No increased cardiovascular mortality among early rheumatoid arthritis patients: a nationwide register study in 2000-2008

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Abstract

Objective

To assess cardiovascular (CV) mortality in early rheumatoid arthritis (RA), and the impact of RA medications on CV mortality.

Methods

We identified all incident RA patients over 18 years of age diagnosed between 2000 and 2007 in Finland. Causes of death were analysed until the end of the year 2008. We used competing-risks regression models to assess the impact of different variables such as RA medications on CV mortality. CV mortality was compared with that of the age- and sex-specific general population.

Results

We identified 14,878 incident RA patients (68% women, 63% rheumatoid factor (RF) positive, mean age 55.8/57.5 years in men/women), of whom more than 80% received RA medications for longer than 90% of their individual patient-years. By the end of 2008, 1,157 patients died, 501 (43%) of whom of CV causes. The standardised mortality ratio (SMR) for CV deaths in the entire RA cohort was 0.57 (95% CI 0.52 to 0.62). Along with traditional CV risk factors, the presence of RF and the use of glucocorticoids was associated with a higher risk of CV death, whereas the use of methotrexate was associated with a lower risk.

Conclusion

These nationwide results suggest that patients with recent-onset RA who receive consistent RA medication have no increased risk for CV mortality compared to the general population, at least in the early years of the disease. The use of methotrexate is associated with lower CV mortality, whereas the use of glucocorticoids is associated with a higher than average CV mortality.

Key words

rheumatoid arthritis, mortality, cardiovascular diseases

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Introduction

A plethora of research data spanning several decades demonstrates that rheumatoid arthritis (RA) patients carry a high risk of cardiovascular (CV) disease. Observational studies have shown that RA leads to an approximately 50% increase in CV mortality in comparison to the general population (1). Most of the evidence on increased CV mortality has been obtained from RA cohorts with established and long-standing disease (1). Although signs of atherosclerosis and CV comorbidities seem to be excessively prevalent even in the early stages of RA (2, 3), studies with inception and early RA cohorts do not always suggest increased CV or all-cause mortality (1, 4-6).

Since the 1990s, improvement in RA treatment strategies has yielded an apparent reduction in RA disease activity (7). However, despite the enhanced control of inflammation, there is not enough evidence to fully confirm a reduction in all-cause or CV mortality in established RA over time (4). Prolonged life expectancy has been observed in some settings (8), but even a widening mortality gap between RA patients and the general population has been suggested (6). A recent British register study indicated that the mortality rates in early inflammatory arthritis have not changed over the past 20 years when accounting for changes in the population rates (9).

The impact of RA medications on CV risk are complex, and may be mediated both through direct effects on the CV system and through an alleviation of the systemic inflammation driving atherosclerosis (10, 11). Methotrexate (MTX), the cornerstone of the initial treatment of RA, and tumour necrosis factor (TNF) inhibitors may decrease the risk of CV events (12, 13). The role of glucocorticoids as predictors of CV mortality remains to be determined – although epidemiological data suggest a positive association between CV mortality and glucocorticoid use (14-16), the evidence of the extent to which confounding by indication is reflected in these results is not sufficient (11).

In this study, we wanted to address the important question whether CV mortality in early RA is still increased in the 2000s, during an era of new RA treatment regimens. We utilised the Finnish Causes of Death Register to compare the CV death rates between RA patients diagnosed in 2000-2007 and the general population in a nationwide setting. In addition, we evaluated the impact of RA medications on CV mortality. During the period between 2000 and 2008, the use of biologic agents was not widespread in Finland compared with some other countries.

Methods

Study population and description of register data

The Finnish national health insurance system entitles all patients with certain chronic and severe diseases such as RA to special reimbursement for outpatient medication costs. After the diagnosis of RA, an examination-based medical certificate issued by a rheumatologist or a physician with experience in rheumatology is sent to the Social Insurance Institution as an enclosure of application for the special reimbursement. The certificate must describe the current status of the patient, relevant diagnostic procedures and a treatment plan. It also includes the ICD-10 code M05 or M06 according to the patient's RF status of present or not present, respectively. The certificates are checked by a medical examiner physician or pharmacist at the regional office of Social Insurance Institution. The diagnosis and date of each medicine reimbursement decision are recorded in a nationwide register. Almost every Finnish RA patient with anti-rheumatic medications receives the reimbursement since it considerably decreases medication expenses. However, medication costs are never reimbursed completely, but the patient has to pay a deductible or a small percentage of the medication expenses with every purchase.

