Tumor Necrosis Factor-α Inhibitor Treatment and the Risk of Incident Cardiovascular Events in Patients with Early Rheumatoid Arthritis: A Nested Case-control Study

Rishi J. Desai, Jaya K. Rao, Richard A. Hansen, Gang Fang, Matthew Maciejewski, and Joel Farley

ABSTRACT. ***Objective.*** To compare the risk of cardiovascular (CV) events between use of tumor necrosis factor-α inhibitors (TNFi) and nonbiologic disease-modifying antirheumatic drugs (DMARD) in patients with early rheumatoid arthritis (RA).

Methods. A nested case-control study was conducted using data from Truven's MarketScan commercial and Medicare claims database for patients with early RA who started treatment with either a TNFi or a nonbiologic DMARD between January 1, 2008, and December 31, 2010. Date of CV event diagnosis for cases was defined as the event date, and 12 age-matched and sex-matched controls were sampled using incidence density sampling. Drug exposure was defined into the following mutually exclusive categories hierarchically: (1) current use of TNFi (with or without nonbiologics), (2) past use of TNFi (with or without nonbiologics), (3) current use of nonbiologics only, and (4) past use of nonbiologics only. Current use was defined as any use in the period 90 days prior to the event date. Conditional logistic regression models were used to derive incidence rate ratios (IRR).

Results. From the cohort of patients with early RA, 279 cases of incident CV events and 3348 matched controls were identified. The adjusted risk of CV events was not significantly different between current TNFi users and current nonbiologic users (IRR 0.92, 95% CI 0.59–1.44). However, past users of nonbiologics showed significantly higher risk compared to current nonbiologic users (IRR 1.47, 95% CI 1.04–2.08).

Conclusion. No differences in the CV risk were found between current TNFi and current nonbiologic DMARD treatment in patients with early RA. (J Rheumatol First Release Aug 1 2014; doi:10.3899/jrheum.131464)

Key Indexing Terms:
EARLY RHEUMATOID ARTHRITIS
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The association between rheumatoid arthritis (RA) and cardiovascular (CV) events has gained increasing recognition in the last decade. Several epidemiological studies indicate that patients with RA have an increased risk of CV-related morbidity and mortality compared to the general population[1,2,3]. Increased inflammation in patients with RA, which is responsible for acceleration of atherosclerosis, may explain the excess CV risk compared to the general population[4,5]. Therefore, inflammation control by disease-modifying antirheumatic drugs (DMARD) may be helpful in managing the increased CV risk. Additionally, the proinflammatory cytokine tumor necrosis factor (TNF)-α, which is found in abundance in patients with RA, may play an important role in the pathophysiology of CV diseases[6]. Therefore, TNF-α inhibitors (TNFi) may have additional benefits in reducing the excess CV risk in patients with RA.

Although several observational studies have evaluated

the association between CV events and TNFi in established patients with RA[7,8,9,10,11,12,13,14,15,16,17], evidence for this association in early RA is scant[18]. Evaluating the association between TNFi treatment and CV risk in patients with early RA is important because it is known that structural damage to joints occurs aggressively within the first few years of RA[19], so it is possible that development of atherosclerosis may also be rapid during this time. A review concluded that the risk of CV events after the diagnosis of RA increases earlier than previously hypothesized[20]. Evidence establishing atherogenic lipid profile and subclinical atherosclerosis as features of early RA also exists[21,22]. However, the epidemiological evidence of the effect of TNFi on CV events among patients with early RA is limited to only 1 study conducted in a Swedish cohort of about 6000 patients, which compared the CV risk between use and nonuse of TNFi[18].

Given the scarcity of epidemiological data on the risk of CV events in patients with early RA, we conducted our study with the primary objective of examining the association of TNFi treatment with the risk of incident CV events among patients with early RA. Our study adds unique knowledge to the existing body of literature by directly comparing the risk of CV events between TNFi and nonbiologic DMARD. The results from our study should contribute to a better understanding of the comparative benefits of TNFi treatment on CV risk in patients with early RA.

