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ORIGINAL RESEARCH

Risks of Myocardial Infarction and Mortality in Patients with Incident Rheumatoid Arthritis Compared with a Matched General Population: A Danish Nationwide Cohort Study

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Background and Aims: Rheumatoid arthritis (RA) is increasingly being recognized as cardiovascular risk factor. We examined temporal trends in the risks of myocardial infarction (MI) and all-cause mortality in patients with newly diagnosed RA without a history of cardiovascular disease (CVD) compared with a matched general population.

Methods and Results: Patients with a first diagnosis of RA without prior CVD (N=20,937) were identified through national health registries between 1996 and 2017. On the index date, each patient was matched by age and sex to five individuals from the general population with neither RA nor CVD (N=104,685) and followed for 5 years. Among patients with RA, the 5-year cumulative incidence proportions for MI declined from 2.6% in 1996–2000 to 1.5% in 2011–2017 (hazard ratio (HR) 0.59; 95% CI 0.45–0.78), whereas all-cause mortality decreased from 9.3% to 7.7% (HR 0.83; 95% CI 0.72–0.95). The reduced risk of MI in patients with RA mirrored the decline observed in a matched general population while the mortality gap between RA and general population individuals was reduced between 1996 and 2010. Statin prescription fillings at 1-year follow-up, a proxy for prophylactic medical intervention, was highest in 2011–2017, reaching 19% among RA patients as well as general population individuals.

Conclusion: Despite a gradual decline in the risk of MI and all-cause mortality from 1996 to 2017, patients with RA remain at higher risk of both MI and death than their matched general population individuals. This increased risk was not reflected by improved primary prophylactic medical interventions.

Plain Language Summary: What is already known about this subject?

- Rheumatoid arthritis (RA) is a cardiovascular risk factor and is associated with an approximately 50% higher relative risk of major adverse cardiovascular events compared with the general population.

Why was the study conducted?

- We aimed to examine how cardiovascular risks and outcomes in people with newly diagnosed RA have changed over time and to identify opportunities to improve prevention and care.

What does this study add?

- This Danish nationwide study of patients with newly diagnosed RA shows substantial improvement in outcomes over two decades. From 1996-2000 to 2011-2017, the 5-year risk of myocardial infarction fell by 41%, and the 5-year risk of all-cause mortality fell by 17%.
- The decline in risk of myocardial infarction paralleled the decline in the general population, so the excess risk of myocardial infarction associated with RA persisted at about 50% across the full study period.

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- All-cause mortality, however, improved only among patients with RA and remained unchanged in the general population. Despite this improvement, RA still carried a 13% higher relative risk of all-cause mortality in 2011-2017.
- Use of preventive cardiovascular disease medications increased steadily in both groups; in the most recent period, 19% of patients with RA received statins within one year after diagnosis.

How might this impact clinical practice or future developments?

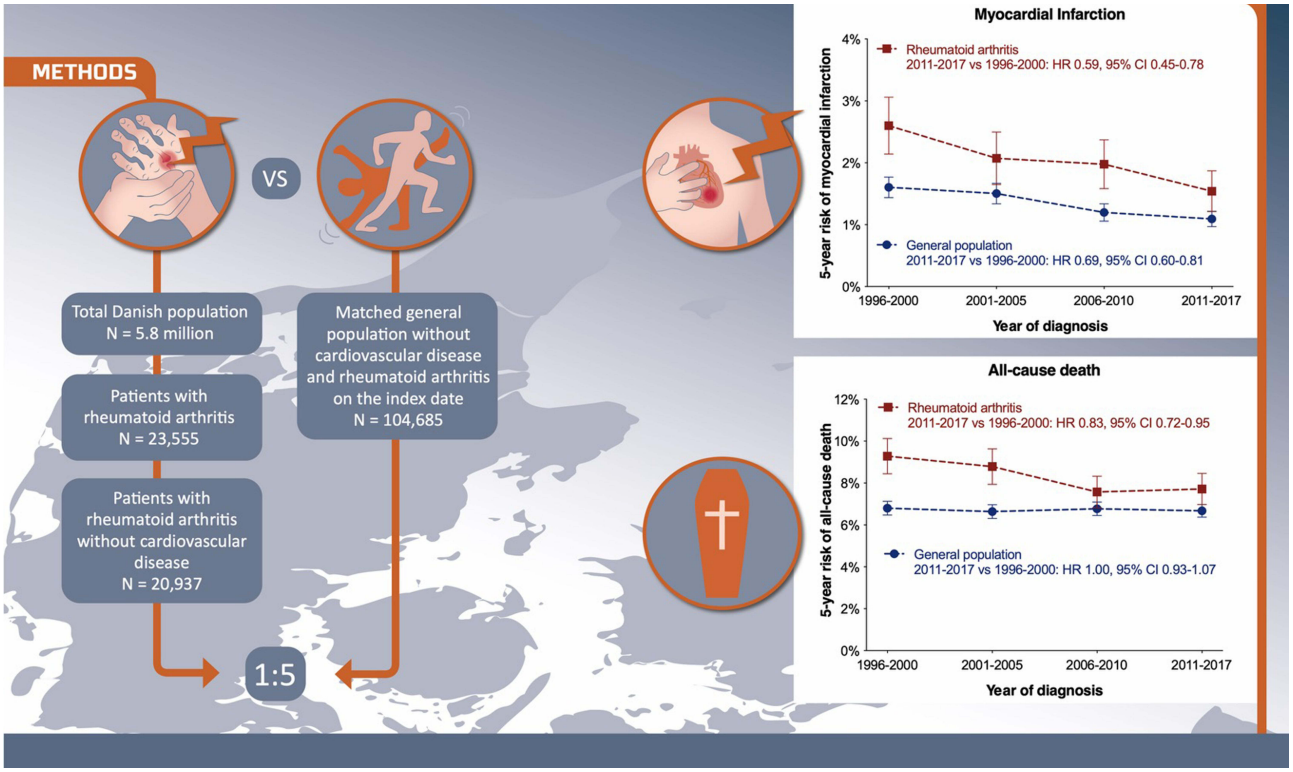
- Clinicians should inform patients with RA about their increased cardiovascular risk and support appropriate risk-reduction strategies.
- These findings underscore the need to clearer guidance on cardiovascular prevention at the time of RA diagnosis.

