Title:
Has the excess risk of acute myocardial infarction in rheumatoid arthritis relative to the general population declined? A population study of trends over time

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Abstract

Objective: To evaluate secular trend in ten-year risk of incident acute myocardial infarction (AMI) in incident rheumatoid arthritis (RA) relative to the general population.

Methods: We conducted a retrospective study of population-based incident RA cohorts with RA incidence from 1997 to 2004 in British Columbia, Canada, with matched general population comparators, using administrative health data. RA and their matched cohorts were divided according to the year of RA incidence, defined according to the first RA visit of the case definition. Incident AMI was defined as the first event occurring within 10 years from RA incidence. Secular trend was assessed using delayed-entry Cox models with an interaction term between the year of RA onset and indicator of RA vs. general population. Linear, quadratic and spline functions of year of RA onset were compared to assess possibility of nonlinear trends. The model with the lowest AIC was selected to interpret the results. Sensitivity analyses were conducted to account for potential effect of unmeasured (e.g. smoking) or partially measured (e.g. obesity) confounders in administrative data, on the interaction term.

Results: Overall**,** 23,237 RA and 46,474 general population controls experienced 1,133 and 1,606 incident AMIs, respectively. A linear Cox model was selected as the model best fitting the AMI events. Overall, RA patients were found to have a 21 % higher risk of AMI than the matched general population controls [1.21 (1.10, 1.32); $p < 0.001$]. A significant linear decline in risk of AMI was observed in RA patients [0.94 (95% CI 0.91, 0.97) $p = <.0001$], and in the general population [0.93 (0.91, 0.95); $p = <.0001$]. The change in AMI risk over time did not differ in RA compared to the general population [p-value of interaction term=0.49]. Our results remained similar after adjusting for the potential effect of confounders on the interaction term, and no

difference in the change in risk of AMI over time was observed between RA and the general population.

Conclusion: Our findings suggest a decline in 10-year risk of AMI in RA, and in the general population. The decline in the risk of AMI over time did not differ between RA and the general population, such that the excess risk of AMI in RA relative to the general population, has remained the same.

Keywords: Rheumatoid arthritis, acute myocardial infarction, cardiovascular disease, temporal trends, administrative data, epidemiology

Key messages

What is already known about this subject?

- Prior studies have found that Rheumatoid arthritis (RA) is associated with a 68% and 59% increase in risk of acute myocardial infarction (AMI) incidence and AMI mortality, respectively.

- A decline in all-cause mortality, as well as cardiovascular mortality, in RA patients with onset in more recent years, compared to the general population has been reported.

What does this study add?

- This study evaluated whether the incidence of AMI in RA patients with incidence in more recent years has improved relative to the general population.

- Our population-based study using administrative health data found an improvement in the 10-year risk of AMI over time in RA patients and in the general population.

- The decline in risk of AMI over time did not differ between RA and the general population.

How might this impact on clinical practice or future developments?

- Despite changes in treatment recommendations aiming at early treatment and eradication of inflammation, and cardiovascular risk management, the risk of AMI remains higher in RA than in the general population and the excess risk has not improved over time.

- There is a need for tailoring cardiovascular risk management strategies specifically at RA patients, in addition to ensuring control of RA inflammation, to reduce the excess risk of AMI.

INTRODUCTION

Cardiovascular diseases (CVD), including acute myocardial infarction (AMI), congestive heart failure, and cerebrovascular accidents are increased in patients with rheumatoid arthritis (RA), with Ischemic Heart Disease (IHD) being the main cause of premature mortality[1] [2]. Meta-analyses of observational studies have reported a 68% increase in incidence of fatal and non-fatal MI events [3], and a 59% increase in risk of death from IHD in patients with RA compared to the general population [4].

Recently published studies, however, are suggesting improvement over time in mortality, particularly cardiovascular (CV) mortality in patients with RA onset in more recent years. In prior work, we found a decline in 5-year all-cause mortality, and CV mortality, in RA relative to general population controls in patients with disease onset in 2001-2006 compared to 1996-2000 [5].

