

EXTENDED REPORT

Longer durations of antitumour necrosis factor treatment are associated with reduced risk of cardiovascular events in patients with rheumatoid arthritis

Michael Nurmohamed,¹ Yanjun Bao,² James Signorovitch,³ Alex Trahey,³ Parvez Mulani,² Daniel E Furst⁴

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¹Departments of Internal Medicine and Rheumatology, VU University Medical Centre, Amsterdam, The Netherlands

²Health Economics and Outcomes Research, AbbVie, North Chicago, Illinois, USA

³The Analysis Group, Boston, Massachusetts, USA

⁴University of California-Los Angeles (UCLA), Los Angeles, California, USA

Correspondence to

Dr Michael Nurmohamed; Nurmohamed@vumc.nl

ABSTRACT

Objective: To assess the effects of treatment with antitumour necrosis factor (TNF) agents, methotrexate, or other non-biological disease-modifying antirheumatic drugs (DMARDs) on cardiovascular event risks among patients with rheumatoid arthritis (RA).

Methods: We conducted a retrospective study using data from the MarketScan claims database. Patients with RA with ≥ 1 prescription for an index drug were included. Each patient's use of an index drug was calculated cumulatively as a time-varying exposure. The incidence of cardiovascular events among patients with RA was determined. Associations between drug exposures and occurrence of cardiovascular events were assessed with Cox proportional hazards models.

Results: Of 113 677 patients identified, 35.8%, 41.1% and 23.1% received anti-TNF agents, methotrexate and other DMARDs, respectively. Patients were treated for an average of 7.6 months; 2138 patients (1.9%) had a cardiovascular event following their index prescription. Each additional 6 months of anti-TNF therapy use versus non-use reduced the risk (HR; 95% CI) for any cardiovascular event by 12% (0.88; 0.81 to 0.95, $p=0.002$). Anti-TNF therapy was associated with a 13% and 12% reduction in cardiovascular events in patients aged ≥ 50 years (0.87; 0.80 to 0.95, $p=0.002$) and in those without prior methotrexate use (0.88; 0.78 to 0.99, $p=0.04$), respectively. Cumulative use of 1, 2 or 3 years of anti-TNF therapy versus non-use is expected to reduce cardiovascular event risks by 21%, 38% and 51%, respectively.

Conclusions: Anti-TNF therapy was associated with a significantly lower risk of cardiovascular events among patients with RA, older patients with RA and patients without prior exposure to methotrexate.

INTRODUCTION

Patients with rheumatoid arthritis (RA) face greater cardiovascular morbidity than the general population, including increased risks of major cardiovascular events, and increased numbers of cardiovascular deaths.^{1–8} The risk of cardiovascular events in patients with RA is

Key messages

What is already known on this subject?

- Rheumatoid arthritis is associated with increased cardiovascular morbidity and mortality.
- Anti-TNF treatment has been associated with cardiovascular risk reduction in multiple observational studies of patients with rheumatoid arthritis.

What does this study add?

- The present study strengthens the evidence for cardiovascular risk reduction with anti-TNF treatment by documenting a quantitative exposure-response relationship: longer cumulative exposures to anti-TNF were associated with greater levels of risk reduction.

How might this impact on clinical practice?

- Patients with longer treatment duration on anti-TNF therapies for RA may derive additional benefits in CV risk reduction.

comparable to that of patients with diabetes.^{9 10} Some of this increased cardiovascular morbidity in RA is explained by a greater prevalence of traditional cardiovascular risk factors, such as diabetes, hyperlipidaemia and hypertension.¹¹ However, traditional risk factors do not fully explain the excess cardiovascular morbidity in RA.^{12 13} Markers of RA disease activity and systemic inflammation have also been associated with cardiovascular event risk in patients with RA. Inflammation has been linked to worsened cardiovascular risk factors, including body composition, glucose metabolism and handling, and lipid function in both the general population^{14–19} and in patients with RA,^{20–23} where chronic, systemic

inflammation is a hallmark of the disease. In response, clinical guidelines suggest managing cardiovascular risk in patients with RA through control of RA disease activity, regular monitoring of cardiovascular risk factors and use of cardiovascular treatments when indicated.²⁴

