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Heart Disease and Rheumatoid Arthritis: *Understanding the Risks*

Sherine E. Gabriel, MD, MSc
Mayo Clinic, Rochester, MN

Abstract

Patients with rheumatoid arthritis (RA) are at increased risk of mortality compared with the general population. Evidence suggests that this increased mortality can largely be attributed to increased cardiovascular (CV) death. In a retrospective study of an inception cohort of RA patients in Rochester, MN, we investigated the contribution of traditional and RA-specific risk factors towards this increased risk of CV morbidity and mortality. Several traditional CV risk factors were found to behave differently in RA patients. In addition, their associations with CV disease are weaker in RA patients as increased inflammation associated with RA appears to also contribute substantially to the increased CV mortality. Furthermore, the impact of disease modifying anti-rheumatic drugs (DMARDs) and biologics on CV disease in RA patients is unclear. CV risk scores for the general population may underestimate risk for RA patients. Together with other studies that have demonstrated similar associations between RA and CV mortality, these data suggest that optimal control of CV risk factors is important, but not sufficient in RA patients. RA-specific CV risk prediction tools are needed, as well as clinical trials to assess the impact of therapies and tight control of inflammation in RA patients on CV outcomes and mortality.

It is now well recognized that people with RA die prematurely[1]. Recent evidence also suggests that the mortality gap between persons with RA and those in the general population has been widening[2]. In other words, persons with RA have not enjoyed the improvements in survival that have been evident in the general population over the past several decades. The increased risk of mortality among persons with RA occurs largely as a result of a higher risk of cardiovascular (CV) death, a higher risk of ischemic heart disease, particularly silent MI and sudden cardiac death as well as a higher risk and poor outcomes associated with heart failure. The goals of this manuscript are to: 1) Review the contribution of traditional CV risk factors towards the excess CV death in RA; 2) To review the contribution of nontraditional risk factors (markers of inflammation, RA features) toward the excess CV risk in RA, and; 3) To discuss the implications of these findings for reduction of CV risk in RA. The epidemiological methods of the research I will discuss are briefly summarized below.

We have assembled a population-based incidence cohort of Olmsted County, Minnesota residents ≥ 18 years of age with RA ascertained according to the 1987 American College of Rheumatology diagnostic criteria. This cohort now contains 822 subjects with a mean follow-up of 14.2 years. We also assembled an age- and gender-matched non-RA comparison cohort identified from the same underlying community. The non-RA cohort is comprised of 603 subjects with a mean follow-up of 16.8 years. Both cohorts have been

followed up retrospectively through the complete medical records, and information on demographics, CV risk factors, comorbidities, and RA characteristics were collected over the entire follow-up period noted above. In addition, information on CV outcomes, including CV death, ischemic heart disease, heart failure, and other clinical outcomes were ascertained. The prevalence of traditional risk factors at RA incidence was described by Gonzalez and colleagues [3]. As seen in Table 1, with the exception of cigarette smoking, which is more prevalent among RA subjects, the prevalence of traditional CV risk factors does not appear to differ between RA and non-RA subjects at the time of RA incidence. Likewise, the development of several CV risk factors over the follow-up period, after disease onset is not significantly different when comparing RA and non-RA subjects for hypertension, high Body Mass Index (BMI), or diabetes mellitus. However, hyperlipidemia was found to be significantly less common over the follow-up period and low BMI was found to be significantly more common over the follow-up period among RA compared to non-RA subjects. Solomon and colleagues[4] using data from the Nurses Health Study also demonstrated that most traditional CV risk factors were similar among subjects with RA when compared to individuals without the disease. In summary, therefore, with the exception of smoking, the prevalence of many of the traditional CV risk factors is similar among RA and matched non-RA subjects. RA subjects are significantly more likely to develop low BMI and less likely to develop dyslipidemia over the course of their disease when compared to non-RA subjects. RA subjects are at similar risk of developing hypertension, less likely to become obese and somewhat less likely to develop diabetes, although the latter differences were not statistically significant.