MATERIALS AND METHODS

Data source. Data from the Truven's MarketScan Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits was used for our study (January 1, 2007–December 31, 2010). The Truven's MarketScan Commercial Claims and Encounters contains healthcare data for nearly 40 million commercially insured individuals, encompassing employees, their spouses, and their dependents from the United States. The Medicare Supplemental and Coordination of Benefits data contains the healthcare experiences of 3.8 million Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. These data have been used widely in health services and pharmacoepidemiological research attributable to their substantial size, longitudinal integrity, and unique data links[23]. For our particular analysis, data from the inpatient services file, the outpatient services file, the outpatient drug claims file, and the enrollment file were merged using unique patient identifiers. Our study was approved by the Institutional Review Board at the University of North Carolina, Chapel Hill.

Study design and patient population. The nested case-control study design was selected to evaluate the association between TNFi and CV events, given the efficiency of this design in dealing with the time-varying nature of treatment exposures without substantial loss in power[24]. This design is also recommended to mitigate selection bias in observational studies of patients with RA[25]. From the MarketScan data files, a base cohort was identified of patients with RA aged 18 years and older who had at least 2 outpatient diagnoses (not on the same date) or 1 inpatient diagnosis of RA [International Classification of Diseases, 9th ed (ICD-9) code: 714.0] followed by at least 1 prescription for a TNFi or a nonbiologic DMARD between January 1, 2008, and December 31, 2010. We used this algorithm because using diagnosis codes in combination with a DMARD prescription has been shown to result in a high positive predicted value (81.1%) for identification of RA in administrative claims[26].

The date of first DMARD prescription filled was defined as the index date, and the 12-month period prior to the index date was used as the baseline period (Figure 1). To be considered for our case-control sampling, patients in the base cohort had to meet the following inclusion criteria: (1) continuous enrollment in their health plans 12 months prior to the first identified RA medical claim to ensure at least 12 months for baseline measurements for everyone, (2) no claim with a diagnosis of RA or DMARD prescription 12 months prior to the first identified RA diagnosis to ensure inclusion of only early RA cases, (3) no diagnosis of tuberculosis (contraindication to biologics use) or inflammatory conditions for which biologic treatment is indicated (i.e., psoriatic arthritis, Crohn's disease) during the baseline period to ensure that all the patients were eligible to receive any DMARD treatment and the biologic use was indeed for RA, (4) no diagnosis of any CV event (as defined under outcome measurement below) during the baseline period to ensure that everyone was at risk of developing an incident CV event, and (5) no initiation of treatment with a non-TNFi biologic (including abatacept, anakinara, tocilizumab, and rituximab) on the index date to ensure the homogeneity of the patients with RA selected by our algorithm because the non-TNFi biologics are generally used as second-line agents.

Nested case-control sampling. All of the patients identified as eligible for sampling from the base cohort were followed from their index date to the earliest of the following events: the outcome (CV event diagnosis), disenrollment from their health plan, addition of a non-TNFi biologic, or the study end date (December 31, 2010). If patients experienced a CV event, they were defined as cases and the date of CV event diagnosis was defined as the event date. Once the cases were identified, an incidence density sampling procedure was used to select controls from the remaining patients of the base cohort who were free from CV event at the event date (Figure 1)[27]. We matched each case with 12 controls based on age (within 2 yrs) and sex. Use of incidence density sampling also ensured matching of cases and controls on person-time at risk.

Classification and measurement of treatment exposure. The TNFi included in this study were adalimumab, certolizumab, etanercept, golimumab, and infliximab. These drugs were defined as nonbiologic DMARD: methotrexate (MTX), hydroxychloroquine, auranofin, injectable gold, penicillamine, minocycline, sulfasalazine, azathioprine, leflunomide, cyclophosphamide, and cyclosporine. The use of these agents was identified using both the national drug codes from outpatient pharmacy files for filled prescriptions and J codes using outpatient services files for injectable/infusion agents administered at physician's office. The following mutually exclusive categories were defined hierarchically: (1) current use of TNFi (with or without nonbiologic DMARD), (2) past use of TNFi (with or without nonbiologic DMARD), (3) current use of nonbiologic DMARD only, and (4) past use of nonbiologic DMARD only. Current use was defined as any drug use in a 90-day period prior to the event date, and past use was defined as any drug use more than 90 days prior to the event date (Figure 1). Current nonbiologic DMARD use was selected as the reference group. The addition of indicators for past use allows for evaluating the effect of the treatment in patients who discontinued therapy and has been advocated as a more valid approach in pharmacoepidemiology studies to minimize the nondifferential exposure misclassification[28].

