The risk of cardiovascular events associated with disease-modifying antirheumatic drugs in rheumatoid arthritis

Gulsen Ozen[1], MD, Sofia Pedro[2], MS, Kaleb Michaud[1, 2], PhD

Affiliations:

[1]*University of Nebraska Medical Center, Omaha, NE*

[2]*FORWARD, The National Databank for Rheumatic Diseases, Wichita, KS*

Competing Interest: None to declare

Funding: Partial funding for this study came from Pfizer through the ASPIRE competitive grant program – no one from Pfizer had input on the final manuscript. Dr. Michaud received additional research grant funding from the Rheumatology Research Foundation.

Address correspondence and requests to: Kaleb Michaud, 986270 Nebraska Medical Center, Omaha, NE 68198. kmichaud@unmc.edu

Running title: Risk of cardiovascular disease in RA with DMARDs

Keywords: rheumatoid arthritis, cardiovascular, DMARDs, biologics, cohort study

Word count: 3530

ABSTRACT/Word count: 241

Objective: To examine the comparative effects of biologic disease-modifying antirheumatic drugs (bDMARDs) and tofacitinib against conventional synthetic (cs) DMARDs on incident cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA).

Methods: RA patients with ≥1-year participation in FORWARD from 1998 through 2017 were assessed for incident composite CVD events (myocardial infarction, stroke, heart failure and CVD-related death validated from hospital/death records). DMARDs were categorized into 7 mutually exclusive groups: (1) csDMARDs-referent (2) TNFi (3) Abatacept (4) Rituximab (5) Tocilizumab (6) Anakinra (7) Tofacitinib. Glucocorticoids were assessed using a weighted cumulative exposure (WCE) model which combines information about duration, intensity, and timing of exposure into a summary measure by using the weighted sum of past oral doses (prednisolone equivalent). Cox proportional hazard models were used to adjust for confounders.

Results: During median (IQR) 4.0 (1.7-8.0) years of follow-up, 1,801 CVD events were identified in 18,754 RA patients. The adjusted model showed CVD risk reduction with TNFi (HR 0.82 [95% CI 0.72-0.94]) and abatacept (HR 0.50 [95% CI 0.30-0.83]) compared to csDMARDs. While higher glucocorticoid exposure as WCE was associated with CVD risk increase (HR 1.15 [95% CI 1.11-1.19]), methotrexate use was associated with CVD risk reduction (use vs. non-use: HR 0.82 [95% CI 0.74-0.90] and high-dose[>15mg/week] vs. low-dose[≤15mg/week]: HR 0.83 [95% CI 0.70-0.99]).

Conclusions: Abatacept and TNFi were associated with decreased risk of CVD compared to csDMARDs. Minimizing glucocorticoid use and optimizing MTX dose may improve CV outcomes in patients with RA.

INTRODUCTION

Cardiovascular disease (CVD) represents the leading cause of death in RA, accounting for approximately 40% of excess mortality (1) which is also 50% higher in RA than the general population (2). This increased risk is driven by systemic inflammation along with traditional CV risk factors and genetics (3, 4). Supporting the role of inflammation on CVD risk, growing evidence suggests that high disease activity was associated with about 50% CVD risk increase in RA patients compared to low disease activity/remission (4, 5). Chronic inflammation, besides its direct vascular effects, is closely linked to development and progression of traditional CVD risk factors including insulin resistance and diabetes, and atherogenic dyslipidemia (6, 7). Based on these data, investigators have examined if the disease-modifying antirheumatic drugs (DMARDs), particularly biologic (b)DMARDs may reduce CVD events in RA patients by controlling the systemic inflammation.

The most studied DMARDs have been methotrexate (MTX), tumor necrosis factor-α inhibitors (TNFi) and glucocorticoids. A systematic review and meta-analysis of observational studies and clinical trials assessing the effects of MTX, TNFi and glucocorticoids on CVD events in RA patients showed a 28% risk reduction with MTX, 30% risk reduction with TNFi and 47% risk increase with glucocorticoids although some studies reported no CVD risk change with these medications (8). However, glucocorticoid associated CVD risk increase may be confounded by disease activity (9). For the non-TNFi bDMARDs, there are data showing favorable effects on surrogate markers of CVD (10, 11). However, only a few observational studies have compared the CVD risk across non-TNFi biologics (12-17). While the results from these studies were not consistent, some indicated a lower CVD risk with abatacept against TNFi and no CVD risk increase with tocilizumab against abatacept or TNFi (12-17).

A recent randomized controlled trial (RCT) testing the effect of canakinumab on the secondary prevention of CVD events in patients with previous myocardial infarction (MI) and high-sensitivity C-reactive protein ≥2mg/L showed 15% reduction in CVD (18). Although anakinra, another interleukin-1 antagonist is thought to be less efficacious than other approved bDMARDs in RA (19), it is unknown whether it exerts similar CVD protective effects as shown for canakinumab.

Lastly, most of our knowledge for tofacitinib comes from the long-term results from the integrated analysis of data from RCTs which showed low CVD event rates that were comparable with placebo (20, 21). However, observational studies including real-world patients are lacking.

With this background, there is still a need to better understand the comparative CVD risk among newer and more traditional DMARDs. In the present prospective cohort study, we sought to examine the comparative effects of bDMARDs and tofacitinib against conventional synthetic (cs) DMARDs on incident CVD in RA patients.