We next examined the impact of traditional risk factors on CV outcome. In these analyses, CV outcome was defined as a combined CV endpoint including: myocardial infarction, heart failure, and CV death[3]. These analyses illustrated that the relative impact of CV risk factors including male gender, current smoking, personal history of ischemic heart disease, family history of ischemic heart disease, hypertension, hyperlipidemia, BMI greater than 30 kg/m2, and diabetes mellitus, differed significantly in RA compared to non-RA subjects (Figure 1). Specifically, the relative impact of several of these risk factors appeared to be significantly less in RA subjects compared to non-RA subjects. While the reasons for this are unclear, we posit the existence of a competing mechanism (perhaps related to chronic systemic inflammation) which imparts additional CV risk in RA but not in non-RA subjects. The presence of an additional mechanism in RA but not in non-RA subjects may result in an apparent dilution effect, making the relative contribution of each individual mechanism or risk factor appear smaller. These findings support the hypothesis that systemic inflammation is a major CV risk factor in RA.

While BMI is considered a traditional CV risk factor, the relationship between BMI and CV mortality in persons with RA is notable. As shown in Figure 2, in the non-RA cohort, low BMI was not associated with an increased risk of CV death. Indeed, if anything, low BMI was somewhat protective for CV death. However, among RA patients, low BMI was associated with a threefold increased risk of CV death. This significant association remained even after adjusting for cardiac history, smoking, diabetes mellitus, hypertension, and malignancy. Thus, unlike the general population, low BMI in persons with RA appears to be associated with a significant risk of CV death. Since low BMI among persons with RA may

indicate active systemic inflammation, this finding lends further support to the hypothesis that inflammation plays a key role in the pathogenesis of CV death[5]. Escalante and colleagues also reported on the “paradoxical effect of BMI on survival in persons with RA” demonstrating that as BMI declined so did survival probability among study subjects with RA[6].

Lipids also appear to have a paradoxical effect on CV risk in persons with RA. As shown in Figure 3, total serum levels of cholesterol and LDL cholesterol decline precipitously during the three to five year period prior to RA incidence[7]. The declines are significantly more marked than those observed in matched non-RA subjects (data not shown).

Thus, while the prevalence of traditional CV risk factors is similar in RA compared to non-RA subjects, their impact on CV outcomes, i.e., the degree to which they impart risk for heart disease, differs in RA compared to non-RA subjects. Most CV risk factors appear to have weaker associations with heart disease in RA subjects and some risk factors have a paradoxical effect when compared to non-RA subjects. Clearly, more research is needed to better understand the mechanisms underlying these relationships.

In addition to traditional CV risk factors, we also evaluated the independent contribution of inflammatory indicators and RA characteristics towards risk of CV death, after adjusting for the aforementioned traditional CV risk factors and after also adjusting for comorbidities[8]. These analyses demonstrated that high erythrocyte sedimentation rate (ESR), small and large joint swelling, destructive changes on joint radiographs, rheumatoid nodules, vasculitis, rheumatoid lung disease, and corticosteroid use were all statistically significantly associated with an increased risk of CV death after adjusting for CV risk factors and comorbidities. We have also previously examined the role of elevated ESR as a CV risk factor in RA. Analyses of ESR levels in 172 RA cases with heart failure demonstrated that the proportion with significantly elevated ESR (≥ 40) was highest during the six month period prior to heart failure diagnosis as compared to any other time over the entire follow-up period[9]. These findings suggest that the six month period immediately preceding heart failure in RA cases is characterized by exceptionally high levels of systemic inflammation. We also examined the risk of CV outcome including myocardial infarction (MI), heart failure, vascular disease, and CV death associated with rheumatoid factor (RF) positivity as well as Antinuclear Antibody (ANA) positivity in the Olmsted County general population both before and after the presence the of rheumatoid disease. Statistical models were adjusted for age, sex, calendar year, and comorbidity. These analyses demonstrated a significantly increased risk of the combined outcome of MI, heart failure or vascular disease as well as overall mortality in subjects testing positive for rheumatoid factor, even after adjusting for the presence of rheumatoid disease. These same relationships were seen for ANA positive patients. The finding that RF and/or ANA positivity alone, even in the absence of rheumatoid disease, was a significant predictor for CV outcome suggests that immune dysregulation may promote CV risk not only in persons with rheumatic disease but also in the general population[10]. In summary, a number of inflammatory indicators, i.e., characteristics of active RA such as joint swelling, vasculitis, and RA lung, as well as high ESR, and rheumatoid factor represent significant independent risk factors for CV morality

