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Subsequent Cardiovascular Events Among Patients With Rheumatoid Arthritis, Psoriatic Arthritis, or Psoriasis: Patterns of Disease-Modifying Antirheumatic Drug Treatment

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Objective. To examine disease-modifying antirheumatic drug (DMARD) treatments and estimate the risk of a subsequent cardiovascular (CV) event following an initial CV event in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or psoriasis.

Methods. We analyzed data from MarketScan claims databases (January 1, 2006 to June 30, 2015) for adults with RA, PsA, or psoriasis and an initial/index CV event (acute myocardial infarction, stroke, or coronary revascularization) while receiving DMARDs (tumor necrosis factor inhibitor [TNFi] biologic DMARDs [bDMARDs], conventional synthetic DMARDs [csDMARDs], or non-TNFi bDMARDs). We studied DMARD treatment patterns following the index event and rates of subsequent CV events. We used Cox regression to investigate predictors of DMARD discontinuation and risk factors for subsequent CV events.

Results. Among 10,254 patients, 15.3% discontinued and 15.5% switched DMARD therapy after the index CV event. Independent predictors of DMARD discontinuation included a psoriasis diagnosis, renal disease, hypertension, heart failure, diabetes mellitus, older age, and baseline csDMARD or non-TNFi bDMARD use (versus TNFi bDMARDs). Rates per 1,000 patient-years of subsequent events were 75.2 (95% confidence interval [95% CI] 54.4–96.0) for patients taking TNFi bDMARDs, 83.6 (95% CI 53.3–113.9) for csDMARDs, and 122.4 (95% CI 60.6–184.3) for non-TNFi bDMARDs. A diagnosis of RA (versus psoriasis) and heart failure at baseline, but not a DMARD pattern after the index event, were independently associated with an increased risk of subsequent CV event.

Conclusion. In this large nationwide study, nearly one-third of patients with RA, PsA, or psoriasis switched or discontinued DMARD therapy following a CV event. There was no association between DMARD class and the risk of a subsequent CV event.

INTRODUCTION

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis are systemic inflammatory diseases that manifest primarily in joints, skin, or both (1). Patients with RA, PsA, or psoriasis have increased rates of cardiovascular (CV) disease as well as excess traditional CV risk factors, increased risk of an initial CV event, and worse outcomes after CV events (2–4). A recent population-based cohort study reported adjusted hazard ratios (HRs) for a major acute CV event (composite outcome) of HR 1.58 (95% confidence interval [95% CI] 1.46–1.70) for patients with RA, HR 1.17 (95% CI 0.95–1.46) for patients with PsA, and HR 1.42 (95% CI 1.17–1.73) for patients with psoriasis treated with disease-modifying antirheumatic drugs (DMARDs) compared with matched controls (5). RA, PsA, and psoriasis are associated with increased prevalence and incidence of traditional CV risk factors of hypertension, diabetes mellitus, hyperlipidemia, and obesity (6). The high systemic inflammatory burden associ-

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SIGNIFICANCE & INNOVATIONS

- Patients with the systemic inflammatory diseases rheumatoid arthritis, psoriatic arthritis, and psoriasis have a high risk of cardiovascular (CV) events, and the effect of treatment for these diseases on the risk of a subsequent CV event is unclear.
- In this large nationwide study reflecting typical clinical care, disease-modifying antirheumatic drug (DMARD) discontinuation and class switches after an initial CV event were common.
- We found that treatment with different classes of DMARDs did not significantly affect the risk of subsequent CV events.

ated with these diseases, which is mediated by proinflammatory cytokines (7), is linked to accelerated atherosclerosis (8,9). Compared with the general population, patients with RA or PsA have excess CV mortality (10–14).

Patients with RA, PsA, or psoriasis are treated with similar classes of medications, including conventional synthetic DMARDs (csDMARDs; e.g., methotrexate, hydroxychloroquine, sulfasalazine), and biologic DMARDs (bDMARDs; e.g., tumor necrosis factor inhibitors [TNFi]), often in combination with a csDMARD (15–17). Some DMARDs may have cardioprotective effects. In patients with RA, for example, the use of methotrexate (versus non-use) was associated with a reduced CV risk of 21% (18), and TNFi bDMARD therapy (versus csDMARD therapy) was associated with a reduced risk of 46% (19). Larger studies to examine this issue are needed (20,21).

