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The Risk of Cardiovascular Events Associated With Disease-modifying Antirheumatic Drugs in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine the comparative effects of biologic disease-modifying antirheumatic drugs (bDMARD) and tofacitinib against conventional synthetic DMARD (csDMARD) on incident cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA).

Methods. RA patients with ≥ 1 year of participation in the FORWARD study, 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). DMARD were categorized into 7 mutually exclusive groups: (1) csDMARD-referent; (2) tumor necrosis factor-α inhibitor (TNFi); (3) abatacept (ABA); (4) rituximab; (5) tocilizumab; (6) anakinra; and (7) tofacitinib. Glucocorticoids (GC) were assessed using a weighted cumulative exposure 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, 1801 CVD events were identified in 18,754 RA patients. The adjusted model showed CVD risk reduction with TNFi (HR 0.81, 95% CI 0.71–0.93) and ABA (HR 0.50, 95% CI 0.30–0.83) compared to csDMARD. While higher GC exposure as weighted cumulative exposure was associated with increased CVD risk (HR 1.15, 95% CI 1.11–1.19), methotrexate (MTX) use was associated with CVD risk reduction [use vs nonuse HR 0.82, 95% CI 0.74–0.90, and high dose (> 15 mg/week) vs low dose (≤ 15 mg/week) HR 0.83, 95% CI 0.70–0.99].

Conclusion. ABA and TNFi were associated with decreased risk of CVD compared to csDMARD. Minimizing GC use and optimizing MTX dose may improve cardiovascular outcomes in patients with RA.

Key Indexing Terms: biologics, cardiovascular, cohort study, DMARD, rheumatoid arthritis

Cardiovascular disease (CVD) represents the leading cause of death in rheumatoid arthritis (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 cardiovascular (CV) risk factors and genetics[3,4]. Supporting the role of inflammation on CVD risk, growing evidence suggests that high disease activity is associated with approximately 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 (DMARD), particularly biologic DMARD (bDMARD), may reduce CVD events in patients with RA by controlling the systemic inflammation.

The most studied DMARD have been methotrexate (MTX), tumor necrosis factor-α inhibitors (TNFi), and glucocorticoids (GC). A systematic review and metaanalysis of observational studies and clinical trials assessing the effects of MTX, TNFi, and GC on CVD events in RA patients showed a 28% risk reduction (RR) with MTX, 30% RR with TNFi, and 47% risk increase with GC, although some studies reported no CVD risk change with these medications[8]. However, GC-associated CVD risk increase may be confounded by disease activity[9]. For the non-TNFi bDMARD, 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[12,13,14,15,16,17]. While the results from these studies were not consistent, some indicated a lower CVD risk with abatacept (ABA) compared to TNFi and no CVD risk increase with tocilizumab (TCZ) compared to ABA or TNFi[12,13,14,15,16,17].

A previous 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 ≥ 2 mg/L showed a 15% reduction in CVD[18]. Although anakinra, another interleukin-1 antagonist, is thought to be less efficacious than other approved bDMARD in RA[19], it is unknown whether it exerts similar CVD protective effects as shown for canakinumab.

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Last, most of our knowledge for tofacitinib comes from the long-term results of the integrated analysis of data from RCT, 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 DMARD. In the present prospective cohort study, we sought to examine the comparative effects of bDMARD and tofacitinib against conventional synthetic DMARD (csDMARD) on incident CVD in patients with RA.

MATERIALS 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 yrs) and completed ≥ 2 semiannual questionnaires during the period of 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, and (4) death from CVD. Possible MI, stroke, and heart failure 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 that were confirmed by medical reviews or death records were included. If hospital or death records were not available, the patient, their physician, 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, 9th and 10th Revisions (ICD-9/10) codes: 410*, I21.*, and I22.* for MI; 433*, 434*, and I63.* for stroke; and 428* and I50.* for heart failure. 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 through 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) csDMARD (MTX, sulfasalazine, hydroxychloroquine, and leflunomide; reference); (2) TNFi [infliximab (IFX), adalimumab (ADA), etanercept (ETN), golimumab, and certolizumab pegol (CZP)]; (3) ABA; (4) rituximab (RTX); (5) TCZ; (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 GC exposure, we used a weighted cumulative exposure model with prednisone (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 in which past GC exposure affects the current risk of the outcome was determined based on the methodology applied by Movahedi, *et al* for diabetes risk[24]. Details of the WCE model are described in the Supplementary Material (available with the online version of this article).

