=Certolizumab pegol; ETN=Etanercept; GLM=Golimumab; HCQ=hydroxychloroquine; IQR=inter-quartile range; IFX=Infliximab; IR=Incidence rate; MTX=methotrexate; nbDMARDs=non-biologic disease-modifying anti-rheumatic drugs; PA=Pennsylvania; PAD=peripheral arterial disease; p-y=person-years; RA=Rheumatoid arthritis; RABBIT=German biologics register Rheumatoid Arthritis: Observation of Biologic Therapy; RIT=Rituximab; SABER=The Safety Assessment of Biologic Therapy; SSZ=sulfasalazine; TCZ=Tocilizumab; TIA=Transient ischemic attack; TNFi=Tumor necrosis factor inhibitors; VA=Veterans Administration]

Exposures classified as: ‘As-treated’ = events on drug + up to 90 days after drug discontinuation, ‘on treatment’ = events on drug, ‘ever-exposed’ = events on drug. nbDMARDs includes 1=methotrexate, 2=hydroxycholorquine, 3=sulfasalazine, 4=leflunomide, 5=azathioprine, 6=auranofin, 7=injectable gold, 8=penicillamine, 9=cyclophosphamide, 10=cyclosporine, 11=minocycline

Covariates: 1=Age, 2=Sex, 3=Smoking status, 4=Diabetes mellitus, 5=hypertension, 6=hyperlipidemia and/or body mass index, 7=history of cardiovascular disease, peripheral artery disease and/or cerebrovascular disease, 8=Other non-cardiovascular comorbidities (chronic lung disease, severe kidney disease, hepatitis C, HIV, dementia), 9=RA disease severity using actual disease activity indices or biochemical markers, 10=RA disease severity based on surrogate measures (articular procedures such as orthopedic procedures or intra-articular injections), 11=RA duration, 12=rheumatoid factor and/or anti- cyclic citrullinated peptide antibodies, 13=RA-related Medications (NSAIDs, corticosteroids), 14=CV-related medications (statins, aspirin, anti-hypertensives, anti-diabetics)

Table 2.