Zhang Y., and colleagues, reported that all-cause mortality in RA compared to the general population improved in patients with RA onset in 2007-2014 versus 1996-2006 [6]. A population-based study from Rochester, USA found that patients with RA incidence in 2000-07 had lower 10-year overall CV mortality and coronary heart disease (CHD) mortality than RA patients diagnosed in 1990-99 [7]. Further, Eswar K., et al., also found a decline in AMI mortality in RA patients with RA onset after 1980 compared to RA patients with RA onset between 1970 and 1980, and RA patients with RA onset before 1970 [8]. In a Swedish population-based cohort, Holmqvist et al., found a steady decline in absolute mortality rates in RA over calendar years 1997 to 2015, but no difference in excess mortality risk relative to the general population after controlling for RA duration[9].

We speculate that this improvement in mortality could be due to improvement in excess risk of CV events, in particular AMI, over time, since they are the leading cause of excess deaths in RA [4 10]. Our objective was to assess secular trend in 10-year risk of incident AMI according to year of RA onset, in incident RA cohorts with onset from 1997 to 2004 compared to general population controls.

METHODS

Study Design

We conducted a retrospective study of a population-based cohort of all incident RA individuals in British Columbia (BC), Canada with matched general population controls, using administrative health data.

BC Cohort Definition and Study Sample

Incident RA Cohort. We identified all patients with incident RA in BC who first met previously published RA criteria [11] between January 1997 and December 2004, using physician billing data with International Classification Disease Codes version 9th for RA (ICD-9: 714.x.). Data were obtained from 01-1990 onwards using Medical Services Plan (MSP), from the Ministry of Health in a universal health care system. Individuals were identified as RA if they had at least two physician visits, at least two months apart, within a 5-year period. We used two physician visits to exclude individuals referred for possible RA evaluation, or in whom an initial impression of possible RA was not subsequently confirmed. The date of first RA visit was defined as time zero, and second RA visit was defined as the "index date", at which time they entered the cohort.

Individuals were excluded, if over a five-year period after their second RA visit (i.e. index date), they had at least two subsequent visits, on two different days, with the same ICD

code for other forms of inflammatory arthritis [Systematic Lupus Erythematosus (SLE), and other connective tissue diseases (CTD), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), and other Spondyloarthropathies]; or if a patient saw a rheumatologist and the diagnosis of RA by a non-rheumatologist was never confirmed by the rheumatologist.

These criteria have been validated in a sub-sample who participated in a RA survey, using impression of an independent rheumatologist reviewing medical records from their treating physician as a gold standard, yielding a positive predictive value (PPV) of 0.82 [12]. To ensure prevalent cases of RA who moved to BC were not erroneously identified as incident RA cases, we excluded RA individuals if they had less than seven years of available data in MSP registry prior to their first RA visit. In a previous study, using the same RA definition, the age and sex standardized RA incidence rates were 58 per 100,000 for the 1996–2000 cohort and 68 per 100,000 for the 2001–2006 cohort, which is consistent with reported RA incidence rates [13 14].

General Population Cohort. General population controls with no diagnoses of inflammatory arthritis (i.e. RA, SLE, CTD, PsA, and Spondyloarthropathies) were randomly selected, using the same administrative databases as for the RA cohort, matching controls to RA cases in a 2:1 ratio on sex and birth year. Controls were assigned the same time 0 (corresponding to the date of RA onset, i.e. first RA visit) and the index date (i.e. date of second RA visit) of the RA patient they were matched to. Individuals were excluded if they had less than 7 years of available data in MSP registry prior to the date corresponding to RA onset.

Exclusion Criteria. We excluded RA and general population individuals with a prior history of MI based on MI diagnoses codes [old MI ICD9/ICD10 codes: 412/I25.2; AMI ICD9/ICD10 codes: 410/I21] in hospitalization data, in any position, or in physician visits in MSP data, over 7 years

prior to index date (i.e. equal duration for all cohorts, regardless of incidence year, to avoid affecting temporal trend).

Data Collection

Data were obtained from administrative databases of the Ministry of Health, through Population Data BC, on all provincially funded health care services, including basic demographics, such as age, sex, postal code (first three digits) used to determine rural vs. urban residence, neighborhood income quintile and local health area, and registration data from Medical Services Plan (MSP) consolidation file [15]; on all physician visits, with one diagnostic code (i.e. ICD-9) per visit representing the reason for the visit, from MSP database [16]; all hospitalizations from Discharge Abstract Database (DAD), which include up to 25 diagnostic codes (i.e. ICD-9/ICD-10) per hospitalization representing either the primary reason for admission or complications during hospitalization [17]. Data from MSP and DAD were obtained from 01/1990 to 12/2014. The PharmaNet database [18] provided information on all prescriptions dispensed by pharmacies in BC from 01/1996 to 12/2014, on all individuals. Information on death and primary cause of death was derived from death certificates using Vital Statistics Data from 01/1996 to 12/2014 [19].