A growing body of observational evidence has described associations between treatments for RA and cardiovascular outcomes. Treatment with methotrexate (MTX) has been associated with reduced risk of cardiovascular events²⁵ and cardiovascular death²⁶ among patients with RA, and among patients with a wide range of inflammation-related conditions.²⁷ Use of low-dose corticosteroids has been associated with increased risks of myocardial infarction and stroke.²⁸ Multiple observational studies and meta-analyses of observational studies have identified associations between antibody inhibition of tumour necrosis factor (TNF) α , and reductions in fatal and non-fatal cardiovascular event rates in patients with RA (see online supplementary table S1).^{12 29 30} Risk reduction with anti-TNF therapy has been observed for myocardial infarction and stroke in a recent meta-analysis of 11 observational studies.³⁰ Associations between anti-TNF treatment and risks of hospitalisation for unstable angina and congestive heart failure are mixed.^{30 31}

We examined associations between anti-TNF use and cardiovascular event risk in terms of the duration of anti-TNF exposure rather than simply exposure versus non-exposure, in essence looking for a cumulative dose-to-risk response. The rationale for focusing on exposure duration is twofold. First, because reductions in systemic inflammation could reduce cardiovascular event risk through multiple pathways, including improvement in traditional cardiovascular risk factors, plaque stabilisation, and improved physical activity, the impacts of treatment on cardiovascular event risk may increase over time. Indeed, the impact of RA on increasing cardiovascular risk is known to increase cumulatively over time, so the potential to achieve increasing levels of risk reduction with anti-TNF exposure is of both scientific and clinical interest.^{32 33} Second, the establishment of a relationship between longer duration of exposure and greater response (ie, a dose-response relationship) is considered a marker of reliability in observational studies,³⁴ and could potentially strengthen the existing evidence linking anti-TNF use to reductions in cardiovascular event risk. To test the hypothesis that longer exposure to anti-TNF treatment is associated with greater cardiovascular risk reductions, we analysed a large claims database, reflecting real-world use of treatments for RA, and the outcomes.

METHODS

Patients

Patients with RA, and at least two claims for RA-related medical services (ICD-9-CM 714.xx), were identified in the *Truven Health MarketScan® Commercial Claims and Medicare Supplemental Databases* (Quarter [Q] 1 2003–Q2

2011). These de-identified and Health Insurance Privacy and Portability Act-compliant databases capture information on the health services of approximately 25 million insured employees, dependents and retirees per year, throughout the USA. The first anti-TNF prescription fill was taken as the index date. Among the remaining patients, a randomly chosen prescription fill, or injection for MTX or other non-biologic disease-modifying antirheumatic drug (DMARD), among all such fills, was taken as the index date. Random index dates for non-biologics were used, as opposed to dates of first use, because the majority of patients with RA receive MTX or other non-biologics before receiving anti-TNF treatment. Patients without prescription fills or injections for the aforementioned drugs were excluded. Index dates were required to follow at least 1 year of continuous eligibility, which served as the baseline period.

Statistics

The presence of cardiovascular events, defined as inpatient diagnoses for myocardial infarction (International Statistical Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM): 410.xx), stroke or transient ischaemic attack (ICD-9 CM: 430.xx-437), congestive heart failure (ICD-9 CM: 402.x1, 404.x1, 428.xx), or unstable angina (ICD-9 CM: 411.1), was assessed following the index date. The primary outcome was the time from the index date to the first cardiovascular event. Times to each type of event were studied as secondary outcomes. The time-to-event outcomes for patients without events were censored at the end of data availability (eg, in Q2 of 2011, or on health plan disenrolment), or 6 months after discontinuation of their index therapy,²⁹ whichever came first.

Each patient's use of anti-TNF agents, MTX, other DMARDs, or corticosteroids, was calculated cumulatively as a time-varying exposure. At each point in time, the patient's cumulative exposure was calculated from prescription claims as the total days of supply dispensed on or after the index date up until that point in time.

