Improved Incidence of Cardiovascular Disease in Patients with Incident Rheumatoid Arthritis in the 2000s: a Population-Based Cohort Study

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Key Indexing Terms: “arthritis, rheumatoid”, “cardiovascular diseases”, “epidemiology”

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Funding: This work was supported by a grant from the National Institutes of Health, NIAMS (R01 AR46849) and NHLBI (HL120859). Research reported in this publication was supported by the National Institute of Aging of the National Institutes of Health under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Dr. Elena Myasoedova is supported by the Louis V. Gerstner, Jr. Fund at Vanguard Charitable.

Conflict of interest: Authors declare no conflict of interest.

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ABSTRACT

Objective: To assess trends in incidence of cardiovascular disease (CVD) and mortality following incident CVD events in patients with rheumatoid arthritis (RA) onset in 1980-2009 versus non-RA subjects.

Methods: We studied Olmsted County, Minnesota residents with incident RA (age ≥18 years, 1987 ACR criteria met in 1980-2009) and non-RA subjects from the same source population with similar age, sex and calendar year of index. All subjects were followed until death, migration, or 12/31/2016. Incident CVD events included myocardial infarction and stroke. Patients with CVD before RA incidence/index date were excluded. Cox models were used to compare incident CVD events by decade, adjusting for age, sex and CVD risk factors.

Results: The study included 905 patients with RA and 904 non-RA subjects. Cumulative incidence of any CVD event was lower in patients with incident RA in 2000s versus 1980s. Hazard Ratio [HR] for any incident CVD 2000s versus 1980s: 0.53; 95% confidence interval (CI): 0.31-0.93. The strength of association attenuated after adjustment for anti-rheumatic medication use: HR 0.64, 95%CI 0.34-1.22. Patients with RA in 2000s had no excess in CVD over non-RA subjects (HR: 0.71, 95%CI:0.42-1.19). Risk of death after a CVD event was somewhat lower in patients with RA after 1980s: HR: 0.54, 95%CI:0.33-0.90 in 1990s and HR: 0.68, 95%CI:0.33-1.41 in 2000s versus 1980s.

Conclusion: Incidence of major CVD events in RA has declined in recent decades. The gap in CVD occurrence between RA patients and the general population is closing. Mortality after CVD events in RA may be improving.

INTRODUCTION

An excess burden of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is an established paradigm. Many epidemiologic studies worldwide have reported 1.5-2-fold increased risk of incident CVD events in RA versus the general population (1-5). Death from CVD is a leading cause of premature mortality in RA (3, 6, 7). Meta-analyses integrating the findings published over the past 50 years showed 2-fold excess risk of CVD death in patients with RA versus the general population, and no apparent decrease in CVD mortality in RA was noted up to the mid-2000s (8, 9).

More recently published population-based studies from Europe, Canada and our group, suggested improving CVD mortality in patients diagnosed with RA after 2000 (10-13). Improved control of RA disease activity following early initiation of anti-rheumatic treatments and the use of biologics were discussed as potential contributors to the decrease in CVD mortality in RA.

Decreased incidence of CVD events and decreased mortality after CVD events could both be contributors to the decreased CVD mortality in RA in recent years. However, longitudinal studies on trends in occurrence of CVD events and mortality after CVD events in patients with RA over time and studies comparing these trends between RA and the general population are scarce (14).

To address this gap in knowledge, we aimed to 1) assess trends in incidence of CVD in patients with incident RA in 1980-2009; 2) compare incidence of CVD in RA patients vs non-RA subjects with RA incidence/index date in 1980-2009; 3) assess mortality following incident CVD events in patients with RA in 1980-2009; and 4)

compare mortality following incident CVD events in patients with RA vs non-RA subjects with RA incidence/index date in 1980-2009.

MATERIALS AND METHODS

The study included a population-based inception cohort of Olmsted County, Minnesota residents aged ≥18 years (1987 American College of Rheumatology [ACR] classification criteria for RA met between 1/1/1980 and 12/31/2009). Patient ascertainment was performed using the Rochester Epidemiology Project (REP), a population-based medical records-linkage system with access to the complete (in-patient and out-patient) medical records from all medical providers in the community (15-18). The RA incidence date was defined as the earliest date of fulfillment of ≥4 1987 ACR criteria for RA. The comparison cohort included randomly selected Olmsted County residents without RA who were of similar age, sex and calendar year of index. Each non-RA subject was assigned an index date corresponding to the incidence date of their matched RA patient. Calendar year of index refers to the year of that index date (e.g., 2010). All subjects were followed through medical record review until death, migration, or 12/31/2016.

Nurse-abstractors reviewed medical records for CVD risk factors: age, smoking, hypertension, diabetes mellitus and dyslipidemia, using standardized criteria as described previously (19). Data on RA characteristics including rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), erythrocyte sedimentation rate (ESR), radiographic joint erosions/destructive changes, and use of systemic corticosteroids, conventional disease-modifying anti-rheumatic drugs (DMARDs) (e.g.,

methotrexate, hydroxychloroquine, other DMARDs), and biologics (i.e., tumor necrosis factor inhibitors [TNFi], anakinra, abatacept, rituximab, tocilizumab) were collected.