We identified all Finnish RA patients over 18 years of age diagnosed between 2000 and 2007 from the special reimbursement register described above. The same RA cohort has been described previously in a study on all-cause mortality by Puolakka and coworkers (5). From the same register, we extracted

data on comorbidities, defined as eligibility for special reimbursement for medications for the disease of interest. The comorbidities included cardiac diseases (coronary heart disease, chronic congestive heart failure, or chronic arrhythmias with or without hypertension), hypertension without cardiac disease, diabetes, asthma, chronic obstructive pulmonary disease (COPD) and malignancies. We were not able to distinguish reliably between patients who had cardiac disease with or without hypertension, because the medications for these diseases overlap substantially, and a patient may have both conditions but be eligible only for the special reimbursement for cardiac disease.

The patients were followed up until death or the end of December 2008, whichever occurred first. The cause of death for each patient as well as for the age-, sex-, and calendar year-specific Finnish population were obtained from the national Causes of death register by Statistics Finland. The validity of this register, particularly regarding CV causes, has been demonstrated (17, 18). In our study, CV disease was identified as the underlying cause of death by the ICD-10 codes I00-99.

From the prescription register maintained by the Social Insurance Institution (19), we extracted data on the use of outpatient medications for RA and CV disease. In the register, all purchases of reimbursable drugs from pharmacies are recorded according to the Anatomical Therapeutic Chemical (ATC) code (20), and the date of purchase is retrievable. The specific RA medications included MTX, hydroxychloroquine, sulfasalazine, glucocorticoids and subcutaneous TNF inhibitors. Intravenous drugs such as infliximab are financed by hospitals and outpatient clinics, and therefore, their use is not recorded in this register. CV disease medications were categorised by ATC code subgroups.

The Social Insurance Institution provides reimbursement for medications for up to three-month use per each purchase. Purchases of more than three months' supply of medications cannot be reimbursed. Therefore, we assumed that one drug purchase corresponds to three months of medication use. Generally, when assessing the total duration of drug use, the number of drug purchases was multiplied with a 3-month period, and the medication use duration was determined as a percentage of patient-years for each RA or CV medication. However, when evaluating the duration of treatment with any RA medication, the remainder of the last and first purchases of the drugs was calculated, and a 3-month period was added.

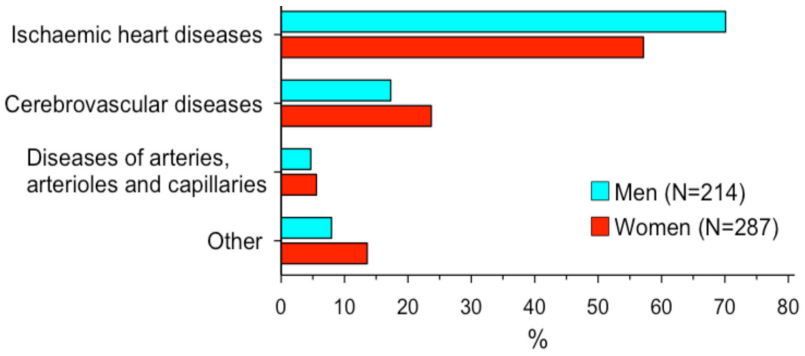


Fig. 1. The proportions of different cardiovascular diseases as causes of cardiovascular deaths in our study population.