Cox proportional hazards models were used to assess associations between drug exposures and the occurrence of cardiovascular events. Multivariable models included time-dependent measures of cumulative drug exposure with adjustment for age; sex; baseline diagnoses (dyslipidaemia, hypertension, diabetes, chronic obstructive pulmonary disease, anaemia, electrolyte disorders, alcohol or drug abuse, obesity); visits to rheumatologists or cardiologists during the baseline period; baseline diagnoses for cardiovascular events (myocardial infarction, stroke, transient ischaemic attack, congestive heart failure or unstable angina); and baseline use of MTX, corticosteroids, cyclo-oxygenase-2 inhibitors, other non-steroidal anti-inflammatory drugs, narcotic analgesics, lipid-lowering medications, antihypertensive medications and smoking deterrents (see online supplementary table S2). Under this model, the effect of drug exposure

depends on the duration of exposure. To facilitate interpretation, adjusted HRs were calculated, based on the fitted model, for cumulative exposures of 1, 2 and 3 years to combination therapy with anti-TNF+MTX versus MTX monotherapy. Cumulative incidence curves were estimated using the multivariable model and Breslow estimate of the background hazard to predict cumulative risk at each year of exposure for a hypothetical patient with average baseline characteristics and continuous use of the given drugs. A test of interaction between exposure to anti-TNF and MTX was conducted. Subgroup analyses were conducted for patients aged 50 years or older (selected based on the mean age of the study cohort), and for patients without prior use of MTX.

All statistical analyses used SAS, V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patients

A total of 113 677 patients met the inclusion criteria. Among them, 37.1% were younger than 50 years, 59.7%

were aged 50–65 years, and 3.2% were older than 65 years. Seventy-six per cent were women. Among the included patients, 40 717 (35.8%) used anti-TNF agents, 46 681 (41.1%) received MTX without anti-TNF agents and 26 279 (23.1%) received other non-biologic DMARDs. Less than 1% used combination therapy with non-MTX DMARDs or non-TNF biologicals. Median follow-up in these groups was 14.9, 3.7 and 3.5 months, respectively. Among prescriptions for oral MTX during the study period, the median dose was 14 mg/week (10.0, 17.7), and the median of patients' maximum oral doses was 19.4 mg/week (15.0, 25.0). Dose data were unavailable for approximately 12% of MTX-treated patients who received injectable MTX.

Baseline characteristics were generally similar across exposure groups, with patients having similar comorbidity profiles, similar cardiovascular event histories and similar rates of cardiovascular-related medication use (table 1). Prevalent baseline cardiovascular risk factors in the full study population included diagnoses for diabetes (12.7%), dyslipidaemia (32.1%) and hypertension (35.0%). Prescriptions were filled for 20.4% and 25% of patients for lipid-lowering drugs and for antihypertensive

Table 1 Baseline characteristics by exposure group

Characteristics	Anti-TNF (n=40 717)	MTX (n=46 681)	Other DMARD (n=26 279)
Demographics			
Mean age (SD), years	51.0±10.4	52.8±9.8*	51.7±10.3*
Female, n (%)	30 414 (74.7)	36 173 (77.5)*	20 237 (77.0)*
Comorbidities, n (%)			
Dyslipidaemia	12 753 (31.3)	14 988 (32.1)*	8703 (33.1)*
Hypertension	13 907 (34.2)	16 482 (35.3)*	9430 (35.9)*
Diabetes	5190 (12.7)	6007 (12.9)	3195 (12.2)*
Chronic obstructive pulmonary disease	4492 (11.0)	4830 (10.3)*	3050 (11.6)*
Deficiency anaemia	6252 (15.4)	6310 (13.5)*	4090 (15.6)
Electrolyte disorder	2684 (6.6)	2694 (5.8)*	1891 (7.2)*
Alcohol-related or drug-related disorder	1775 (4.4)	1912 (4.1)	1163 (4.4)
Obesity	1590 (3.9)	1739 (3.7)	1051 (4.0)
Baseline medical service use, mean±SD			
Rheumatologist visit	2.8±3.7	2.3±3.5*	1.9±3.1*
Cardiologist visit	0.3±1.4	0.3±1.3*	0.4±1.5*
Prior cardiovascular diagnoses, n (%)			
Myocardial infarction	528 (1.3)	562 (1.2)	326 (1.2)
Stroke/transient ischaemic attack	1812 (4.5)	2134 (4.6)	1369 (5.2)*
Unstable angina	645 (1.6)	664 (1.4)*	425 (1.6)
Congestive heart failure	1152 (2.8)	1439 (3.1)*	959 (3.6)*
RA-related medications, n (%)			
Methotrexate	23 725 (58.3)	24 347 (52.2)*	1736 (6.6)*
Corticosteroids	27 509 (67.6)	30 135 (64.6)*	15 325 (58.3)*
Cardiovascular-related medications, n (%)			
COX-2-selective NSAIDs	9039 (22.2)	9801 (21.0)*	5351 (20.4)*
Other non-selective NSAIDs	17 899 (44.0)	22 477 (48.2)*	12 143 (46.2)*
Narcotic analgesic	22 161 (54.4)	23 766 (50.9)*	13 452 (51.2)*
Lipid-lowering medication	7988 (19.6)	9736 (20.9)*	5494 (20.9)*
Antihypertensive medication	9896 (24.3)	11 892 (25.5)*	6613 (25.2)*
Smoking deterrent	533 (1.3)	603 (1.3)	299 (1.1)