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 the end of study period. CVD events were attributed to the corresponding DMARD group when the treatment was ongoing or discontinued ≤ 3 months before CVD. The risk window after discontinuation of a DMARD was included in the follow-up period.

Covariables. Several confounder variables that were collected semiannually by study questionnaires were adjusted for in the analyses: age; sex; ethnicity; location of residence (rural vs urban)[26]; education level (yrs); employment (yes/no); insurance type (Medicare vs others); BMI in World Health Organization categories (normal weight reference); smoking (ever vs never); Rheumatic Disease Comorbidity Index (RDCI) not including diabetes and hypertension[27]; hypertension; diabetes; chronic kidney disease (CKD); prior CVD; RA duration; Health Assessment Questionnaire (HAQ); pain and patient global scores (0–10); use of other drugs influencing the CVD risk (statins, acetylsalicylic acid, nonsteroidal antiinflammatory drugs); number of previous csDMARD and bDMARD WCE-prednisone; and calendar year. The Patient Activity Scale (PAS), which is a patient-reported composite disease activity scale calculated by using HAQ and 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 patients with RA 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 1000 patient-years (PY) of follow-up with 95% CI.

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

In sensitivity analyses, as MTX has been shown to decrease CVD risk[30], we explored the association of bDMARD and tofacitinib with CVD risk compared to MTX (reference: MTX ± other csDMARD). Additionally, because the majority of the bDMARD are more efficacious with MTX than as monotherapy, we tested if bDMARD and tofacitinib with concomitant MTX use conferred any CVD benefits over MTX alone. For this analysis, we selected the patients using MTX alone or in combination with any bDMARD or tofacitinib. Also, in this subgroup analysis, we included the MTX dose in the model as a binary variable (MTX dose > 15 mg/week: yes/no). We also separately analyzed individual TNFi against csDMARD. Last, we performed the same analysis in patients without prior CVD.

Although WCE-prednisone has been shown to be superior to conventional GC exposure assessment methods (dose, duration, or combined variables) in the assessment of diabetes and serious infection risks in patients with RA, it has not been used for the CVD risk assessment before. Therefore, we created a different model with a dose-duration–combined GC 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 2-sided, conducted at a significance level of 0.05. All statistical analyses were performed using Stata version 14.0 (StataCorp.).

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 PY. 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; more likely to be male; had longer disease duration; had higher HAQ, disease activity by PAS, and RDCI scores; and had more frequent prior CVD, diabetes, hypertension, and GC use (Table 1). The use of other DMARD 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 1 (available with the online version of this article).

During the study period, we identified 1801 composite CVD events yielding an incidence rate of 1.78 (95% CI 1.69–1.87) per 1000 PY. The incidence rates were slightly higher in GC and anakinra users and slightly lower in ABA 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 Table 2 and Table 3.

The fully adjusted model for the composite CVD events showed that TNFi (HR 0.81, 95% CI 0.71–0.93) and ABA (HR 0.50, 95% CI 0.30–0.83) were associated with a significant CVD RR compared to csDMARD. The other bDMARD and tofacitinib were not associated with any CVD risk alteration against csDMARD (Table 2). Approximately 80% of the non–TNFi bDMARD users were previously exposed to TNFi. When patients with prior TNFi use were excluded, the risk with non-TNFi remained similar but had wider CI (ABA HR 0.46, 95% CI 0.15–1.43; data not shown for other bDMARD). In the analysis of CVD risk with individual TNFi, we found that all TNFi except for CZP tended to decrease CVD risk compared to csDMARD, but the RR reached statistical significance with only IFX (HR 0.83, 95% CI 0.69–0.99) and ETN (HR 0.76, 95% CI 0.63–0.92; Table 2). When patients with prior CVD were excluded (839 CVD events), TNFi were again associated with reduced CVD risk (HR 0.83, 95% CI 0.69–0.99). The RR with ABA was no longer statistically significant (HR 0.77, 95% CI 0.42–1.43), likely due to reduction in sample size and event number. The association of other RA-related factors and traditional CVD risk factors and CV events are shown in Supplementary Table 2 (aviailable with the online version of this article).

