The Role of Traditional Cardiovascular Risk Factors Among Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** People with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease (CVD) compared with the general population. We investigated the relative contribution of traditional cardiovascular risk factors to this elevated risk.

Methods. Fifty RA subjects and 150 age and sex matched controls attended a cardiovascular risk assessment clinic between March and July 2006. Traditional cardiovascular risk factors and the absolute risks of CVD (calculated from application of a Framingham risk equation) were compared between the 2 groups.

Results. Compared with the controls, RA subjects were more likely to smoke ($p < 0.001$), be physically inactive ($p = 0.006$), and have higher mean measurements of body mass index ($p = 0.040$) and waist circumference ($p = 0.049$). No significant differences were found in mean levels of plasma lipid or glucose, or in the prevalences of diabetes and hypertension. Overall, the mean absolute risk of CVD was higher in the RA group, even after excluding smokers ($p = 0.036$).

Conclusion. Smoking and physical inactivity are important risk factors in the management of cardiovascular risk among patients with RA. Subjects with RA seem to have higher absolute risks of CVD compared with controls, even independently of smoking. This highlights the importance of treating all modifiable risk factors in those with RA although, individually, few may be conspicuous. (First Release Nov 15 2008; J Rheumatol 2009;36:34–40; doi:10.3899/jrheum.080404)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CARDIOVASCULAR DISEASES RISK FACTORS

It is well known that there is an increased risk of cardiovascular disease (CVD) among patients with rheumatoid arthritis (RA). Indeed, CVD constitutes the leading cause of death in these patients[1]. RA specifically increases the risk of coronary heart disease[2-6], heart failure[7-9], and possibly also cerebrovascular disease[4,5,10]. Further, patients with RA have been found to be significantly more likely to experience silent myocardial ischemic episodes[11,12] and present with collapse and sudden cardiac death compared to persons without RA[12].

The exact reasons for the strong association between RA and CVD are unclear, but are likely to relate to both "traditional" and "novel" cardiovascular risk factors, the latter including systemic inflammation[13,14]. In terms of traditional cardiovascular risk factors, a consistent finding among RA patients is low levels of high-density lipoprotein (HDL) cholesterol[15-19]. Further, RA patients have been noted to have higher levels of small, dense low-density lipoprotein (LDL) cholesterol, known to be more atherogenic than regular LDL cholesterol[20]. Lipoprotein(a), a cholesterol-rich lipoprotein known to be associated with CVD[21], has also been found to be significantly higher among RA patients[19,22], even in those with median disease activity[23].

Further evidence suggests that RA patients are more likely to smoke than the general population[3]. In a subset of the Nurses' Health Study population comprising 87,306 women, RA patients were more likely to be past-smokers compared with controls (48% vs 38%, respectively; $p < 0.001$), but there was no difference between the groups in terms of current-smoker status[24].

However, while traditional cardiovascular risk factors appear to play an important role, they do not fully account for the increased risk of CVD seen among patients with RA[4,6,25].

Inflammation features most prominently among the novel cardiovascular risk factors, being common to both CVD and RA[13,14]. There are similarities between the inflammatory responses seen in atherosclerosis and RA. For example, collagen degradation, which occurs through the activation of macrophages and mast cells, appears to play a major role in the destabilization of atherosclerotic plaques and is also a vital component in the pathogenesis of inflammatory conditions

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such as RA[26]. Further, the association between RA and CVD might also be attributable to the atherogenic side effects of corticosteroids and selective cyclooxygenase-2 inhibitors, which are commonly used in RA[27,28].

We investigated the relative contribution of traditional risk factors to elevated cardiovascular risk among patients with RA.

MATERIALS AND METHODS

Study design. A cross-sectional study of traditional cardiovascular risk factors was undertaken in patients with RA and age and sex matched controls. Subjects with RA were drawn from the rheumatology outpatient clinic at the Alfred Hospital, a major tertiary referral hospital in Melbourne. The clinic serves a patient population with a broad range of conditions, among which RA constitutes approximately 15%.