Data on CVD events (i.e., myocardial infarction [MI], including MI without ST-elevation [non-STEMI], and stroke – ischemic or hemorrhagic) were collected throughout the follow-up using standardized diagnostic criteria, including laboratory and electrocardiographic (ECG) criteria for MI, and clinical diagnosis by a neurologist confirmed by imaging for stroke (20, 21). MIs were adjudicated by a cardiologist (VLR) to ensure there were no alternative causes for ECG changes or elevated biomarkers. Silent MIs were excluded. Information on coronary revascularization procedures (i.e., percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]) was collected.

Vital status information was obtained from state and local death certificates as well as the National Death Index Plus. This study was approved by institutional review boards of Mayo Clinic (IRB #17-002593) and Olmsted Medical Center (IRB #017-omc-17). The need for informed consent was waived. Patients who declined the use of their medical records for research purposes were not included in the study, per Minnesota law.

Statistical Methods

Descriptive characteristics (means, percentages, etc.) were used to summarize the data. Comparisons of characteristics between cohorts were performed using Chi-square and rank sum tests. MI and stroke were examined separately, and a combined outcome of “any CVD event” defined as first of either MI or stroke was also examined.

For patients who experienced both a stroke and an MI, both events were counted in the analyses of the individual events, respectively.

Patients with CVD events before RA incidence/index date were excluded. Cumulative incidence of CVD events adjusted for the competing risk of death was calculated. Cox models were used to compare CVD events by decade, adjusting for age and sex (Model 1); age, sex, smoking (current and former), obesity, diabetes mellitus, hypertension, dyslipidemia (Model 2); age, sex, highest ESR in the first year of RA incidence (Model 3); variables from Model 2 and time-dependent exposure to conventional DMARDs and biologics (Model 4). With the use of Cox model calculations which occur at each event time, no comparisons between groups are made after the follow-up ends for one of the groups, thus shorter length of follow-up in more recent cohorts versus earlier cohorts does not affect the validity of the comparisons. Sensitivity analyses were performed using an outcome of first of either MI or revascularization procedure. Kaplan-Meier methods were used to estimate all-cause mortality following CVD occurrence. Cox models were used to compare all-cause mortality after CVD event by decade adjusting for age, sex and RA duration. Analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics of patients with and without RA

The study included 905 patients with RA (a total of 12,808 person-years of follow-up), of whom 201 were incident RA during 1980-89, 299 during 1990-99 and 405 during 2000-09. Patients with RA onset in different decades were similar in their

demographics (Table 1). The percentage of current smokers, the highest ESR in the first year of RA and the use of other DMARDs in the first year of RA incidence declined, while obesity, hypertension, dyslipidemia, use of methotrexate, hydroxychloroquine, biologics and corticosteroids increased in patients with more recent RA onset versus those with RA in earlier decades. Time from RA incidence to initiation of the first DMARD declined dramatically over the decades (Table 1).

The comparison population comprised 904 subjects without RA (a total of 13,095 person-years of follow-up), including 201 non-RA subjects in 1980-89, 299 in 1990-99 and 404 in 2000-09. Apart from lower rates of smoking, hypertension and dyslipidemia in non-RA subjects, there were no significant differences in demographics and CVD risk factors between RA and non-RA subjects overall (Table 1). Non-RA subjects were more likely to have experienced a stroke before RA incidence/index date (p=0.02). Characteristics of patients without previous CVD events (Supplemental Table 1) were similar to those for patients with or without underlying CVD events (Table 1).

Risk of CVD events by decade of RA incidence

Figure 1 shows trends in incidence of any CVD event, MI and stroke by decade of RA incidence. Adjusting for age and sex, the risk of any CVD event in patients with RA in 2000s was 42% lower than in 1980s (Table 2). The risk of MI was 56% lower in patients with RA in 2000s vs 1980s, while risk of stroke was similar in patients with RA across the decades. These results remained consistent after adjustment for age, sex, smoking, obesity, diabetes mellitus, hypertension, and dyslipidemia (Table 2). Adjusting for age, sex and highest ESR during the first year of RA incidence, the results remained similar for MI, but the strength of association for risk of any CVD event in patients with

RA onset in 2000s vs 1980s was attenuated. Adjustment for antirheumatic medications use further attenuated the strength of associations (Table 2).

When revascularizations were combined with MI, the results were similar to the trends for MI alone (Table 2). Results were similar after adjustment for age, sex, smoking status, obesity, diabetes, hypertension, dyslipidemia, highest ESR and anti-rheumatic medication use.

Trends in incident CVD events and coronary revascularizations among RF-positive and RF-negative patients were similar to the RA cohort overall. However, differences in CVD incidence between the decades did not reach statistical significance in either subgroup. For example, the HR for any CVD event in patients with positive RF was 0.58 (95%CI 0.31-1.11) for the 2000s vs 1980s, and in RF-negative patients, the HR was 0.50 (95%CI 0.19-1.33) for the 2000s vs 1980s, adjusting for age and sex. As anti-CCP testing was not widely available until the 2000s, analysis comparing multiple decades for anti-CCP-positive vs negative patients was not possible. A sensitivity analysis by RF/anti-CCP positivity showed results similar to those by RF-positivity alone.