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 csDMARD, without any increased risk in heart failure (HR 0.87, 95% CI 0.73–1.03). ABA was only associated with a decreased MI risk (HR 0.37, 95% CI 0.15–0.91) compared to csDMARD, 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 bDMARD and tofacitinib again did not change individual CVD event risk compared to csDMARD (Table 3).

We also assessed MTX use and its relationship with CVD risk in a separate model. We found that MTX use compared to nonuse was associated with an 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 csDMARD to MTX ± other csDMARD and found that TNFi (HR 0.91, 95% CI 0.78–1.05) and ABA (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 the analysis of the individual CVD outcomes with bDMARD 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 > 15 mg/week than with lower doses (HR 0.83, 95% CI 0.70–0.99; adjusted for CKD).

In analyzing the relationship between disease activity, GC 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 GC exposure as WCE-prednisone was associated with increased CVD risk (HR 1.15, 95% CI 1.11–1.19). In the sensitivity analysis, we included a

Table 1. Baseline characteristics of rheumatoid arthritis (RA) patients by incident cardiovascular disease (CVD)[a].

	RA Patients Who Did Not Develop CVD, N = 16,953	RA Patients Who Developed CVD, N = 1801	*P*
Age, yrs	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, yrs	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
GC 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
No. prior bDMARD, median (IQR)	0 (0–1)	0 (0–0)	< 0.001
No. prior csDMARD, median (IQR)	2 (1–3)	2 (1–3)	0.111
NSAID use, %	61.0	59.4	0.205
Acetylsalicylic acid use, %	15.6	22.6	< 0.001
Statin use, %	11.6	11.6	0.970

[a] Values are mean (SD) unless indicated otherwise. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; GC: glucocorticoid; HAQ: Health Assessment Questionnaire; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; PAS: Patient Activity Scale; RDCI: Rheumatic Diseases Comorbidity Index; TNFi: tumor necrosis factor-α inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

Table 2. Crude incidence rates and risk of composite CVD events in patients with rheumatoid arthritis by disease-modifying antirheumatic drug (DMARD) treatment.

	No. Events/Exposures	Patient-years	Incidence Rate (95% CI)[a]	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
All patients	1801/18,754	94,781	1.78 (1.69–1.87)	–	–
Glucocorticoids	726/9544	32,287	2.25 (2.10–2.42)	1.19 (1.16–1.22)	1.15 (1.11–1.19)
DMARD					
csDMARD	1361/15,541	69,213	1.84 (1.74–1.95)	Ref	Ref
TNFi	395/7724	21,983	1.68 (1.51–1.87)	0.58 (0.52–0.65)	0.81 (0.71–0.93)
Infliximab	174/2888	56,649	1.45 (1.39–1.53)	0.95 (0.81–1.12)	0.83 (0.69–0.99)
Etanercept	142/3850	19,213	0.77 (0.62–1.29)	0.50 (0.42–0.59)	0.76 (0.63–0.92)
Adalimumab	62/2150	44,878	0.99 (0.92–1.32)	0.39 (0.30–0.50)	0.87 (0.66–1.14)
Golimumab	3/286	3085	0.61 (0.21–2.39)	0.21 (0.07–0.65)	0.73 (0.23–2.28)
Certolizumab pegol	14/521	12,922	1.01 (0.44–2.98)	0.32 (0.19–0.54)	1.14 (0.64–2.04)
Non–TNFi-bDMARD and tsDMARD					
Abatacept	20/1147	19,213	0.79 (0.48–1.32)	0.24 (0.15–0.37)	0.50 (0.30–0.83)
Rituximab	13/552	6122	2.01 (1.11–3.63)	0.47 (0.27–0.81)	0.84 (0.48–1.47)
Tocilizumab	7/414	4594	1.36 (0.61–3.03)	0.32 (0.15–0.68)	0.92 (0.41–2.10)
Anakinra	4/160	1764	2.82 (1.06–7.51)	0.79 (0.30–2.11)	0.63 (0.23–1.68)
Tofacitinib	1/301	2301	0.57 (0.10–4.01)	0.10 (0.01-0.56)	0.23 (0.03–1.62)