*p Value <0.05 for comparison to the anti-TNF group.

COX-2, cyclo-oxygenase-2; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Table 2 Patient counts, event counts and unadjusted incidence rates

Exposure categories	Description*	Number of patients	Total patient-years (×100)	Cardiovascular events/100 patient-years of exposure
Exposure to anti-TNF	Anti-TNF use, with possible use of MTX or other DMARDs	40 717	768.9	1.7
Exposure to MTX	MTX use with possible use of other DMARDs, but no anti-TNF	46 681	230.7	2.0
Exposure to other DMARDs	Use of other DMARDs, without use of MTX or anti-TNF	26 279	129.2	2.7

*Defined hierarchically as in Greenberg *et al.*^{29–40}

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumour necrosis factor.

drugs, respectively. A total of 9872 patients (8.7%) experienced a prior diagnosis for myocardial infarction, stroke/transient ischaemic attack, unstable angina or congestive heart failure during the baseline period. Differences across exposure groups included patients in the anti-TNF exposure group having a higher rate of rheumatologist visits and a slightly lower rate of women, and patients in the other DMARD group having less prior use of MTX (table 1).

Primary outcomes

A total of 2138 patients (1.9%) had at least one cardiovascular event during the study period; 459 patients had a myocardial infarction, 845 patients had a stroke or transient ischaemic attack, 461 patients had unstable angina and 845 had congestive heart failure. The unadjusted incidence of the primary composite event, consisting of inpatient diagnosis for myocardial infarction, stroke/transient ischaemic attack, unstable angina or heart failure, was 1.7/100 patient-years (PY) among anti-TNF or anti-TNF combination-treated patients, 2.0/100 PY among the MTX or MTX and DMARDs-treated patients and 2.7/100 PY among patients receiving only other non-biological DMARDs aside from MTX (table 2). The majority of events (1784) occurred among patients aged 50 years or older, with only 354 events occurring among patients younger than 50 years.

In the adjusted Cox models, each additional 6 months of anti-TNF treatment was significantly associated with a 12% reduction in cardiovascular event risk (HR 0.88, 95% CI 0.81 to 0.95, $p=0.002$; figure 1A). In addition to adjusting for patient baseline characteristics, this analysis adjusted for cumulative exposures to MTX, other non-biologic DMARDs and corticosteroids during the study period. Use of MTX or other DMARDs was not significantly associated with a significant reduction in cardiovascular event risk (figure 1A). However, each additional 6 months of treatment with corticosteroids was associated with a 7% increase in the risk of cardiovascular events (HR 1.07, 95% CI 1.03 to 1.10, $p<0.001$). It is worth noting that the three exposure groups into which patients were hierarchically classified for tables 1 and 2 are not included in this time-to-event analysis, where

cumulative exposures to each type of treatment were measured separately to reflect real-world use.