Outcome measurement. The outcome of interest, CV event, was defined as a composite measure consisting of acute myocardial infarction (ICD-9 code 410)[29], unstable angina (ICD-9 code 411)[30], angina pectoris (ICD-9 code 413)[29], chronic heart failure (ICD-9 codes 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93)[31], other forms of chronic heart diseases (ICD-9 code 414)[29], and cerebrovascular events (ICD-9 codes 433.x1, 434.x1, 435.x, 436.x, 437.1x, 437.9x)[31]. To improve the specificity of the identified cases for each of the component events, we further required the patients to have at least 2 outpatient claims (not on the same date) or 1 inpatient claim with the ICD-9 codes listed above for the respective event. For patients meeting this criterion, the date of their earliest eligible claim was defined as the outcome date.

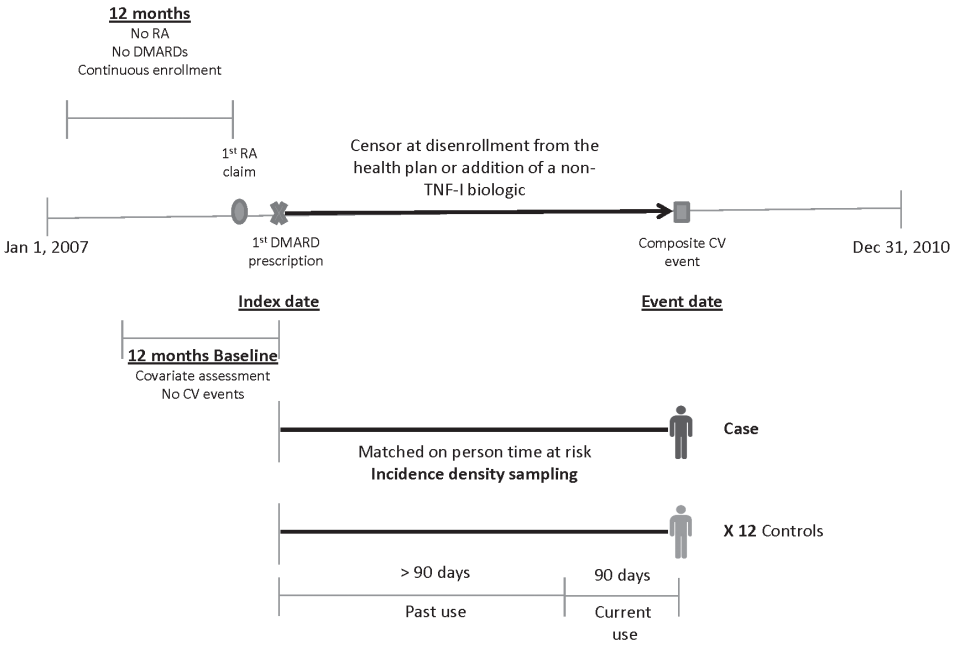

Figure 1. Timeline of the study. RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; TNF-I: tumor necrosis factor-α inhibitor; CV: cardiovascular.

Covariates. The following covariates were identified in the baseline period: CV risk factors including hypertension (HTN), hyperlipidemia, and diabetes mellitus; and other comorbidities including chronic obstructive pulmonary disease (COPD) and any malignancy. We also considered concurrent use of other treatments including lipid-lowering agents, β blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, other CV drugs (cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents, and phosphodiesterase inhibitor), nonselective nonsteroidal antiinflammatory drugs, and cyclooxygenase inhibitors (COX)-2, and defined exposure to these medications as a binary variable based on a filled prescription 90 days prior to the event date. Because of the reports of steroids being associated with an increased CV risk[15], we defined use of these agents using time-specific definitions into following mutually exclusive categories to minimize confounding: (1) never use, (2) past use (any use more than 90 days prior to the event date), and (3) concurrent use (any use 90 days prior to the index date).