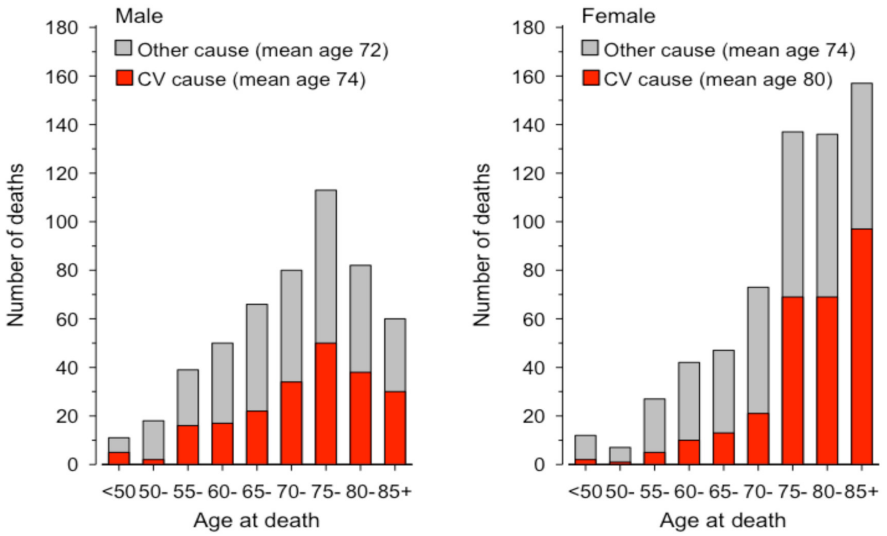


Fig. 2. The number of cardiovascular (CV) and other deaths by sex and age group.

Statistical analysis

The expected number of deaths was calculated on the basis of sex-, age- and calendar-period-specific mortality rates in the Finnish population. The standardised mortality ratio (SMR) was calculated as the ratio of observed and expected number of CV deaths. Cumulative CV mortality was assessed using the cumulative incidence competing risks method. Competing-risks regression model was used to assess the impact of sex, age, RF, comorbidities, and RA medications on CV mortality.

Ethical considerations

We used only officially archived, unidentifiable register data, which can be used for research purposes without an approval by an ethics committee or patient-specific consents. Permission for the usage of the data was obtained from the administrator of each register.

Results

During the 8-year period, 14,878 new RA patients were identified. RF was present in 9,319 (63%) patients. A total of 10,119 (68%) patients were women, 62% of whom were RF positive. Correspondingly, 4,759 men were identified, 64% of whom were RF positive. The mean age was 55.8 (SD 15.8) years in

women and 57.5 (SD 13.9) years in men at the time of RA diagnosis.

From a total of 71,769 person-years (22,471 in men and 49,298 in women), 1,157 patients died. The median (range) duration of individual follow-up was 4 (1-9) years. CV disease was the underlying cause of death in 501 patients, representing 43% of deaths due to any cause (Supplementary Table I). Other important causes of death were neoplasms (27%) and diseases of the respiratory system (7%). The most frequent CV causes of death were ischaemic heart diseases, comprising 63% of all CV deaths (Supplementary Table II). Cerebrovascular disease accounted for one fifth of CV deaths (Supplementary Table II). These proportions were similar in both men and women (Fig. 1). Only one death was caused by carditis, specifically recorded as chronic adhesive pericarditis (I31.0).

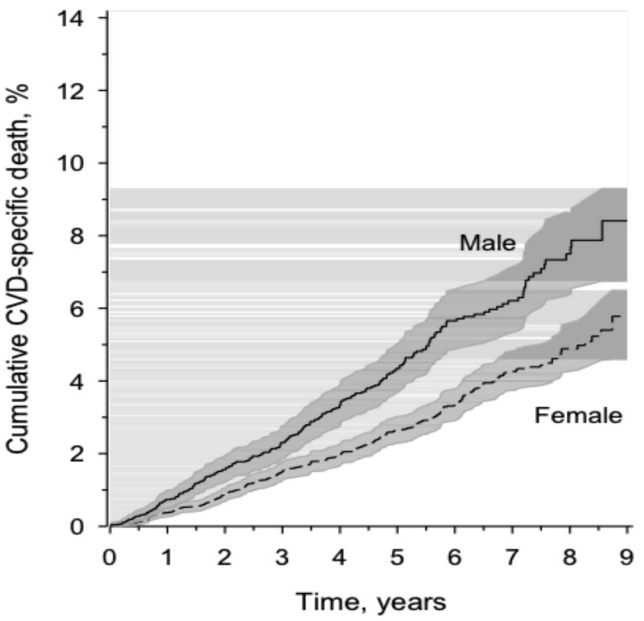
The quota of CV deaths out of all deaths increased towards the older age groups in both men and women (Fig. 2). The cumulative incidence of CV death was 2.6% among women and 4.4% among men at five years after the diagnosis of RA and reached 5.8% and 8.4%, respectively, at the end of the follow-up (Fig. 3).

As to RA medications, Supplementary Figure 1 illustrates that more than 80% of the patients were treated for longer than 90% of their individual patient-years with any RA medication (glucocorticoids included). Glucocorticoid use was more common among those who died than those who survived, whereas MTX use was most common among those who survived (Fig. 4). The prevalence of comorbidities differed in predictable ways among those who died of CV disease, those who died of other causes, and those who survived (Supplementary Table III). Regarding CV disease medications, the percentages of drug use duration per individual patient-years were generally higher among those who died of CV disease than among other patient subsets, although statins formed an exception in this respect (Supplementary Table IV).