[a] Per 1000 patient-years. [b] Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension, diabetes, comorbidity index, BMI, HAQ, NSAID, statins, prior count of csDMARD and bDMARD, prior CVD history, and year of entry. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; HAQ: Health Assessment Questionnaire; NSAID: nonsteroidal antiinflammatory drug; TNFi: tumor necrosis factor-α inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

Table 3. Crude incidence rates and risk of individual CVD events in patients with rheumatoid arthritis with biologic disease-modifying antirheumatic drug (DMARD) and tofacitinib treatment against csDMARD.

	MI	Stroke	Heart Failure	CVD-related Death
No. events	878	211	1088	942
Incidence rate (95% CI)[a]	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 DMARD[b]				
csDMARD	Ref	Ref	Ref	Ref
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)	–

[a] Per 1000 patient-years. [b] Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension, diabetes, comorbidity index, BMI, HAQ, NSAID, statins, prior count of csDMARD and bDMARD, prior CVD history, and year of entry. csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; MI: myocardial infarction; TNFi: tumor necrosis factor-α inhibitor.

dose-duration–combined categorical GC variable to the model instead of WCE-prednisone. We observed an increasing trend of CVD risk as the dose and treatment duration of GC 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); and ≥ 7.5 mg/day for ≥ 3 months (HR 1.47, 95% CI 1.26–1.71). The results for the DMARD were similar with the categorical GC variable. However, the model fit was worse than the one with the WCE-prednisone variable. Also, interaction analysis showed that concomitant use of GC with DMARD abated the protective effects of TNFi (HR 1.10, 95% CI 0.91–1.32), ABA (HR 0.63, 95% CI 0.33–1.19), and MTX (HR 0.96, 95% CI 0.84–1.11).

DISCUSSION

CVD is the major cause of death, healthcare utilization, and overall costs that 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

Table 4. Crude incidence rates and risk of individual CVD events in patients with rheumatoid arthritis with bDMARD and tofacitinib treatment against MTX ± other csDMARD.

	Composite CVD events	MI	Stroke	Heart failure	CVD-related death
No. events	1801	878	211	1088	942
Incidence rate (95% CI)[a]	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 DMARD[b]					
MTX ± csDMARD	Ref	Ref	Ref	Ref	Ref
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 csDMARD	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)

[a] Per 1000 patient-years. [b] Adjusted for age, sex, disease duration, socioeconomic status (employment and education level, insurance, location of residency), ethnicity, smoking, hypertension, diabetes, comorbidity index, BMI, HAQ, NSAID, statins, prior count of csDMARD and bDMARD, prior CVD history, and year of entry. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CVD: cardiovascular disease; DMARD: biologic disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; MI: myocardial infarction; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; TNFi: tumor necrosis factor-α inhibitor.

risk in patients with RA. Thus, knowing how bDMARD and targeted synthetic DMARD (tsDMARD) influence CVD risk is important to be able to improve CV outcomes in RA patients. In this observational cohort study conducted across the United States, we found that ABA and TNFi (notably IFX and ETN) were associated with a reduced risk of composite CVD compared to csDMARD (mostly non-MTX csDMARD). Moreover, whereas GC use was associated with an increase in CVD risk, MTX use was associated with an 18% CVD RR, which was more prominent in doses over 15 mg/week. The RR with bDMARD mentioned above was not pronounced against MTX ± other csDMARD except for a reduced risk of MI with TNFi.