The model predicted that cumulative use of 1, 2 or 3 years of anti-TNF+MTX treatment would reduce the cardiovascular event risks by 21%, 38% and 51%, respectively, compared to use of MTX alone during those time periods, adjusting for baseline characteristics and concurrent use of other DMARDs and corticosteroids (figure 2). Predicted cumulative incidence curves for continuous treatment with anti-TNF+MTX or with MTX are shown in figure 3. On the log-hazard scale, no significant interaction was detected between effects on cardiovascular risk of exposure to anti-TNF and exposure to MTX. This indicates that anti-TNF combination therapy and anti-TNF monotherapy are associated with similar levels of cardiovascular risk reduction, which is greater than that associated with MTX monotherapy.

In the subgroup analyses, each additional 6 months of TNF treatment was associated with a 13% reduction in composite cardiovascular event risk (HR 0.87, 95% CI 0.80 to 0.95; $p=0.002$) among patients aged ≥ 50 years, and with a 12% reduction (HR 0.88, 95% CI 0.78 to 0.99, $p=0.04$) among patients without prior MTX (figure 1B). Estimated effects were numerically similar among patients aged younger than 50 years (HR=0.86, 95% CI 0.72 to 1.04; $p=0.12$), and among patients with prior MTX (HR=0.88, 95% CI 0.80 to 0.98; $p=0.02$). In the full study population, when individual types of cardiovascular events were analysed as secondary outcomes, each additional 6 months of anti-TNF treatment was associated with statistically significant reductions in the risk of myocardial infarction by 18% (HR 0.82, $p=0.01$), unstable angina by 23% (HR 0.77, $p=0.002$) and congestive heart failure by 20% (HR 0.80, $p<0.001$). No association was observed between cumulative use of anti-TNF and the hazard of stroke (HR 0.98, $p=0.706$).

DISCUSSION

This study used a large retrospective database to investigate associations between durations of exposure to treatments for RA and cardiovascular risk. In this study, we added an estimate of continued treatment with anti-TNF