In the multivariable competing-risks regression (Table I), factors associated with an increased risk of CV death included age, presence of RF, cardiac disease, hypertension, diabetes and the use of glucocorticoids. A decreased risk of CV death was associated with female sex, the presence of asthma or COPD and the use of MTX. Treatment with sulfasalazine, hydroxychloroquine, subcutaneous TNF inhibitors and other anti-rheumatic drugs did not associate with CV mortality in our analysis, nor did prior malignancies.

The SMR for CV deaths in the entire RA cohort was 0.57 (95% CI 0.52 to 0.62). The SMRs in subgroups according to sex and RF status varied from the lowest value of 0.43 among the RF negative women to 0.70 among the RF positive men, this subgroup difference being statistically significant (Table II).

Fig. 3.
Cumulative cardiovascular mortality among men and women with RA.
Cumulative incidence functions with adjustment for competing risks of cardiovascular-disease-specific (CVD-specific) death among men and women with RA.
Grey area shows 95% confidence intervals.



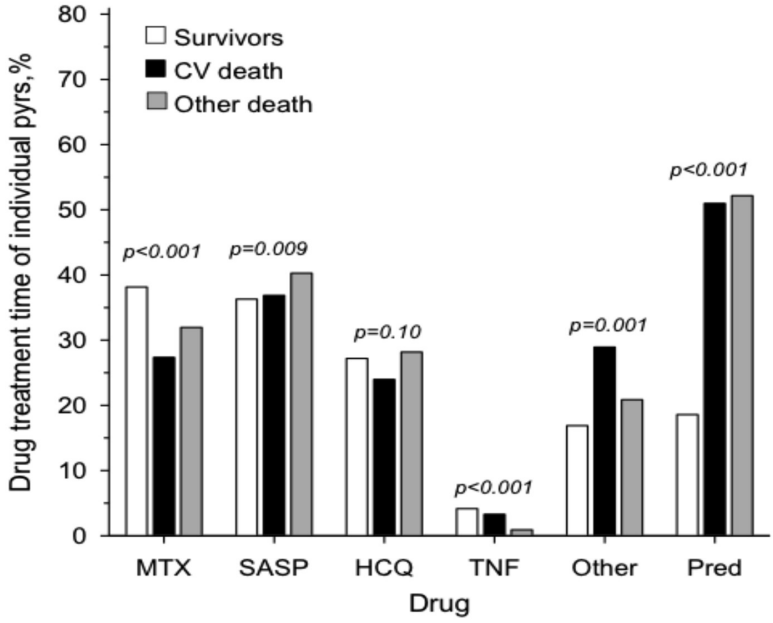


Fig. 4. Duration of the use of anti-rheumatic agents among the rheumatoid arthritis cohort.
The percentages of drug use duration per individual patient-years (pyrs) in patients who died of cardiovascular disease (n=501), those who died of other causes (n=656), and those who survived (n=13,721). For differences between groups, the age- and sex-adjusted *p*-values are given on top of the bars.

Discussion

In this Finnish register study, we observed no increased CV mortality among incident RA patients compared

Table I. The impact of different variables on the risk of cardiovascular death in a multivariable competing-risks regression. Regarding RA medications, sub-hazard ratios are given for the impact of drug use duration of 10% of individual patient-years.

Variable	sHR (95% CI)	*p*-value
Patient characteristics		
Female sex	0.68 (0.57 to 0.82)	<0.001
Age	1.07 (1.06 to 1.08)	<0.001
RF	1.30 (1.07 to 1.57)	0.009
Comorbidities		
Cardiac disease*	2.90 (2.30 to 3.66)	<0.001
Hypertension without cardiac disease	2.01 (1.60 to 2.52)	<0.001
Diabetes	2.12 (1.63 to 2.75)	<0.001
Asthma or COPD	0.72 (0.54 to 0.96)	0.024
Prior malignancy	0.54 (0.23 to 1.26)	0.154
RA medications		
MTX	0.95 (0.92 to 0.98)	<0.001
OXI	1.00 (0.97 to 1.04)	0.963
Glucocorticoids	1.26 (1.22 to 1.30)	<0.001
SASP	1.00 (0.97 to 1.02)	0.975
TNF inhibitors	0.98 (0.94 to 1.02)	0.267

*includes CHD, chronic CHF, chronic cardiac arrythmias (with or without hypertension and hyperlipidaemia)
sHR: sub-hazard ratio; RF: rheumatoid factor; RA: rheumatoid arthritis; MTX: methotrexate; OXI: hydroxychloroquine; SASP: sulfasalazine; TNF: tumour necrosis factor.