After a CV event in patients with RA, PsA, or psoriasis, adverse events may be more likely to occur and to have serious clinical consequences, or DMARDs may be contraindicated because of organ dysfunction resulting from the CV event. However, DMARD therapy may be required for underlying rheumatic disease control. Moreover, recent data support the potential benefit of immunomodulators in patients who have experienced a CV event (22). The aims of this study were to describe patterns and predictors of changes in DMARD treatment patterns after an initial CV event, to estimate the risk of subsequent CV events, and to compare the risk of subsequent CV events among patients with RA, PsA, or psoriasis.

PATIENTS AND METHODS

Study design. This retrospective cohort study used administrative claims data from the MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases. The study period was January 1, 2006 through June 30, 2015. The index date was the hospital discharge date for the first nonfatal CV event during the study period. Index CV events included acute myocardial infarction (MI), stroke, or coronary revascularization procedure (percutaneous coronary intervention, stent, or coronary artery bypass grafting). The baseline period was the 12 months preceding (and including) the index date. Follow-up started on the day after the index date and continued for at least 30 days until disenrollment from MarketScan, a CV event of interest, diagnosis of an exclusionary event, or the end of the study period. During follow-up, patients were assessed for treatment and subsequent CV events.

Patients. Patients were adults (age ≥18 years) with a diagnosis of RA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 714.0), PsA (ICD-9-CM code 696.0), or psoriasis (ICD-9-CM code 696.1) and an index CV event. Patients with RA were identified using a previously validated algorithm (23). All patients had ≥1 claim for a TNFi bDMARD, csDMARD, or a non-TNFi bDMARD within 12 months before the index event. Continuous enrollment for the 12-month baseline period and ≥30 days of follow-up after the index event were required. Patients with inflammatory bowel disease, juvenile idiopathic arthritis, ankylosing spondylitis, cancer (except nonmelanoma skin cancer), HIV, systemic lupus erythematosus, organ transplant, or dialysis utilization were excluded.

Diagnoses of RA, PsA, and psoriasis were based on ≥1 inpatient diagnosis or outpatient diagnosis claim, a practice that is known to accurately classify patients with RA (23). Outpatient claims had to be accompanied by another RA, PsA, or psoriasis outpatient diagnosis claim within ≥30 days and ≤365 days of the original outpatient claim; the latter claim was defined as the diagnosis date. Patients with multiple diagnoses were classified according to a hierarchy. Patients with a dual diagnosis of RA and either PsA or psoriasis were included in the RA cohort. Patients with a dual diagnosis of PsA and psoriasis on the same date were assigned to the PsA cohort; if the psoriasis diagnosis preceded the PsA diagnosis, the patients were assigned to the psoriasis cohort until the PsA diagnosis, and were then censored from the psoriasis cohort and included in the PsA cohort.

Outcomes. Study outcomes included DMARD treatment patterns across all patients after an initial CV event and the incidence of subsequent CV events in patients who received DMARD therapies after the initial CV event. We grouped patients by DMARD class (TNFi bDMARD, csDMARD, or non-TNFi bDMARD) because of the limited number of subsequent CV events for each individual DMARD.

Outcome 1: DMARD treatment patterns after initial CV event. Treatment pattern outcomes included the proportion of patients receiving TNFi bDMARD therapy, csDMARD therapy, or non-TNFi bDMARD therapy at the time of the initial CV event, and whether patients persisted with initial therapy, switched to another therapy, or discontinued all DMARD therapy following the index CV event. Treatment assessments were based on pharmacy claim records

(National Drug Codes) for medications administered subcutaneously or orally and procedure claim records (Current Procedure Terminology [CPT] and/or Healthcare Common Procedure Coding System) for intravenously administered medications.

The csDMARD therapies included methotrexate, hydroxychloroquine, leflunomide, azathioprine, cyclophosphamide, cyclosporine, D-penicillamine, gold, mycophenolate mofetil, or sulfasalazine as monotherapy or in combination with another csDMARD. TNFi bDMARD therapies included adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab with or without a csDMARD. Non-TNFi bDMARD therapies included abatacept, anakinra, rituximab, secukinumab, tocilizumab, tofacitinib, or ustekinumab with or without a csDMARD. Tofacitinib, a small molecule, was included with the non-TNFi bDMARD group because it is a targeted medication with biologic effects that are more similar to bDMARDs than to csDMARDs. Baseline therapies during the 12 months before the index event were based on the last 2 treatments before the index date (all patients were taking at least 1 DMARD). Postindex therapies were based on the first 2 treatments after the index date. Patients who were using combination therapies with csDMARDs and bDMARDs were included in the bDMARD cohorts based on the type of bDMARD (TNFi or non-TNFi).