Statistical analyses. Descriptive statistics were used to summarize the patient characteristics for our cases and controls. Numbers of each of the component events from our composite CV outcome were presented. The incidence rate ratios (IRR) for the CV events were estimated by OR calculated from conditional logistic regression models that appropriately accounted for the matched sampling technique. Results from both unadjusted and risk adjusted models were presented. All analyses were conducted using SAS version 9.2 (SAS Institute Inc.).

Sensitivity analyses. Multiple sensitivity analyses were conducted to evaluate the strength of the findings. First, we conducted a separate analysis after excluding congestive heart failure (CHF) cases because TNFi are contraindicated in CHF and it is possible that patients showing early signs of CHF, which is not recorded in claims, may be intentionally withheld from TNFi treatment. Further, we conducted a sensitivity analysis in which we used only inpatient claims to define the outcome to detect bias owing to less well-defined diagnoses used in the composite outcome. Next, because our database did not contain information about the severity of RA, we designed a sensitivity analysis in which we controlled for the number of nonbiologic DMARD used, number of visits to rheumatologists, and number of RA-related hospitalizations prior to the event date as a proxy for unmeasured disease severity. Finally, we varied the definition of current use to 30 days and 180 days from the 90-day definition used in the original analysis.

RESULTS

The base-cohort consisted of 10,316 patients with a new diagnosis of RA, who started treatment with either TNFi or nonbiologic DMARD. Of the 10,316 patients in the base cohort, 279 cases of an incident CV event were identified during followup (Figure 2). These cases were age-matched and sex-matched with 3348 controls (12 cases per control) using incidence density sampling. Table 1 compares the case and control patients' baseline characteristics. Cases and their matched controls were 64 years old at the index date, and 65.2% of the cases and controls were women. The mean followup time was 238 days for the cases and controls. Cases had a higher prevalence of CV risk factors (hyperlipidemia, HTN, and diabetes mellitus) and COPD. Concurrent use of CV medications was higher in cases compared to controls. Concurrent use of pain-relieving medications, including nonsteroidal antiinflammatory drugs, COX-2 inhibitors, and steroids, was similar between cases and controls.

Of the 279 cases identified, 18 were diagnosed with acute myocardial infarction, 36 with angina, 54 with CHF, 102 with other forms of chronic heart diseases, 54 with cerebrovascular events, and 17 with multiple diagnoses from this list. The majority of our sample was classified as current nonbiologic users (n = 2582 or 71.1%), followed by