Keywords: rheumatoid arthritis, cardiovascular disease, coronary heart disease, acute myocardial infarction, mortality, outcome, statins, medical treatment, cohort study

Introduction

Rheumatoid arthritis (RA) has emerged as an established risk factor for cardiovascular disease (CVD), with studies reporting up to a 2-fold greater risk of incident CVD compared with the general population.[1–4] Meta-analyses of observational studies have reported a 68% relative elevation in the incidence of fatal and non-fatal myocardial infarction (MI) and a 59% relative elevation in the risk of mortality in patients with RA compared with the general population.[1,5,6] The elevated risk may partly be explained by the well-documented association between RA and traditional atherogenic risk factors, such as dyslipidemia, diabetes mellitus, smoking, obesity, physical inactivity, inflammation, and arterial hypertension.[7–9] Consequently, current guidelines recommend management of CVD risk factors for patients with RA, including lifestyle interventions such as smoking cessation and physical activity, CVD risk assessment at least once every 5 years, and intense RA disease management. For patients with RA, current recommendations suggest use of

Graphical Abstract



antihypertensive agents and statins in the same manner as in the general population, in addition to a CVD risk prediction model adapted for patients with RA by using a 1.5 multiplication factor.[10] Despite the awareness of the association between RA and atherosclerotic CVD, temporal cohort studies have not shown decreases in cardiovascular (CV) mortality in patients with RA in the five decades between the 1960s and 2010s.[5,11,12] Furthermore, studies have suggested that the mortality gap observed between patients with RA and the general population has not narrowed significantly.[11,13,14] A few cohort studies have demonstrated declines in major CV events and mortality rates; however, most of those studies included patients with prevalent RA or prior atherosclerotic CVD, or low numbers of patients with incident RA.[15,16] Furthermore, these studies represent older eras of management of patients with RA and consequently would not be expected to indicate the benefits of the present treatment algorithms. Evidence on whether RA-specific treatments improve cardiovascular outcomes is inconsistent, with some studies showing benefit – mainly for methotrexate and TNF inhibitors – while others report neutral or even increased risk. These discrepancies largely reflect differences in study design, cohorts, and outcome definitions.[17] Despite increased awareness of the CVD risk associated with RA, CV risk stratification is not performed regularly, and the CV prophylaxis in patients with RA is reported to be sub-optimal in clinical practice.[18]

In the current study, we examined temporal trends in the risk of MI and all-cause mortality in a Danish nationwide cohort of patients with incident RA, but no prior CVD diagnosed from 1996 through 2017. To study whether the gaps in the risks of MI and all-cause mortality between patients with RA and the general population decreased during the study period, we used a matched general population comparison cohort. We hypothesized that: i) the risks of MI and mortality in patients with incident RA and no prior CVD have decreased over the past 20 years, ii) the gaps in the risks of MI and all-cause mortality between patients with incident RA and no prior CVD and general population individuals have narrowed over time, and iii) these trends temporally coincide with intensified use of statin treatment, a proxy for optimized medical prophylactic therapy.

Materials and Methods

Settings

We used administrative health data to identify a nationwide population-based cohort of patients with incident RA patients from January 1, 1996, to December 10, 2017, with follow-up until December 10, 2018, in Denmark. This cohort was matched to a general population cohort.

Denmark has a population of approximately 5.8 million inhabitants. All Danish citizens are guaranteed unrestricted and free access to hospitals and general practitioners. All Danish citizens are assigned a unique civil personal registration (CPR) number enabling complete long-term follow-up. Because the CPR number is used in all Danish registries, individual-level linkage between all registries is possible.

Data Sources

We used the following registries in the current study: the Danish National Patient Register (DNPR), which contains data on all hospitalizations since 1977, as well as outpatient clinic diagnoses since 1995; the Danish Civil Registration System (CRS), which maintains data on all Danish residents´ vital status (dead, alive, or emigrated); and the Danish Prescription Registry, which records data on all reimbursed prescriptions redeemed at Danish pharmacies.[19–22]

Since this was a non-interventional study ethical approval was unnecessary. The study was reported to the Danish Data Protection Agency via registration at Aarhus University (Record number AU-2016-051-000001, sequential number 438). Patient consent is not necessary for studies based on registry data.