Outcome 2: subsequent CV events. Following the initial CV event, subsequent CV events were identified based on inpatient ICD-9-CM codes for MI (410.x) or stroke (430.x, 431.x, 432.x, 433.x1, 434.x1, 435.x, 436.x, 437.1x, 437.9x). Subsequent CV events were also identified based on procedure codes for coronary revascularization (ICD-9-CM procedure codes: 36.10–36.17, 36.19, 36.2, 36.3x, 36.0x, 00.66; and/or CPT procedure codes: 33510–33523, 33533–33536, G0290, G0291, 92980, 92981, 92982, 92995).

Statistical analysis. Descriptive statistics for categorical variables were presented as proportions, and for continuous variables were presented as mean ± SDs or as medians and interquartile ranges. Proportions of patients who persisted with, switched, or discontinued DMARD therapy following the index CV event were calculated. Rates of subsequent CV events were calculated and age- and sex-standardized to the MarketScan general population. Rate ratios (RRs) with 95% CIs were calculated using TNFi bDMARD therapy as reference.

Logistic regression was used to estimate odds ratios (ORs) with 95% CIs for discontinuation from all DMARD therapy following the index CV event. Covariates used in regression analyses included demographic characteristics (age and sex), disease indication (RA, PsA, or psoriasis), comorbid conditions (obesity, hyperlipidemia, hypertension, diabetes mellitus, chronic pulmonary disease, and unstable angina), DMARD treatment prior to the index CV event, medication use in the baseline period (oral glucocorticoids, statins, and antihypertensives), and the type of index CV event (MI, stroke, or coronary revascularization procedure). Only patients who were receiving TNFi bDMARDs, csDMARDs, or non-TNFi bDMARDs after the initial CV event were included in the analyses of subsequent CV events.

Cox proportional hazards models were fit to estimate adjusted HRs and 95% CIs for the risk of subsequent CV events. The proportional hazards assumption was tested by plotting standardized score residuals over time and was met in all analyses. Data were standardized by age and sex using standard methods (24). For each sex category, 4 age strata were examined: ≤54 years, 55–64 years, 65–74 years, and ≥75 years, for a total of 8 strata.

Model 1 was adjusted for age (per 10 years) and sex. Model 2 was adjusted for age (per 10 years), sex, disease indication (RA, PsA, and psoriasis), index CV event (acute MI, stroke, coronary revascularization), baseline comorbidities (heart failure, chronic pulmonary disease, diabetes mellitus, hyperlipidemia, hypertension,