Table II. Number of cardiovascular (CV) deaths and standardised mortality ratios (SMR) by sex and rheumatoid factor (RF) status.

		n	CV deaths	SMR (95%CI)
Total				
	Men	4,759	214	0.63 (0.55 to 0.72)
	Women	10,119	287	0.53 (0.48 to 0.60)
RF+				
	Men	3,055	148	0.70 (0.60 to 0.83)
	Women	6,264	198	0.60 (0.52 to 0.69)
RF-				
	Men	1,704	66	0.51 (0.40 to 0.65)
	Women	3,855	89	0.43 (0.35 to 0.53)

with the general population. In fact, the CV disease-specific SMR was less than one in the entire RA population and in every subgroup according to sex and RF status. Previous studies have generally shown higher SMRs for CV death. A meta-analysis including mainly studies among long-standing RA cohorts showed that SMRs for CV death have varied between 0.91 and 2.20, leading to a meta-SMR of 1.6 (21). Another meta-analysis reported a combined SMR for CV death of 1.5 (1). However, our study was an inception cohort study, which limits its comparability to established RA cohorts. Indeed, in the latter meta-analysis, the four inception cohort studies included did not indicate an increased risk of CV death, the meta-SMR being 1.19 (95% CI 0.86–1.68) (1). Moreover, in a previous Finnish study on the same early RA cohort and with the same short follow-up, there was no difference in all-cause mortality between RA patients and the general population (all-cause SMR was 0.97 (95% Cl 0.91–1.02) (5).

Not only the severity but also the duration of systemic inflammation is central to the detrimental effects of RA on the vasculature (22). As demonstrated by previous studies, CV mortality in RA may not rise until 7–10 years from the diagnosis (6, 23-25). The earliest time point in RA disease course with epidemiological evidence of increased CV mortality is five years after RA diagnosis, the observation made solely among RF positive patients in a British multicentre inception cohort study (26). In the light of this data, it may be speculated whether we would observe increased CV mortality after longer follow-up in our cohort as well.

Our results indicate that, along with traditional risk factors and the presence of RF, the use of glucocorticoids increase the risk of CV death–glucocorticoid use for 10% of individual patient-years yielded a sHR for CV death of 1.26 (95% CI 1.22–1.30, $p<0.001$) (Table I). Our observation extends the earlier epidemiological findings of an association between glucocorticoids and CV mortality or CV events (14, 27, 28). Glucocorticoids may theoretically increase the CV risk through their deleterious effects on lipid and glucose metabolism, blood pressure, weight and fat distribution (29). However, a more robust explanation may be that the use of glucocorticoids acts as a marker of uncontrolled RA activity and systemic inflammation that increases the risk of CV events (30, 31). In this respect, glucocorticoids may hypothetically even decrease the risk of CV events by alleviating inflammation (11). However, a recent German study on 8,908 RA patients reported that treatment with glucocorticoids (dosage >5mg/day) was significantly associated with increased all-cause mortality in a dose-dependent manner, and this study reduced the impact of channelling bias by taking into account disease activity and functional capacity as time-varying covariates (15). The methodological advantages of our study were the competing-risks approach and the evaluation of drug use not only at baseline or during a short period of time but during the entire follow-up.

This study mainly reflects the impact of conventional DMARDs on CV mortality. During the study period between 2000 and 2008, the use of biologic agents was rather limited in Finland, while the early initiation of combinations of synthetic DMARDs became increasingly prevalent (32).

In our RA population, MTX use was associated with a decreased risk of CV death. MTX together with sulfasalazine was the most commonly prescribed anti-rheumatic drug, as its use covered almost 40% of all patient-years in the cohort. Regarding earlier studies, MTX appears to decrease the risk of CV

events in RA patients by approximately 21% when the results of the most relevant studies are collated (33). In one prospective study on 1,240 RA patients, CV death was reduced by as much as 70% among patients ever *versus* never treated with MTX (34). Moreover, a recent study on 5,626 RA patients found a propensity-adjusted association of MTX with a 70% reduction in overall mortality (35). However, not all studies have observed decreased rates of CV events or deaths associated with MTX (36).