Study Population

Patients with RA

Patients were classified as having incident RA based on two criteria. First, patients should receive at least one prescription for a disease-modifying antirheumatic drug (DMARD) between 1996 and 2017 (codes L01BA01, L04AX03, A07EC01, L04AX01, P01BA02, M01CB, L04AA13 and L04AA01). Second, patients were required to be

registered in the DNPR with a primary or secondary diagnosis of RA (International Classification of Diseases (ICD)-10 codes DM05.0-DM05.9 and DM06.0-DM06.9) during hospitalization, or a visit to an outpatient clinic within 1-year before or after the first prescription.

To ensure that only incident cases of RA between 1996 and 2017 were included, we excluded patients who had been prescribed any disease-modifying antirheumatic drug (DMARD) during the period of 1994–1995 (referred to as the "washout period").

The index date for RA was defined as the latest date of either the first-time DMARD dispensing date or the date of hospital diagnosis. Patients with peripheral vascular disease, heart failure, previous MI, stroke, percutaneous coronary intervention or coronary artery bypass grafting before to the RA index date were excluded from the analysis.

General Population

At the index date, individuals from the general population were corresponding to RA index data. For each patient with RA, we selected five individuals from the general population (with replacement), matched by age and sex, who had no previous history of heart failure, MI, percutaneous coronary intervention, coronary artery bypass grafting, stroke, or peripheral vascular disease, and were not diagnosed with RA at the time of matching.

Outcomes

The study outcomes were MI and all-cause mortality. Myocardial infarction was identified using primary and secondary ICD-10 codes from the DNPR (ICD-10 codes DI-21) and mortality was identified using the vital status listed in the CRS.

Prophylactic Cardiovascular Medications

Records of treatment with statins, beta-blockers, ACE inhibitors/AT II receptor blockers, loop diuretics, and platelet inhibitors were obtained from the Danish Prescription Registry. Treatment at baseline (study inclusion) was defined as redemption of one or more prescriptions within 12 months before or on the index date. Follow-up treatment with the same drugs was defined as redemption of one or more prescriptions within 12 months after the index date.

Statistical Analysis

We described characteristics of patients with incident RA and the general population, both overall and in the following calendar periods: 1996–2000, 2001–2005, 2006–2010, and 2011–2017.

Study participants were followed from the index date until the occurrence of death, emigration, a maximum of 5 years of follow-up, or December 10th, 2018, whichever came first.

We computed 5-year cumulative incidence proportions (CIPs) of MI and all-cause mortality for each calendar period and for patients with RA and the general population separately, using the Kaplan-Meier estimator for mortality ant the Aalen-Johansen estimator for MI, treating mortality as a competing event for MI. Furthermore, after checking the proportional hazards assumption graphically we calculated hazard ratios (HRs) for MI and all-cause mortality within each cohort, using the time period 1996–2000 as a reference. For each time period, we also computed HRs between the RA cohort and the general population, using the general population as the reference group and after checking the proportional hazards assumption graphically.

The Charlson Comorbidity Index (CCI) was calculated based on primary or secondary diagnoses from in- or outpatient records in the DNPR based on ICD-10 codes, by using a 10-year lookback period from the index date.

All estimates are presented with 95% confidence intervals.

Cumulative incidence curves of mortality were plotted for each time period and cohort. The difference in 5-year cumulative incidence over time between cohorts was plotted against calendar year.

The same analyses were performed for MI, and mortality was considered as a competing risk in calculating the 5-year CIP and constructing the cumulative incidence curve.

Results

Baseline Characteristics of the Study Cohorts

The flowchart of the study is depicted in Central Illustration. We included 20,937 patients with incident RA and no prior CVD. These patients with RA were matched with 104,685 individuals, all without RA or prior CVD from the general population. The baseline characteristics of the patient and comparison cohorts are presented in Table 1. The proportion of individuals with female sex was 69.3% overall and this sex distribution remained largely unchanged throughout the four study periods. We observed an increasing prevalence of diabetes (2.8% (year 1996–2000) versus 5.0% (year 2011–2017)), hypertension (3.5% (year 1996–2000) versus 14.1% (year 2011–2017)) and atrial fibrillation (1.5% (year 1996–2000) versus 3.5% (year 2011–2017)) in the RA cohort over the study period.

Outcomes in the RA and General Population Cohorts

Number of events, 5-year risk differences, 5-year CIPs, and HRs for patients with RA and the general population for MI and all-cause mortality are presented in Table 2 and Supplementary Figure 1. We observed a decline in the 5-year CIPs for MI in patients with RA from 2.6% in 1996–2000 to 1.5% in 2011–2017 (HR 0.59; 95% CI 0.45–0.78), corresponding to a 1.1% absolute risk reduction. In the matched general population, we observed a decline in CIPs for MI going from 1.6% in 1996–2000 to 1.1% in 2011–2017 (HR 0.69; 95% CI 0.60–0.81) corresponding to a 0.5% absolute risk reduction. Although risk differences between the RA and the general population cohorts decreased over time, the relative risk remained elevated in the RA versus the general population cohort in 2011–2017 (HR 1.41; 95% CI 1.11–1.79).

All-cause mortality also declined in the RA cohort during follow-up. The CIPs for all-cause mortality in patients with RA decreased from 9.3% in 1996–2000 to 7.7% in 2011–2017 (HR 0.83; 95% CI 0.72–0.95), corresponding to a 1.6% absolute mortality reduction. In contrast, we observed no reduction in mortality in the matched general population (HR in 2011–2017 relative to 1996–2000: 1.00 (95% CI 0.93-1-07)).