The presence of RA was based on the 1987 American College of Rheumatology criteria[29]. There were no exclusion criteria and all eligible subjects attending the clinic from March to July 2006 were invited to participate. Consenting subjects were referred to the Baker Heart Risk Clinic (BHRC) of the Baker Heart Research Institute for cardiovascular assessment. Among those who declined the cardiovascular risk assessment, information regarding their reason(s) for refusal was collected, where possible.

Three unidentified controls from the BHRC database were randomly selected for every RA subject, matched for age and sex. Controls were drawn from the same general population as RA subjects. The BHRC and the Alfred rheumatology clinic are located on the same premises and both service the Bayside and inner Eastern suburbs of Melbourne. Controls comprised people referred to the BHRC for cardiovascular risk assessment from sources other than the Alfred rheumatology clinic. People who attend the BHRC are generally members of the community seeking assessment; workers who need to obtain an annual medical screen for their occupation; people referred to the clinic by their general practitioner or other allied health professional; those who have experienced a previous myocardial infarction; or patients taking part in research projects. People usually hear about the BHRC and its services through word of mouth, although some advertising does operate within local clubs and businesses. These controls were selected because they had the advantage of being predominantly from the general population and were assessed in the same way as RA subjects. They were eligible to participate in the study if their assessment at the BHRC occurred within the same time period as the RA subjects (March to July 2006).

Cardiovascular risk assessment. Subjects completed an interviewer-administered survey, and information was collected on the following variables: sex, date of birth, smoking habits, alcohol consumption, presence or absence of diabetes, detailed dietary habits, family history of "heart disease" (including whether the family member(s) died before or after the age of 55 years), and physical activity.

The questionnaire completed by all participants differentiated nonsmokers, smokers of a cigar or pipe, smokers of ≤ 10 cigarettes per day, and smokers of 10 cigarettes per day. It also asked how many cigarettes were smoked per day. Smokers (of any number of cigarettes) were added to form one group, "current smokers," and nonsmokers formed the second group. Data were not collected that could identify participants who were ex-smokers, nor was it possible to calculate pack-years from the data collected.

Other questions included whether subjects had been "previously diagnosed with any cardiovascular problem" or whether they suffered from any "chest pain at rest or under exertion." Subjects were additionally questioned on their use of medications for high blood pressure and dyslipidemia.

The following examination findings were recorded for study subjects: body mass index (BMI; weight measured using a beam balance scale and height measured by a stadiometer), waist and hip circumference (tape measure), and 2 measurements of blood pressure performed by the same nurse (mercury sphygmomanometer). Assessments were undertaken by one of 3 experienced nurses with similar training. Each was aware of the study subjects' RA status.

Plasma analyses at the BHRC were performed for the following cardiovascular risk factors: total, HDL and LDL cholesterol, triglycerides, and glucose (Cholestech LDX; Cholestech Corp., Hayward, CA, USA). Where possible, testing was undertaken after an overnight fast from 10 P.M. the night before.

Among patients with RA, information regarding disease status (e.g., duration, severity, and clinical course) and treatment history was not available.

Statistical analysis. Independent sample t-tests were used to compare the mean values of continuous variables between the RA and control groups, and chi-square tests of significance were applied to comparisons of proportions within categorical variables. Five and 10-year absolute risks of CVD (comprising coronary heart disease, stroke, heart failure, and peripheral vascular disease) were also assessed in all study participants using a risk equation derived from the Framingham Heart Study[30]. The variables for the equation comprised age, sex, smoking (yes/no), diabetes (yes/no), systolic blood pressure (SBP), ratio of total to HDL cholesterol, and left ventricular hypertrophy based on electrocardiographic assessment. As electrocardiographs were not performed on study participants, an assumption was made that none of the subjects had left ventricular hypertrophy.

All analyses were undertaken on SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Sample-size calculation was focused on a difference in the mean 10-year absolute risk of CVD between the RA and control groups. Assuming a standard deviation of 2.5% in absolute risk in each group and a 2-sided level of significance of 0.05, having 80% power to detect a 1% difference in mean absolute risk between the 2 groups required 200 subjects, with 100 in each group. Given the demanding logistics of recruiting 100 patients with RA, a target of 50 RA subjects was selected, with 3-to-1 matching of control subjects. Maintaining the same set of assumptions, this study sample allowed for 80% power to detect a 1.1% difference in mean absolute risk between the 2 groups.