Risk of CVD events in patients with RA versus non-RA subjects by decade of RA incidence/ index

Unlike the over 50% excess risk of any CVD event in patients with RA in 1980s and 1990s, patients with incident RA in 2000s had no excess in any CVD events over non-RA subjects, adjusting for age and sex (Table 3). Adjustment for age, sex, smoking, obesity, diabetes mellitus, hypertension, dyslipidemia has attenuated associations for the 1980s and 1990s, while not altering the results for the 2000s. The HR for the

incident MI in patients with RA versus non-RA subjects has declined from ~1.6 in 1980s and 1990s to ~0.6 in the 2000s, but these associations did not reach statistical significance in either of the adjustment models (Table 3).

For the combined outcome of MI and/or revascularization, the risk was similar in patients with and without RA across the decades of incidence/ index, adjusting for age, sex, smoking, obesity, diabetes mellitus, hypertension, dyslipidemia.

Mortality after CVD events by decade of RA incidence/index

The 120 RA patients and 94 non-RA subjects who developed an incident CVD event following RA incidence/ index date were comparable in age at diagnosis of stroke/MI, years since RA incidence/index at CVD event, and smoking status (Table 4). During follow-up (median 3.3 years for RA and 4.2 years for non-RA), there were 68 deaths in the 1980-89 cohort (41 RA; 27 non-RA), 45 deaths in the 1990-99 cohort (30 RA; 15 non-RA), and 26 deaths in the 2000-09 cohort (12 RA; 14 non-RA).

Among RA patients with incident CVD events, mortality was somewhat lower, particularly in patients with RA onset in 1990s (HR 0.54, 95%CI:0.33-0.90), while not reaching statistical significance for patients with RA onset in 2000s (HR 0.68, 95%CI:0.33-1.41) compared to 1980s, adjusting for age, sex and RA duration. Figure 2 shows mortality following incident CVD event in RA by decade of RA incidence.

Among patients with incident CVD, mortality was similar between RA and non-RA subjects with incidence/index date in 1980-89 (HR 1.38, 95%CI:0.84-2.27), 1990-99 (HR 1.18, 95%CI:0.62-2.23), and 2000-09 (HR 1.87, 95%CI:0.82-4.26), adjusting for age, sex and years since RA incidence/index.

DISCUSSION

This study shows a decrease in the *incidence* of major CVD events in successive population-based incident RA cohorts. This improvement appears to be largely driven by an over 50% decline in the incidence of MI in patients with RA onset in 2000s versus 1980s, concomitant with the declining incidence of MI in the general population (22).

Trends in Incidence of Myocardial Infarction in RA

Coronary artery disease (CAD) is an established contributor to excess CVD risk and mortality in RA (3, 6, 23). A meta-analysis of observational studies estimated a 68% increase in the risk of acute MI in patients with RA vs the general population (pooled relative risk [RR] 1.68; 95% CI 1.40–2.03), with significantly increased risk in both sexes (1). This is consistent with our estimates of about 60%-increase in risk of MI in patients with RA onset in 1980s and 1990s versus the non-RA subjects. While not reaching statistical significance in any of the decades, one may appreciate reversal of the risk estimate for incident MI in RA versus non-RA subjects from ~1.6 in 1980s and 1990s to ~0.6 in the 2000s. Taken together with statistically significant decline in the risk of incident MI in RA in 2000s versus 1980s, this suggests that the rate of improvement in MI risk in RA may be outpacing that in the general population. While data on trends in incidence of CVD events in RA are scarce, a recent nation-wide cohort study from Sweden showed about 40% decline in incidence of acute coronary syndrome (ACS) in the general population and in patients with RA (14). Unlike in patients with new-onset RA in late 1990s and 2000s, who had persistent ~40% excess risk of ACS as compared to the general population, in patients with new-onset RA in 2011-14 the hazard ratio for ACS was not statistically significant (1.19, 95%CI 0.85-1.67), potentially suggesting an emerging decrease in excess ACS risk in RA. Preliminary findings from the British

Columbia population have suggested a decreased risk of incident MI in patients diagnosed with RA in 1997-2004 and followed up though 2014, and a parallel decline in the risk of MI in matched comparators from the general population (24). Our study extends these studies by reporting results from successive incidence RA cohorts in a geographically different population and strengthens the evidence of declining MI incidence in patients with RA in recent years.

Coronary revascularization procedures are increasingly widespread therapeutic interventions for patients with CAD with potential impact on subsequent CVD events (25, 26). The trends by decade of RA incidence for the combined outcome of MI or revascularization were similar to the trends for MI alone.