Cardiovascular Medical Treatment

Medical treatment within 1-year before or after the index date is presented in Table 3. The proportion of redeemed prescriptions of ACE-inhibitors/ARBs, beta-blockers, and statins increased over time for both cohorts. For example, use of ACE-i/ARBs within 1-year after the index date increased from 7.1% in 1996–2000 to 23.8% in 2011–2017, and use of statins increased from 1.2% to 19.0% in the same periods among patients with RA. However, the baseline and 1-year use of CV medications were similar for patients with RA and general population individuals.

Rheumatic Medical Treatment

Medical rheumatic treatment within 1-year after the index date is shown in Table 4. The choice of rheumatic drugs changed over time, use of methotrexate and hydroxychloroquine increased; use of corticosteroids, sulfasalazine, and azathioprine decreased. We observed unaltered use of NSAIDs, while gold therapy, leflunomide, and cyclosporine were all rarely used.

Discussion

In this Danish nationwide cohort study, we compared trends in the 5-year risks of MI and all-cause mortality among 20,937 patients with incident RA and no prior CVD and a matched general population cohort of 104,685 individuals without RA or prior CVD. Our study revealed the following novel results: i) Among patients with incident RA, the 5-year risk of MI and mortality steadily decreased from period of 1996–2000 to the last period of 2011–2017, while the mortality risk decreased up to 2010 with no further decline thereafter. ii) The decline in risk of MI in the RA cohort was mirrored by an almost similar decline in the general population. This finding suggests that a major part of the temporal reduction in MI observed within the study period reflects a general reduced risk, at least in Denmark, rather than optimized RA treatment; iii) In contrast to the MI findings, the gap in risk of all-cause mortality between the RA population and the general population decreased over time. iv) Although the use of prophylactic CVD medications increased gradually from 1996 to 2017, the increase did not differ between the RA cohort and the matched general

Table 1 Baseline Characteristics of Patients with Incident Rheumatoid Arthritis and Matched Individuals from the General Population

	1996-2000		2001-2005		2006-2010		2011-2017		Total period	
	RA (n = 4576)	**GP (n = 22,880)**	**RA (n = 4288)**	**GP (n = 21,440)**	**RA (n = 4758)**	**GP (n = 23,790)**	**RA (n = 7315)**	**GP (n = 36,575)**	**All Patients with RA (n = 20,937)**	**Total General Population (n = 104,685)**
Age										
Median age, years (IQR)	59.2 (48.8;69.7)	59.3 (48.9;69.8)	59.5 (48.9;69.7)	59.4 (48.8;69.6)	59.3 (49.0;69.3)	59.3 (49.1;69.2)	61.9 (51.5;70.9)	61.9 (51.5;70.9)	60.2 (49.8;70.1)	60.2 (49.8;70.1)
Sex										
Female, n (%)	3264 (71.3)	16,320 (71.3)	3031 (70.7)	15,155 (70.7)	3314 (69.7)	16,570 (69.7)	4904 (67.0)	24,520 (67.0)	14,513 (69.3)	72,565 (69.3)
Male, n (%)	1312 (28.7)	6560 (28.7)	1257 (29.3)	6285 (29.3)	1444 (30.3)	7220 (30.3)	2411 (33.0)	12,055 (33.0)	6424 (30.7)	32,120 (30.7)
Charlsons Comorbidity Index score										
0, n (%)	2390 (52.2)	20,160 (88.1)	2480 (57.8)	18,426 (85.9)	3012 (63.3)	20,039 (84.2)	4657 (63.7)	29,619 (81.0)	12,539 (59.9)	88,244 (84.3)
1-2, n (%)	2020 (44.1)	2455 (10.7)	1634 (38.1)	2689 (12.5)	1555 (32.7)	3280 (13.8)	2307 (31.5)	5880 (16.1)	7516 (35.9)	14,304 (13.7)
≥3, n (%)	166 (3.6)	265 (1.2)	174 (4.1)	325 (1.5)	191 (4.0)	471 (2.0)	351 (4.8)	1076 (2.9)	882 (4.2)	2137 (2.0)
Comorbidity										
Diabetes, n (%)	128 (2.8)	390 (1.7)	138 (3.2)	474 (2.2)	210 (4.4)	634 (2.7)	366 (5.0)	1305 (3.6)	842 (4.0)	2803 (2.7)
Hypertension, n (%)	158 (3.5)	687 (3.0)	322 (7.5)	1125 (5.2)	515 (10.8)	1998 (8.4)	1030 (14.1)	4452 (12.2)	2025 (9.7)	8262 (7.9)
Atrial fibrillation, n (%)	69 (1.5)	255 (1.1)	87 (2.0)	359 (1.7)	130 (2.7)	502 (2.1)	258 (3.5)	1080 (3.0)	544 (2.6)	2196 (2.1)
Rheumatological treatment (up to 1 year prior to the index date)										
Methotrexate, n (%)	311 (6.8)	0 (0.0)	492 (11.5)	0 (0.0)	776 (16.3)	0 (0)	1105 (15.1)	0 (0)	2684 (12.8)	0 (0)
Corticosteroids, n (%)	1682 (36.8)	1025 (4.5)	1594 (37.2)	870 (4.1)	1731 (36.4)	1001 (4.2)	2537 (34.7)	1489 (4.1)	7544 (36.0)	4385 (4.2)
Sulfasalazine, n (%)	715 (15.6)	0 (0.0)	599 (14.0)	0 (0.0)	430 (9.0)	0 (0)	351 (4.8)	0 (0)	2095 (10.0)	0 (0)
Azathioprine, n (%)	45 (1.0)	0 (0.0)	29 (0.7)	0 (0.0)	22 (0.5)	0 (0)	23 (0.3)	0 (0)	119 (0.6)	0 (0)
HCL, n (%)	65 (1.4)	0 (0.0)	61 (1.4)	0 (0.0)	86 (1.8)	0 (0)	125 (1.7)	0 (0)	337 (1.6)	0 (0)
Gold therapy, n (%)	16 (0.3)	0 (0.0)	<5 (<0.1)	0 (0.0)	0 (0.0)	0 (0)	0(0.0)	0 (0)	<20 (<0.4)	0 (0)
Leflunomide, n (%)	<5 (<0.1)	0 (0.0)	8 (0.2)	0 (0.0)	<5 (<0.1)	0 (0)	5 (0.1)	0 (0)	19 (0.1)	0 (0)
Cyclosporine, n (%)	<5 (<0.1)	<5 (<0.1)	<5 (<0.1)	<5 (<0.1)	5 (0.1)	<5 (<0.1)	<5 (<0.1)	0 (0)	10 (0.0)	<5 (<0.1)
NSAIDs, n (%)	2357 (51.5)	2664 (11.6)	1953 (45.5)	2419 (11.3)	2556 (53.7)	3226 (13.6)	4469 (61.1)	5857 (16.0)	11,335 (54.1)	14,166 (13.5)