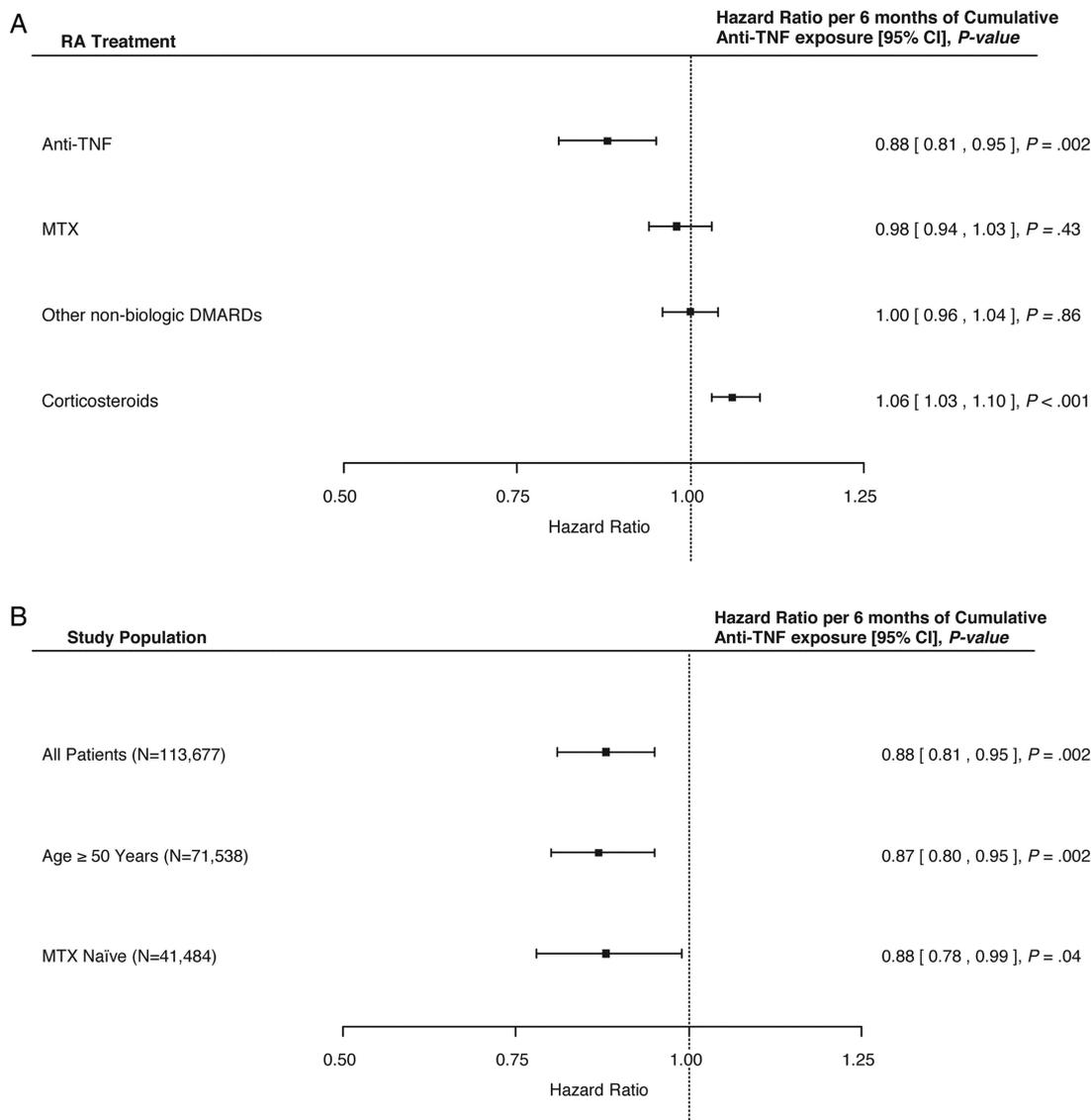


Figure 1 HRs for composite cardiovascular events. (A) RA treatments, (B) anti-TNF treatment in subpopulations. *Adjusted for baseline demographics, comorbidities, prior cardiovascular events, RA medications and cardiovascular-related medications (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor).

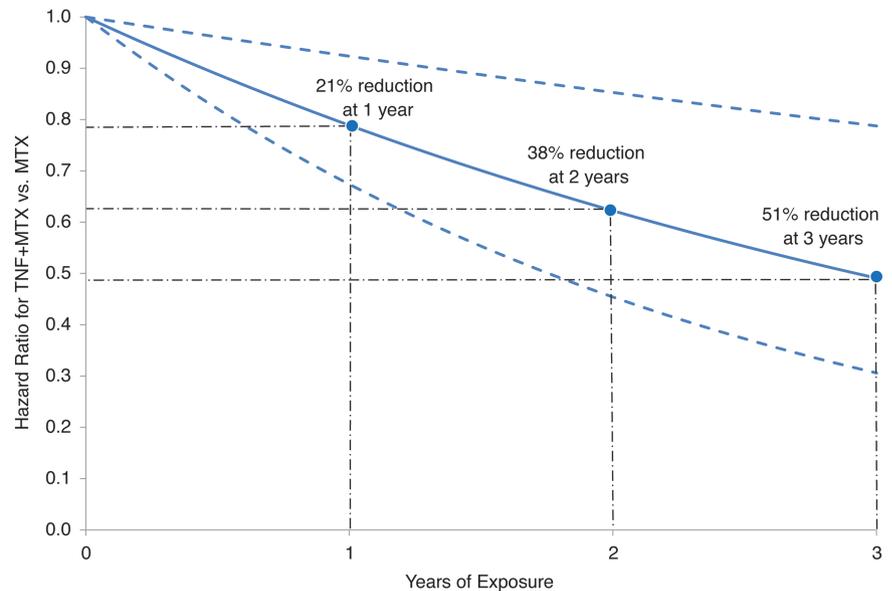
agents and MTX as well as cumulative exposure to other therapies. Longer exposure to anti-TNF therapy was found to be associated with significantly reduced cardiovascular event risk after adjusting for concurrent use of MTX, other DMARDs and corticosteroids, in addition to patient baseline characteristics. Cumulative exposures to MTX or other DMARDs were not significantly associated with reduced cardiovascular event risk in comparison with no exposure to these drugs. Longer exposure to corticosteroids was associated with significantly increased cardiovascular event risk.