Trends in Incidence of Stroke in RA

Unlike the improving incidence of MI, in this study, no statistically significant differences in the risk of ischemic or hemorrhagic stroke by decade of RA incidence or by RA status were found. Reasons for this lack of improvement are not immediately apparent from our observational study. The association between RA and risk of stroke is weaker and less consistent across studies, compared to the well-established association between RA and risk of MI (1). Difference in the pathogenesis of cerebrovascular disease versus coronary artery disease (i.e. potentially longer time to occurrence of cerebrovascular events compared to coronary events), stemming from difference in anatomy and physiology of cerebrovascular and cardiovascular beds have been suggested as potential explanations for differences in strength of association between RA and stroke vs RA and MI (27-29). Similar reasoning may relate to our finding of lack of significant decline in the incidence of stroke. However, other

explanations (e.g. population-specific environmental effects and difference in impact of preventive practices on MI and stroke) should be considered. There is emerging evidence of decline in incidence of ischemic stroke in the population of British Columbia after 1999 (30). These findings based on trends in ischemic stroke by cohort year 1997-2004 are not directly comparable to ours based on trends in ischemic and hemorrhagic stroke by decade of RA incidence/ index (1980-2000). Further studies evaluating trends in incidence of stroke in RA are warranted.

Mortality after incident CVD events in RA

While earlier observational studies from different populations have reported increased mortality after acute MI in patients with RA versus non-RA subjects, including 30-day and 1-year mortality (31-33), a recent National Inpatient Sample database analysis showed no increase in in-hospital mortality following acute MI in patients with RA in 2005-2014 (34). In our study, mortality following incident MI and/or stroke showed potential improvement in patients with RA diagnosed after 1980s, while relative mortality was similar in patients with RA and non-RA subjects across the decades of the study.

What are the reasons for the improved CVD Incidence in RA?

The reasons are likely several-fold. Improvement in CVD health in patients with RA onset in recent decades may reflect improvement in CVD morbidity and mortality in the general population following implementation of effective CVD prevention and management strategies. We observed some improvement in CVD risk factor profile in RA patients across the decades of study. While smoking and dyslipidemia were more prevalent in RA versus non-RA in earlier decades, prevalence of these and other major CVD risk factors (i.e., obesity, diabetes mellitus, hypertension) was similar in RA

patients versus non-RA subjects with incidence/ index dates in the 2000s. Measures for improved awareness and timely management of CVD risk factors in patients with RA (i.e., increase in statin prescribing and diagnosis of hypertension) may be contributing to the improving CVD risk factor profile and declining CVD incidence in RA (35, 36).

The improved incidence of CVD events in RA versus non-RA implies a closing gap in CVD occurrence between RA and the general population and suggests RA-specific reasons for these trends. The pivotal role of inflammation in the pathogenesis of CVD has been shown both in RA and the general population, with a dose-response relationship between chronicity and severity of inflammation and the acuity and severity of CVD outcomes (14, 37-43). Implementation of treat-to-target strategies, early initiation of DMARDs and the rapidly increasing use of biologic DMARDS have revolutionized rheumatology care, leading to substantial outcome improvement in RA, including CVD outcome improvement, which is largely attributable to improved control of systemic inflammation (44, 45). A systematic review and meta-analysis of observational studies and randomized controlled trials showed a 28% reduction in CVD events in patients with RA on methotrexate and a 30% reduction with TNFi (45). In our study, the use of methotrexate and biologics has increased in patients with more recent RA onset, while time from RA incidence to initiation of the first DMARD has drastically declined over the decades. These therapeutic changes were accompanied by decline in the highest ESR in the first year of RA over the decades of RA incidence, suggesting that improved control of RA disease activity can be contributing to the observed improvement in incidence of CVD events in RA.

Implications of the study findings

This study has a number of important implications. The major decline in the incidence of CVD events in RA and equilibration of CVD incidence between RA and the general population, augmenting the previously reported decline in CVD mortality in RA patients suggests an emerging paradigm shift from the well-established concept of substantially increased CVD incidence and CVD mortality in RA. It can be hypothesized that the decrease in incidence of acute MI as the major driver for the improved incidence of CVD events overall in patients with RA is a likely contributor to improved CVD mortality in RA over time. Both improved control of inflammation and increasing efforts for optimization of CVD risk management in RA in recent years could be important contributors to these trends, particularly to the closing gap in CVD occurrence in RA versus non-RA subjects. Future studies aimed at understanding the underlying nature for these trends, together with studies evaluating trends in non-cardiac peripheral vascular disease may aid in improving CVD risk management strategies in patients with rheumatic diseases as well as in the general population.

Limitations and strengths

There are some potential limitations to this study. There is a chance for miscoding of the CVD events. However, this would affect all subjects in the study and thus is unlikely to significantly bias the comparisons. In an unlikely possibility that non-STEMI events were missed in the earlier decades due to less sensitive diagnostic assays compared to the 2000s, this would be expected to comparably affect both the RA and non-RA cohorts and no differential misclassification bias would be expected. Patients with chronic inflammatory conditions other than RA were not excluded from either the RA or the non-RA cohort to minimize selection bias. Applying this inclusion

criterion to both cohorts likely minimizes any differential impact of these conditions on the comparisons. The reasons for the emerging improvement in mortality following CVD events in RA warrant further study. During the period of investigation, the population of Olmsted County, Minnesota was predominantly white. Thus, the results should be replicated in different populations.