The study was approved by both the Alfred Hospital and Monash University Institutional Ethics Committees.

RESULTS

Study sample. Within the period of study recruitment, 92 eligible patients with RA were identified, of whom 50 (54%) agreed to participate and underwent cardiovascular risk assessment. One hundred fifty age and sex matched controls were selected. Age matching was within 2 years, except for 2 controls for whom the differences in age to the index RA subjects were 3 and 5 years. Each group comprised 76% females, with 114 female and 36 male controls and 38 female and 12 male patients with RA. The mean ages of the RA subjects and controls were 64.9 and 64.8 years, respectively.

Of the 42 RA subjects who declined to undergo the cardiovascular assessment, 20 (48%) declined because they were already being managed by their general practitioners and/or cardiologists and 8 (19%) because of logistical difficulties in attending the BHRC. For 10 (24%), reasons were not provided. There was no significant difference in sex distribution between those who took part and those who did not (76% and 71% females, respectively). However, participants were on average older than nonparticipants (64.9 vs 56.3 yrs).

Cardiovascular risk factors. Key results for the modifiable and nonmodifiable cardiovascular risk factors are summarized in Tables 1 to 3.

Compared with the control group, subjects with RA were significantly more likely to smoke ($p < 0.001$) and were more

Table 1. Modifiable cardiovascular risk factors in the rheumatoid arthritis (RA) and control groups. Values are expressed as means or percentages, unless stated otherwise. Mean values are accompanied by standard deviation in parentheses.

Risk Factor	RA Group, n = 50	Controls, n = 150	p
Diabetes, %	8.0	7.14	1.00
Current smoker, %	24.0	4.67	< 0.001
Cholesterol ratio*	3.58 (1.26)	3.53 (0.99)	0.760
Total cholesterol, mmol/l**	5.07 (1.09)	5.15 (0.83)	0.564
LDL cholesterol, mmol/l**	2.88 (0.92)	3.06 (0.69)	0.160
HDL cholesterol mmol/l**	1.53 (0.47)	1.55 (0.40)	0.816
Triglycerides, mmol/l**	1.34 (0.66)	1.24 (0.78)	0.460
Glucose, mmol/l**	5.21 (1.92)	5.15 (1.35)	0.829
Systolic blood pressure, mm Hg	148.08 (20.12)	142.20 (20.08)	0.075
Diastolic blood pressure, mm Hg	82.24 (9.94)	82.72 (10.22)	0.771
Physical inactivity†	36.73%	15.15%	0.006
Waist circumference, cm	91.39 (13.94)	86.96 (13.31)	0.049
Waist-hip ratio	0.87 (0.08)	0.85 (0.08)	0.137
Body Mass Index, kg/m^2	28.05 (7.07)	26.25 (4.59)	0.040

* Cholesterol ratio = total cholesterol/HDL cholesterol. ** Three RA and 12 control subjects had not fasted (7.5% of sample).† Subjects were defined as physically inactive if they engaged in no regular exercise and were physically inactive at work. LDL: low-density lipoprotein; HDL: high-density lipoprotein; CVD: cardiovascular disease.

Table 2. Dietary habits in the RA and control groups.

Risk Factor	RA Group, n = 50	Controls, n = 150	p
Heavy alcohol intake*, %	0.0	4.03	—
Salt added to food†, %	70.0	53.33	0.060
≥ 1 take-away meal per week, %	40.0	43.33	0.735
Daily cake or biscuits, %	36.0	38.52	0.863
Do not use low-fat dairy products, %	50.0	14.75	< 0.001
Eat meat or poultry ≥ 7 times per week, %	10.0	8.2	0.884
Eat > 3 eggs per week, %	40.0	22.5	0.025
Fried food more than twice per week, %	8.0	8.26	0.482

* Heavy alcohol intake was defined as drinking ≥ 3 alcoholic drinks 5 to 7 times per week or drinking > 4 alcoholic drinks 3 or more times per week. A p value could not be evaluated as there were fewer than 5 subjects in the analysis. † Salt was added to food either before or after cooking.