In a recent meta-analysis of 11 studies, Barnabe *et al*³⁰ found anti-TNF treatment was associated with significantly reduced risks of composite cardiovascular events, myocardial infarction and stroke (see online supplementary table S1). In addition to the present study, two other observational studies were published

subsequent to the Barnabe *et al*³⁰ meta-analysis, and provided consistent findings (see online supplementary table S1). Greenberg *et al*²⁹ found significant associations between anti-TNF treatment, and reduced risk of a composite cardiovascular event and myocardial infarction. Anti-TNF treatment was numerically associated with reduced risk of stroke, but the association was not statistically significant. Ljung *et al*³¹ studied acute coronary syndromes and did not detect a statistically significant association with anti-TNF treatment, but observed a numerical 20% risk reduction, similar to that of Barnabe *et al*,³⁰ Greenberg *et al*²⁹ and the present study.

The present study also adds to the evidence for effects of anti-TNF treatment on cardiovascular risk reduction by associating longer anti-TNF exposures with greater risk reduction. This cumulative relationship between drug exposure (measured as the duration of use) and its effect

Figure 2 Cardiovascular hazard reduction associated with longer anti-TNF exposure (MTX, methotrexate; TNF, tumour necrosis factor).



on reducing cardiovascular risk is of real interest. Another aspect needed to assess the credibility of an observational study is a plausible scientific explanation for the result, which was found in this case.^{14 35–39} Finally, the fact that other observational studies generally support our finding adds credibility to the findings.^{12 29–31} A strength of the current study is that data were available for all patients meeting the inclusion criteria, even those who subsequently disenrolled from their health plan, and drug exposure histories were calculated as time-dependent variables.

The lack of a significant association between MTX treatment and cardiovascular risk reduction in the present study is consistent with Greenberg *et al.*²⁹ When interpreting this result, it is important to consider that all

patients in this study received at least one oral DMARD. It is possible that MTX and other non-biological DMARDs reduce cardiovascular risk versus the absence of DMARD treatment,⁴⁰ although MTX was not associated with such reduction in this study. It should be noted that the doses of MTX recorded in the present study were consistent with aggressive treatment, with a median maximum dose of approximately 19 mg/week. However, the lack of statistical significance in the present study does not rule out an association between use of MTX and reduced cardiovascular risk. The significant association between use of corticosteroid and increased cardiovascular risk observed in the present study is consistent with prior studies^{29 41} and with the European League Against Rheumatism guidance for managing cardiovascular risk in patients with RA.²⁴ Previous studies associated higher maximum corticosteroid dose with greater cardiovascular risk, whereas, the present study associated longer duration of corticosteroid exposure with greater cardiovascular risk.

The significant association between longer duration of anti-TNF exposure and reduced cardiovascular risk in the present study was based on a composite cardiovascular end point consisting of inpatient diagnoses for myocardial infarction, stroke, congestive heart failure and unstable angina. When studied separately, risks for each of these events were significantly reduced with longer durations of anti-TNF treatment except for stroke. The reason for lack of association with stroke is unclear, but could be due to lower precision in detecting true stroke events based on claims and, by a truly smaller association, to chance; or it might be mediated by effects on blood pressure. Greenberg *et al.*²⁹ also observed no statistically significant association between anti-TNF use and stroke.

Studies of associations between anti-TNF treatment and congestive heart failure risk in RA have produced mixed findings, with some studies observing a significant reduction in congestive heart failure risk,^{42 43} some