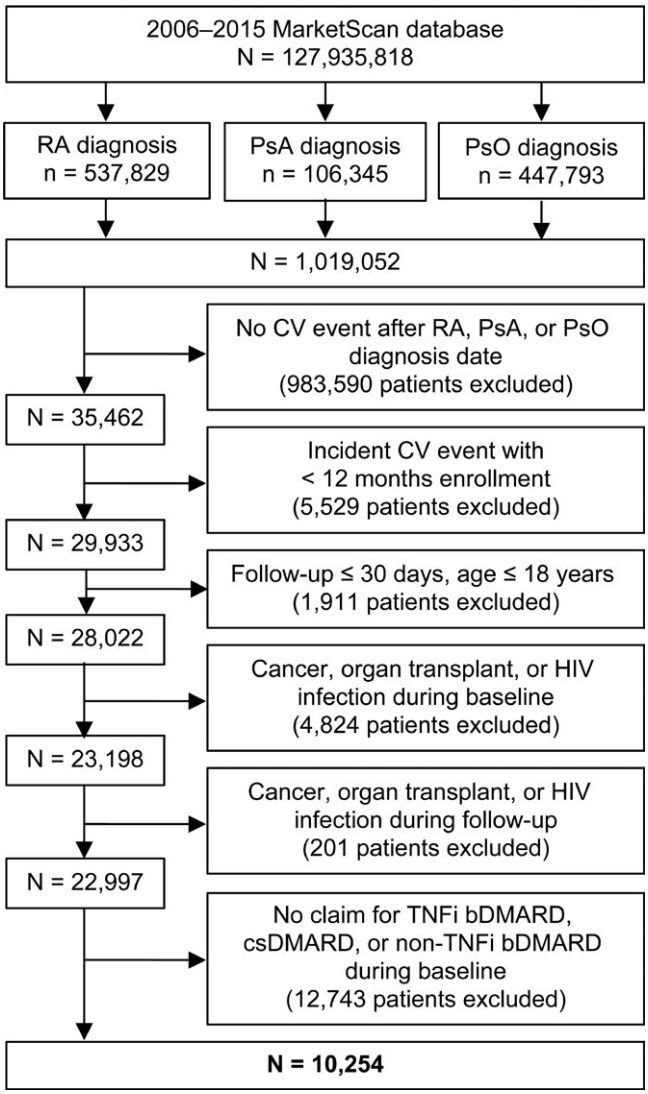

Figure 1. Identification of study sample. RA = rheumatoid arthritis; PsA = psoriatic arthritis; PsO = psoriasis; CV = cardiovascular; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD.

obesity, unstable angina, and renal disease), the number of baseline unique DMARDs used, and baseline medication exposures (statins, oral glucocorticoids, angiotensin-converting enzyme inhibitor, and beta blockers). Model 3 used backward elimination, retaining covariates of age, sex, disease indication, baseline comorbidities (heart failure, diabetes mellitus, renal disease), and baseline oral glucocorticoid use.

RESULTS

Patients and baseline medication. Data from 10,254 patients were analyzed (Figure 1), including 8,475 patients (82.7%) with RA, 794 patients (7.7%) with PsA, and 985 patients (9.6%) with psoriasis (Table 1). In the total study sample, the mean ± SD age was 67.2 ± 11.9 years, and 59.1% were women. The most common index CV event was stroke (42.7%), followed by coronary revascularization (39.2%) and acute MI (18.1%). The most commonly used medication class to treat RA, PsA, or psoriasis in the baseline period was csDMARDs (76.8%). Nearly one-half of all patients (48.7%) were receiving a statin during the baseline period, and 52.2% were receiving oral glucocorticoids. Patients taking csDMARDs were older (mean ± SD age 69.7 ± 11.4 years) compared to patients taking TNFi bDMARDs (63.7 ± 11.1 years) or non-TNFi bDMARDs (64.6 ± 12.0 years). Fewer women were in the TNFi bDMARD cohort (53.4%) than in the csDMARD cohort (61.3%) or non-TNFi bDMARD cohort (59.4%).

Treatment patterns after index CV event and predictors of DMARD discontinuation. Across all therapies, most patients persisted with their index DMARD following the index CV

Table 1. Pre-index demographic and clinical characteristics of patients according to the class of DMARD treatment after an initial cardiovascular event (n = 10,254)*

Characteristics	TNFi bDMARD (n = 3,077)	csDMARD (n = 4,663)	Non-TNFi bDMARD (n = 947)	No DMARD (n = 1,567)
Age, mean ± SD years	63.7 ± 11.1	69.7 ± 11.4	64.6 ± 12.0	68.7 ± 12.9
Women	1,642 (53.4)	2,860 (61.3)	563 (59.4)	990 (63.2)
Disease indication				
Rheumatoid arthritis	2,315 (75.2)	4,223 (90.6)	750 (79.2)	1,187 (75.7)
Psoriatic arthritis	411 (13.4)	218 (4.7)	54 (5.7)	111 (7.1)
Psoriasis	351 (11.4)	222 (4.8)	143 (15.1)	269 (17.2)
Index event				
Acute myocardial infarction	452 (14.7)	883 (18.9)	184 (19.4)	342 (21.8)
Stroke	1,196 (38.9)	2,014 (43.2)	378 (39.9)	787 (50.2)
Coronary revascularization	1,429 (46.4)	1,766 (37.9)	385 (40.7)	438 (28.0)
Comorbidities				
Chronic pulmonary disease	689 (22.4)	1,294 (27.8)	280 (29.6)	494 (31.5)
Diabetes mellitus	928 (30.2)	1,336 (28.7)	326 (34.4)	571 (36.4)
Heart failure	433 (14.1)	979 (21.0)	212 (22.4)	429 (27.4)
Hyperlipidemia	1,435 (46.6)	1,983 (42.5)	506 (53.4)	751 (47.9)
Hypertension	1,968 (64.0)	3,109 (66.7)	662 (69.9)	1,200 (76.6)
Obesity	292 (9.5)	351 (7.5)	142 (15.0)	198 (12.6)
Renal disease	237 (7.7)	472 (10.1)	115 (12.1)	272 (17.4)
Unstable angina	414 (13.5)	532 (11.4)	128 (13.5)	146 (9.3)
Medication exposure during baseline				
TNFi bDMARD	2,883 (93.7)	332 (7.1)	153 (16.2)	386 (24.6)
csDMARD	1,788 (58.1)	4,607 (98.8)	487 (51.4)	997 (63.6)
Non-TNFi bDMARD	158 (5.1)	168 (3.6)	766 (80.9)	361 (23.0)
Oral glucocorticoids	1,457 (47.4)	2,655 (56.9)	479 (50.6)	763 (48.7)
Statin	1,479 (48.1)	2,454 (52.6)	393 (41.5)	669 (42.7)
ACEi	939 (30.5)	1,550 (33.2)	241 (25.5)	447 (28.5)
Beta blocker	1,341 (43.6)	2,429 (52.1)	401 (42.3)	744 (47.5)