PATIENTS and METHODS

Patients were participants in FORWARD, the National Databank for Rheumatic Diseases longitudinal prospective observational study (22).We included adult patients with RA (age ≥18 years) and completed ≥2 semiannual questionnaires during the period January 1998 through December 2017.

The primary outcome of the study was a composite of incident nonfatal and fatal CV events: (1) MI; (2) stroke; (3) hospitalized heart failure (HF); (4) death from CVD. Possible MI, stroke, and HF were identified from study questionnaires, hospitalization/procedural records, physician reports, and death records. Previous studies from FORWARD showed that reports of CVD events were valid in more than 90% of cases (23). Only the events which were confirmed by medical reviews or death records were included. If hospital/death records were not available, patient's physician, the patient or family were contacted with a structured, protocolized interview designed to address the reported condition.

To identify and validate the CVD events, we used the following International Classification of Diseases, Ninth and Tenth Revision (ICD-9/10) codes: 410*, I21.* and I22.* for MI; 433*, 434* and I63.* for stroke; 428* and I50.* for HF. Any death with these codes was regarded as CVD-specific mortality. The first of any of these CVD events for a patient during follow-up was assessed. We did not include hemorrhagic cerebrovascular events or transient ischemic attacks as "stroke" due to difficulty in confirming the event and uncertainty of the underlying atherosclerotic process. The secondary outcomes were the individual CV endpoints of the primary outcome.

The study was approved by Ascension via Christie Hospitals Wichita Inc. (Institutional Review Board number: IRB00001674). Informed consent was obtained from all patients at the cohort entry.

Treatment exposure and follow-up

We assessed DMARD exposure in mutually exclusive, hierarchical categories: 1. csDMARDs (MTX, sulfasalazine, hydroxychloroquine and leflunomide) (reference), 2. TNFi (infliximab, adalimumab, etanercept, golimumab, certolizumab), 3. Abatacept, 4. Rituximab, 5. Tocilizumab, 6. Anakinra and 7. Tofacitinib (7). This DMARD variable was time-varying and allowed patients to contribute to different DMARD groups throughout the follow-up. MTX was also evaluated separately as an independent treatment exposure.

For the assessment of glucocorticoid exposure, we used a weighted cumulative exposure model (WCE-prednisone) which combines information about duration, intensity, and timing of exposure into a summary measure by using the weighted sum of past oral doses (prednisolone equivalent). The weights assigned to past doses were estimated using a flexible cubic spline-based method (24, 25). The time window which past glucocorticoid exposure affects the current risk of the outcome was determined based on the methodology applied by Mohavedi et al. for diabetes risk (24). Details of the WCE model are described in the supplementary material.

The study follow-up started at the cohort entry and continued until the participant developed an outcome or was censored at death, loss to follow-up, or end of study period. CVD events were attributed to the corresponding DMARD group when the treatment was ongoing or discontinued ≤3 months before the CVD. The risk window after discontinuation of a DMARD was included in the follow-up period.

Covariables

Several confounder variables which were collected semiannually by study questionnaires were adjusted for in the analyses. These were age, gender, ethnicity, location of residence (rural vs. urban) (26), education level (years), employment (yes/no), insurance type (Medicare

vs. others), body mass index (BMI) in WHO categories (normal weight-reference), smoking (ever vs. never), rheumatic disease comorbidity index (RDCI) not including diabetes and hypertension (27), hypertension, diabetes, and chronic kidney disease, prior CVD, RA duration, Health Assessment Questionnaire (HAQ), pain and patient global scores (0-10), use of other drugs influencing the CVD risk (statins, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]), number of previous csDMARDs and bDMARDs, WCE-prednisone and calendar year. Patient activity scale (PAS) which is a patient-reported composite disease activity scale calculated by using HAQ, pain and patient global scores was also assessed in a separate model (28). We categorized disease activity as remission/low disease activity (PAS≤3.70) and moderate/high disease activity (PAS>3.70). All confounders and treatment exposures were time-varying.

Statistical analysis

Baseline characteristics of RA patients by the outcomes and DMARD use at the time of initiation were summarized by using descriptive statistics. CVD incidence rates were calculated by dividing the number of events per 1,000 patient-years of follow-up with 95% CI.

To examine the association between CVD risk and bDMARDs and tofacitinib, we constructed multivariable Cox proportional hazards models to adjust for confounders mentioned above. We determined the goodness of model fit using Akaike information criterion (AIC) (29).

In sensitivity analyses, as MTX has been shown to decrease CVD risk (30), we explored the association of bDMARDs and tofacitinib with CVD risk against MTX (reference: MTX ± other csDMARDs). Additionally, because the majority of the bDMARDs are more efficacious with MTX than bDMARD monotherapy, we tested if bDMARDs and tofacitinib with

concomitant MTX use conferred any CVD benefits over MTX. For this analysis, we selected the patients using MTX alone or in combination with any bDMARDs or tofacitinib. Also, in this subgroup analysis, we included MTX dose in the model as a binary variable (MTX dose >15mg/week: yes/no). We also separately analyzed individual TNFi against csDMARDs. Lastly, we performed the same analysis in patients without prior CVD.