Abbreviations: RA, rheumatoid arthritis; GP, general population; HCL, Hydroxychloroquine; NSAIDs, Non-steroid anti-inflammatory drugs.

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Table 2 Risk and Risk Difference of Myocardial Infarction and All-Cause Mortality in Patients with Incident Rheumatoid Arthritis and Matched Individuals from the General Population Cohort

	Rheumatoid Arthritis				General Population				Rheumatoid Arthritis vs General Population	
	Individuals (Events), n	5-Year CIP (95% CI)	5-Year Risk Diff. (95% CI)	HR within RA Patients (95% CI)	Individuals (Events), n	5-Year CIP (95% CI)	5-Year Risk Diff. (95% CI)	HR within General Population (95% CI)	5-Year Risk Diff. Between RA Cohort and the General Population (95% CI)	HR, RA Patients vs General Population (95% CI)
Myocardial infarction					Myocardial infarction					
1996-2000	4576 (118)	2.58 (2.15–3.07)	Ref.	Ref.	22,880 (366)	1.60 (1.44–1.77)	Ref.	Ref.	0.98 (0.49–1.47)	1.64 (1.33–2.01)
2001-2005	4288 (88)	2.05 (1.66–2.51)	−0.53 (−1.15–0.10)	0.79 (0.60–1.04)	21,440 (322)	1.50 (1.34–1.67)	−0.10 (−0.33–0.13)	0.94 (0.81–1.09)	0.55 (0.10–1.01)	1.38 (1.09–1.75)
2006-2010	4758 (93)	1.96 (1.59–2.38)	−0.62 (−1.23–0.02)	0.75 (0.57–0.99)	23,790 (283)	1.19 (1.06–1.34)	−0.41 (−0.62 - −0.20)	0.74 (0.64–0.87)	0.77 (0.35–1.18)	1.66 (1.31–2.10)
2011-2017	7315 (87)	1.52 (1.22–1.88)	−1.05 (−1.62 - −0.49)	0.59 (0.45–0.78)	36,575 (310)	1.09 (0.97–1.22)	−0.51 (−0.72 - −0.31)	0.69 (0.60–0.81)	0.43 (0.08–0.79)	1.41 (1.11–1.79)
All-cause death					All-cause death					
1996-2000	4576 (424)	9.27 (8.45–10.13)	Ref.	Ref.	22,880 (1554)	6.80 (6.47–7.13)	Ref.	Ref.	2.47 (1.57–3.37)	1.38 (1.24–1.54)
2001-2005	4288 (376)	8.77 (7.95–9.64)	−0.49 (−1.69–0.70)	0.94 (0.82–1.08)	21,440 (1421)	6.63 (6.31-6-97)	−0.16 (−0.63–0.30)	0.98 (0.91–1.05)	2.14 (1.23–3.05)	1.33 (1.19–1.50)
2006-2010	4758 (359)	7.56 (6.83–8.33)	−1.71 (−2.84 - −0.58)	0.81 (0.70–0.93)	23,790 (1608)	6.77 (6.45–7.09)	−0.03 (−0.48–0.43)	1.00 (0.93–1.07)	0.79 (−0.03–1.60)	1.12 (1.02–1.26)
2011-2017	7315 (417)	7.70 (6.98–8.46)	−1.57 (−2.69 - −0.45)	0.83 (0.72–0.95)	36,575 (1853)	6.67 (6.37–6.98)	−0.12 (−0.57–0.33)	1.00 (0.93–1.07)	1.02 (0.22–1.82)	1.13 (1.01–1.25)

Abbreviations: CIP, cumulative incidence proportion; HR, Hazard Ratio; RA, Rheumatoid arthritis.

