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Why do persons with rheumatoid arthritis still die prematurely?

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Keywords

Rheumatoid arthritis; mortality; cardiovascular disease

It has been recognized for decades that survival among persons with Rheumatoid Arthritis (RA) is significantly worse compared to survival in the general population^{1–5}. Figure 1 shows significantly reduced survival among residents of Rochester, Minnesota, with a first diagnosis of RA between 1955 and 1995 with follow-up to the present compared to expected survival.

Trends in RA survival over time have also been examined⁶. These data disappointingly demonstrate that RA mortality does not appear to have improved over the past three to four decades. In fact, when trends in RA mortality are compared to trends in expected mortality in the same population over a long period of time, it is clear that there is a widening mortality gap between persons with RA and the general population. This is because mortality in persons with RA has remained unchanged while mortality in the general population has improved over the past several decades. Thus, overall survival in persons with RA is significantly reduced compared to in the general population and the mortality gap between RA and the general population appears to be widening over time.

Ischemic Heart Disease

Much recent literature has demonstrated that the excess mortality in persons with RA is largely attributable to cardiovascular disease⁷. The most common cardiovascular disease is ischemic heart disease. In our own studies, ischemic heart disease was described according to five distinct constructs: hospitalized myocardial infarction (MI) (defined according to standard epidemiological criteria as definite, probable, suspect, or no MI based on the presence of cardiac pain, biomarker values, and the Minnesota coding of the electrocardiogram), silent MI (defined by a characteristic electrocardiogram in a non-acute setting), coronary revascularization procedures (including percutaneous transluminal angioplasty and coronary artery bypass graft), angina pectoris (physician defined recognition of cardiac pain in the absence of other causes), and sudden cardiac death (defined as out-of-hospital deaths occurring in emergency departments, private homes, public places, nursing homes, and containing ICD-9 CM codes for 410-414 as the underlying cause of death on death certificates).

Research from our group and others has repeatedly demonstrated that the risk of ischemic heart disease is significantly higher among persons with RA compared to controls^{8–16}. We have recently compared the prevalence of ischemic heart disease in a population-based incidence

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cohort of 603 RA patients and a matched non-RA comparison group from the same underlying population. These comparisons demonstrate that at index date (i.e., the date of first fulfillment of the ACR RA criteria for RA subjects and a comparable date for non-RA subjects), RA subjects are at a more than 3.17 fold higher risk of having had a hospital MI (multivariable odds ratio: 3.17, 95% CI, 1.16, 8.68) and a nearly 6 fold increased risk of having had a silent MI (multivariable odds ratio 5.86, 95% CI, 1.29, 26.64). Our data also demonstrated that the cumulative incidence of silent MI following incidence/index date continues to rise over time (fig. 2). The cumulative incidence of silent MI after 30 years of follow-up, adjusted for competing risks of death, is approximately 6.0% in the RA and 3.7% in the non-RA cohorts ($p=0.050$).

Likewise, the cumulative incidence of sudden death after 30 years of follow-up adjusted again for the competing risk of death by other causes, was 6.7% in the RA and 3.8% in the non-RA cohorts ($p=0.052$).

In contradistinction, both the prevalence of angina pectoris at incidence/index date as well as the cumulative risk of angina pectoris after 30 years of follow-up are significantly lower in persons with RA compared to the general population⁸. Indeed, after 30 years of follow-up, incident angina was identified in only 9.5% of the RA cohort compared to 14% of the non-RA cohort.

In summary, persons with RA are at increased risk of ischemic heart disease. The increased risk appears to precede the ACR criteria based diagnosis of RA. The increased risk of ischemic heart disease may remain silent and may first manifest as sudden cardiac death in persons with RA.

Heart Failure

An emerging body of literature now indicates that persons with RA are also at increased risk for heart failure. These studies typically classify heart failure according to the traditional Framingham Heart Study criteria¹⁷. We have previously demonstrated that the cumulative incidence of heart failure following incident RA is statistically significantly higher in persons with RA compared to those without the disease in a population-based setting¹⁸.