Outcome Assessment

The outcome of interest was time to first AMI occurring within 10 years from RA onset (i.e., first RA visit), with follow-up starting from index date (i.e., second RA visit). AMI events were identified using diagnostic codes (ICD-9/ICD-10 Codes: 410/I21) in hospitalization data in any position, or in vital statistics data as primary cause of death, to ensure capture of fatal events without hospitalization. A previous validation study in Canada evaluating the validity of

administrative data to identify MI found that sensitivity and specificity of hospitalization data for identifying MI in most [≥50%] studies was ≥86%, and PPV in most studies was ≥93%.[20].

Statistical Analysis

RA and general population cohorts were divided according to the year of RA incidence, defined as the first RA visit. We used Cox multivariable models [21] that were fitted to all RA and matched general population cohorts, pooled across all years of RA incidence. To ensure comparability of follow-up across subjects, time zero was defined as the date of first RA visit; however, to avoid immortal time bias, we used delayed-entry models with subjects contributing person years (PYs) of follow-up, from index date (i.e. second RA visit), which is when they met the criteria for inclusion in our cohort and became at risk of developing the outcome of interest [22] [23].

We followed the well-established procedure for cause-specific hazard regression that treats all competing events as censored observations [24]. Thus, censoring was done at ten years from RA incidence, or last health care utilization due to death related to non-AMI events or migration, whichever occurred first. To complement the cause-specific hazard regression in accounting for competing risk of death due to non-AMI fatal events, we also performed a sensitivity analysis using the Fine-Gray sub-distribution hazard model, based on cumulative incidence function [25].

All multivariable Cox models included terms for (i) calendar year of cohort entry (year of RA incidence), modeled as a continuous variable to examine proper functional form of incident year effects; (ii) binary indicator of RA patient vs. matched control, and (iii) two-way interaction between year of RA onset and RA vs. general population indicator. The interaction term was tested to assess the change in incidence of AMI in RA relative to the general population over time. In the

case of statistically non-significant interaction ($p>0.05$ for a 2-tailed Wald chi-square test, representing no change in AMI incidence in RA relative to the general population over time), the final multivariable model was examined without the interaction term to yield the adjusted Hazard Ratios for (i) change over time in the AMI incidence, in RA and general population cohorts, and (ii) excess risk of AMI associated with RA, relative to the general population, pooled across all years of RA incidence.

To assess possible non-linear patterns of change in AMI incidence across the calendar years of RA onset, Cox models with linear, quadratic and flexible spline functions for year of RA incidence were compared, and the model with the lowest Akaike Information Criterion (AIC) [26], i.e. best fitting the AMI events, was selected to interpret the results. We used data-driven stepwise selection approaches to select the numbers and locations of the knot(s) for the spline Cox regression, which allows for more flexible modeling of possible changes across years of RA incidence than parametric (i.e. linear or quadratic) functions [27].

Potential confounders known to be associated with risk of AMI were selected from the variables listed in *Table 1* and were controlled for as time-invariant covariates at baseline, i.e. at or over one year prior to RA incidence, as appropriate. Variables were included in the final model if they altered the hazard ratio by more than 5%, or if they were significant at an alpha level < 0.05. In a sensitivity analysis, we also fitted the model including all variables in *Table 1*.

The description of covariates assessed and how they were measured is included in *Supplementary Material, Appendix 1.* To control for overall comorbidity burden, a Romano

modification of the Charlson comorbidity score for use with administrative data (with RA excluded from comorbidities) was calculated using data over one year prior to RA onset[28].

In sensitivity analyses, to test the robustness of our results to the potential effect on the interaction term of confounders that are unmeasured (e.g. smoking) or partially measured (e.g. obesity) in administrative data, we modelled hypothetical confounders that varied differentially over time in RA and in the general population and included them in the multivariable Cox models. For these analyses, we used age- and gender-specific BC rates of smoking and obesity[29] for the general population controls, we assumed a 50% higher prevalence of smoking and obesity in RA than in the general population in the year 1997 based on the literature [30 31], we assumed relative risks of AMI with smoking and obesity of 2.0 [32]and 1.5[33], respectively, and we modeled a 50% differential change over time in the confounder prevalence at index date in RA relative to the general population, as a plausible worst case scenario."[34].