and CV events in RA. RF and ANA appear to be associated with CV events and overall mortality even in the absence of rheumatoid diseases.

We then sought to determine how much of the increased incidence of heart disease in RA can be attributed to traditional (and thus potentially modifiable) CV risk factors such as smoking or hypertension. These analyses required the estimation of attributable risk or etiologic fraction, which is defined as the proportion of disease in a population that could, hypothetically, be prevented by elimination of a risk factor. In this analysis, the outcome was heart failure. We first estimated how much of the heart failure risk is attributable to hypertension and determined that to be approximately 60% in non-RA subjects and 18–20% in RA subjects. In other words, if all hypertension was eliminated, 60% of heart failure risk would be eliminated among non-RA subjects while only 18–20% of heart failure risk would be eliminated among RA subjects. This analysis was repeated and summed for all CV risk factors, including past history of ischemic heart disease. As shown in Figure 4, if all known CV risk factors and the past history of ischemic heart disease were magically eliminated, that would eliminate approximately 80% of all heart failure risk among non-RA subjects; however, it would only eliminate approximately 40% of heart failure risk among RA subjects[11]. These results clearly demonstrate that a much larger proportion of heart failure risk can be explained in non-RA compared to RA subjects. Once again we posit that the systemic inflammation and immune dysregulation that characterizes that characterizes RA may represent the ‘unexplained risk’ in RA subjects.

Maradit Kremers et al [12] reported the 10-year absolute CV risk in persons with RA and demonstrated that while relative risk information is useful, estimating absolute risk by age group is much more clinically meaningful. In this analysis, we demonstrated a high 10-year absolute CV risk at RA onset across the four age groups from 40 through 80 years of age. When compared to non-RA, the absolute CV risk in RA subjects was equivalent to that in non-RA subjects who were five to ten years older. These results combined with the finding that traditional CV risk factors behave differently in RA subjects (above) suggest that risk scores based on these traditional CV risk factors are likely to underestimate CV risk in RA. Indeed, such risk scores have been demonstrated to underestimate CV risk in other chronic diseases such as chronic kidney disease and diabetes[13–16].

In conclusion, traditional CV risk factors are important in individuals with RA; however, they are relatively less important in terms of the risk they impart in RA as compared to non-RA subjects. Indeed, some risk factors may act in the opposite direction as one would expect based on evidence from the general population. Inflammatory markers and markers of rheumatoid disease are highly significant predictors of CV outcome even after adjusting for demographics and CV risk factors. Together, these findings suggest that the systemic inflammation and immune dysregulation associated with RA appears to promote CV disease and CV death. These findings also suggest that effective, even optimal control of traditional risk factors alone may be insufficient in reducing CV risk for persons with RA and highlight the need for RA specific clinical risk prediction tools to accurately estimate CV risk in persons with RA. Finally, the CV impact of immune modulating agents and especially biological agents used in the treatment of RA is unknown. Large simple trials are needed to elucidate the impact of these agents on CV outcomes and mortality.