* Values are the number (%) unless indicated otherwise. DMARD = disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; ACEi = angiotensin-converting enzyme inhibitor.

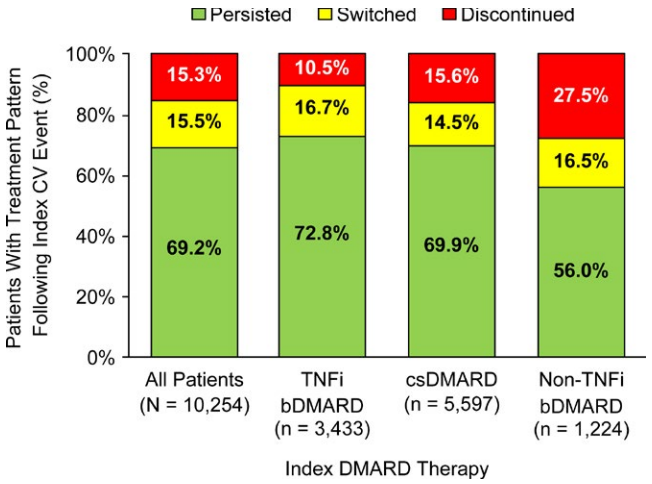

Figure 2. Treatment patterns following index cardiovascular (CV) event. The percentages of patients who persisted with the index disease-modifying antirheumatic drug (DMARD) (green bars), switched to a different DMARD (yellow bars), or discontinued all DMARD therapy (red bars) are shown. bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; TNFi = tumor necrosis factor inhibitor.

event (Figure 2). Nearly one-third of patients (30.8%) discontinued or switched from index therapy following the index CV event. There were 540 infliximab users (18.5% of TNFi bDMARDs) during the baseline period; of these, 382 patients (70.7%) re-initiated infliximab as their first DMARD after the index date. There were 100 rituximab users (11.5% of non-TNFi bDMARDs) during the baseline period; of these, 39 patients (39.0%) re-initiated rituximab as their first DMARD after the index date.

Regression analyses showed that older patients and those with a comorbidity of renal disease, hypertension, heart failure, or diabetes mellitus were more likely to discontinue DMARD therapy following the index CV event (Figure 3). Compared to patients taking TNFi bDMARDs after the index CV event, patients taking csDMARDs (odds ratio [OR] 1.61 [95% CI 1.41–1.85]) or non-TNFi bDMARDs (OR 2.61 [95% CI 2.19–3.11]) were more likely to discontinue DMARD therapy after the index CV event.

Risk of subsequent CV events. Age- and sex-standardized rates for a subsequent CV event were highest for patients taking non-TNFi bDMARDs (rate 122.4 [95% CI 60.6–184.3] events per 1,000 patient-years) followed by patients taking csDMARDs (rate 83.6 [95% CI 53.3–113.9] events per 1,000 patient-years) and patients taking TNFi bDMARDs (rate 75.2 [95% CI 54.4–96.0] events per 1,000 patient-years) (Table 2). Compared to TNFi bDMARDs, the RRs for subsequent CV events were 1.11 (95% CI 0.70–1.75) for csDMARDs and 1.63 (95% CI 0.92–2.90) for non-TNFi bDMARDs.

The type of DMARD used after the initial nonfatal CV event was not associated with an increased risk for subsequent CV events among patients with RA, PsA, or psoriasis in any of the models tested (Table 3). The model 3 multivariable HR for risk of subsequent CV events was 0.98 (95% CI 0.82–1.17) for csDMARDs (versus TNFi bDMARDs), and 1.16 (95% CI 0.86–1.57) for non-TNFi bDMARDs (versus TNFi bDMARDs). Patients with RA (HR 1.55 [95% CI 1.00–2.39] versus patients with psoriasis) and patients with heart failure (HR 1.39 [95% CI 1.13–1.72]) had an increased risk of a subsequent CV event independent of other factors, including age, sex, medication use, type of index CV event, and other baseline comorbidities.