Furthermore, to gain insight into potential explanations for the observed patterns of change in 10 year risk of AMI according to calendar years of RA incidence, we assessed temporal trends in cumulative use of statins, glucocorticoids, NSAIDs, Cox2 Inhibitors, biologics and DMARDs over the 10 years of follow-up, according to the year of RA incidence.

All analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

Ethics

The study received ethics approval from the University of British Columbia's Behavioral Research Ethics Board (H00-80305). Population Data BC provided data linkage and access, no personal identifying information was provided to the investigators, and procedures were compliant with BC's Freedom of Information and Privacy Protection Act.

RESULTS

The sample included 23,237 RA individuals (66.4% women; mean [SD] age 58 [16.8] years) and 46,474 matched general population controls. Mean [SD] years of follow-up were 8.9 [2.2] years in the RA cohort and 8.9 [2.3] years in the general population. A total of 1,133 and 1,606 incident AMI events were observed in RA and in controls, respectively; of which 60 in RA, and 13 in the general population, were fatal events identified through death certificates.

Baseline characteristic of the RA and the general population cohorts are described in *Table 1.* Crude 10-year incidence rates of AMI per 1000 PYs in RA and general population cohorts are shown in *Table 2.* In RA, the crude 10-year incidence (95% CI) of AMI decreased from 6.06 per 1000 PYs (5.16, 7.05), in people with RA onset in 1997, to 4.42 (3.68, 5.26) in people with RA onset in 2004, with some fluctuations observed over time. There was an unexplained peak in incidence, at 7.11 per 1000PYs (6.11, 8.2) in 1999, with a subsequent decline to 4.94 (4.13, 5.84) in 2000. In the general population, the crude 10-year incidence of AMI declined over time, from 4.80 per 1000PYs (4.22, 5.42) in 1997 to 2.88 (2.45, 3.36) in 2004, following a linear trend. The graphical representation of crude AMI incidence rates in RA and general population cohorts is provided in *Figure 1*.

Cox models with linear, quadratic, and spline functions of incidence year effects were fitted. Using stepwise selection, the best spline model with piecewise linear functions contains zero knot which coincides with the Cox model with linear function of RA incidence years. However, for comparison purpose, we forced a knot at year 1999 appearing as a potential peak year in *Figure 1* in the Cox spline model, which was compared with Cox models with linear and quadratic functions of incident years (*Supplementary Table 1)*. The linear Cox model was selected, as the model best fitting the incident AMI events (lowest AIC). In analyses not reported here, Cox

spline models using polynomial basis functions (i.e., piecewise quadratic and cubic functions) performed worse than the linear Cox model according to the AIC statistics.

Table 3 shows the results of the adjusted and unadjusted analyses for the cause-specific hazard regression models estimating risk of AMI. We observed a significant decline in the risk of AMI with increasing calendar years of incidence in both RA [aHR per year of incidence (95% CI) 0.94 (0.91, 0.97) p = <0.0001] and the general population [0.93 (0.91, 0.95); p = <.0001]. The decline in risk over time (temporal trend) did not differ significantly between RA and the general population, as demonstrated by the interaction term tested in the Cox model [1.01 (0.98, 1.05); p =0.49]. When models were examined without the interaction term to estimate the main effect of RA on incidence of AMI, pooled across all calendar years of RA incidence, the RA patients were found to have a 21 % higher risk of AMI than the matched population controls, after controlling for potential confounders [1.21 (1.10, 1.32); p < 0.001].

In sensitivity analyses using Fine-Gray method, the decline in sub-distribution hazard of AMI also did not differ between RA and the general population (p = 0.8). Our results also did not change when all variables described in *Table 1* were forced as covariates in the Cox model (p= 0.43), and according to AIC statistics, this model did not outperform the model selected to interpret the results.

Sensitivity analyses modeling a potential confounding effect of obesity and smoking on the interaction term did not alter the coefficient estimate for the interaction term or the conclusions about secular trend differences between RA and the general population. The decline in risk of AMI in RA did not differ from that in the general population (p = 0.45).

DISCUSSION

The 10-year risk of AMI has improved over time in patients with more recent RA onset and in general population controls. However, the decline in the risk of AMI over time did not differ between RA and the general population, such that the excess risk of AMI in RA relative to the general population, has remained essentially the same in patients with earlier or more recent RA onset.