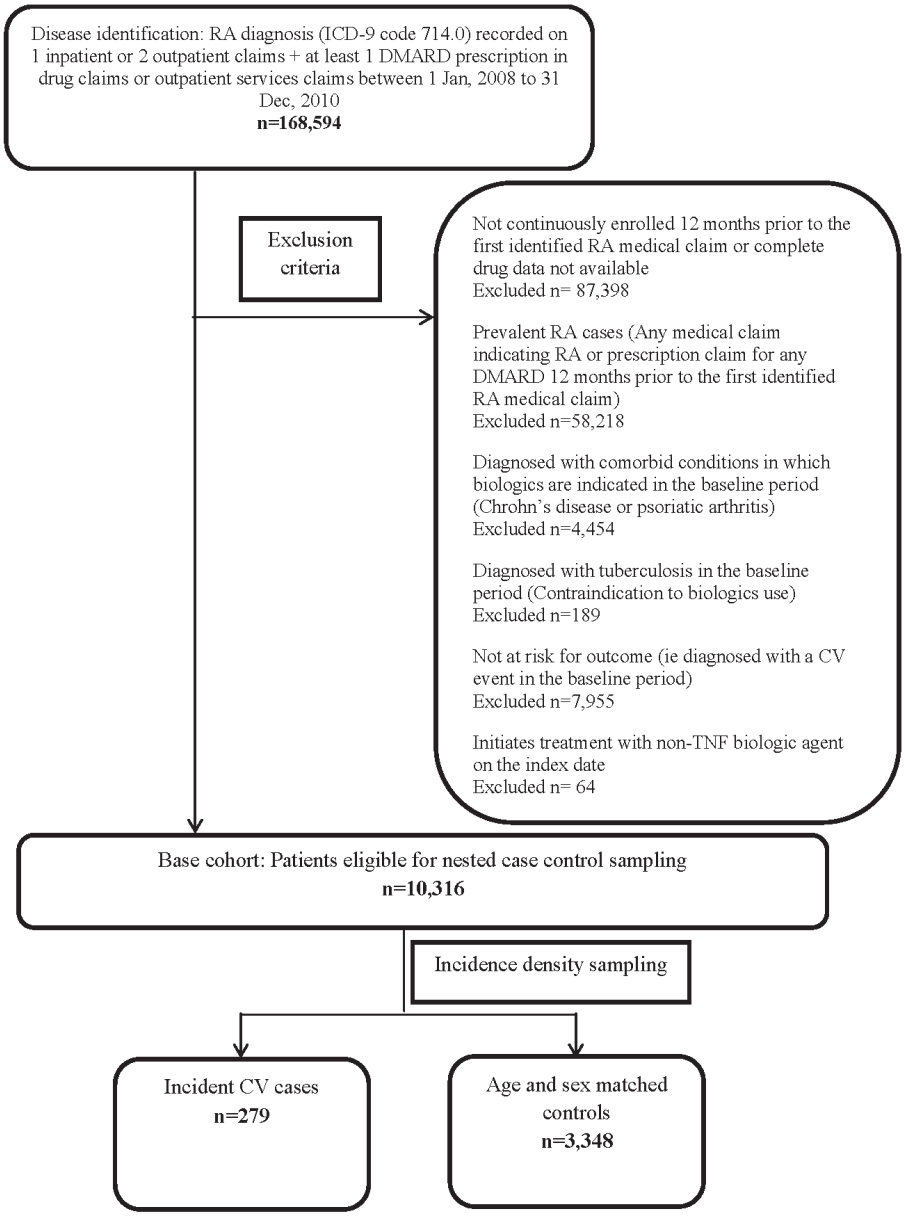

Figure 2. Sample derivation flow chart. RA: rheumatoid arthritis; ICD-9: International Classification of Diseases, 9th ed; DMARD: disease-modifying antirheumatic drug; CV: cardiovascular; TNF: tumor necrosis factor.

past nonbiologic users (15.8%), current TNFi users (11.3%), and past TNFi users (1.8%).

Table 2 shows results from our multivariate analysis. We did not observe any statistically significant difference between current use of TNFi and current use of nonbiologic DMARD or past use of TNFi and current use of nonbiologic DMARD in reducing the risk of CV events in our risk-adjusted analysis (IRR 0.92, 95% CI 0.59–1.44 and IRR 0.99, 95% CI 0.38–2.60, respectively). However, we did observe a statistically significant 47% increase in the risk of CV events among past users of nonbiologic DMARD compared to current users of nonbiologic DMARD (IRR 1.47, 95% CI 1.04–2.08).

Estimates from our sensitivity analyses, in which we varied the "current use" definition, outcome definition, and adjusted for various proxy measures of RA severity prior to the event date, were found to be consistent with the primary model (Figure 3). While estimates for some exposure categories were no longer statistically significant, potentially because of loss of power with smaller sample size in

Table 1. Baseline comparison of cases of incident cardiovascular (CV) events and controls sampled from a cohort of patients with early rheumatoid arthritis.