Despite the recent therapeutic advances, it is still not clear whether the new b/tsDMARD reduce the incidence of CVD in patients with RA. Over the last 2 decades, a number of studies have examined the potential CVD benefits of these therapies in RA[13–17,23,32,33,34]. As 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 metaanalysis of RCT and observational studies estimated the RR 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 metaanalysis. Moreover, our study is the first to assess the dose effect of MTX for CVD risk, to our knowledge. The doses over 15 mg/week were associated with lower CVD compared to 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 United States[35]. Our findings suggest that optimal use of MTX may reduce CVD risk along with its well-known disease activity control.

Several publications have also suggested that TNFi might have beneficial effects on CVD[8,23,32,33,34,36,37,38]. The most significant RR with TNFi was reported in studies comparing CVD risk with TNFi against non-MTX csDMARD (HR range 0.39–0.45)[32,37]. However, the studies comparing the risk against csDMARD including MTX reported less significant CVD RR with TNFi and some showed CVD RR only in responders[34,38]. Consistent with our results, the above-mentioned systematic review and metaanalysis estimated a 30% CVD RR 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 0.36–0.97) and stroke (RR 0.57, 95% CI 0.35–0.92)[8]. This RR we observed with TNFi persisted for MI when we compared the risks with TNFi against MTX ± other csDMARD. Interestingly, we observed that only IFX and ETN were associated with CVD RR. 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 bDMARD or tsDMARD have been limited. Favorable effects on surrogate markers of CVD have been reported with tofacitinib and RTX[10,11]. Few observational studies have compared the CVD risk across these bDMARD[12,13,14,15,16,17]. 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 ABA compared to TNFi[12,13,17]. However, this RR with ABA against TNFi was only reported for Medicare patients[12,13,17]. None of these studies compared CVD risk with bDMARD against csDMARD or MTX. In our analysis, although we found a CVD RR with ABA compared to csDMARD, we did not observe any RR with ABA compared to TNFi (data not shown).

Regarding the other non-TNFi bDMARD, 4 studies using administrative data reported inconsistent results[13,14,15,16]. The multidatabase cohort studies found similar CVD risk among patients starting starting TCZ or TNFi, and TCZ or ABA[14,15]. Two other studies using Medicare and MarketScan data showed a lower composite CVD risk with TCZ compared