Table 3. Nonmodifiable cardiovascular risk factors and other variables in the RA and control groups.

Variable	RA Group, n = 50	Controls, n = 150	p
Family history of CVD, %	36.0	59.33	0.005
History of CV problem, %	20.0	23.81	0.698
Prevalence of chest pain*, %	6.0	11.56	0.416
Use of antihypertensive medication, %	36.0	30.82	0.490
Use of cholesterol-lowering medication, %	18.0	17.69	1.0

* Chest pain was defined as any chest pain at rest or under exertion. CV: cardiovascular.

physically inactive, with fewer RA subjects engaging in regular exercise compared with controls (p = 0.006). RA subjects also had a significantly higher mean BMI (p = 0.040) and waist circumference (p = 0.049) compared with controls. Mean SBP was higher among those with RA, but the difference was not significant. There were no other differences in the composition of other modifiable cardiovascular risk factors.

After stratification for the use of cholesterol-lowering medications, antihypertensive medications, and diabetes status, the differences between the groups in terms of mean lipid con-

centrations (all 4 masures), blood pressure (diastolic and systolic), and glucose levels, respectively, remained statistically insignificant.

In terms of dietary habits (Table 2), RA subjects were less likely to consume low-fat dairy products ($p < 0.001$) but more likely to eat more than 3 eggs per week ($p = 0.025$). No subject within the RA group consumed alcohol "heavily" (defined as ≥ 3 alcoholic drinks 5 to 7 times/week or > 4 alcoholic drinks ≥ 3 times per week), compared to 4% of the control group. The 2 groups were equally as likely to eat takeaway meals, meats, cakes or biscuits, salt-enriched food, and fried food.

Compared with the control group, subjects with RA were less likely to have a family history of CVD ($p = 0.005$). There were no differences between the 2 groups with regard to a history of CVD ($p = 0.698$).

The proportions of subjects experiencing chest pain and using antihypertensive and cholesterol-lowering medications are presented in Table 3. No statistically significant differences were found, although there was a tendency among RA subjects to experience less chest pain.

Absolute risk of cardiovascular disease. There were statistically significant differences in the mean levels of both the 5- and 10-year absolute risks of CVD, with RA subjects exhibiting greater risks (Table 4). The differences remained significant even after exclusion of those with a previously diagnosed cardiovascular problem.

To examine the influence of smoking (which was much more prevalent among the RA group) on mean absolute risk of CVD between the 2 groups, absolute risk data were stratified by smoking status, excluding subjects with previously diagnosed CVD (Table 4). Among nonsmokers, a significantly higher absolute risk of CVD remained for the RA group. Among smokers, no differences in absolute risks of CVD were noted between the groups, mindful of the fact that there were very few subjects who smoked (11 RA and 3 control subjects).

DISCUSSION

RA subjects demonstrated an increased prevalence of smoking and physical inactivity, a higher BMI and waist circumference, and a decreased likelihood of having a family history of CVD. No significant differences were found in waist-hip ratio, plasma lipid or glucose levels, or rates of diabetes, hypertension or preexisting CVD.

The reasons behind the greater prevalence of smoking among the RA group are likely to be multiple. Other studies have found RA subjects to be more likely to be past or current smokers than the general population[3,24]. Further, smoking may increase the risk of developing RA[31,32] and positivity for rheumatoid factor[33-35], thus potentially being part of the causal pathway for RA. However, another likely explanation is an abnormally low smoking prevalence among the control group compared to the general population[36], which may reflect selection bias towards recruitment of a healthier control group. (This limitation will be discussed below.)

Physical inactivity, while not used in the calculation of absolute risk of CVD, is an important cardiovascular risk factor. RA subjects were less likely to participate in regular physical activity than the controls, probably because functional disabilities, joint pain, and stiffness are commonly experienced by those with RA, but as mentioned, a healthily-biased control group may also have contributed.

Further, waist circumference and BMI were significantly higher among the RA subjects, which probably relates to their being less physically active. There is no consistency in the literature about BMI measurements among patients with RA compared to non-RA patients; RA patients have been found to have higher[6,18], the same[3,24], and lower BMI[37,38]. In terms of association with CVD, limited data indicate that RA patients with low BMI (< 20 kg/m^2)[39,40] are those with higher cardiovascular risk. This situation probably reflects RA severity, as systemic inflammation often leads to weight loss, and even cachexia.