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Table 3 Cardiovascular Medical Treatment and Change in the Rheumatoid Arthritis Population and General Population Within 1 year Before or After the Index Date

	RA n (%)	**GP n (%)**	**RA n (%)**	**GP n (%)**	**RA (%)**	**GP (%)**
Statin treatment						
Year	1 year *up to* index date		1 year *after* index date		Change in treatment from *up to* index date to 1 year *after* index date	
1996-2000	38 (0.8)	283 (1.2)	54 (1.2)	390 (1.7)	0.4	0.5
2001-2005	175 (4.1)	936 (4.4)	244 (5.7)	1392 (6.5)	1.6	2.1
2006-2010	586 (12.3)	3109 (13.1)	675 (14.2)	3635 (15.3)	1.9	2.2
2011-2017	1369 (18.7)	6536 (17.9)	1388 (19.0)	6942 (19.0)	0.3	1.1
All periods	2168 (10.4)	10,864 (10.4)	2361 (11.3)	12,359 (11.8)	0.9	1.4
ACE-inhibitor/ARB treatment						
1996-2000	260 (5.7)	1249 (5.5)	323 (7.1)	1516 (6.6)	1.4	1.1
2001-2005	465 (10.8)	2216 (10.3)	573 (13.4)	2649 (12.4)	2.6	2.1
2006-2010	857 (18.0)	4065 (17.1)	958 (20.1)	4520 (19.0)	2.1	1.9
2011-2017	1700 (23.2)	7910 (21.6)	1738 (23.8)	8404 (23.0)	0.6	1.4
All periods	3282 (15.7)	15,440 (14.7)	3592 (17.2)	17,089 (16.3)	1.5	1.6
Beta-blocker treatment						
1996-2000	245 (5.4)	1412 (6.2)	301 (6.6)	1555 (6.8)	1.2	0.6
2001-2005	381 (8.9)	1760 (8.2)	455 (10.6)	1996 (9.3)	1.7	1.1
2006-2010	489 (10.3)	2217 (9.3)	545 (11.5)	2425 (10.2)	1.2	0.9
2011-2017	750 (10.3)	3459 (9.5)	826 (11.3)	3708 (10.1)	1.0	0.6
All periods	1865 (8.9)	8848 (8.5)	2127 (10.2)	9684 (9.3)	1.3	0.8
Platelet inhibitors						
1996-2000	254 (5.6)	1265 (5.5)	328 (7.2)	1530 (6.7)	1.6	1.2
2001-2005	343 (8.0)	1611 (4.4)	417 (9.7)	2021 (9.4)	1.7	5.0
2006-2010	500 (10.5)	2298 (9.7)	559 (11.7)	2608 (11.0)	1.2	1.3
2011-2017	735 (10.0)	3326 (9.1)	783 (10.7)	3602 (9.8)	0.7	0.7
All periods	1832 (8.8)	8500 (8.1)	2087 (10.0)	9761 (9.3)	1.2	1.2
Loop diuretics						
1996-2000	381 (8.3)	1030 (4.5)	410 (9.0)	1207 (5.3)	0.7	0.8
2001-2005	348 (8.1)	830 (3.9)	339 (7.9)	982 (4.6)	−0.2	0.7
2006-2010	357 (7.5)	919 (3.9)	345 (7.3)	1077 (4.5)	−0.2	0.6
2011-2017	485 (6.6)	1328 (3.6)	487 (6.7)	1599 (4.4)	0.1	0.8
All periods	1571 (7.5)	4107 (3.9)	1581 (7.6)	4865 (4.6)	0.1	0.7

Abbreviations: RA, rheumatoid Arthritis; GP, general population.

Table 4 Rheumatic Medical Treatment 1-year After Index Date in Patients with Incident Rheumatoid Arthritis and Matched Individuals from the General Population Cohort

	1996-2000		2001-2005		2006-2010		2011-2017		Total Period	
	RA (n = 4576)	GP (n = 22,880)	RA (n = 4288)	GP (n = 21,440)	RA (n = 4758)	GP (n = 23,790)	RA (n = 7315)	GP (n = 36,575)	All Patients with RA (n = 20,937)	Total General Population (n = 104,685)
Rheumatic treatment										
Methotrexate	2258 (49.3)	14 (0.1)	2935 (68.4)	18 (<0.1)	3868 (81.3)	33 (<0.1)	6307 (86.2)	49 (<0.1)	15,368 (73.4)	114 (0.1)
Corticosteroids	2163 (47.3)	1103 (4.8)	2112 (49.3)	991 (4.6)	1991 (41.8)	1072 (4.5)	2736 (37.4)	1658 (4.5)	9002 (43.0)	4824 (4.6)
Sulfasalazine	2633 (57.5)	19 (0.1)	1985 (46.3)	10 (<0.1)	1570 (33.0)	11 (<0.1)	1969 (26.9)	9 (<0.1)	8157 (39.0)	49 (<0.1)
Azathioprine	181 (4.0)	5 (<0.1)	111 (2.6)	6 (<0.1)	87 (1.8)	13 (<0.1)	86 (1.2)	14 (<0.1)	465 (2.2)	38 (<0.1)
HCL	374 (8.2)	8 (<0.1)	456 (10.6)	<5 (<0.1)	693 (14.6)	<5 (<0.5)	1078 (14.7)	12 (<0.1)	2601 (12.4)	27 (<0.1)
Gold therapy	46 (1.0)	0 (0)	9 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	55 (0.3)	0 (0)
Leflunomide	54 (1.2)	0 (0)	61 (1.4)	0 (0)	11 (0.2)	0 (0)	25 (0.3)	0 (0)	151 (0.7)	0 (0)
Cyclosporine	25 (0.5)	<5 (<0.1)	0 (0)	<5 (<0.1)	0 (0)	0 (0)	0(0)	<5 (<0.1)	44 (0.2)	<5 (<0.1)
NSAIDs	1518 (33.2)	2483 (10.9)	1163 (27.1)	2495 (11.6)	1505 (31.6)	3302 (13.9)	2637 (36.9)	6039 (16.5)	6823 (32.6)	14,319 (13.7)

Abbreviations: RA, Rheumatoid arthritis; GP, general population; HCL, Hydroxychloroquine; NSAIDs, Non-steroid anti-inflammatory drugs.