DISCUSSION

Patients with RA, PsA, or psoriasis have an inherently high risk for CV disease, and our study showed that these patients are

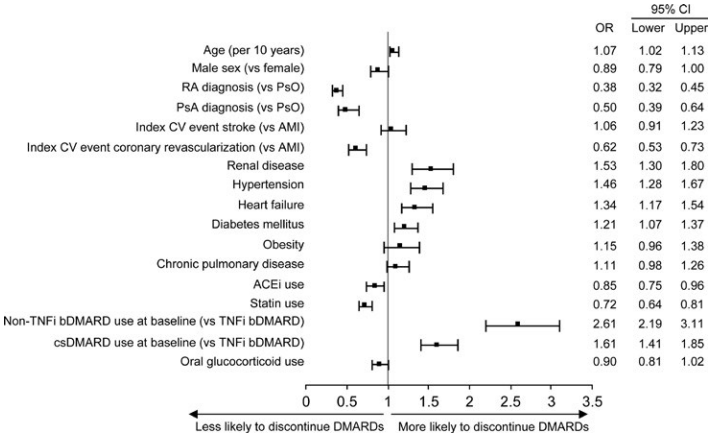

Figure 3. Predictors of discontinuation from all disease-modifying antirheumatic drugs (DMARDs) following the index cardiovascular (CV) event. Odds ratios (ORs) with 95% confidence intervals (95% CIs) for the risk of discontinuation are shown. The vertical line represents OR = 1. RA = rheumatoid arthritis; PsO = psoriasis; PsA = psoriatic arthritis; AMI = acute myocardial infarction; ACEi = angiotensin-converting enzyme inhibitor; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD.

Table 2. Subsequent CV events (acute myocardial infarction, stroke, or coronary revascularization) in patients receiving DMARD therapy following the index CV event*

	TNFi bDMARD	csDMARD	Non-TNFi bDMARD
Follow-up			
Patient-years	2,744.4	2,984.7	482.0
Mean ± SD years	0.99 ± 1.21	0.69 ± 0.87	0.69 ± 0.92
Subsequent CV events, no.	230	288	53
Rate per 1,000 patient-years (95% CI)†	75.2 (54.4–96.0)	83.6 (53.3–113.9)	122.4 (60.6–184.3)
RR (95% CI)†	Ref.	1.11 (0.70–1.75)	1.63 (0.92–2.90)

* CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; csDMARD = conventional synthetic DMARD; 95% CI = 95% confidence interval; RR = rate ratio.
† Rates and RRs are age- and sex-standardized to the MarketScan general population.

also at high risk for a subsequent CV event following an initial CV event. Clinicians may focus on the CV disease immediately following an initial event, and management of other chronic illnesses may have low priority. The frequent discontinuation observed in this study of all DMARD therapies (over 15% of all patients) following the initial CV event suggests that RA, PsA, and psoriasis disease management was secondary to CV disease management in many patients. Notably, the risk of a subsequent CV event did not differ by type of DMARD therapy in this analysis.

Although high rates of CV risk factors and the high risk of CV disease in patients with RA, PsA, or psoriasis have been thoroughly documented, few studies have examined recurrent or subsequent CV events in these patient populations. Of the few studies conducted in patients with RA, all showed that patients with RA and a prior CV event had worse outcomes compared to patients without RA. For example, a small study of patients with acute coronary syndrome from a coronary care admission register showed that recurrent cardiac events were more common in patients with RA (57.5%) compared to controls (30%; $P = 0.013$) (25). An increased risk for acute coronary syndrome recurrence in RA patients was also found in a cohort study (HR 1.30 [95% CI 1.04–1.62]) versus matched controls (26). In a cohort study of statin use, crude event rates for a nonfatal MI were 81.6 events per 1,000 patient-years (95% CI 30.6–217.5) for secondary prevention patients with RA who were statin-naive (27). Notably, statin use was associated with a reduced rate of nonfatal MI in RA patients (47.6 [95% CI 24.8–91.5] events per 1,000 patient-years) (27). In a recent analysis of nationwide health claims data in Taiwan, patients with RA were significantly more likely to have a subsequent major acute coronary event compared to controls (HR 1.20 [95% CI 1.07–1.34]; $P < 0.01$) (28). These results are consistent with our observation that patients with RA are at high risk for a subsequent CV event, and that CV risks in patients with RA, PsA, or psoriasis need to be aggressively managed.