This study has several important strengths. Our study takes advantage of its population-based design and use of a comprehensive medical record linkage system including all in-patient and out-patient care from all local providers. Standardized case ascertainment and inclusion of successive incidence cohorts strengthen the study. Our study also takes advantage of the long and complete follow-up of all subjects and the availability of a non-RA comparison cohort from the same underlying population. Use of uniform classification of CVD events and available data on CVD risk factors for both cohorts, as well data on RA characteristics and medications also strengthens the study.

In conclusion, following decades of increased CVD risk in RA, a reduction in incidence of major CVD events was found. The reduction was primarily in acute MI and was not explained by earlier revascularization interventions. The gap in CVD occurrence between RA patients and the general population is closing. There was also some improvement in mortality following CVD events in RA in recent decades. Taken collectively, these findings highlight an important milestone in CVD disease management, opening grounds for investigation of the reasons for these trends with implications for patients with rheumatic diseases and beyond.

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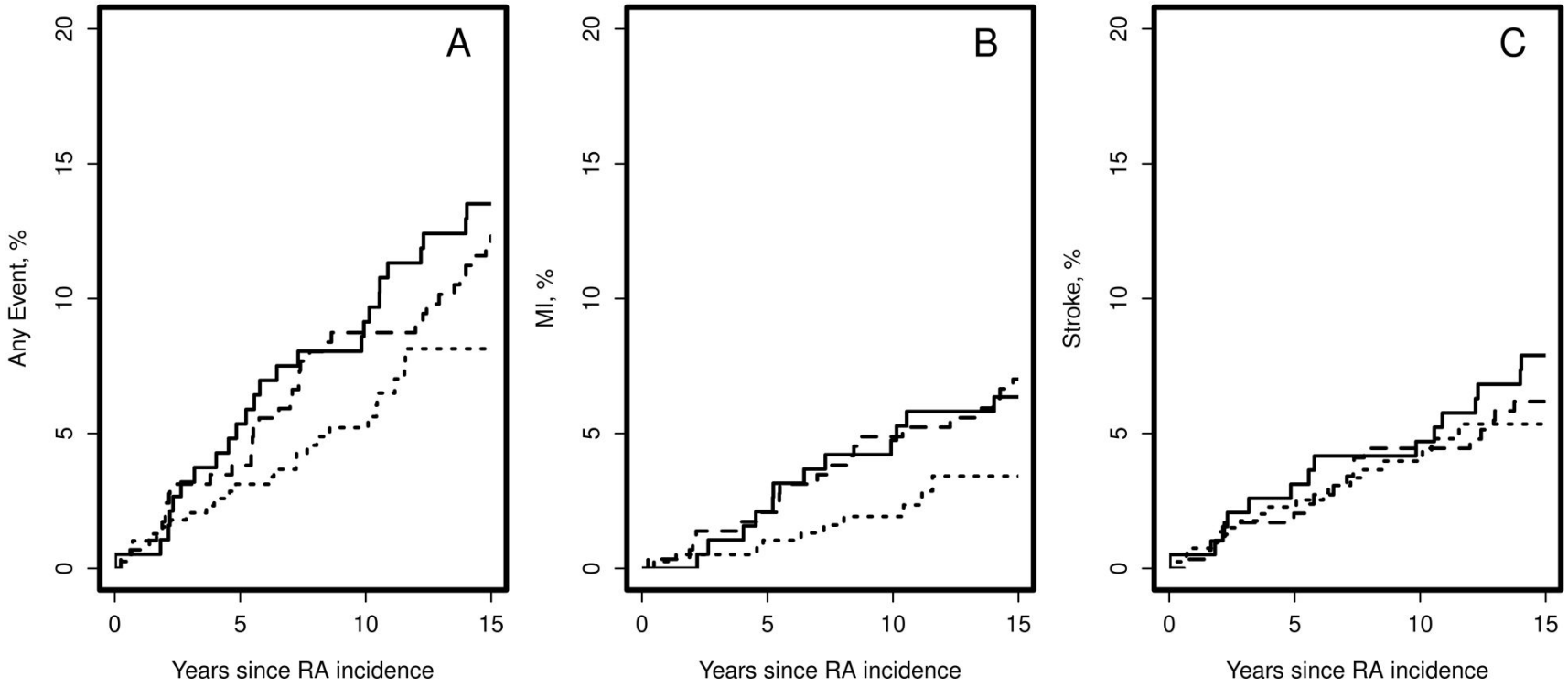
FIGURE LEGENDS

Figure 1. Cumulative incidence of Cardiovascular Disease (CVD) Events in patients with Rheumatoid Arthritis (RA) by decade of RA incidence