Although WCE-prednisone has been shown to be superior to conventional glucocorticoid exposure assessment methods (dose, duration or combined variables) in the assessment of diabetes and serious infection risks in RA patients, it has not been used for the CVD risk assessment before. Therefore, we created a different model with dose-duration combined glucocorticoid exposure variable to compare the model fit and the results of that with the WCE-prednisone model.

In order to prevent bias from removing observations due to missing data, unanswered covariates of completed questionnaires were replaced by using multiple imputation by chained equations to create imputed datasets for analyses (annual income had 4% missing, all other variables had < 1% missing). For nonconsecutive observations (8%), the last observation was carried forward. All *P* values were two-sided, conducted at a significance level of 0.05. All statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 18,754 RA patients were followed for a median (IQR) of 4.0 (1.7-8.0) years and 94,781 patient-years. The study population was predominantly female (79.4%) and white (93.7%), mean (SD) age was 58.6 (13.3) years, and disease duration was 14.2 (12.7) years. Patients who developed CVD were older and more likely to be male, had longer disease duration, higher HAQ, disease activity by PAS, and RDCI scores, and more frequent prior CVD, diabetes, and hypertension and glucocorticoid use (Table 1). The use of other DMARDs was not different in patients who did and did not develop CVD. Baseline characteristics of RA patients by medication use are shown in supplementary Table 1S.

During the study period, we identified 1,801 composite CVD events yielding an incidence rate of 1.78 (1.69-1.87) per 1,000 patient-years. The incidence rates were slightly higher in glucocorticoid and anakinra users and slightly lower in abatacept and tofacitinib users compared to the other DMARD groups (Table 2). The incidence rates for the individual TNFi and individual CVD events are shown in Tables 2 and 3.

The fully adjusted model for the composite CVD events showed that TNFi, HR 0.81 (95%CI 0.71, 0.93), and abatacept, HR 0.50 (95% CI 0.30-0.83) were associated with a significant CVD risk reduction compared to csDMARDs. The other bDMARDs and tofacitinib were not associated with any CVD risk alteration against csDMARDs (Table 2). About 80% of the non-TNFi bDMARD users were exposed to TNFi priorly. When patients with prior TNFi use were excluded, the risk with non-TNFi remained similar but wider CIs (Abatacept HR 0.46 [95% CI 0.15-1.43], data not shown for other bDMARDs). In the analysis of CVD risk with individual TNFi, we found that all TNFi except for certolizumab tended to decrease CVD risk against csDMARDs, but the risk reduction reached statistical significance with only infliximab, HR 0.81 (95% CI 0.71-0.93) and etanercept, HR 0.81 (95% CI 0.71-0.93) (Table 2). When patients with prior CVD excluded (839 CVD events), TNFi were again associated

with reduced CVD risk, HR 0.83 (95% CI 0.69-0.99). The risk reduction with abatacept was no longer statistically significant, HR 0.77 (95% CI 0.42-1.43), likely due to reduction in sample size and event number.

For the individual CVD outcomes, the fully adjusted models showed that TNFi were associated with a decreased risk of MI (HR 0.78 [95% CI 0.66-0.96]), stroke (HR 0.67 [95% CI 0.46-0.97]) and CVD-related death (HR 0.76 [95% CI 0.62-0.92]) compared to csDMARDs without any risk increase in HF (HR 0.87 [95% CI 0.73-1.03]). Abatacept was only associated with a decreased MI risk (HR 0.37 [95% CI 0.15-0.91] compared to csDMARDs with a tendency of lower risk of stroke (HR 0.53 [95% CI 0.17-1.73]) and CVD-related death (HR 0.44 [95% CI 0.20-1.00]) (Table 3). The other bDMARDs and tofacitinib again did not change individual CVD event risk compared to csDMARDs (Table 3).

We also assessed MTX use and its relationship with CVD risk in a separate model. We found that MTX use compared to non-use was associated with 18% reduction in CVD risk (HR 0.82 [95% CI 0.74-0.90]). Due to this protective effect, we changed the referent group from csDMARDs to MTX±other csDMARDs, and found that TNFi (HR 0.91 [95% CI 0.78-1.05]) and abatacept (HR 0.62 [95% CI 0.37-1.03]) again tended to decrease CVD risk, but the association was no longer statistically significant (Table 4). In analysis of the individual CVD outcomes with bDMARDs and tofacitinib against MTX treatment, TNFi were only associated with decreased MI risk (HR 0.85 [95% CI 0.66-0.96]) (Table 4).

In the subgroup analysis of patients using MTX, we observed no risk change with any bDMARD use in combination with MTX over MTX monotherapy (Figure 1). We also found that CVD risk was lower with MTX doses >15mg/week than lower doses (HR 0.83 [95% CI 0.70-0.99]) (adjusted for chronic kidney disease).