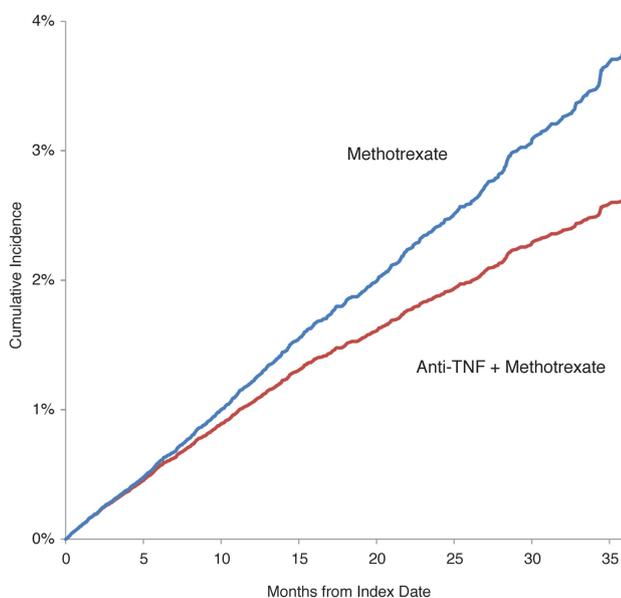


Figure 3 Adjusted cumulative incidence of composite cardiovascular events. (TNF, tumour necrosis factor).

observing non-significant associations^{44 45} and some observing associations with increased congestive heart failure risk.^{46 47} A study by Curtis *et al*⁴⁶ was based on small numbers of events and did not utilise multivariable adjustments to account for differences between patients using and not using anti-TNF agents. Setoguchi *et al*⁴⁷ exclusively studied Medicare patients, whereas the present study included largely non-Medicare patients.

This study has some limitations. Although we adjusted for a large number of baseline characteristics in the multivariable models, confounding due to unobserved factors may remain. For example, using claims data, we could not directly adjust for important cardiovascular risk factors such as blood pressure, low-density lipoprotein and high-density lipoprotein levels, smoking history, family history of cardiovascular events, use of over-the-counter aspirin and body mass index. Disease duration of RA was another potential confounder that is not available in claims data. In addition, death was not observable in claims data and could not be studied as an end point. Claims data may also contain misreported diagnoses and fills for prescriptions that were not fully used, which would be expected to bias towards null associations between exposure and risk. Furthermore, because employees and their dependents in the USA often switch health insurance providers when they change their employment status, the present study had limited follow-up durations and could not reliably assess drug exposure durations longer than 3 years. There were also limited sample sizes to study DMARDs aside from TNF inhibitors and MTX, and complete dose data were not available for MTX or steroids. Finally, the present study does not distinguish among different anti-TNF agents, which could have different effects on cardiovascular risk. Further studies are needed to assess the extent to which associations between anti-TNF use and cardiovascular risk reduction represent a class effect.

The present study cannot identify the mechanism for associations between anti-TNF treatment and cardiovascular risk reduction, but several mechanisms have been hypothesised. First, inhibition of TNF- α may improve lipoprotein composition, stabilise plaques and reduce systemic inflammation that contributes to cardiovascular risk.^{14 35–39} Second, anti-TNF treatment may improve patients' abilities to participate in physical activities, which may reduce cardiovascular risk. This explanation seems unlikely to account for the findings of the current study; MTX and other DMARDs are also effective in reducing disease activity, yet they were not associated with cardiovascular risk reduction. Third, anti-TNF treatment may reduce the need for corticosteroids, which can reduce steroid-associated cardiovascular risks. The present study accounted for this hypothesis by adjusting for cumulative use of corticosteroids during the study period.

After accounting for cumulative exposures to treatments for RA, treatment with anti-TNF agents was

associated with significantly lower risk of cardiovascular events (for inpatient myocardial infarction, stroke, unstable angina or congestive heart failure). The cardiovascular risk reduction associated with longer exposure to anti-TNF therapy was primarily driven by reductions in myocardial infarction, unstable angina and congestive heart failure.

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Dedication This manuscript is dedicated to the memory of Parvez Mulani, AbbVie colleague and friend (1974–2014), who continues to be a great inspiration.

Contributors YB, PM and JS provided the study concept and design. Acquisition of data was provided by JS. Analysis and interpretation of data were performed by DEF, MN, JS, AT, YB and PM. The manuscript was drafted by MN, JS and AT. Statistical analysis was carried out by JS and AT. Critical revision of manuscript for important intellectual content was performed by DEF, MN, JS, YB and PM. All authors approved the version submitted for publication.

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