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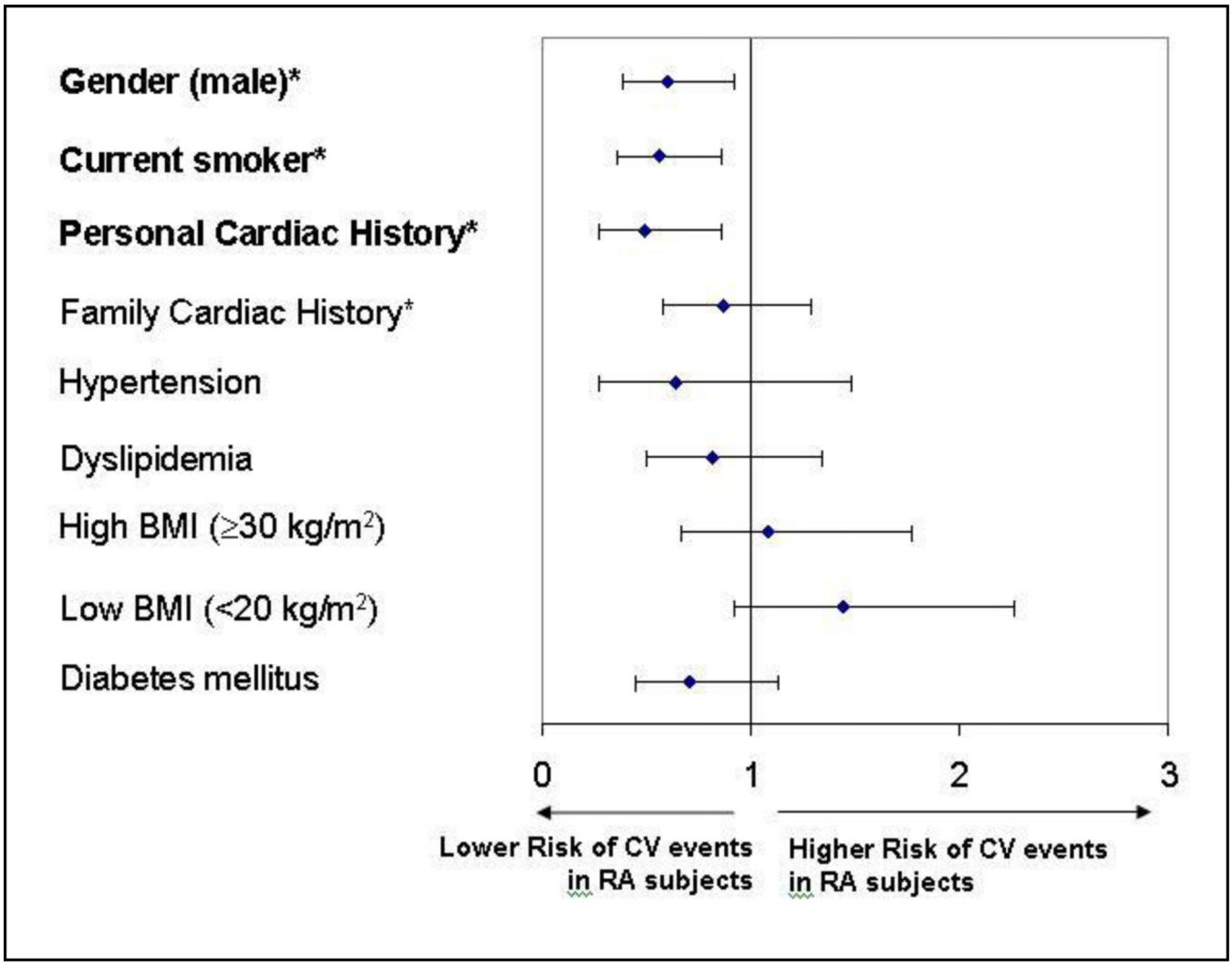

Figure 1.
Relative Impact of Traditional CV Risk Factors on Combined CV Endpoint in RA and Non-RA Subjects[3].