Our results are consistent with other reports in the literature. A Swedish study observed that the increased risk of incident CVD, which consisted primarily of CAD, in RA relative to the general population, was similar for patients with RA onset in 1978 and in 1995 [35]. Holmqvist et al., in a population-based study of RA patients with RA onset between 1997 and 2014, found a decline in incidence of acute coronary syndrome (ACS) in RA and in the general population with increasing calendar years of RA onset, however, the excess risk of ACS in RA relative to the general population remained the same [36]. Our study confirms these findings in another population-based sample in a different country.

In contrast to our results, a study in Spain, published in abstract form, using national hospitalization data, found a 5% increase in annual incidence of AMI among prevalent cases of RA who were admitted to hospital between 1999 and 2015 [37]. Their study sample, however, included prevalent RA cases who may have had onset of their disease much prior to 1999 when treatment paradigms for RA differed; the temporal trend evaluated over years 1999 to 2015 represented the time when the AMI outcomes were measured, whereas in our study the years 1999 to 2004 represent the year of RA incidence and the AMI risk was assessed over 10 years after RA onset. Their study also did not include general population comparators. Furthermore, their cohort

identified RA cases who had been hospitalized, who likely had more comorbidities, and therefore may have had a greater risk of MI.

Results of a population-based study of Olmsted County, USA, also published in abstract form, found, there was no excess incidence of CVD events in incident RA patients diagnosed in the 2000's compared to controls without RA. They report that results were similar when they examined AMI separately from other CVD events [38]. However, the sample size of their cohort was small (total number of RA individuals = 906) and few cardiovascular events were observed.

We had anticipated to observe an improvement in the excess risk of AMI in RA relative to the general population in patients with more recent RA incidence, due to better control of inflammation in recent years from earlier and more aggressive RA treatment recommendations, aimed at achieving remission, or low disease activity [39], as well as with the advent of more effective RA therapies, such as biologic agents. However, this was not observed, despite evidence suggesting that RA patients may be experiencing milder disease in recent years [40].

It is possible that the improvements in RA inflammation achieved in recent years are not sufficient to reduce the excess risk of AMI. It could also be due to the population-based nature of our sample and the fact that a significant portion of the RA population are not receiving treatment according to the treat-to-target approach, and/or the targeted remission or low disease activity states are not achieved. This hypothesis is supported by quality of care studies showing that clinical practice lags behind evidence and that when care is evaluated at the population level, a large proportion of patients are not receiving care as recommended [41 42]. Additionally, our cohort includes patients with RA incidence until the year 2004, followed over 10 years of disease, which represents a relatively early era of biologics availability. Therefore, it is possible that evaluating more recent incident cohorts may yield different results. Of note, selecting years

of RA incidence until 2004 allowed 10 years of follow-up for assessment of AMI risk (data available until 2014), which was necessary since studies suggest that the excess risk of AMI may only become apparent 7 to 10 years after RA onset [43 44].

Other possible explanations include the fact that RA patients have higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension, and hyperlipidemia; yet, despite the increased burden of CVD, as we and others previously identified, screening and management of these risk factors for MI in RA remain suboptimal in clinical practice[11 45].

When we looked at patterns of RA medication use over the 10 years of follow-up according to the year of RA incidence to assess whether they could explain our findings, we found that cumulative use of DMARDs (traditional and biologics) over the 10 years after RA onset increased in cohorts with more recent RA onset, use of glucocorticosteroids decreased slightly, and use of traditional NSAIDs decreased, while use of COX2-selective NSAIDs increased, in the RA cohorts. Use of statins increased in both the RA and general population cohorts, with a similar increase in both groups ($p = 0.2$). Antihypertensive use increased in RA and in the general population, and this increase over time did not differ between two groups ($p=0.8$)).

The overall improvement in MI over time observed in RA and in the general population is in line with the general population literature [46]. Improvements in treatment of risk factors and improvement in cardiac care have been held responsible for the reduction in ischemic heart disease events over time in the general population [47]. It is important to note that the incidence rates observed in our general population controls do not necessarily reflect rates observed in the BC general population, given that the age and sex distribution of our controls matched those of our RA sample and are therefore, not representative of the entire general population.

Limitations of this study are those inherent to observational studies and studies using administrative data. Misclassification of RA diagnosis identified using administrative data is possible. However, we used previously published criteria that were validated in a subsample who participated in a RA survey, with a positive predictive value of 0.82.