Characteristics of patients included in the identified studies

First author, Year, ref.	Age, mean (SD), males (%)	Smoking, ever (%)	Diabetes mellitus (%)	Hypertension/ Hyperlipidemia (%)	Prior CAD or CVA (%)	Other medications		
						Prednisone (%)	NSAIDs/COX inhibitor (%)	Statins or other lipid-lowering agents (%)
Cohort studies (comparison of patients exposed to specific medications)								
Al-Aly, 2010(21)	E: 57±12; 91 C: 63±12; 91	NR	E: 31 C: 31	E: 68, 52 C: 68, 52	E: 38 C: 36	NR		
Bili, 2014(22)	TNFi (E1): 52±13; 28 MTX (E2): 56±14; 27 nbDMARDs (C): 57±14; 25	E1: 42 E2: 41 C: 41	E1: 18 E2: 17 C: 21	E1: 38, 34 E2: 35, 35 C: 40, 38	E1: 0 E2: 0 C: 0	E1: 94 E2: 92 C: 90	E1: 79 E2: 76 C: 81	E1: 30 E2: 34 C: 35
Low, 2017(14)	E: 56±12; 22 C: 60±13; 25	E: 59 C: 62	E: 6 C: 6	E: 28, NR C: 30, NR	E: 0 C: 0	E: 44 C: 22	E: 63 C: 56	E: 5 C: 9
Low, 2016(13)	E: 56±12; 23 C: 60±12; 26	E: 60 C: 63	E: 6 C: 7	E: 30, NR C: 31, NR	E: 0 C: 0	E: 44 C: 22	E: 63 C: 55	E: 7 C: 13
Greenberg, 2011(20)	TNFi (E1): 56±15; 23 MTX (E2): 59±15; 83 nbDMARDs (C): 59±14; 25	E1: 16 E2: 15 C: 17	E1: 6 E2: 6 C: 5	E1: 22, 9 E2: 24, 10 C: 24, 10	E1: 5 E2: 5 C: 6	E1: 39 E2: 39 C: 37	E1: 52 E2: 50 C: 52	NR
Solomon, 2013(26)	E: 55±14; 13 C: 56±14; 14	NR	E: 24 C: 23	E: 42, 52 C: 42, 54	E: 2/2 C: 2/2	E: 81 C: 79	E: 84 C: 85	E: 23 C: 23
Generali, 2018(18)	E: 55±13; 29 C: 57±13; 18	NR	E: 9 C: 8	E: 17, 16 C: 19, 19	E: 6 C: 9	E: 59 C: 72	E: 64 C: 73	NR
Zhang, 2016(24)	IFX (E1): 66, 17 TCZ (E2): 64, 16 RIT (E3): 65, 13 ABA (C): 66, 13	NR	E1: 14 E2: 14 E3: 15 C: 14	E1: 30, 23 E2: 28, 24 E3: 30, 22 C: 30, 22	E1: 0 E2: 0 E3: 0 C: 0	E1: 60 E2: 61 E3: 67 C: 61	E1: 53 E2: 46 E3: 45 C: 47	E1: 30 E2: 27 E3: 25 C: 28
Kim, 2017; (16) Medicare	E: 72±6; 15 C: 72±6; 15	NR	E: 31 C: 30	E: 84, 66 C: 84, 67	E: 8, 3 C: 7, 3	E: 32 C: 33	E: 45 C: 44	E: 44 C: 45
PharMetrics	E: 51±12; 19 C: 51±12; 18		E: 14 C: 14	E: 49, 35 C: 50, 36	E: 2, 1 C: 2, 1	E: 32 C: 33	E: 51 C: 50	E: 20 C: 21
MarketScan	E: 53±12; 18 C: 53±13; 17		E: 15 C: 16	E: 46, 33 C: 48, 34	E: 2, 1 C: 2, 1	E: 30 C: 31	E: 50 C: 49	E: 23 C: 22
Kim, 2018; (17) - Medicare	E: 72±6; 17 C: 72±6; 17	NR	E: 30 C: 30	E: 83, 68 C: 83, 69	E: 8, 3 C: 8, 3	E: 34 C: 35	E: 44 C: 44	E: 45 C: 45
- PharMetrics	E: 51±12; 20 C: 51±12; 20		E: 14 C: 14	E: 49, 35 C: 49, 36	E: 2, 1 C: 2, 1	E: 33 C: 33	E: 49 C: 48	E: 19 C: 19

First author, Year, ref.	Age, mean (SD), males (%)	Smoking, ever (%)	Diabetes mellitus (%)	Hypertension/ Hyperlipidemia (%)	Prior CAD or CVA (%)	Other medications		
						Prednisone (%)	NSAIDs/COX inhibitor (%)	Statins or other lipid-lowering agents (%)
- MarketScan	E: 54±13; 18 C: 53±13; 19		E: 16 C: 16	E: 47, 34 C: 48, 35	E: 3, 1 C: 3, 1	E: 29 C: 29	E: 45 C: 45	E: 21 C: 21
Kang, 2018(15) - Medicare, DM	E: 74±6; 20 C: 73±6; 20	E: 17 C: 17	E: 100 C: 100	E: 90, 82 C: 91, 82	E: 44, 9 C: 43, 9	E: 30 C: 34	E: 52 C: 52	E: 58 C: 58
- Medicare, non-DM	E: 74±6; 15 C: 74±7; 16	E: 15 C: 14	E: 0 C: 0	E: 75, 63 C: 75, 63	E: 26, 7 C: 26, 6	E: 33 C: 35	E: 47 C: 48	E: 38 C: 37
- MarketScan, DM	E: 60±11; 20 C: 60±12; 21	E: 9 C: 9	E: 100 C: 100	E: 67, 56 C: 66, 54	E: 21, 4 C: 22, 4	E: 21 C: 21	E: 41 C: 42	E: 38 C: 39
- MarketScan, non-DM	E: 56±13; 17 C: 56±14; 18	E: 9 C: 9	E: 0 C: 0	E: 39, 28 C: 39, 29	E: 11, 3 C: 10, 2	E: 23 C: 20	E: 38 C: 39	E: 15 C: 15
Case-control studies (comparison of cases with CV events and controls without CV event)								
Desai, 2014(23)	CS: 64±12; 35 CR: 64±12; 35	NR	CS: 29 CR: 17	CS: 35, 59 CR: 35, 47	CS: 0 CR: 0	CS: 48 CR: 47	CS: 18 CR: 16	CS: 31 CR: 26
Meissner, 2016(19)	CS: 64±9; 43 CR: 64±9; 43	CS: 54 CR: 38	CS: 23 CR: 13	CS: 60, 17 CR: 61, 16	CS: 25 CR: 23	CS: 94 CR: 78	CS: 55 CR: 55	NR
Solomon, 2006(25)	CS: 81±6; 11 CR: 80±6; 8	NR	CS: 14 CR: 10	CS: 60, NR CR: 55, NR	CS: 10, 20 CR: 7, 12	NR	CS: 32 CR: 36	CS: 17 CR: 16