In analyzing the relationship between disease activity, glucocorticoid use and CVD risk, we found that high/moderate disease activity by PAS was associated with an 18% increase in CVD compared to remission/low disease activity (HR 1.18 [95% CI 1.06-1.32]). Similarly, higher glucocorticoid exposure as WCE of prednisone was associated with increased CVD risk (HR 1.15 [95% CI 1.11-1.19]). In the sensitivity analysis, we included a dose-duration combined categorical glucocorticoid variable to the model instead of WCE-prednisone. We observed an increasing trend of CVD risk as the dose and treatment duration of glucocorticoids increased (<7.5 mg/day for <3 months HR 0.90 [95% CI 0.40-2.01]; <7.5 mg/day for ≥3 months HR 1.11 [95% CI 0.99-1.25]; ≥7.5 mg/day for <3 months HR 1.18 [95% CI 0.63-2.20]; ≥7.5 mg/day for ≥3 months HR 1.47 [95% CI 1.26-1.71]). The results for the DMARDs were similar with the categorical glucocorticoid variable. However, the model fit was worse than the one with WCE-prednisone variable. Also, interaction analysis showed that concomitant use of glucocorticoids with DMARDs abated the protective of TNFi (HR 1.10 [95% CI 0.91-1.32]), abatacept (0.63 [95% CI 0.33-1.19]) and MTX (0.96 [95% CI 0.84-1.11]).

DISCUSSION

CVD is the major cause of death, healthcare utilization, and overall costs occurs earlier and at a greater rate in patients with RA than the general population (1, 2, 31). Systemic inflammation is one of the main drivers leading to increased CVD risk in RA patients. Thus, knowing how bDMARDs and targeted synthetic (ts) DMARDs influence CVD risk is important to be able to improve CV outcomes in RA patients. In this US-wide observational cohort study, we found that abatacept and TNFi (notably infliximab and etanercept) were associated with a reduced risk of composite CVD compared to csDMARDs, mostly non-MTX csDMARDs. Moreover, while glucocorticoid use was associated with an increase in CVD risk, MTX use was associated with an 18% CVD risk reduction which was more prominent in doses over 15mg/week. The risk reduction with bDMARDs mentioned above was not pronounced against MTX±other csDMARDs except for a reduced risk of MI with TNFi.

Despite the recent therapeutic advances, it is still not clear whether the new b/tsDMARDs reduce the incidence of CVD in patients with RA. Over the last two decades, a number of studies have examined the potential CVD benefits of these therapies in RA (13-17, 23, 32-34). The most studied DMARD, MTX has been repeatedly shown to be associated with a reduced risk of CVD events although some studies reported no CVD benefits (8, 23, 30). A systematic review and meta-analysis of RCTs and observational studies estimated the risk reduction with MTX as 28%, RR 0.72 (95% CI 0.57-0.91), in RA (8). Our results regarding the cardioprotective effects of MTX were consistent with the systematic review and meta-analysis. Moreover, our study is the first to assess the dose-effect of MTX for CVD risk. The doses over 15mg/week were associated with lower CVD than lower MTX doses which might be due to better disease activity control or direct vascular effect with higher doses. This is clinically important as MTX has been shown to be used in suboptimal doses in the US (35). Our findings

suggest that optimal use of MTX may reduce CVD risk besides well-known disease activity control.

Several publications have also suggested that TNFi might have beneficial effects on CVD (8, 23, 32-34, 36-38). The most significant risk reduction with TNFi was reported in studies comparing CVD risk with TNFi against non-MTX csDMARDs (HR ranged between 0.39 and 0.45) (32, 37). However, the studies comparing the risk against csDMARDs including MTX reported less significant CVD risk reduction with TNFi and some showed CVD risk reduction only in responders (34, 38). Consistent with our results, the above-mentioned systematic review and meta-analysis estimated a 30% CVD risk reduction with TNFi in patients with RA (RR 0.70, 95% CI 0.54-0.90), with protective associations specifically for MI (RR 0.59, 95% CI 0.36 to 0.97) and stroke (RR 0.57, 95% CI 0.35 to 0.92) (8). This risk reduction we observed with TNFi persisted for MI when we compared the risks with TNFi against MTX ± other csDMARDs. Interestingly, we observed that only infliximab and etanercept were associated with CVD risk reduction. It is likely that the reason for not finding a significant association with other TNFi was the relatively lower number of patients who were on these TNFi.

Data on CVD risk with other b/tsDMARDs has been limited. Favorable effects on surrogate markers of CVD have been reported with tofacitinib and rituximab (10, 11). Few observational studies have compared the CVD risk across these bDMARDs (12-17). Most of these studies used patients from administrative data (Medicare and Truven MarketScan). Although not consistent in all studies and for all CVD outcomes, some reported low CVD risk with abatacept compared to TNFi (12, 13, 17). However, this risk reduction with abatacept

against TNFi was only reported for Medicare patients (12, 13, 17). None of these studies compared CVD risk with bDMARDs against csDMARDs or MTX. In our analysis, although we found a CVD risk reduction with abatacept compared to csDMARDs, we did not observe any risk reduction with abatacept compared to TNFi (data not shown).

Regarding the other nonTNFi bDMARDs, four studies using administrative data reported inconsistent results (13-16). The multi-database cohort studies found similar CVD risk among patients starting tocilizumab and TNFi and abatacept (14, 15). But then, two other studies using Medicare and MarketScan data showed a lower composite CVD risk with tocilizumab compared to TNFi and abatacept (17, 18). The reason for these discordant results despite using similar datasets might be due to the differences in addressing confounders. Although we did not find any CVD risk change with tocilizumab, rituximab, and anakinra and tofacitinib against csDMARDs and among each other (data not shown), the numbers of patients who were on these nonTNFi bDMARDs and tofacitinib were low. Further pharmacovigilance studies of CVD risk with these DMARDs are needed.