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population cohort. For example, in the last study period, from 2011 to 2017, "only" 19% of RA patients received medical prophylaxis with a statin one year after RA diagnosis. This proportion of statin users exactly matched that of the general population comparison cohort, and was much lower than the 60% prevalence of prophylactic statin use previously reported for a nationwide incident diabetes cohort where a major reduction in the 7-year gap of risk of MI versus a matched general population was reported.[23] These results are important for the societies writing the RA guidelines, for clinicians treating patients with RA, and for patients either having or who are being diagnosed with RA. Despite RA being a recognized risk factor for MI and mortality, cardiovascular medical preventive management seems underutilized in RA patients, and we believe that our results highlight a need for clarification of appropriate medical cardiovascular prophylaxis when RA is diagnosed. This finding may reflect challenges in the implementation of cardiovascular risk management in routine clinical practice, including potential under-recognition of cardiovascular risk in RA or uncertainty regarding responsibility between specialties. Current EULAR guidelines recommend regular cardiovascular risk assessment and appropriate preventive treatment in patients with RA;[10] however, translating these recommendations into practice may be challenging. The observed patterns of medication use may therefore reflect physician inertia – as an explanation for the gap between guideline recommendations and real-world clinical practice.

Closing the Gap in Myocardial Infarction Between Patients with RA and the General Population

As hypothesized, we observed steady reductions in 5-year rates of MI from 1996 to 2017 in both patients with RA and matched population individuals. This result is concordant with the observations in Danish patients with incident diabetes compared to a matched general population.[23] However, in contrast to our hypothesis and expectations, we did not find a narrowing of the gap in MI risk between the RA and the general population cohort. In our opinion, these results underline the importance of a matched general population to differentiate between treatment optimization and influence of societal changes. Here, the results suggest that societal changes related to a more aggressive medical risk factor modification, plus other risk factors such as smoking habits, education, diet, pollution, etc. are more likely to explain the reduced risk of MI than the RA-related treatment. In a recent retrospective Canadian cohort included in 1997–2004, the authors reported a 21% higher 10-year risk of MI in patients with incident RA versus matched general population controls.[24] A Swedish population-based study of patients with RA onset between 1997 and 2014 demonstrated a 41% higher risk of MI and a numerically similar decline in incidence of acute coronary syndrome in RA and general population individuals within their study period. Like in our study, the excess and the relative risk of MI in RA relative to the general population remained the same.[25] In contrast to these results, a relatively smaller population-based study from Olmsted County, USA, found no excess risk of MI in a cohort of 905 patients diagnosed with RA in 2000–2009 when compared to 904 non-RA subjects.[26] In fact, this is the only study where a numerically lower risk in the RA cohort was reported (HR 0.58; 95% CI 0.26–1.28). Our results provide a more contemporary dataset, which provides a stronger probability for new treatment strategies to be implemented. Still, our results are consistent with the Canadian and Swedish results.

Closing the Gap in Mortality Between Patients with RA and the General Population

As hypothesized, we report a gradual decrease in all-cause mortality and a substantial reduction in excess mortality when compared with the matched general population.

Our nationwide results are consistent with findings from Northern Italy demonstrating higher risks of mortality and CV outcomes among patients diagnosed with RA from 2005 to 2008 compared with the general population. However, the comparison cohort in the Italian study was not age- and sex-matched, the RA cohort was significantly older (mean age 59 versus 45 years), had a higher prevalence of female sex (73% versus 51%), and an almost doubled prevalence of diabetes, liver- and gastrointestinal diseases, chronic obstructive pulmonary disease and cancer diseases at baseline compared with the unmatched general population cohort.[27] These major differences between the RA cohort and their non-matched control group limit the interpretation and comparability of the study findings. A more recent study from the Australian Rheumatology Association Database investigated 1895 patients with RA and reported no decrease in mortality over the first 10 years of follow-up when compared to an age- and sex-matched expected survival calculation from the Australian

population mortality rates.[28] Compared to our nationwide cohort study, patients were included in the registry on a voluntary basis, had a significantly lower mean age, included both incident and prevalent RA, and used life tables rather than a matched comparison cohort. Importantly, it is unlikely that the use of life tables is an optimal comparison to patients included on a voluntary basis. A large UK-based study using primary healthcare records for incident RA between 1990 and 2009, reported comparable mortality rates from 1990 to 2004 and a decrease in mortality risk thereafter when compared with matched non-RA controls.[29] In contrast to the present study, only participants contributing with acceptable quality data were included and the study also included juvenile arthritis. This could explain our observation of a decrement trend at an earlier time point. Furthermore, our study showed that a mortality gap persists. The study by Holmqvist et al observed a steady decline in absolute mortality rates over time in patients with newly diagnosed RA and in the general population.[16] However, despite this overall improvement, patients with RA continued to experience excess mortality compared to the general population, particularly evident five years after diagnosis. Notably, the study did not find a clear trend toward reduced excess mortality in patients diagnosed more recently, suggesting that the increased relative mortality risk associated with RA persists.