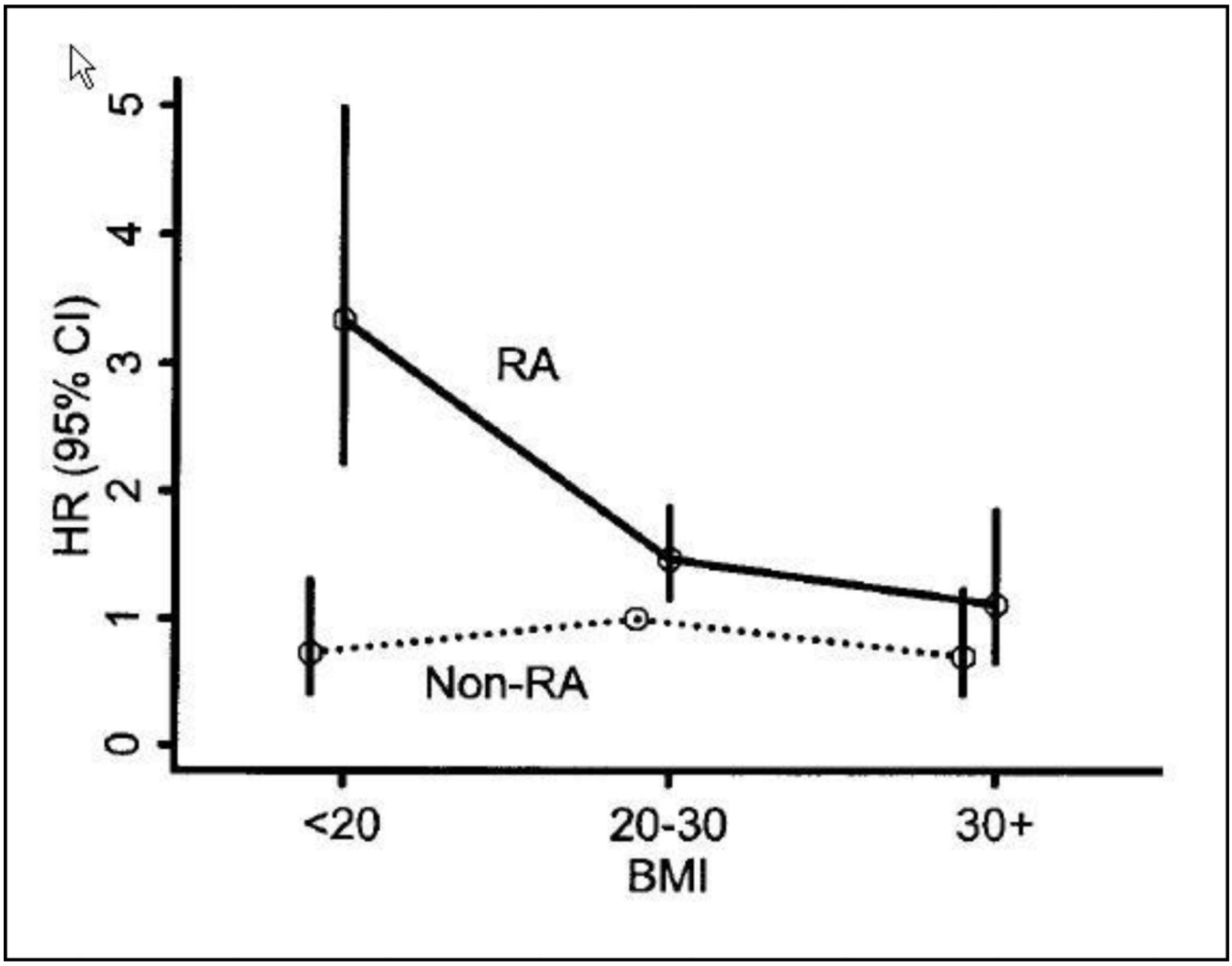

Figure 2.
Traditional CV Risk Factors in RA COMPARED TO NON RA SUBJECTS – Paradoxical effect of BMI. Arthritis Rheum 2004;50(11);3453. Permission to reprint requested from John Wiley & Sons, Inc.