Another noteworthy finding of our study is the CVD risk increase with glucocorticoid use. Although this has been shown in previous studies (23), our study employed a WCE model for glucocorticoids which considered the impact of dosage, duration, and timing of glucocorticoid use on the risk of CVD. This approach has been shown to be superior to conventional glucocorticoid exposure assessment in serious infection and diabetes risk in RA patients (24, 39), but has not been used for CVD risk assessment. We found the model fit to be better with WCE-prednisone than conventional glucocorticoid exposure variables. CVD risk increase with glucocorticoids can be attributed to cardiometabolic changes including increased risk of hypertension, diabetes, weight gain, and metabolic syndrome (7, 40, 41) as well as disease severity channeling.

Our study has some limitations. We included both prevalent and new users, and as an observational cohort, the patients were not randomly assigned to the assessed medications. Despite the inclusion of several CVD-related covariables in the analyses, channeling bias cannot be fully excluded, and there might be unmeasured factors. The number of CV events and accordingly incidence rates reported were lower than in previous observational studies, which may be due to the differences in study populations and the application of the strict validation process in FORWARD, which increases the accuracy of the events reported. Additionally, patients who are in better health may be more likely to participate in FORWARD than those who are frail and at higher risk of CVD. This participation bias can also explain the low incidence rates of the events, although this should not greatly impact the comparative results by treatment. Also, our smaller sample sizes for tocilizumab, anakinra, and tofacitinib limited us in drawing conclusions regarding their associated CVD risk. Lastly, traditional CV risk factors have gained more importance in CV outcomes of RA with the advent of new potent DMARDs and more aggressive treat to target approaches (42). About 50% of the CVD in RA can be explained by CVD risk factors (42). Although we adjusted for multiple traditional CV risk factors, we did not have data about how well-controlled these factors were such as A1c.

In conclusion, abatacept and TNFi (notably infliximab and etanercept) were associated with lower risk of composite CVD than csDMARDs whereas glucocorticoids were associated with increased risk. However, only TNFi were associated with decreased risk of CVD (specifically MI) compared to MTX. Despite reported similar efficacies of bDMARDs in RA, the difference in CVD benefits may be due to drug-specific mechanisms directly influencing atherosclerosis or metabolic changes. Besides disease activity control, MTX dose should be optimized (>15 mg/week), glucocorticoid use should be minimized, and lastly, traditional CVD risk factors should not be forgotten to improve CV outcomes in RA patients.

REFERENCES

1. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008;26:S35-61.

2. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524-9.

3. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015;11:390-400.

4. Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015;67:1449-55.

5. Curtis JR, Xie F, Chen L, Saag KG, Yun H, Muntner P. Biomarker-related risk for myocardial infarction and serious infections in patients with rheumatoid arthritis: a population-based study. Ann Rheum Dis 2018;77:386-92.

6. Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. Ann Rheum Dis 2014;73:1281-3.

7. Ozen G, Pedro S, Holmqvist ME, Avery M, Wolfe F, Michaud K. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. Ann Rheum Dis 2017;76:848-54.

8. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. 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. Ann Rheum Dis 2015;74:480-9.

9. van Sijl AM, Boers M, Voskuyl AE, Nurmohamed MT. Confounding by Indication Probably Distorts the Relationship between Steroid Use and Cardiovascular Disease in Rheumatoid Arthritis: Results from a Prospective Cohort Study. PLoS One 2014; 9: e87965.

10. Hsue PY, Scherzer R, Grunfeld C, Imboden J, Wu Y, Del Puerto G, et al. Depletion of B-cells with rituximab improves endothelial function and reduces inflammation among individuals with rheumatoid arthritis. J Am Heart Assoc 2014;3:e001267.

11. Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. J Rheumatol 2011;38:2169-71.

12. Jin Y, Kang EH, Brill G, Desai RJ, Kim SC. Cardiovascular (CV) Risk after Initiation of Abatacept versus TNF Inhibitors in Rheumatoid Arthritis Patients with and without Baseline CV Disease. J Rheumatol 2018;45:1240-8.

13. Kang EH, Jin Y, Brill G, Lewey J, Patorno E, Desai RJ, et al. Comparative Cardiovascular Risk of Abatacept and Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis With and Without Diabetes Mellitus: A Multidatabase Cohort Study. J Am Heart Assoc 2018;7. pii: e007393.

14. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. Arthritis Rheumatol 2017;69:1154-64.

15. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, et al. No difference in cardiovascular risk of tocilizumab versus abatacept for rheumatoid arthritis: A multi-database cohort study. Semin Arthritis Rheum 2018; 48:399-405.

16. Xie F, Yun H, Levitan EB, Muntner P, Curtis JR. Tocilizumab and the risk for cardiovascular disease: a direct comparison among biologic disease-modifying antirheumatic drugs for rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2019;71:1004-1018.

. Zhang J, Xie F, Yun H, Chen L, Muntner P, Levitan EB, et al. Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1813-8.

18. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119-31.

19. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev 2009:CD005121.

20. Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, Boy M, Zuckerman A, Soma K, et al. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. Semin Arthritis Rheum 2016;46:261-71.

21. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017;76:1253-62.

22. Michaud K. The National Data Bank for Rheumatic Diseases (NDB). Clin Exp Rheumatol 2016;34:S100-S1.

23. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: a cohort and nested case-control analysis. Arthritis Rheumatol 2008;58:2612-21.

24. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, et al. Risk of Incident Diabetes Mellitus Associated With the Dosage and Duration of Oral

Glucocorticoid Therapy in Patients With Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1089-98.

25. Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. Stat Med 2009;28:3437-53.

26. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/

27. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21:885-906.

28. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies, and clinical trials: the patient activity scale (PAS/PAS-II). J Rheumatol 2005;32:2410-5.

29. Akaike H. A new look at the statistical model identification. Automatic Control, IEEE Transactions on 1974;19:716-23.

30. Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 2010;49:295-307.

31. Han GM, Han XF. Comorbid conditions are associated with healthcare utilization, medical charges and mortality of patients with rheumatoid arthritis. Clin Rheumatol 2016;35:1483-92.

32. Bili A, Tang X, Pranesh S, Bozaite R, Morris SJ, Antohe JL, et al. Tumor necrosis factor alpha inhibitor use and decreased risk for incident coronary events in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66:355-63.

33. Ljung L, Askling J, Rantapaa-Dahlqvist S, Jacobsson L, Group AS. The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour necrosis factor inhibitors and the risk in the general population: a national cohort study. Arthritis Res Ther 2014;16:R127.

34. Solomon DH, Curtis JR, Saag KG, Lii J, Chen L, Harrold LR, et al. Cardiovascular risk in rheumatoid arthritis: comparing TNF-alpha blockade with nonbiologic DMARDs. Am J Med 2013;126:730 e9- e17.

35. Rohr MK, Mikuls TR, Cohen SB, Thorne JC, O'Dell JR. Underuse of Methotrexate in the Treatment of Rheumatoid Arthritis: A National Analysis of Prescribing Practices in the US. Arthritis Care Res (Hoboken) 2017;69:794-800.

36. Dixon WG, Symmons DP. What effects might anti-TNFalpha treatment be expected to have on cardiovascular morbidity and mortality in rheumatoid arthritis? A review of the role of TNFalpha in cardiovascular pathophysiology. Ann Rheum Dis 2007;66:1132-6..

37. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576-82.

38. Dixon WG, Watson KD, Lunt M, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre C, Silman AJ, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheumatol 2007;56:2905-12.

39. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis 2012;71:1128-33.

40. Baker JF, Sauer BC, Cannon GW, Teng CC, Michaud K, Ibrahim S, et al. Changes in Body Mass Related to the Initiation of Disease-Modifying Therapies in Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1818-27.

41. Wilson JC, Sarsour K, Gale S, Petho-Schramm A, Jick SS, Meier CR. Incidence and risk of glucocorticoid-associated adverse effects in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;71:498-511.

42. Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel PLCM, Gabriel SE, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis 2018; 77: 48–54.

Figure 1. The risk of cardiovascular disease in patients with rheumatoid arthritis with bDMARDs and tofacitinib a. Against csDMARDs; b. Against Methotrexate ± other csDMARDs; c. Against Methotrexate ± other csDMARDs when bDMARDs or tofacinitib were used concomitantly with methotrexate

bDMARDs= Biologic disease-modifying antirheumatic drugs; csDMARDs= Conventional disease-modifying antirheumatic drugs; MTX= Methotrexate; TNFi= Tumor necrosis factor-α inhibitors; HR= Hazard ratio; CI= Confidence interval

Table 1. Baseline characteristics of rheumatoid arthritis patients by incident cardiovascular disease*

Variables	RA patients who did not develop CVD N=16,953	RA patients who developed CVD N=1,801	P value
Age, years	57.5 (13.3)	67.5 (10.4)	<0.001
Female, %	80.6	70.4	<0.001
White, %	93.5	95.3	0.003
Medicare, %	41.7	68.1	<0.001
Disease duration, years	14.0 (12.5)	16.6 (13.3)	<0.001
BMI, kg/m^2	28.1 (6.7)	28.6 (7.0)	0.994
Obesity, %	32.2	34.1	0.137
RDCI (0-9)	1.6 (1.5)	2.2 (1.6)	<0.001
Ever-smoked, %	42.5	48.3	<0.001
Diabetes, %	8.2	16.4	<0.001
Hypertension, %	31.0	42.0	<0.001
Pulmonary disease, %	5.9	11.6	<0.001
Prior CVD , %	4.2	15.7	<0.001
HAQ disability (0-3)	1.1 (0.7)	1.2 (0.7)	<0.001
PAS (0-10)	3.6 (2.2)	4.0 (2.2)	<0.001
Glucocorticoid use, %	35.7	45.6	<0.001
MTX use, %	52.2	51.6	0.589
TNFi use, %	22.7	13.3	<0.001
Other b/tsDMARD use, %	3.6	1.1	<0.001
Number of prior bDMARDs, median (IQR)	0 (0-1)	0 (0-0)	<0.001

Number of prior csDMARDs, median (IQR)	2 (1-3)	2 (1-3)	0.111
NSAID use, %	61.0	59.4	0.205
Aspirin use, %	15.6	22.6	<0.001
Statin use, %	11.6	11.6	0.970