Abbreviations: C=Comparator; CAD=Coronary artery disease; CR=Control; CS=Case; CVA=Cerebrovascular accident; DM=Diabetes mellitus; E=Exposed; nbDMARDs=non-biologic disease-modifying anti-rheumatic drugs; NR=Not reported; TNFi=Tumor necrosis factor inhibitors;

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Table 3.

Subgroup analysis for comparison of non-TNFi biologics and csDMARDs vs. TNFi in modifying the risk of major adverse cardiovascular events in patients with rheumatoid arthritis

Exposures	Subgroup types (P-value for difference between subgroups)	Subgroups	# of cohorts	OR (95% CI)	I^2
Non-TNFi biologic DMARDs (vs. TNFi)	Adjusted for RA disease activity ($P_{interaction}$=0.63)	Assessed through surrogate measures	3	0.70 (0.37-1.33)	0
		Not assessed	4	0.83 (0.63-1.09)	55
	Included only patients with incident CVD ($P_{interaction}$=0.03)	Yes	1	0.99 (0.85-1.15)	0
		No	6	0.73 (0.57-0.93)	0
	Analysis involved propensity score methods ($P_{interaction}$=0.88)	Yes	2	0.71 (0.29-1.70)	71
		No	5	0.76 (0.59-0.97)	0
	Geographic location ($P_{interaction}$=0.09)	USA	6	0.92 (0.81-1.05)	0
		Outside USA	1	0.39 (0.15-1.04)	NA
csDMARDs (vs. TNFi)	Adjusted for RA disease activity ($P_{interaction}$=0.25)	Assessed using objective measures	4	1.72 (1.23-2.40)	6
		Not assessed	1	0.59 (0.17-1.99)	0
		Assessed through surrogate measures	1	1.54 (0.89-2.65)	0
	Included only patients with incident CVD ($P_{interaction}$=0.48)	Yes	2	1.74 (1.24-2.46)	0
		No	4	1.37 (0.77-2.42)	37
	Analysis involved propensity score methods ($P_{interaction}$=0.48)	Yes	2	1.74 (1.24-2.46)	0
		No	4	1.37 (0.77-2.42)	37
	Study design ($P_{interaction}$=0.17)	Cohort	3	1.84 (1.31-2.57)	0
		Nested case-control	3	1.24 (0.79-1.93)	6
	Database type ($P_{interaction}$=0.37)	Claims-based	2	1.12 (0.46-2.71)	50
		Clinical registries	4	1.72 (1.23-2.40)	6
	Geographic location ($P_{interaction}$=0.73)	USA	5	1.37 (0.83-2.27)	69
		Outside USA	2	1.53 (1.07-2.17)	0

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