Variable	Cases, n = 279		Controls, n = 3348	
	n	%	n	%
Matching variables				
Patient age, yrs, mean ± SD	64 ± 12		64 ± 12	
Mean followup time, days, mean ± SD	238 ± 196		238 ± 196	
Female	182	65.2	2184	65.2
CV risk factors				
Diabetes mellitus	82	29.4	564	16.8
Hyperlipidemia	98	35.1	1162	34.7
Hypertension	165	59.1	1571	46.9
Other comorbid conditions				
COPD	61	21.9	484	14.5
Any malignancy	22	7.9	287	8.6
Concurrent drug use†				
Pain relievers				
COXIB	21	7.5	205	6.1
NSAID	29	10.4	320	9.6
Steroids	135	48.4	1569	46.9
CV medications				
ACE inhibitors	53	19	573	17.1
β blockers	68	24.4	541	16.2
Lipid-lowering agents	85	30.5	858	25.6
Calcium channel blockers	61	21.9	494	14.8
Other CV drugs‡	74	26.5	560	16.7

† Concurrent drug use was defined as any use in the period of 90 days prior to the event date; ‡ Other CV drugs include cardiac glycosides, antiarrhythmic agents, hypotensive agents, vasodilating agents, and phosphodiesterase inhibitor. COXIB: cyclooxygenase inhibitors; NSAID: nonsteroidal antiinflammatory drugs; ACE: angiotensin-converting enzyme; COPD: chronic obstructive pulmonary disease.

Table 2. Relative measures of association of an incident cardiovascular event by exposure status in patients with early rheumatoid arthritis.

Exposure†	No. Cases	No. Controls	Unadjusted IRR, (95% CI)	Adjusted‡ IRR, (95% CI)
Current nonbiologic DMARD	191	2391	Ref.	Ref.
Current TNFi	26	383	0.87 (0.56–1.35)	0.92 (0.59–1.44)
Past nonbiologic DMARD	57	515	1.44 (1.03–2.03)	1.47 (1.04–2.08)
Past TNFi	5	59	1.11 (0.43–2.85)	0.99 (0.38–2.60)

† TNF inhibitors include infliximab, etanercept, adalimumab, certolizumab, and golimumab. Nonbiologic DMARD include methotrexate, hydroxychloroquine, auranofin, injectable gold, penicillamine, sulfasalazine, azathioprine, leflunomide, minocycline, cyclophosphamide, and cyclosporine. Other biologic agents include abatacept, anakinara, rituximab, and tocilizumab; ‡ Adjusted for preindex diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, any malignancy, current use of NSAID, COXIB, and CV medications, and current and past use of steroids, in addition to matching with age and sex. Unadjusted associations are estimated in age-matched and sex-matched sample. IRR: incidence rate ratios; DMARD: disease-modifying antirheumatic drug; TNFi: tumor necrosis factor-α inhibitor; NSAID: nonsteroidal antiinflammatory drugs; COXIB: cyclooxygenase inhibitors; CV: cardiovascular.

those categories, the estimates generally trended in the direction of the original results.

DISCUSSION

In this observational study of patients with early RA, we noted that the risk of incident CV events did not differ between current use of TNFi and current use of nonbiologic DMARD. Further, we observed that past users of nonbiologic DMARD had a 47% greater risk of an incident CV event compared to current users of nonbiologic DMARD.

Our study adds new knowledge to the limited body of literature documenting the association between TNFi and CV events in patients with early RA by directly comparing effects of these agents with nonbiologic DMARD. Our