**Values are mean (SD) unless indicated otherwise.*

CVD= Cardiovascular disease; BMI= Body mass index; RDCI= Rheumatic Diseases Comorbidity Index; HAQ= Health Assessment Questionnaire; PAS=Patient Activity Scale; MTX= Methotrexate; TNFi= Tumor necrosis factor-α inhibitors; bDMARDs= Biologic disease-modifying antirehumatic drugs; tsDMARDs= Targeted synthetic disease-modifying antirheumatic drugs; csDMARDs= Conventional synthetic disease-modifying antirheumatic drugs; NSAID= Nonsteroidal anti-inflammatory drugs; IQR= Interquartile range

Table 2. Crude incidence rates and risk of composite cardiovascular disease events in patients with rheumatoid arthritis by DMARD treatment

	No. of events/exposure	Patient-years	Incidence rate (95% CI)*	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
All patients	1,801/18,754	94,781	1.78 (1.69-1.87)	-	-
Glucocorticoids	726/9,544	32,287	2.25 (2.10-2.42)	1.19 (1.16-1.22)	**1.15 (1.11-1.19)**
DMARD Category					
csDMARDs	1,361/15,541	69,213	1.84 (1.74-1.95)	Referent	Referent
TNFi	395/7,724	21,983	1.68 (1.51-1.87)	0.58 (0.52-0.65)	**0.81 (0.71-0.93)**
Infliximab	174/2,888	56,649	1.68 (1.51-1.87)	0.95 (0.81-1.12)	**0.81 (0.71-0.93)**
Etanercept	142/3,850	19,213	0.79 (0.48-1.32)	0.50 (0.42-0.59)	**0.50 (0.30-0.83)**
Adalimumab	62/2,150	44,878	2.01 (1.11-3.63)	0.39 (0.30-0.50)	0.84 (0.48-1.47)
Golimumab	3/286	3,085	1.36 (0.61-3.03)	0.21 (0.07-0.65)	0.92 (0.41-2.10)
Certolizumab	14/521	12,922	2.82 (1.06-7.51)	0.32 (0.19-0.54)	0.63 (0.23-1.68)
NonTNFi bDMARDs and tsDMARDs					
Abatacept	20/1,147	19,213	0.79 (0.48-1.32)	0.24 (0.15-0.37)	**0.50 (0.30-0.83)**
Rituximab	13/552	6,122	2.01 (1.11-3.63)	0.47 (0.27-0.81)	0.84 (0.48-1.47)
Tocilizumab	7/414	4,594	1.36 (0.61-3.03)	0.32 (0.15-0.68)	0.92 (0.41-2.10)
Anakinra	4/160	1,764	2.82 (1.06-7.51)	0.79 (0.30-2.11)	0.63 (0.23-1.68)
Tofacitinib	1/301	2,301	0.57 (0.10-4.01)	0.10 (0.01-0.56)	0.23 (0.03-1.62)

**Per 1,000 patient-years*

‡Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension ,diabetes, comorbidity index, BMI, HAQ, NSAIDs, statins, prior count of csDMARDs and bDMARDs, prior CVD history and year of entry

DMARD= Disease-modifying antirheumatic drug; csDMARDs=Conventional synthetic disease-modifying antirheumatic drugs; TNFi= Tumor necrosis factor-α inhbitors; bDMARDS=Biologic disease-modifying antirheumatic drugs; tsDMARDs=Targeted synthetic disease-modifying drugs; HR= Hazard ratio; CI= Confidence interval

Table 3. Crude incidence rates and risk of individual cardiovascular disease events in patients with rheumatoid arthritis with bDMARD and tofacitinib treatment against csDMARDs

	MI	Stroke	Heart failure	CVD-related death
Number of events	878	211	1,088	942
Incidence rate (95% CI)*	0.92 (0.86-0.99)	0.22 (0.19-0.25)	1.14 (1.08-1.21)	0.99 (0.93-1.05)
Adjusted HR (95% CI) for DMARDs ⁑				
csDMARDs	Referent	Referent	Referent	Referent
TNFi	**0.78 (0.66-0.96)**	**0.67 (0.46-0.97)**	0.87 (0.73-1.03)	**0.76 (0.62-0.92)**
Abatacept	**0.37 (0.15-0.91)**	0.53 (0.17-1.73)	0.74 (0.40-1.36)	0.44 (0.20-1.00)
Rituximab	0.48 (0.18-1.30)	1.30 (0.46-3.66)	1.00 (0.47-2.15)	0.66 (0.29-1.51)
Tocilizumab	0.71 (0.17-2.91)	1.05 (0.14-7.77)	0.95 (0.30-3.02)	0.75 (0.18-3.07)
Anakinra	0.74 (0.18-3.02)	1.10 (0.15-7.98)	0.60 (0.15-2.42)	0.41 (0.06-2.94)
Tofacitinib	-	-	0.43 (0.06-3.08)	-

**Per 1,000 patient-years*

⁑Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension ,diabetes, comorbidity index, BMI, HAQ, NSAIDs, statins, prior count of csDMARDs and bDMARDs, prior CVD history and year of entry

bDMARDs=Biologic disease-modifying antirheumatic drugs; csDMARDs=Conventional synthetic disease-modifying antirheumatic drugs; MI= Myocardial infarction; CVD= Cardiovascular disease; TNFi= Tumor necrosis factor-α inhbitors; HR= Hazard ratio; CI= Confidence interval

Table 4. Crude incidence rates and risk of individual cardiovascular disease events in patients with rheumatoid arthritis with bDMARD and tofacitinib treatment against methotrexate ± other csDMARDs