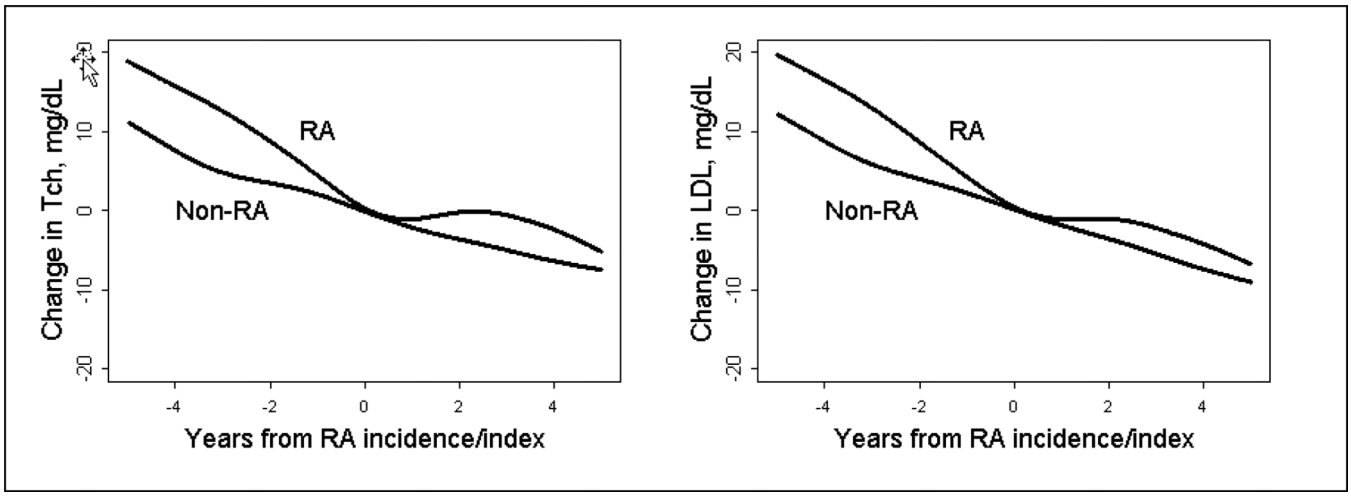

Figure 3.
Traditional CV Risk Factors – Paradoxical Effect of Lipids

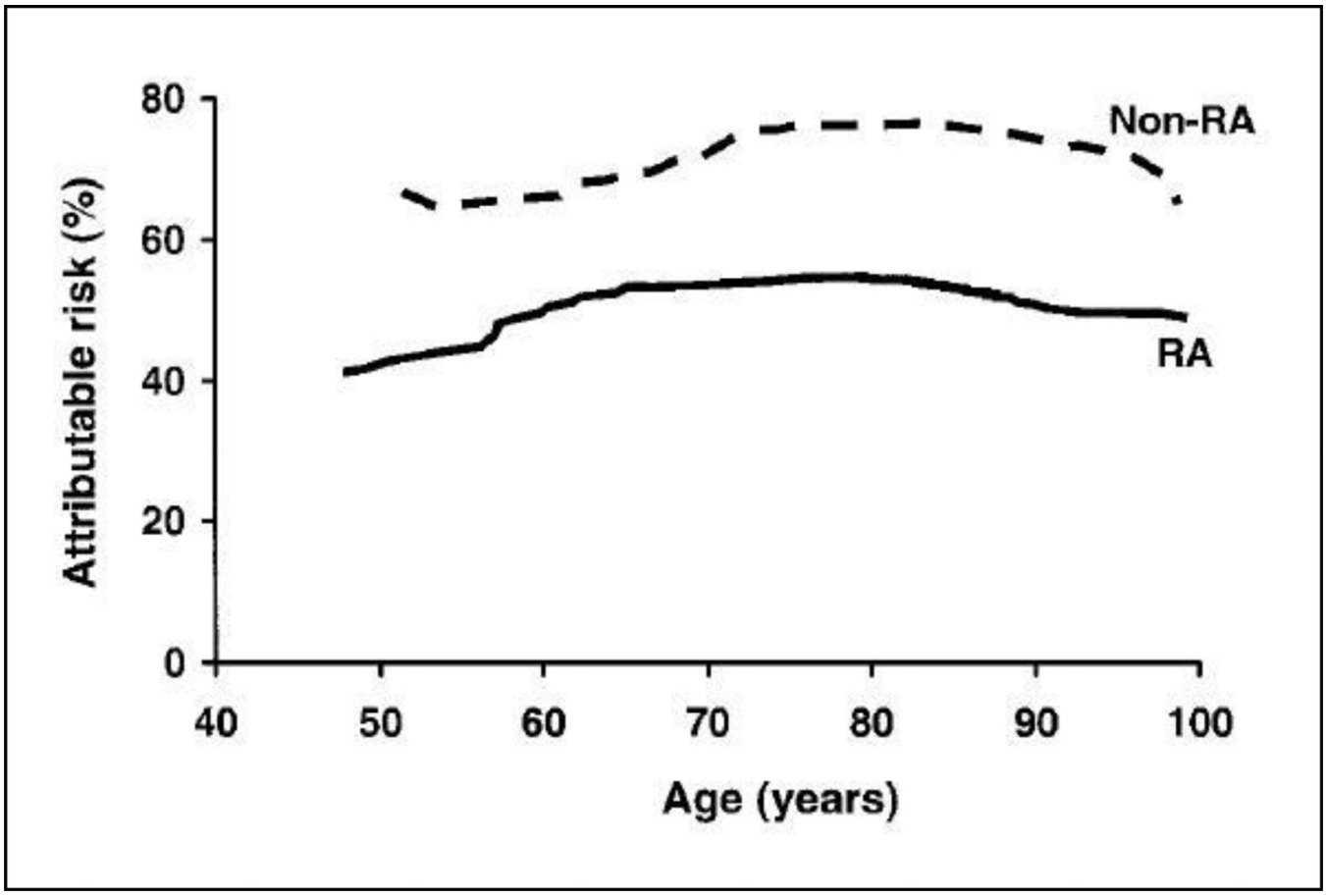

Figure 4.

How much of the Heart Failure Risk is Attributable to all CV Risk Factors and IHD together in RA compared to non RA subjects? Arthritis Rheum 2005;52(10);3042. Permission to reprint requested from John Wiley & Sons, Inc.

Table 1

Prevalence of traditional CV risk factors at RA incidence in RA and non RA subjects

CV Risk Factor	RA subjects N (%)	Non-RA subjects N (%)	p-value
Cigarette smoking			<0.001
Never	285 (47)	341 (57)	
Former	148 (25)	118 (19)	
Current	170 (28)	144 (24)	
Hypertension	312 (52)	298 (49)	0.42
Dyslipidemia	163 (49)	169 (52)	0.45
High BMI (≥30 kg/m2)	71 (13)	68 (13)	0.98
Low BMI (<20 kg/m2)	73 (13)	63 (12)	0.50
Diabetes mellitus	44 (7)	41 (7)	0.74
Family cardiac history	287 (48)	284 (47)	0.86
Personal cardiac history	77 (13)	72 (12)	0.66

Table 2

Incidence of CV risk factors over follow-up in RA and non RA subjects

CV Risk Factor	Rate per 100 person-years *(Number of cases)*		Rate Ratio (95% CI)
	RA	Non-RA	
Hypertension	3.67 (179)	3.59 (215)	1.02 (0.84, 1.25)
Hyperlipidemia	2.71 (158)	3.64 (228)	0.75 (0.61, 0.91)
High BMI (≥30 kg/m2)	0.47 (35)	0.63 (54)	0.75 (0.48, 1.13)
Low BMI (<20 kg/m2)	1.17 (83)	0.65 (53)	1.79 (1.28, 2.54)
Diabetes mellitus	0.79 (66)	1.02 (98)	0.78 (0.57,1.06)