In fact, even after adjusting for competing risks of death, the cumulative risk of heart failure in the RA cohort was significantly higher than in the non-RA cohort throughout follow-up. Indeed, persons with RA reached the same cumulative incidence of heart failure as subjects without RA in about half the time. For example, after ten years of follow-up, an RA patient had the same probability of developing heart failure as an age-and-sex matched individual without RA after 20 years of follow-up. This effect was constant across all ages. At any particular age, the incidence of heart failure in RA subjects was approximately twice the incidence in non-RA subjects. Data from multivariable Cox models from our group showed that RA subjects had about twice the risk of developing heart failure and that this risk changed little after accounting for the presence of ischemic heart disease, other risk factors, and the combination of the above.

In subset analyses, this risk appeared to be largely confined to rheumatoid factor positive RA cases. Indeed, rheumatoid factor positive RA patients had a risk of developing heart failure that was 2.5 times higher than that of non-RA subjects. Notably, this excess risk of heart failure is very similar to that experienced by persons with Diabetes Mellitus.

Davis and colleagues examined the presentation of heart failure in RA compared to presentation of heart failure in the general population¹⁹. He reported that RA patients with heart failure presented with a different constellation of signs and symptoms than non-RA subjects with heart

failure. In particular, RA subjects with heart failure were less likely to be obese, hypertensive, or to have had a history of ischemic heart disease. RA subjects with heart failure were also less likely to present with the more typical signs and symptoms of heart failure, i.e., RA patients with HF were less likely to be obese, hypertensive, or to have a history of ischemic heart disease. Davis went on to describe echocardiographic features in RA subjects with heart failure compared to non-RA subjects with heart failure. He demonstrated that the proportion of RA subjects with preserved ejection fraction ($\geq 50\%$) was significantly higher for RA compared to non-RA subjects with heart failure (58.3% vs. 41.4%, $p = 0.02$). Mean ejection fraction was also shown to be higher among RA subjects compared to non-RA subjects (50% vs. 43%, $p=0.007$).

Indeed the likelihood of preserved ejection fraction at the onset of heart failure was 2.57 times more likely in heart failure subjects with RA vs. those without RA (odds ratio 2.57, 95% CI, 1.20, 5.49). Other investigators also reported that heart failure is more common in persons with RA²⁰, and a number of echocardiographic series have reported preserved ejection fraction and/or diastolic functional impairment in persons with RA²¹⁻²³.

In summary, persons with RA appear to have an increased risk of heart failure. Heart failure in persons with RA can present in an atypical manner with fewer typical signs and symptoms. Persons with RA are more likely to have heart failure with preserved ejection fraction.

Other Comorbidities

Persons with RA have also been shown to be at increased risk of other important comorbidities. These include infection^{24, 25} and hypertension²⁶, as well as other conditions²⁷. There is no evidence that trends in comorbidity among persons with RA, when compared to persons without RA, have changed significantly over time.

Not only do persons with RA appear to be at increased risk for a number of important comorbidities, but outcome after comorbidities has also been shown to be poorer in persons with RA compared to the general population. In our own studies, mortality following myocardial infarction was significantly higher in MI cases with RA compared to MI cases who do not have RA (hazard rate for mortality in RA vs. non-RA: 1.46, 95% CI, 1.01, 2.10, adjusted for age, sex and calendar year). Likewise, six month mortality following heart failure is significantly worse in heart failure cases with RA vs. those without.

The risk of mortality at 30 days following heart failure was 2.57 fold higher for RA subjects compared to non-RA subjects after adjusting for age, sex, and calendar year, while the risk of mortality at six months following heart failure was 1.94 fold higher for RA subjects compared to non-RA subjects after similar adjustment. These comparisons were both highly statistically significant²⁸.

In summary, there is strong evidence that persons with RA are at high risk for developing several comorbid disorders. Comorbid conditions in persons with RA may have atypical features and thus may be difficult to diagnose. There is no evidence that the excess risks of these comorbidities have declined. Emerging evidence points to poorer outcomes after comorbidity, in persons with RA compared to the general population.