The capture of comorbidities may be incomplete since it relies on diagnostic codes used for billing physician visits or extracted from hospitalization discharge summaries. Although we adjusted for baseline characteristics, unmeasured or residual confounding from lack of or incomplete information on known (e.g. smoking, obesity) or unknown risk factors could have influenced the results. For these to influence the difference in secular trends, they would have to change differentially across calendar years in RA compared to the general population. However, in sensitivity analyses, our results remained robust to including in the model hypothetical confounding variables, selected to model the potential confounding effect of smoking and obesity on the interaction term, with no significant difference observed in the time trend.

It is possible that our incident cohort includes prevalent RA patients with an RA visit >7 years prior to the first RA visit captured in our data. However, consecutive visits >7 years apart is very infrequent in our cohort. In a prior study using this definition, we found that only 0.44% of periods between consecutive RA visits were >6 years, 94.3% were <1 year, and 97.3% were <2 years[5].

Administrative data does not include information on onset of clinical symptoms, therefore RA onset reflects first RA visit to a physician. We also did not have information on RA disease activity or severity, which may have helped us understand why we did not observe an improvement over time in the excess risk of AMI in RA relative to the general population.

Strengths of our study include the population-based and incident nature of our cohort capturing all individuals in BC with RA incidence in 1997-2004; the large sample allowing a sufficient number of events; and, the long follow-up of 10 years.

Conclusion

In conclusion, our population-based study showed that the 10-year incidence of AMI has improved over time, with lower AMI risk in patients with more recent RA onset; however, the decline in incidence of AMI did not differ from that in the general population. This suggests that despite changes in treatment recommendations aiming at early treatment and eradication of inflammation, the risk of MI remains higher in RA than in the general population, and the excess risk has not improved over time. There is a need for cardiovascular risk management strategies tailored to RA populations, including adequate screening and management of cardiovascular risk factors, as part of cardiovascular prevention care in RA.

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DECLARATIONS

Contributors: All authors contributed to the study conception and design. KY contributed to data analysis and interpretation of results, manuscript preparation and revision. DL contributed to data acquisition, guiding data analysis, intepretation of results, and manuscript revisions. YZ and HX were responsible for data analysis and interpretation of results and manuscript revisions. HX, AZ, MA contributed to the interpretation of results and manuscript revision.

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Competing Interest: None declared.

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Table 1. Baseline characteristics of incident RA and general population cohorts

Baseline Characteristics	RA (n = 23,237)	General Population (n = 46,474)	p-value
Demographics *			
Women	15, 421 (66.4)	30,842 (66.4)	1
Mean Age (yrs.)	58.0 (16.8)	58.0 (16.8)	1
Rural vs. Urban [#]	4322 (18.6)	6392 (13.8)	<0.001
Regional Health Authority			
Interior	5112 (22.0)	8372 (18.0)	<0.001
Fraser	6918 (29.8)	14235 (30.6)	
Vancouver Coastal	4386 (18.9)	11042 (23.8)	
Vancouver Island	4839 (20.8)	8733 (18.8)	
Northern	1891 (8.1)	2857 (6.1)	
Neighborhood Income Quintile [‡]			
1 (Lowest)	5034 (21.7)	8757 (18.8)	<0.001
2	4655 (20.0)	8576 (18.5)	
3	4361 (18.8)	8636 (18.6)	
4	4281 (18.4)	8733 (18.8)	
5 (Highest)	4018 (17.3)	9169 (19.7)	
Health Care Utilization [Ω]			
Median No. Physician Visits per yr	28.0	13.0	<0.001
Prior Hospitalizations, yes	3840 (16.5)	6222 (13.4)	<0.001
Comorbidities [Ω]			
Romano Charlson index [¥]	0.42 (0.92)	0.29 (0.82)	<0.001
Diabetes	1160 (5.3)	2178 (4.7)	<0.001
Alcoholism	379 (1.7)	256 (0.6)	<0.001
Hypertension	5288 (23.0)	8305 (17.9)	<0.001
COPD	686 (3.0)	823 (1.8)	<0.001
Angina	876 (3.8)	1163 (2.5)	<0.001
Atrial fibrillation	190 (0.8)	296 (0.6)	0.005
Medications [Ω]			
Anticoagulation	582 (2.7)	908 (2.0)	<0.001
CVD Medications [§]	7005 (32.2)	10688 (23.0)	<0.001
Fibrates	215 (1.0)	337 (0.7)	<0.001
Statin	1951 (9.0)	3374 (7.3)	<0.001
Hormone Replacement Therapy	2834 (13.0)	4126 (8.9)	<0.001
Traditional NSAIDs	10260 (47.2)	5469 (11.8)	<0.001
COX2 Inhibitors	3516 (16.2)	1313 (2.8)	<0.001
Contraceptives	621 (2.9)	1299 (2.8)	0.67
Glucocorticoids	3281 (15.1)	1207 (2.6)	<0.001

Values represent number (%) unless where indicated, values represent mean (SD).