Most of the protective effect of MTX is likely to be due to a reduction in systemic inflammation. Nevertheless, direct cardioprotective effects may also exist, for example, MTX has been implied to facilitate reverse cholesterol transport and downregulate foam cell formation in human THP-1 macrophages (37). Interestingly, a trial on the use of low-dose MTX as a cardioprotective therapy in 7,000 non-RA patients with stable coronary heart disease and either type 2 diabetes or metabolic syndrome is underway (38). If MTX reduces CV events in this trial, it will strongly support the inflammatory hypothesis of atherothrombosis, and provide novel directions for the secondary prevention of CV events (38).

TNF inhibitors have reduced the risk of CV events in some settings (12, 36). One mechanism leading to lower CV risk among TNF users may be reduction in endothelial activation (39). In the already-mentioned German study on 8,908 RA patients, TNF inhibitor and rituximab users had significantly lower mortality rates than MTX users (15). In our RA cohort, the use of subcutaneous TNF inhibitors did not have any impact on CV mortality, perhaps due to their infrequent use (Fig. 4). Hydroxychloroquine may have cardioprotective properties through its beneficial effects on fasting lipid profiles (40, 41), but it failed to show a protective effect in our analysis. All in all, it must be noted that the impacts of CV comorbidities on CV mortality were generally greater in magnitude than those imposed by RA medications; the sHRs for diabetes, hypertension and cardiac disease were 2.02–2.90, whereas the sHRs for RA medications were smaller, 0.95–1.26 (Table I).

The initial treatment of RA intensified in 2000–2007, in this RA population, the use of MTX during the first 3 months of RA treatment increased from 43.8% to 69.0% and a combination therapy of at least two DMARDs from 37.5% to 55.3% (32). Moreover, 93%–95% of the patients in the cohort already received DMARDs within the first 3 months after the diagnosis (32). These trends in the treatment of RA may have affected the patients' CV prognosis favourably. Theoretically, the regular follow-up visits in the Finnish health care system may influence the intensity of the primary and secondary prevention of CV events among RA patients. However, most existing data suggest that RA patients are less likely to be prescribed CV drugs than non RA-patients, both in terms of primary and secondary prevention (42, 43).

Male sex and the presence of RF increased the risk of CV death in our study population. Regarding the absolute risk, this is consistent with previous reports on both RA cohorts (26, 44) and non-RA cohorts (45). Regarding the relative risk, earlier observations have shown the presence of RF to associate with higher SMRs for CV death (46). Male sex, on the contrary, has been linked to mainly similar (1) or even lower (47, 48). SMRs in comparison to female RA patients.

The genetics, course, severity, as well as clinical and radiological expression of RA may differ between different countries and continents, also between Northern and Southern Europe (49-53). Moreover, the prevalence of CV risk factors and their impact on the risk of atherosclerosis may differ between populations from different ethnic origins (54). These factors may cause differences in CV mortality rates between different geographical areas and ethnic groups, and thus limit the generalisability of our results to non-Finnish RA populations.

The major strength of this study lies in its nationwide setting with a high coverage of RA patients: practically all RA patients diagnosed in Finland in 2000-2007 were identified and compared with the age-, sex-, and calendar-year-specific general population. Moreover, we were able to retrieve data on the total duration of medication use throughout the follow-up. Our follow-up period was short for a mortality study, which can be considered as the main limitation. Other limitations of our study arise from the deficiencies in the register data used – we had no data on the clinical characteristics of RA except for RF status. Therefore, we were not able to adjust for disease severity or the degree of inflammation in our analysis, and confounding by indication is most likely to have affected our results on RA medications since more active RA is both an indication for glucocorticoids and a risk factor for CV diseases. We also lack data on CV risk factors such as obesity and smoking. Competing causes of death may have affected the point estimate of SMR for CV deaths. Moreover, the RA case definition is a clinical one, and no data on the fulfillment of any classification criteria is available.

In summary, these nationwide results suggest that patients with recent-onset RA who receive consistent RA medication have no increased risk for CV mortality compared to the general population, at least in the early years of the disease. Furthermore, the use of MTX had a decreasing impact on the risk of CV death, whereas glucocorticoids increased the risk. Studies with a longer follow-up are needed to demonstrate whether the low CV mortality remains in more established RA populations, and studies accounting for confounding by indication are warranted to assess the true effect of RA medications on CV mortality.

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