Taken together, our nationwide study with a randomly selected general population comparison cohort and a long inclusion period provides the currently most solid and reliable estimates of the development of all-cause mortality over the past 20 years. These data suggest that not only is mortality declining, the mortality gap between RA and general population individuals is closing too. Furthermore, our study and the above-mentioned studies collectively suggest that despite advancements in RA management, including the introduction of biologic treatments and early, aggressive intervention strategies, RA patients continue to face an elevated mortality risk compared to the general population. The persistent excess mortality underscores the need for ongoing efforts to optimize RA management, address comorbidities, and develop strategies to further reduce mortality risk in this patient population.

Medical Management of Rheumatoid Arthritis

We observed an increase in the inflammatory treatment of RA with increasing use of methotrexate and a decline in the use of NSAIDs. Despite the observed positive trends in decreasing risks of MI and all-cause mortality in RA, the need for CV risk management tailored to RA populations remains, including relevant risk stratification and management of CV risk factors. Whether there has been an improvement in RA-associated risk of MI and mortality in recent years is a relevant question given the increasing availability in RA treatment strategies. The improved control of RA disease activity over the past three decades starting with the initiation of combination therapy in the 90´s,[30,31] anti-TNF therapy around the millennium[32] in combination with improved early diagnostic strategies[33] and later the option of several other targeted biological treatments like anti-CD20 therapy,[34] anti CD28/CD86 therapy, anti-IL6 therapy[35,36] and more recently JAk inhibition,[37] strengthened the ability to personalize and optimize relevant immunosuppressive "treat-to-target" strategies for patients with RA. These aspects might potentially have contributed to the observed decline in CVD. However, the similar decline observed in the non-RA control cohort does not support that. This may be a potential contributor to the observed declines in MI and mortality observed.

The prognostic improvements documented in this cohort study could also be due to the change in RA treatment algorithms since we found no significant difference in the use of prophylactic CV treatment between patients with RA and the general population cohorts. Despite an increase in the prevalence of hypertension during the study period, most likely representing the increased focus on diagnosing and treating this risk factor, we observed no corresponding increase in the use of beta-blockers or loop diuretics as hypertensive treatment. We observed an increase in the use of statins overall in the RA cohort. In the most contemporary study period from 2011 to 2017, however, the use of statins 1 year after the diagnosis of RA was observed in only 19% of the RA population, matching the 19% rate of statin use in the general population. In the same time period, reflecting recent guidelines in CV prevention in RA, a 0.9 percentage point increase in use of statins in RA patients within the first year after RA diagnosis compared to 1.4 percentage points in the general population is worrisome. Our data represent daily clinical practice in Denmark showing the current multifactorial cardiovascular prophylaxis algorithm in incident patients with incident RA without prior CVD. All current guidelines on the prevention of CV disease in clinical practice recommend the assessment of CV risk. Patients with a higher CV risk should receive more intensive interventions. However, despite RA remains associated with an increased risk of MI and

death, the RA patients did not receive a more intensive medical CV prophylaxis than the general population. We have previously reported that 50–60% of patients with incident diabetes filled a prescription for a statin within the first year after their diagnosis.[38] However, CV risk algorithms developed for the general population are not accurate in RA patients. These predictive tools were not specifically developed in patients with RA and the performance is suboptimal because traditional CV risk factors do not fully explain the increased CV risk. Recent data show that CV risk stratification varies according to the strategies used.[39] These authors report a higher incidence of statins treatment for primary prophylactic use (24.7%) compared to our incidence 1-year after diagnosis (11.3%). Evidence have shown significant benefit of statin treatment in patients with RA.[40] Awareness and wider use of prophylactic CV treatment hopefully will lead to further reductions in especially MI incidence and ultimately death.

Strengths and Limitations

Strengths of our study include the use of nationwide population-based registries in a tax-supported, public health care system with virtually complete follow-up, thereby minimizes the risk of selection bias and representing daily clinical practice. All registries have been fully validated. DNPR has been validated extensively, but almost always for specific diagnoses, procedures, and research purposes rather than via a single blanket validation study. The positive Predictive Value (PPV) for the RA diagnosis in DNPR is 79% which we in our paper increased by adding the treatment criteria.[41] The PPV for first-time myocardial infarction is >90%.[42]

The Danish Prescription Registry contains individual-level data on all prescription drugs dispensed at Danish community pharmacies since 1995. It has been found to be valid and reliable with a PPV for prescriber types (general practitioner, hospital physician) were 94–99%.[43]

We acknowledge that we lacked information on socioeconomic status and lifestyle changes such as eating habits, physical activity, and smoking habits. Furthermore, no data regarding laboratory test results, especially regarding lipid parameters, were available.

Conclusion

In a nationwide cohort of patients with incident RA, the risks of MI and death declined gradually from 1996 to 2017 but patients with RA remained at higher risk of both MI and death than their matched general population individuals. These results suggest that cardiovascular prevention has not been improved in patients diagnosed with RA despite the potential benefit of surveillance bias associated with the RA diagnosis and subsequent regular clinical follow-up. Considering that focus on cardiovascular prevention is recommended by RA guidelines, the low use of statins and hypertensive medications is concerning and highlights a need for clarification of appropriate medical CVD prophylaxis when RA is diagnosed in patients with no prior CVD.

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