***** Measured at RA incidence (i.e. first RA visit)
Ω Measured over one year prior to RA incidence

Rural vs. Urban: based on postal code, where a zero '0' in the second position indicates a rural area;
‡ Income quintile is a measure of neighborhood socioeconomic status derived from postal code that divides the population into 5 income groups (from lowest income to highest income);
¥ Romano Charlson refers to Romano adaptation of the Charlson co-morbidity score developed for use with administrative health data, excluding RA as a comorbidity;

§ CVD Medications included antihypertensive, Beta-blockers, cardiac glycosides, diuretics, antiarrhythmic, nitrates.

Abbreviations: RA: rheumatoid arthritis; yrs: years; no.: number; Hosp: hospitalization; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSAIDs: non-steroidal anti-inflammatory drugs; COX-2 inhibitors: cyclooxygenase 2 selective anti-inflammatories;

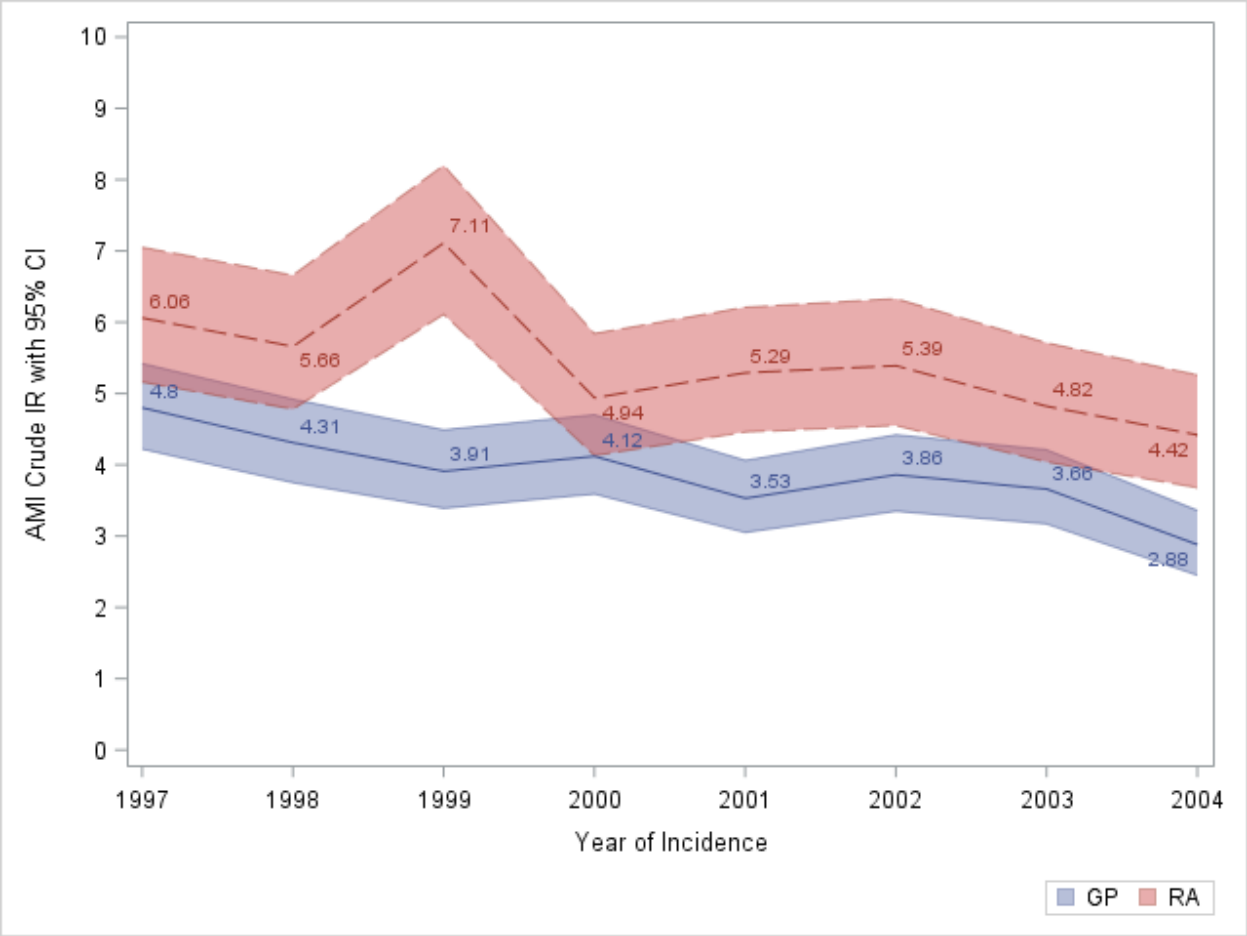
Table 2. Crude 10-year incidence rates of AMI per 1000 PYs in RA and general population cohorts, and crude incidence rate ratio, according to year of RA incidence.