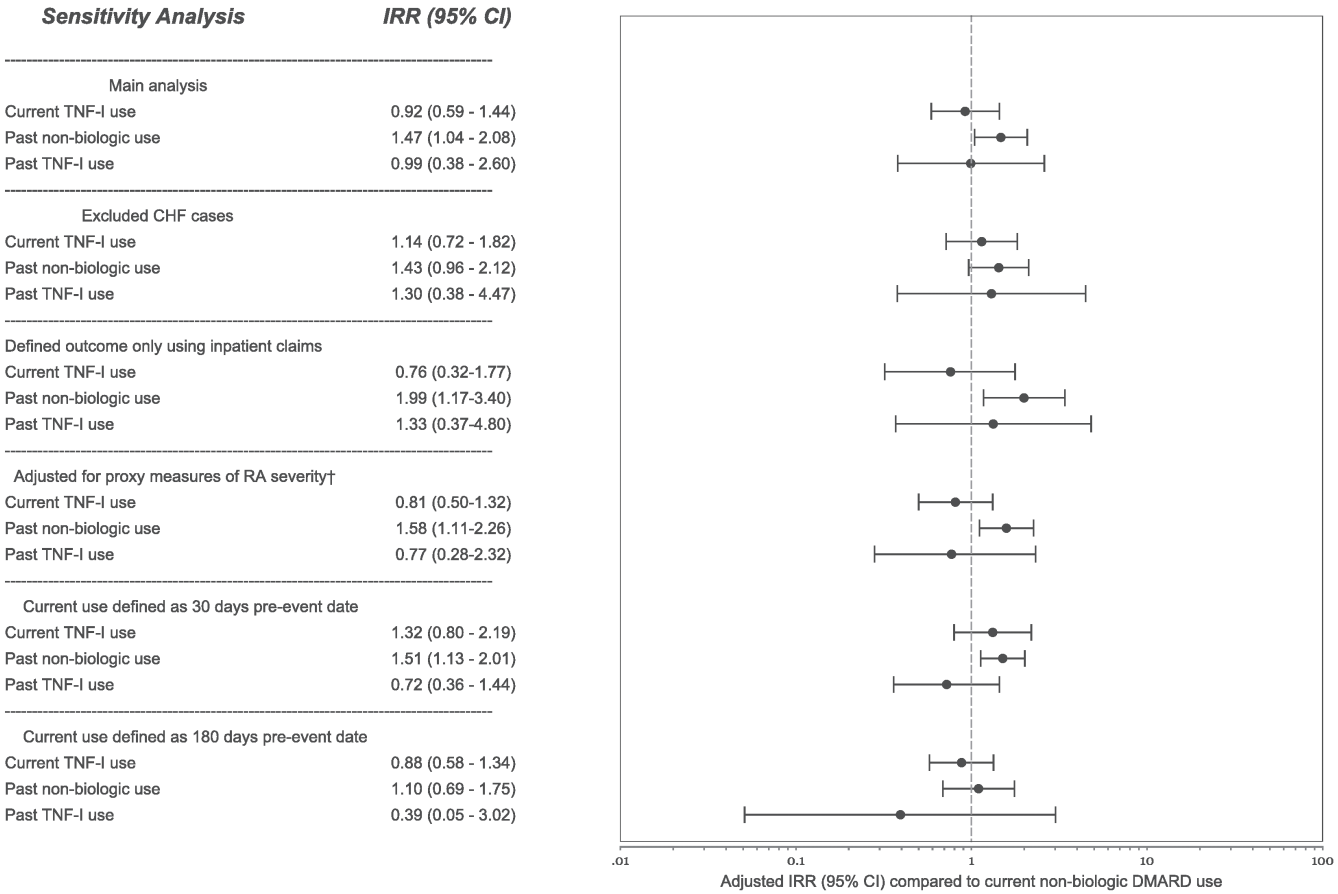

Figure 3. Sensitivity analyses. † RA proxy measures include number of nonbiologic DMARD used, number of visits to rheumatologists, and number of RA-related hospitalizations prior to the event date. IRR: incidence rate ratios; TNF-I: tumor necrosis factor-α inhibitor; CHF: congestive heart failure; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug.

findings suggest that in the early stages of the disease, treatment with TNFi may not be superior to nonbiologic DMARD in reducing the risk of an incident CV event. An earlier study by Ljung, *et al*[18] also did not observe any statistically significant risk reduction in acute coronary syndrome risk after TNFi treatment in a Swedish cohort of patients with early RA [propensity score adjusted hazard ratio (HR) 0.80, 95% CI 0.52–1.24 for TNFi use vs nonuse]. However, a few prior longitudinal observational studies have observed a significant lowering of CV risk after treatment with TNFi[7,16,17]. There are several unique differences between our study and the previous studies in terms of patient population and study design features such as choice of the comparator group, certain exclusion criteria, and exposure definition, that may have contributed to these differential findings. First, the prior studies by Jacobsson, *et al*[7] and Greenberg, *et al*[16] were conducted in patients with longstanding RA (mean disease duration 6–12 years) compared to an early RA cohort in our study. Similarly, Solomon, *et al*[17] compared TNFi and nonbiologic DMARD when both were added to an existing MTX regimen and therefore their analysis may also represent a population of patients that are at a later stage of the disease. Further, Jacobsson, *et al*[7] used nonusers of TNFi as their comparator group instead of our active comparator approach, and hence their comparator group may include a mix of users of nonbiologic DMARD and nonusers of any DMARD. Greenberg, *et al*[16] allowed prevalent use of DMARD at the beginning of the followup, while we initiated followup at the first DMARD prescription. It is worth noting that in a sensitivity analysis where Greenberg, *et al*[16] restricted their cohort to only the new DMARD users, their findings were no longer statistically significant (TNFi vs non-MTX nonbiologic DMARD HR 0.45, 95% CI 0.13–1.56). Finally, unlike our approach of excluding patients with existing CV events, Solomon, *et al*[17] did not exclude these patients from their cohort. In a sensitivity analysis where they excluded patients with known coronary artery disease (or diabetes), an approach that closely resembles our approach, nonstatistically significant findings similar to our study were observed (TNFi vs non-MTX nonbiologic DMARD HR 0.81, 95% CI 0.55–1.23)[17].