The difference between the 2 groups in terms of family his-

Table 4. Absolute risk of cardiovascular disease in the RA and control groups. Data are mean (SD).

Absolute Risk of CVD	RA Group	Controls	p
All subjects			
Mean 5-year risk of CVD, %	9.87 (7.24)	7.36 (4.78)	0.013
Mean 10-year risk of CVD, %	20.22 (11.98)	16.02 (8.99)	0.018
Subjects without a previously diagnosed cardiovascular problem			
Mean 5-year risk of CVD, %	9.8 (6.97)	7.01 (4.87)	0.017
Mean 10-year risk of CVD, %	20.16 (11.70)	15.3 (9.21)	0.019
Nonsmokers*			
Mean 5-year risk of CVD, %	9.51 (6.58)	6.86 (4.87)	0.033
Mean 10-year risk of CVD, %	19.72 (11.19)	15.01 (9.21)	0.036
Smokers*			
Mean 5-year risk of CVD, %	10.58 (8.21)	10.18 (4.32)	0.937
Mean 10-year risk of CVD, %	21.31 (13.45)	21.53 (7.89)	0.979

* Excluding subjects with a previously diagnosed cardiovascular problem.

tory of CVD was probably partly due to the well recognized fact that when a person develops CVD, it induces vigilance among family members, of which submission to cardiovascular screening is a consequence. While this motivation would probably have been present in both groups, it is likely to have been more prominent in the control group, with their cardiovascular screening at the BHRC having been more self-driven than in the RA subjects.

Against the weight of evidence[15-19], no differences in mean HDL cholesterol were found between the 2 groups. It was possible that RA medications and/or inflammatory activity may have affected lipid levels and hence obscured any true differences between the 2 groups, but this theory could not be tested in our study.

Despite the similarities across most of the traditional cardiovascular risk factors used in the calculation of absolute risk, mean absolute risks of CVD for both the 5- and 10-year prediction periods were greater for RA subjects than for controls. The differences remained statistically significant even after excluding smokers. This suggests that slight differences across multiple cardiovascular risk factors have combined to produce a significantly elevated overall risk. Of note, although the differences between the 2 groups in terms of mean SBP were not statistically significant, SBP was higher in the RA group by 6 mm Hg. Despite the lack of statistical significance ($p = 0.075$), it is important to emphasize the clinical significance of blood pressure control. It is well known that even modest reductions in blood pressure reduce cardiovascular risk.

Very few studies have assessed absolute risk of CVD using risk equations in RA populations. Of those that have, absolute risk of CVD was found to be elevated in only one study[41]. The other studies found patients with RA had risk no different from that of patients without RA[42], or a comparison with control subjects was not performed[43].

There have been suggestions that absolute risk scores based on traditional cardiovascular risk factors be modified for RA patients or interpreted differently in order to improve their validity. Suggestions have included doubling of the absolute risk scores such that they approximate true cardiovascular risk in RA patients[44], automatic allocation of people with RA to at least an "intermediate risk" category[45], and the use of lower thresholds of intervention among those with RA[42]. Indeed, there is growing support for the idea that a level of attention for cardiovascular risk similar to that applied to diabetic patients can be applied to patients with RA[46]. Despite an absence of longterm studies that demonstrate benefits of intensive cardiovascular risk management in RA populations, it seems prudent that RA populations should receive traditional cardiovascular risk factor modification that is at least as aggressive as the general population.

Our findings imply that in terms of managing traditional risk factors, particular attention should be devoted to addressing smoking and physical inactivity among subjects with RA. The importance of assessing and treating absolute cardiovascular risk (as opposed to targeting risk factors in isolation) is also highlighted. That is, among patients with RA, all modifiable risk factors should be optimized, despite the fact that individually, few may be greatly elevated. Further rationale for aggressive treatment of known traditional risk factors among people with RA stems from there being much that remains unknown, or at least untreatable, in this subpopulation. "Nontraditional" risk factors are not as easily measured or targeted for treatment.