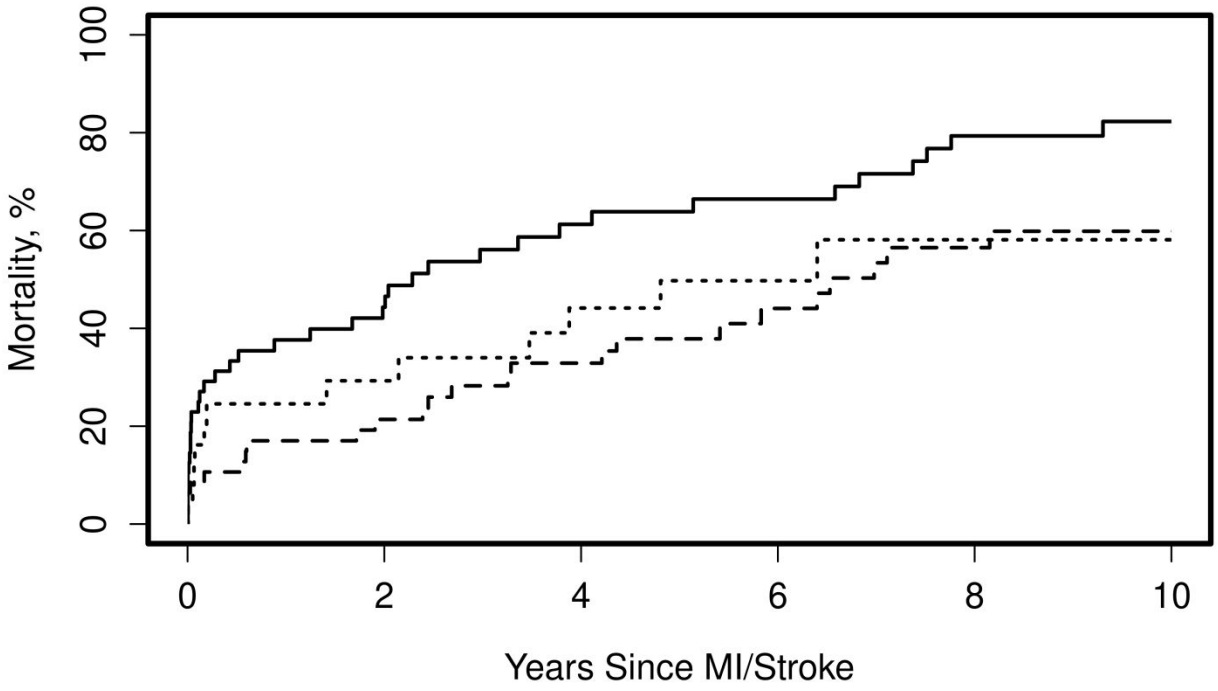
Figure 2. Mortality following an incident Cardiovascular Disease (CVD) Event in patients with Rheumatoid Arthritis (RA) by decade of RA incidence

Figure 1. Cumulative incidence of Cardiovascular Disease (CVD) Events in patients with Rheumatoid Arthritis (RA) by decade of RA incidence



Footnote: trends by decades of RA incidence are shown as follows: black solid line = 1980-1989; dashed line = 1990-1999; dotted line = 2000-2009. A=Any event; B=myocardial infarction (MI); C=Stroke (Ischemic or hemorrhagic)

Figure 2. Mortality following an incident Cardiovascular Disease (CVD) Event in patients with Rheumatoid Arthritis (RA) by decade of RA incidence



Footnote: trends by decade of RA incidence are shown as follows: black solid line = 1980-1989; dashed line = 1990-1999; dotted line = 2000-2009.

Abbreviation: MI=myocardial infarction

Table 1: Characteristics of study subjects

	RA cohort				Non-RA cohort			
Incidence/ index	Overall	1980-89	1990-99	2000-09	Overall	1980-89	1990-99	2000-09
Variables	(n=905)	(n=201)	(n=299)	(n=405)	(n=904)	(n=201)	(n=299)	(n=404)
Age, years	55.9 (15.6)	57.2 (15.8)	56.2 (15.9)	55.0 (15.4)	55.9 (15.6)	57.3 (15.7)	56.3 (15.8)	55.0 (15.4)
Female sex	621 (69%)	137 (68%)	197 (66%)	287 (71%)	620 (69%)	137 (68%)	197 (66%)	286 (71%)
CVD risk factors, at incidence/ index								
Cigarette smoking, at RA incidence	189 (21%)	67 (33%)	60 (20%)	62 (15%)	158 (17%)	52 (26%)	40 (13%)	66 (16%)
- Current								
- Former	303 (33%)	55 (27%)	115 (38%)	133 (33%)	254 (28%)	48 (24%)	94 (31%)	112 (28%)
Obesity (BMI≥30 kg/m^2), at RA incidence	284 (31%)	33 (16%)	83 (28%)	168 (41%)	259 (29%)	30 (15%)	70 (23%)	159 (39%)
Hypertension	366 (40%)	77 (38%)	105 (35%)	184 (45%)	323 (36%)	65 (32%)	88 (29%)	170 (42%)
Diabetes Mellitus	97 (11%)	22 (11%)	24 (8%)	51 (13%)	80 (9%)	15 (7%)	18 (6%)	47 (12%)
Dyslipidemia	512 (57%)	82 (41%)	172 (58%)	258 (64%)	456 (50%)	63 (31%)	147 (49%)	246 (61%)
*CVD events prior to or on RA incidence/ Index date***								