	Composite CVD events	MI	Stroke	Heart failure	CVD-related death
Number of events	1,801	878	211	1,088	942
Incidence rate (95% CI)*	1.78 (1.69-1.87)	0.92 (0.86-0.99)	0.22 (0.19-0.25)	1.14 (1.08-1.21)	0.99 (0.93-1.05)
Adjusted HR (95% CI) for DMARDs ⁑					
MTX +/- csDMARDs	Referent	Referent	Referent	Referent	Referent
TNFi	0.91 (0.78-1.05)	**0.85 (0.66-0.96)**	0.72 (0.48-1.09)	0.95 (0.78-1.16)	0.83 (0.67-1.04)
Abatacept	0.62 (0.37-1.03)	0.43 (0.17-1.06)	0.57 (0.18-1.88)	0.91 (0.49-1.68)	0.54 (0.23-1.22)
Rituximab	1.04 (0.59-1.82)	0.56 (0.21-1.53)	1.52 (0.53-4.33)	1.22 (0.57-2.63)	0.72 (0.31-1.64)
Tocilizumab	1.20 (0.53-2.73)	0.92 (0.23-3.78)	1.16 (0.16-8.73)	1.23 (0.39-3.90)	0.92 (0.22-3.75)
Anakinra	0.79 (0.29-2.12)	0.86 (0.21-3.47)	1.20 (0.16-8.77)	0.73 (0.18-2.95)	0.48 (0.07-3.44)
Tofacitinib	0.29 (0.04-2.11)	-	-	0.52 (0.07-3.72)	-
Non-MTX csDMARDs	1.31 (1.17-1.48)	1.16 (0.98-1.36)	1.03 (0.73-1.43)	1.34 (1.15-1.56)	1.35 (1.15-1.59)

**Per 1,000 patient-years*

⁑Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension ,diabetes, comorbidity index, BMI, HAQ, NSAIDs, statins, prior count of csDMARDs and bDMARDs, prior CVD history and year of entry

bDMARDs=Biologic disease-modifying antirheumatic drugs; csDMARDs=Conventional synthetic disease-modifying antirheumatic drugs; CVD= Cardiovascular disease; MI= Myocardial infarction; MTX= Methotrexate; TNFi= Tumor necrosis factor-α inhbitors; HR= Hazard ratio; CI= Confidence interval

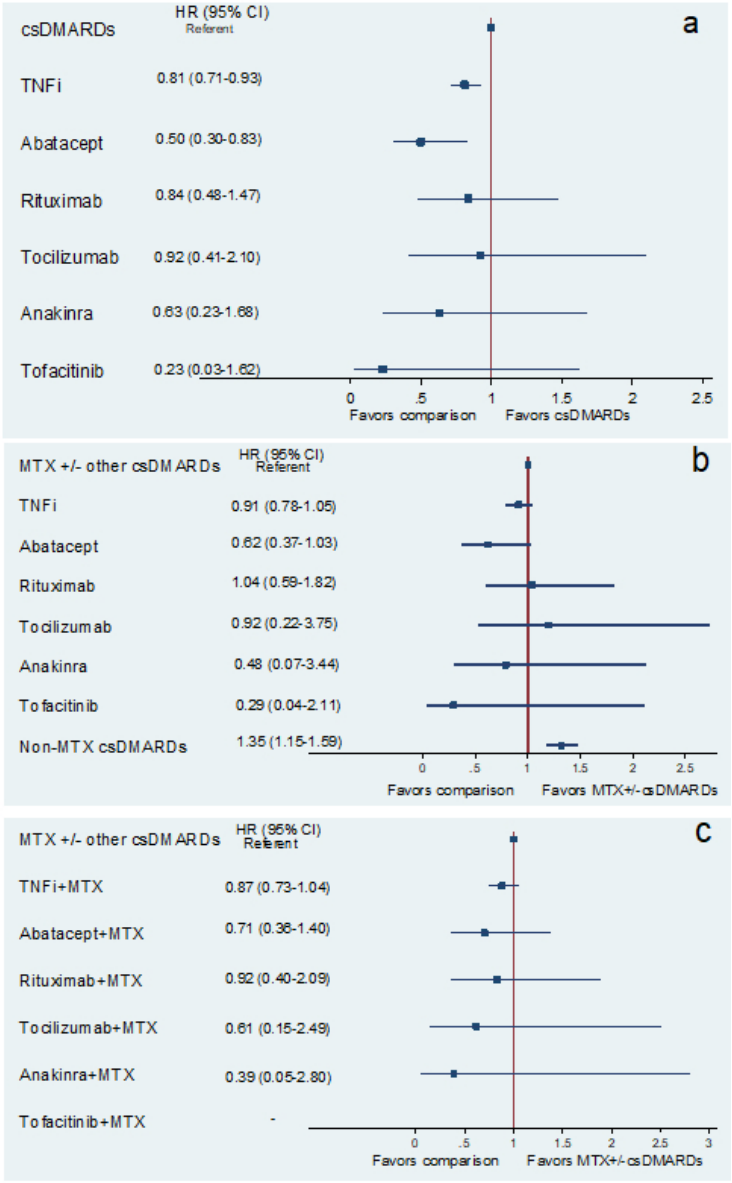

Figure 1.

64x104mm (192 x 192 DPI)