After a CV event, patients may experience a profound decline in functional status and worsened organ function that are not adequately captured in administrative claims database studies such as ours. These complex factors likely affect the decision for DMARD treatment for both clinicians and patients. For example, patients with systemic rheumatic disease in remission or low disease activity may not resume medications after a CV event, particularly if disease activity remains stable or if new medical complications persist after the CV event. Patients may also experience a flare from their underlying rheumatic disease but be hesitant to restart DMARD treatment because of a perceived risk of adverse events, such as serious infection. Clinicians may be reluctant to prescribe DMARDs if new contraindications have developed, such as heart failure or renal insufficiency. While our study could not investigate the complexities of these treatment decisions, we were able to capture an overall view of DMARD treatment patterns following CV events. We found that >30% of patients switched or discontinued DMARD therapy after an initial CV event. In our study, patients taking non-TNFi bDMARDs at baseline were at much higher risk to discontinue DMARD therapy after the index CV event compared to those patients taking TNFi bDMARDs. This finding is perhaps surprising given some conflicting evidence of the effect of TNFi on heart failure (29,30), which presumably occurred in some patients after the index CV event. Some residual confounding may have occurred, because patients in the TNFi group may have been slightly healthier based on the inclusion of heart failure in the warnings and precautions on TNFi labels (31).

Patients with multimorbidities at baseline were more likely to discontinue all DMARDs after a CV event, perhaps because these patients were in relatively poor health both before and after the CV event, which made prescribers and patients reluctant to continue DMARDs. Patients with RA and PsA were less likely to discontinue all DMARDs compared to patients with psoriasis. While we were not able to determine levels of disease activity, we used glucocorticoid therapy as a surrogate. While there was no statistically significant association between glucocorticoid use and DMARD discontinuation, the point estimate

Table 3. Hazard ratios for risk of subsequent cardiovascular events*

	Model 1 (age, sex, DMARD type)	Model 2 (multivariable)	Model 3 (multivariable, parsimonious)
csDMARD vs. TNFi bDMARD	1.03 (0.86–1.23)	0.97 (0.80–1.18)	0.98 (0.82–1.17)
Non-TNFi bDMARD vs. TNFi bDMARD	1.23 (0.91–1.66)	1.17 (0.86–1.58)	1.16 (0.86–1.57)
Age per 10 years	1.05 (0.97–1.13)	1.01 (0.93–1.10)	1.02 (0.94–1.10)
Men vs. women	1.11 (0.94–1.31)	1.15 (0.96–1.37)	1.13 (0.96–1.34)
Rheumatoid arthritis vs. psoriasis	–	1.58 (1.01–2.46)	1.55 (1.00–2.39)
Psoriatic arthritis vs. psoriasis	–	1.45 (0.86–2.44)	1.43 (0.85–2.40)
Stroke vs. acute MI	–	1.20 (0.93–1.56)	–
Coronary revascularization vs. acute MI	–	1.14 (0.88–1.56)	–
Chronic pulmonary disease	–	0.97 (0.80–1.18)	–
Heart failure	–	1.42 (1.41–1.77)	1.39 (1.13–1.72)
Diabetes mellitus	–	1.16 (0.96–1.40)	1.16 (0.97–1.39)
Hyperlipidemia	–	0.95 (0.80–1.14)	–
Hypertension	–	0.99 (0.83–1.19)	–
Obesity	–	1.09 (0.80–1.49)	–
Unstable angina	–	0.96 (0.75–1.25)	–
Renal disease	–	1.28 (0.96–1.69)	1.27 (0.96–1.67)
No. of unique baseline DMARDs	–	0.98 (0.88–1.10)	–
Baseline oral glucocorticoid use	–	1.14 (0.96–1.35)	1.14 (0.96–1.35)
Statin use	–	0.98 (0.82–1.17)	–
ACEi use	–	1.00 (0.84–1.21)	–
Beta blocker use	–	1.12 (0.94–1.22)	–

* Values are the hazard ratio (95% confidence interval). DMARD = disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic DMARD; MI = myocardial infarction; ACEi = angiotensin-converting enzyme inhibitor.

suggested that patients taking glucocorticoids were less likely to discontinue DMARDs, perhaps because of active inflammation requiring continuation of DMARDs even after a CV event. Our findings describe the result of these complex clinical scenarios on a nationwide scale, but we cannot make conclusions about the validity of those clinical decisions.