- Myocardial infarction	24 (3%)	6 (3%)	7 (2%)	11 (3%)	27 (3%)	4 (2%)	12 (4%)	11 (3%)
- Stroke (ischemic or hemorrhagic)	10 (1%)	5 (2%)	2 (1%)	3 (1%)	23 (3%)	5 (2%)	10 (3%)	8 (2%)
Revascularization procedures prior to or on RA incidence/ index date	40 (4%)	2 (1%)	16 (5%)	22 (5%)	26 (3%)	4 (2%)	8 (3%)	14 (3%)
Years from RA diagnosis to last follow up	14.2 (7.9)	18.8 (10.9)	16.5 (6.9)	10.2 (3.8)	14.5 (8.1)	20.3 (11.0)	17.0 (6.5)	9.7 (3.5)
RA disease characteristics								
RF/CCP positivity, at incidence/ index	607 (67%)	134 (67%)	205 (69%)	268 (66%)				
Missing	3	2	0	1				
Highest ESR, during the 1st year of RA incidence, mm/hr, mean (SD)	32.4 (25.7)	38.9 (27.6)	31.5 (25.1)	30.0 (24.8)	--			
Missing	34	13	10	11				
Erosions/destructive changes, during the 1st year of RA incidence	243 (27%)	51 (25%)	75 (25%)	117 (29%)	--			
Antirheumatic medication use, during the first year of RA incidence								
Time from RA incidence to initiation of the first DMARD, months (median (IQR))	0.7 (0.0-4.4)	4.5 (0.8-23.3)	0.9 (0.1-5.3)	0.3 (0.0-1.6)				
Methotrexate	323 (36%)	4 (2%)	83 (28%)	236 (58%)	--			
Hydroxychloroquine	410	50	134	226	--			

	(45%)	(25%)	(45%)	(56%)	
Other DMARDs	137 (15%)	56 (28%)	44 (15%)	37 (9%)	--
Biologics	39 (4%)	0 (0%)	1 (0%)	38 (9%)	--
Glucocorticoids	510 (56%)	51 (25%)	179 (60%)	280 (69%)	--

Abbreviations: RA = Rheumatoid Arthritis; BMI = body mass index; CVD = cardiovascular disease; RF = rheumatoid factor; CCP=cyclic citrullinated peptide; ESR = erythrocyte sedimentation rate; DMARDs = disease modifying antirheumatic drugs; IQR=interquartile range.

Footnote: *Values in the table are mean (SD) for continuous characteristics unless otherwise specified, and N (%) for discrete characteristics; ** Patients with prior CVD events were excluded from analyses of CVD outcomes

- Significant differences between the RA and non-RA cohorts overall included smoking status (p=0.001), hypertension (p=0.039) and dyslipidemia (p=0.009). Significant differences between decades among the RA included smoking status, obesity, hypertension, dyslipidemia, ESR, time from RA incidence to initiation of the first DMARD, use of methotrexate, hydroxychloroquine, other DMARDs, biologics, glucocorticoids in the first year of RA incidence (all p<0.001, except hypertension, p=0.018). Significant differences between decades among the non-RA included smoking status (p=0.006), obesity (p<0.001), hypertension (p=0.001), diabetes (p=0.026), dyslipidemia (p<0.001).

Table 2. Risk of incident Cardiovascular Disease (CVD) and revascularization procedures in Rheumatoid arthritis (RA) by decade of RA incidence

Event Type	Decade	Total† (Events)	HR (95% CI)*	p-value	HR (95% CI)**	p-value	HR (95% CI)***	p-value	HR (95% CI)****	p-value
Any CVD Event (Myocardial infarction/stroke)	1980-89	191 (48)	Reference	--	Reference	--	Reference	--	Reference	--
	1990-99	291 (47)	0.84 (0.55-1.29)	0.43	0.89 (0.57-1.39)	0.60	0.87 (0.56-1.36)	0.55	1.02 (0.63-1.64)	0.94
	2000-09	392 (25)	0.58 (0.34-0.98)	0.043	0.53 (0.31-0.93)	0.028	0.63 (0.37-1.08)	0.095	0.64 (0.34-1.22)	0.18
Myocardial infarction	1980-89	195 (26)	Reference	--	Reference	--	Reference	--	Reference	--
	1990-99	292 (24)	0.82 (0.45-1.49)	0.51	0.77 (0.41-1.45)	0.43	0.76 (0.41-1.40)	0.38	0.95 (0.48-1.86)	0.87
	2000-09	394 (10)	0.44 (0.20-0.97)	0.042	0.36 (0.16-0.81)	0.013	0.45 (0.20-0.99)	0.046	0.47 (0.18-1.19)	0.11
Stroke (ischemic or hemorrhagic)	1980-89	196 (27)	Reference	--	Reference	--	Reference	--	Reference	--
	1990-99	297 (28)	0.84 (0.48-1.46)	0.53	0.95 (0.53-1.70)	0.86	0.97 (0.54-1.73)	0.91	1.05 (0.57-1.94)	0.87
	2000-09	402 (18)	0.75 (0.38-1.45)	0.38	0.77 (0.38-1.56)	0.47	0.88 (0.44-1.73)	0.70	0.92 (0.41-2.04)	0.83
Myocardial infarction/ revascularization procedure	1980-89	194 (36)	Reference	--	Reference	--	Reference	--	Reference	--
	1990-99	281 (37)	0.83 (0.51-1.33)	0.43	0.82 (0.49-1.34)	0.42	0.81 (0.49-1.32)	0.40	0.99 (0.58-1.71)	0.97
	2000-09	382 (13)	0.36 (0.18-0.70)	0.003	0.30 (0.15-0.59)	<0.001	0.37 (0.19-0.72)	0.003	0.40 (0.18-0.87)	0.022