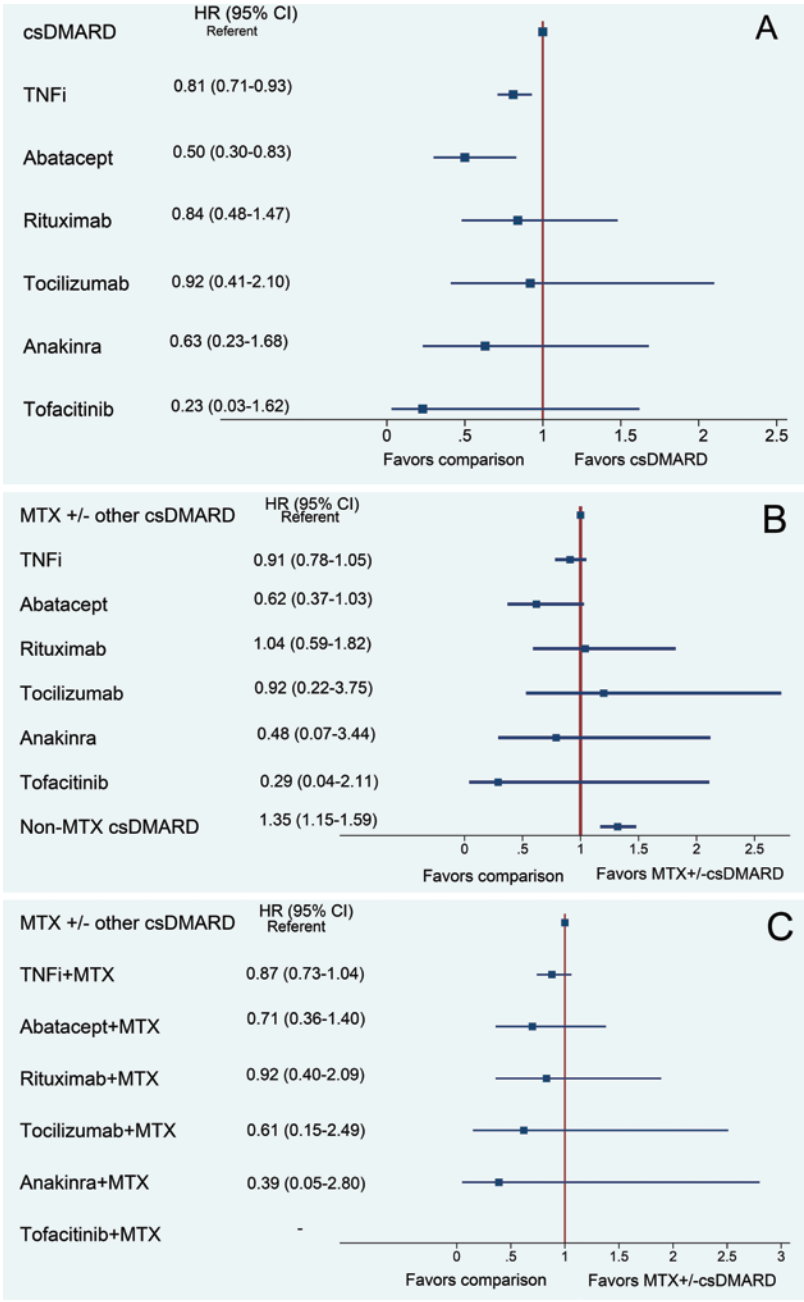

Figure 1. The risk of cardiovascular disease in patients with rheumatoid arthritis with bDMARD and tofacitinib (A) compared to csDMARD; (B) compared to MTX ± other csDMARD; (C) compared to MTX ± other csDMARD when bDMARD or tofacinitib was used concomitantly with MTX. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate; TNFi: tumor necrosis factor-α inhibitor.

to TNFi and ABA[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 TCZ, RTX, and anakinra, and tofacitinib against csDMARD and among each other (data not shown), the numbers of patients who were on these non-TNFi bDMARD and tofacitinib were low. Further pharmacovigilance studies of CVD risk with these DMARD are needed.

Another noteworthy finding of our study is the CVD risk increase with GC use. Although this has been shown in previous studies[23], our study employed a WCE model for GC, which considered the effect of dosage, duration, and timing of GC use on the risk of CVD. This approach has been shown to be superior to conventional GC exposure assessment in serious infection and diabetes risk in patients with RA [24,39] but has not been used for CVD risk assessment. We found the model fit to

be better with WCE-prednisone than conventional GC exposure variables. CVD risk increase with GC 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 corresponding incidence rates reported were lower than in previous observational studies, and may be due to the differences in study populations, as well as 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 affect the comparative results by treatment. Also, our smaller sample sizes for TCZ, anakinra, and tofacitinib limited us in drawing conclusions regarding their associated CVD risk. Last, traditional CV risk factors have gained more importance in CV outcomes of RA with the advent of new potent DMARD and more aggressive treat-to-target approaches[42]. Approximately 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 glycosylated hemoglobin.

In conclusion, ABA and TNFi (notably IFX and ETN) were associated with lower risk of composite CVD than csDMARD, whereas GC were associated with increased risk. However, only TNFi were associated with a decreased risk of CVD (specifically MI) compared to MTX. Despite reported similar efficacies of bDMARD 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), GC use should be minimized, and last, traditional CVD risk factors should not be forgotten in order to improve CV outcomes in patients with RA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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