Preventive Care

Another possible reason why persons with RA continue to die prematurely relates to the utilization or implementation of preventive care for persons with RA. Our group reported in 2003²⁹ that patients with RA do not receive optimal health maintenance and preventive care services when compared to their peers in the general population. Some years ago our group

examined the degree to which patients with RA receive health maintenance and preventive care procedures as recommended by the United States Preventive Services Task Force, a government appointed independent expert panel whose recommendations are based on systematic review of the evidence of effectiveness of clinical preventive services. Such services included blood pressure testing, lipids profile testing, flu vaccination, pneumococcal vaccination, mammograms, and cervical cancer screening. We showed that persons with RA do not receive optimal health maintenance and preventive care services. Davis and colleagues also showed that RA subjects with a clinical diagnosis of heart failure were less likely to undergo echocardiography and less likely to be prescribed cardiovascular medications, e.g., ACE inhibitors, beta blockers and diuretics¹⁹. Thus, although few studies have examined preventive care in RA, results do suggest that persons with RA may not receive optimal primary and/or secondary preventive care.

Cardiovascular Risk Factors

A number of investigators have examined the contribution of traditional cardiovascular risk factors as well as markers of inflammation towards the excess cardiovascular and overall morbidity and mortality in persons with RA^{7, 30-33}. Together these results indicate that while traditional cardiovascular factors are important in persons with RA, they alone do not explain the excess cardiovascular risk in this population. Indeed, some evidence suggests that some risk factors may act differently in persons with RA compared to the general population. For example, the balance of cardiovascular risks and potential cardiovascular benefits associated with corticosteroid use may be different in persons with RA compared to those in the general population³⁴. Also, the benefit of low BMI in cardiovascular protection may be different in persons with RA vs. those in the general population because in RA low BMI often reflects disease activity. In addition, inflammatory markers such as ESR, CCP, Rheumatoid factor, large joint swelling, the presence of vasculitis, and lung disease are highly significant predictors of cardiovascular outcome and mortality even after adjustment for other confounders.

Conclusion

In conclusion, three lines of evidence can explain why persons with RA die prematurely and why the mortality gap between RA and the general population appears to be widening. First, not only do persons with RA have a higher risk of multiple comorbid conditions but persons with RA tend to experience worse outcomes following the occurrence of these comorbid illnesses. Second, persons with RA may not receive optimal primary or secondary preventive care. And third, the systemic inflammation and immune dysfunction associated with RA appears to promote and accelerate comorbidity and mortality. These findings indicate that effective, even optimal control of traditional risk factors alone, while important, will be insufficient in reducing the excess mortality in RA.

In order to eliminate premature death in persons with RA, a new research strategy is needed that is specifically focused on this goal. Such studies should investigate the role of tight control of inflammation as an intervention and the impact of comorbidity on outcome; and should include large, simple, randomized control trials complemented by well designed observational studies.

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Figure 1. Survival Among Rochester Residents with RA first diagnosed 1955-1995, with follow-up to present day, compared to expected survival in the same underlying population
Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 2003;48(1):54-8. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

Figure 2. Cumulative Incidence of Silent MI in a population-based incidence cohort of 603 RA patients and a matched non-RA comparison group of 603 non-RA subjects from the same underlying population

Increased unrecognized coronary heart disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52(2)402-411. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

Figure 3. Cumulative Incidence of Sudden Cardiac Death in a population-based incidence cohort of 603 RA patients and a matched non-RA comparison group from the same underlying population Increased unrecognized coronary heart disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52(2)402-411. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

Figure 4. Distribution of EF at onset of HF

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Figure 5.
Trends in Comorbidities in Persons with RA vs. non-RA.

Figure 6. Six Month Mortality Following HF

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Table 1
Heart Failure in RA

Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 2003;48(1):54-8. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

Models	All RA vs non-RA	RF+RA vs non-RA
Age & sex-adjusted	1.96 (1.54; 2.49)	2.49 (1.90; 3.26)
Age, sex & IHD	1.95 (1.53; 2.49)	2.83 (2.14; 3.73)
Age, sex, risk factors	1.82 (1.43; 2.32)	2.29 (1.74; 3.02)
Age, sex, IHD & risk factors	1.87 (1.47; 2.39)	2.59 (1.95; 3.43)

Hazard ratios (95% CI) from multivariable Cox models