Footnote: †Excludes patients with events prior to RA incidence/index *Adjusted for age and sex

** Adjusted for age, sex, current and former smoking, obesity, diabetes, hypertension, dyslipidemia

*** Adjusted for age, sex, and highest ESR

**** Adjusted for age, sex, current and former smoking, obesity, diabetes, hypertension, dyslipidemia, time-dependent MTX, time-dependent HCQ, time-dependent other DMARDs, and time-dependent biologics

Table 3. Risk of incident Cardiovascular Disease (CVD) in patients with rheumatoid arthritis (RA) versus non-RA subjects by decade of RA incidence/ index

Decade	Outcome	Total† (Event) in RA	Total† (Event) in non-RA	HR (95% CI)*	p-value	HR (95% CI)**	p-value
Any CVD Event	1980-1989	191(48)	192 (38)	1.66 (1.08-2.56)	0.020	1.46 (0.94-2.27)	0.095
	1990-1999	291(47)	278 (24)	2.08 (1.27-3.40)	0.004	1.91 (1.15-3.18)	0.012
	2000-2009	392 (25)	385 (32)	0.71 (0.42-1.19)	0.19	0.71 (0.42-1.19)	0.20
Myocardial infarction	1980-1989	195 (26)	197 (21)	1.59 (0.89-2.85)	0.12	1.36 (0.74-2.48)	0.32
	1990-1999	292 (24)	287 (16)	1.60 (0.85-3.01)	0.15	1.31 (0.68-2.54)	0.42
	2000-2009	394 (10)	393 (16)	0.58 (0.26-1.28)	0.18	0.57 (0.26-1.27)	0.17
Stroke (ischemic or hemorrhagic)	1980-1989	196 (27)	196 (23)	1.51 (0.86-2.65)	0.15	1.29 (0.72-2.29)	0.40
	1990-1999	297 (28)	289 (14)	2.27 (1.19-4.32)	0.013	2.25 (1.16-4.34)	0.016
	2000-2009	402 (18)	396 (22)	0.78 (0.42-1.45)	0.43	0.79 (0.42-1.48)	0.46
Myocardial infarction/revascularization	1980-1989	194 (36)	194 (31)	1.37 (0.85-2.23)	0.20	1.10 (0.67-1.81)	0.71
	1990-1999	281 (37)	284 (20)	2.09 (1.21-3.60)	0.008	1.64 (0.94-2.87)	0.084
	2000-2009	382 (13)	388 (20)	0.62 (0.31-1.25)	0.184	0.62 (0.31-1.26)	0.19

Footnote: †Excludes patients with events prior to RA incidence/index *Adjusted for age and sex

** Adjusted for age, sex, current and former smoking, obesity, diabetes, hypertension, dyslipidemia

Table 4: Characteristics of patients with incident Cardiovascular Disease (CVD) events during the follow-up, by decade of RA incidence/index

	RA cohort				Non-RA			
Variable	Overall (N=120)	1980-89 (n=48)	1990-99 (n=47)	2000-09 (n=25)	Overall (N=94)	1980-89 (n=38)	1990-99 (n=24)	2000-09 (n=32)
Age (yrs) at MI/ Stroke	75.2 (12.0)	76.7 (10.1)	75.0 (13.4)	72.7 (12.6)	75.4 (11.9)	77.1 (10.8)	73.7 (13.3)	74.6 (12.3)
Female sex	71 (59%)	32 (67%)	26 (55%)	13 (52%)	62 (66%)	25 (66%)	15 (63%)	22 (69%)
Years from RA/ index to MI /Stroke	11.1 (8.3)	14.8 (9.8)	10.1 (6.4)	5.8 (3.8)	10.6 (7.5)	14.5 (8.9)	10.3 (5.2)	6.2 (3.9)
RF/CCP positive	86 (72%)	32 (67%)	36 (77%)	18 (72%)	--	--	--	--
Ever smoker	75 (63%)	33 (69%)	29 (62%)	13 (52%)	51 (54%)	20 (53%)	16 (67%)	15 (47%)
Years from MI /Stroke to last follow-up (median (IQR))	3.3 (0.6-7.2)	2.0 (0.1-6.7)	4.7 (2.3-8.8)	3.5 (0.2-6.1)	4.2 (0.5-8.2)	3.4 (0.1-8.9)	5.2 (1.3-8.1)	4.1 (1.1-6.7)

Abbreviations: RA = Rheumatoid Arthritis; MI=myocardial infarction; RF = rheumatoid factor; CCP=cyclic citrullinated peptide; IQR=interquartile range.

Footnote: *Values in the table are mean (SD) for continuous characteristics unless otherwise specified, and N (%) for discrete characteristics.

- There were no significant differences in characteristics of the RA and non-RA cohorts overall or by decade of RA incidence/ index. Significant differences between decades among the RA cohort and among the non-RA cohort included years from RA/ index date to MI/ stroke (both $p<0.001$).