In the present study, we investigated the risk of a subsequent CV event using a large nationwide database of patients with rheumatic diseases taking DMARDs prior to the initial CV event. The secondary prevention of CV diseases using antiinflammatory drugs is currently being investigated in large randomized clinical trials as a way to understand the contribution of inflammation to CV disease. A large placebo-controlled trial recently showed that canakinumab lowered the risk of recurrent CV events independent of lipid-lowering effect, providing evidence supporting the "inflammatory hypothesis" underlying CV disease (22). A similarly designed placebo-controlled randomized clinical trial is investigating the safety and efficacy of methotrexate for risk of recurrent CV events (32,33). However, these studies were conducted in patient populations without systemic rheumatic diseases, because large-scale placebo-controlled trials with lengthy follow-ups are not feasible for patients with systemic rheumatic disease who require DMARDs.

We investigated the risk of a subsequent CV event among patients with rheumatic diseases who were taking DMARDs prior to the index CV event. We did not analyze patients who discontinued DMARD therapy after their index CV event because these patients may have been more likely to die or have new contraindications to DMARDs. We found no significant differences between the classes of DMARDs for risk of a subsequent CV event after controlling for confounders. All DMARDs investigated possibly had truly similar cardioprotective effects, but perhaps there were subtle differences that we were unable to detect. Because of the number of outcomes, we grouped different DMARDs into the same class. For example, we grouped tocilizumab and abatacept as non-TNFi bDMARDs even though they have different mechanisms of action and therefore may have different effects on CV disease. However, a recent large

observational study comparing tocilizumab to TNFi bDMARDs reported no difference in CV event rates, consistent with our results (34). We also found no difference for risk of a subsequent CV event between csDMARDs and bDMARDs. Patients receiving bDMARDs may be inherently different from patients who can be maintained only using csDMARDs. Since we found no difference between these DMARD classes, confounding by indication or channeling bias probably does not explain these null results. Overall, our study does not provide guidance on DMARD class and risk of CV event, so the decision of DMARD use should be related to the relative risks and benefits for a given patient's clinical scenario.

The current study was subject to inherent limitations of analyses of claims databases and observational studies. The study population was not randomized, but selected from the database based on claims codes. A preliminary review of data from patients who discontinued all DMARD therapy following the index CV event suggested that those patients were clinically different from patients who continued to receive DMARD therapy, and therefore the data from those patients would not be generalizable to the overall RA, PsA, or psoriasis populations. Additionally, the study population was insured, and results of the analysis may not be generalizable to uninsured or underinsured patients. Obesity, a risk factor for CV disease, was identified based on coded diagnoses, and rates of obesity may have been underestimated. Similarly, smoking, another risk factor for CV disease, was not well captured in the database. Information on disease activity and severity is not available from claims databases, which may affect the interpretation of the results. To address this issue, glucocorticoid use at baseline was used as a surrogate for moderate to severe disease prior to initial CV event. There was no adjudication of CV outcomes. Deaths are not well captured in this type of database. This limitation was mitigated in the analysis of subsequent CV event risk by requiring 30 days of follow-up after the initial CV event and excluding patients who did not receive DMARDs after the initial CV event. Although patients in this database filled these prescriptions, there were no measures of medication adherence, and we could not determine whether medications were used as prescribed. Discontinuation of treatment was assumed when prescriptions were not refilled, but patients possibly could have continued taking their medications from a home supply; a 60-day window around medication supply was used to minimize this possibility. Mean follow-up after the initial CV event was <1 year for each class of DMARD; this duration of follow-up may have been too short to detect a true biologic effect on subsequent CV events.

In conclusion, patients with RA, PsA, or psoriasis remain at high risk for a subsequent CV event following an initial CV event. Our study suggests that DMARD therapy for the underlying RA, PsA, or psoriasis does not appear to affect the risk for subsequent CV events, and clinicians should carefully consider continuing DMARD therapy as well as appropriate therapies for CV disease.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Sparks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sparks, Lesperance, Accortt, Solomon.

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ROLE OF THE STUDY SPONSOR

Amgen Inc. designed the study in collaboration with the non-Amgen authors and was involved in the collection, analysis, and interpretation of the data. Both the Amgen and non-Amgen authors participated in writing the manuscript and provided approval to submit the manuscript for publication.

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