RA Cohort					General Population				Crude IRRs (95% CI)
Cohort Year of Incidence *	N	AMI	PYs	Crude IRs (95%CI)	N	AMI	PYs	Crude IRs (95%CI)	
1997	2934	158	26073	6.06 (5.16, 7.05)	5868	248	51696	4.80 (4.22, 5.42)	1.26 (1.03, 1.54)
1998	2741	140	24715	5.66 (4.78, 6.66)	5482	211	48983	4.31 (3.75, 4.92)	1.31 (1.06, 1.63)
1999	2827	178	25049	7.11 (6.11, 8.2)	5654	196	50080	3.91 (3.39, 4.49)	1.82 (1.48, 2.22)
2000	2907	129	26128	4.94 (4.13, 5.84)	5814	214	51926	4.12 (3.59, 4.7)	1.20 (0.96, 1.49)
2001	2951	140	26470	5.29 (4.46, 6.21)	5902	187	52968	3.53 (3.05, 4.06)	1.50 (1.20, 1.86)
2002	2917	140	25969	5.39 (4.55, 6.33)	5834	201	52099	3.86 (3.35, 4.42)	1.40 (1.12, 1.73)
2003	2954	128	26534	4.82 (4.04, 5.71)	5908	193	52662	3.66 (3.17, 4.21)	1.32 (1.05, 1.64)
2004	3006	120	27146	4.42 (3.68, 5.26)	6012	156	54139	2.88 (2.45, 3.36)	1.53 (1.21, 1.94)

Abbreviations: RA: rheumatoid arthritis; N: Number of individuals; AMI: acute myocardial infarction; PYs: Person-years of follow-up; IRs: incident rates; IRRs: incident rate ratios (IR in RA / IR in General Population); CI: confidence interval

*Year of incidence of RA cohort, defined based on first RA visit.

Figure 1. Crude 10-year risk of AMI according to year of incidence (1997-2004) in RA and general population cohorts



Abbreviations: AMI: acute myocardial infarction; IR: incidence rate; CI: confidence interval; GP: general population; RA: rheumatoid arthritis

Table 3. Secular trend in 10-year risk of AMI in RA relative to the general population

Secular Trends in 10-year risk of AMI	Unadj. HR (95% CI)	p-value	Adj. HR Ω (95% CI)	p-value
RA cohort*	0.95 (0.93, 0.98)	0.0002	0.94 (0.92, 0.97)	<.0001
general population**	0.95 (0.93, 0.97)	<.0001	0.93 (0.91, 0.95)	<.0001
Secular Trend in RA relative to the General Population***	1.01 (0.98, 1.04)	0.59	1.01 (0.98, 1.05)	0.49

Ω covariates included in the final multivariable model include: age ; sex; income quintile; health care authority; rural vs. urban; number of physician visits; prior hospitalization ; angina; COPD; alcoholism; CV medications; diabetes; fibrates; statins; cox2 inhibitors; glucocorticoids

*HR represents the change in AMI risk in the RA population per increasing calendar year of incidence.

** HR represents the change in AMI risk in the general population per increasing calendar year of index date (corresponding to the year of RA incidence of the RA case they are matched to).

*** HR represents the HR for the interaction term between indicator of RA vs. general population and year of incidence.

Abbreviations: RA: rheumatoid arthritis; GP: general population; Unadj. HR: unadjusted hazard ratio; Adj. HR: adjusted hazard ratio; CI: confidence interval

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