Selection biases represented the main limitation of our study. The study sample, having been drawn from people specifically referred for cardiovascular risk assessment, may have been biased toward those with high cardiovascular risk. On the other hand, people with very high cardiovascular risks may already have been assessed (for example, by a cardiologist) and hence declined further assessment. Ambulant people, who were able to commute to and from the BHRC, were more likely to have been recruited. Any selection bias arising from targeting patients attending the BHRC would at least have applied to both the RA and control groups, meaning that it would not have influenced the differences observed between the 2 groups.

The RA group selected for study was drawn from a community-based sample of patients attending a specialty rheumatology outpatient clinic. It may not have been representative of this group, as 54% of eligible patients participated and participants were older. However, it is notable that any bias resulting from this age difference would not have affected the observed differences between the RA and control groups, since they were matched for age. Differences in other factors, like disease status, were not assessable.

One of the major limitations to the use of subjects from the BHRC as controls was that they may not have been representative of the general population in terms of their cardiovascular risk profiles. To assess for potential selection bias in the control subjects recruited from the BHRC, data from the control group were compared to those from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, a community-based cross-sectional study of 11,247 participants[47]. Compared with age and sex matched AusDiab subjects, members of the control group were less likely to be smokers (4.1% vs 14.0%) and had lower measurements of total cholesterol (5.2 mmol/l vs 5.9 mmol/l), LDL cholesterol (3.1 mmol/l vs 3.6 mmol/l), waist circumference (86.9 cm vs 90.2 cm), and BMI (26.2 kg/m^2 vs 27.6 kg/m^2). However, the prevalence of diabetes (6.3% vs 6.0%), mean SBP (142 mm Hg vs 134 mm Hg), and mean 5- and 10-year absolute risk scores were higher (6.8% vs 6.1%; 14.9% vs 13.3%). The direction of selection bias arising from use of this control group is not clear, but at least in terms of absolute cardiovascular risk, the group did not appear to be healthier than a community sample.

Overall, it was not clear in what direction the results were influenced by potential selection biases.

Another limitation was that control subjects were not specifically assessed for presence of RA. If any controls did indeed have RA, this would have served to underestimate the differences observed between the 2 study groups. However, since the prevalence of RA in the general population is approximately 1%[48], it is unlikely that this would have significantly affected the results.

The Framingham risk equation used in our study (like all other currently available equations) was based only on a selection of traditional risk factors. It did not take into account the effects of some other important traditional risk factors (such as abdominal obesity, triglycerides, family history, and physical activity) or novel risk factors (such as C-reactive protein, fibrinogen, homocysteine, and psychosocial factors). This is a particularly limiting factor when applying the risk equation to those with RA, whereby the mechanisms of CVD are less well defined, and possibly more reliant on novel risk factors in comparison with the general population.

With all Framingham risk equations having been based on a circumscribed US population initially recruited over 40 years ago, there are uncertainties about their applicability to more contemporary populations. However, the validity of Framingham risk equations and their generalizability to populations around the world have been extensively studied and they have generally been found to be reasonably accurate[49], including among Australians[50]. Additionally, any lack of applicability would have been equally relevant to both the RA and control groups and hence little bias would have arisen. Further, this limitation applies to the calculation of the actual risk score itself, whereas this study focused on the differences in scores between the 2 groups.

In this study, RA subjects were more likely to smoke, be physically inactive, and have a higher BMI and waist circumference, which suggests that these risk factors may warrant greater attention in the management of cardiovascular risk among patients with RA. A higher absolute risk of CVD was found in patients with RA compared to the general population, even without considering the effects of inflammation and other nontraditional risk factors. This highlights the importance of treating all modifiable cardiovascular risk factors in patients with RA, despite the fact that individually, few risk factors may be significantly elevated.

Our findings address the relative importance of the traditional cardiovascular factors in patients with RA, and will help to inform the management of cardiovascular risk in this population. It is hoped that our study will also raise awareness of the important, yet often unacknowledged, association between CVD and RA. The ultimate aim is reduction of the significant burden of disease in RA that is attributable to CVD, for which the potential remains great.

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