Another important contribution of our study is that it provides evidence for the importance of persistence on DMARD treatment in managing CV risk by reporting a higher CV risk among patients who stopped treatment with nonbiologic DMARD (past users) compared to patients receiving treatment with these agents (current users). Persistence on DMARD therapy has been shown to result in favorable outcomes related to RA severity such as lower disease activity and sustained remission in patients with early RA[32]. Markers of RA severity are known to be associated with increased CV risk[33]. Our findings suggest that improved inflammation control through persistence on DMARD treatment may be associated with a decreased risk of incident CV events. Unfortunately, discontinuation of DMARD treatment is very common in RA, reported to be in the range of 54% to 66% in prior studies[32,34]. Special attention should be given to improving persistence with DMARD because, in addition to resulting in better RA-related outcomes, improving persistence to DMARD may also lead to improved CV outcomes.

Our study has several unique strengths. First, our study has high external validity because we used real-world data from patients typically seen in day-to-day clinical practice. Next, we used rigorous evaluation techniques including a study design that is advocated to appropriately account for time-varying exposures and use of an active comparator that is very important to avoid confounding by indication in pharmacoepidemiology studies.

Our study also has some limitations. As with any other study using administrative claims, we were not able to validate the diagnoses of the disease condition as well as the outcome. However, to address this limitation, we used algorithms that have been validated for their use in identifying these conditions in electronic databases whenever possible[26,29,31]. Further, the administrative claims contain very limited information on clinical status of patients with RA, such as disease activity and swollen joint count. Therefore, we were not able to detect and control for the exact severity of RA in our cohort of patients. To address this limitation, we designed a sensitivity analysis in which we tried to control for RA severity by adjusting for the number of nonbiologic DMARD used prior to the event date. Because we used a baseline period of 12 months to define prior CV events and comorbidities, events not recorded in this time frame may have been misclassified as nonevents. Additionally, because the claims data do not have reliable information on patient vital status, our study is limited by the competing risk of death. It must also be noted that certain exposure categories had small numbers of patients, which may lead to limited power to detect differences between the groups. Further, our database did not contain information on important variables such as tobacco use, which is a risk factor for both RA and CV events. We were also not able to identify the over-the-counter use of certain pain relievers, which are commonly used by patients with RA. Therefore, there may be some residual confounding in our exposure-outcome association even after multivariate risk adjustment. Finally, given the limited number of composite CV events identified, we were not able to conduct comparisons across individual CV endpoints. Future studies should be designed to evaluate the effect of these treatments on various individual CV endpoints. Because of these limitations, our findings should be considered hypothesis-generating rather than hypothesis-confirming. Future prospective studies with precise covariate and outcome measurement and sufficient followup time should be considered to evaluate the comparative effect of TNFi on incident CV events.

We observed that there was no difference between current treatment with TNFi and current treatment with nonbiologic DMARD in reducing the risk of CV events in patients with early RA. We also observed that past users of nonbiologic DMARD had a higher risk of incident CV events compared to current users of these agents, implying that inflammation control through persistence of treatment with these agents is extremely important in managing CV risk even in early stages of RA.

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