Current limitations in the management of cardiovascular risk in rheumatoid arthritis

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Abstract

Objective

Rheumatoid arthritis (RA) is associated with excess cardiovascular (CV) disease. Many studies have shown subclinical atherosclerosis in RA is associated with CV risk factors and inflammation. Their relationship with CV events has however received less attention. Furthermore, except for hypertension CV risk factor management has not been examined in a UK RA population. We therefore evaluated the contribution of RA specific and CV risk factors to CV events alongside the management of CV risk factors in RA patients.

Methods

We assessed the prevalence, screening and treatment of CV risk factors in a cross-sectional survey of RA patients consecutively attending specialist clinics. We used binary logistic regression to examine relationships between CV events and RA and CV risk factors.

Results

We enrolled 309 patients (81% female; median age 60 years; median disease duration 8 years). 27 (9%) had previous CV events. 56% had hypertension, 42% hyperlipidaemia, 11% diabetes, 52% were ex/current smokers and 26% obese. Lipid status was unknown in one third. 47% of patients on anti-hypertensive agents were undertreated. CV events were associated with hyperlipidaemia (OR 13.5; 95% CI 3.9, 45.9), hypertension (OR 6.4; 95% CI 1.9, 21.9), having ever smoked (OR 2.7; 95% CI 1.1, 6.5), RA duration (OR 1.09; 95% CI 1.06, 1.13) and erosions (OR 2.9; 95% CI 1.1, 8.2).

Conclusion

CV events are prevalent in RA. They are associated with CV risks and RA factors. Despite this burden we found CV risk factors were inadequately managed. A robust system to identify and treat CV risks in RA is required.

Key words

rheumatoid arthritis, cardiovascular diseases, inflammation

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Introduction

The increased cardiovascular (CV) morbidity of rheumatoid arthritis (RA) is well established. It equals that of diabetes mellitus, which is widely regarded as an independent CV risk factor (1). Both conventional CV risk factors and RA inflammation contribute to RA atherosclerosis (2). Research has mainly focussed on subclinical atherosclerosis in RA using blood vessel imaging. The factors driving actual CV events have received less attention.

UK and other national guidelines recommend annual CV risk factor screening in RA (3). The implementation of these recommendations is uncertain. Panoulas *et al*. found only 22% of treated hypertensive RA patients had adequate blood pressure (BP) control (4). The management of other CV risk factors in UK RA patients has not been examined.

We therefore evaluated the screening and treatment of CV risk factors in RA patients. We also examined their relative contributions alongside disease specific factors to CV events in RA.

Materials and methods

Patients

Between October 2009 and February 2010 we evaluated 309 consecutive patients with diagnoses of RA attending outpatient rheumatology clinics in two South London hospitals (University Hospital Lewisham and King's College Hospital). Patients met the 1987 RA classification criteria. Information was captured both prospectively (*e.g*. BP measurements) and retrospectively (*e.g*. reviewing medical records for diagnoses of CV events).

Most patients (81%) were female. 68% were Caucasian; 80% sero-positive for rheumatoid factor. 80% received disease modifying anti-rheumatic drugs (DMARDs), comprising methotrexate in 58%, sulphasalazine 20%, leflunomide 9%, hydroxychloroquine 20%, azathioprine 1% and gold 1%. 54 (17%) received biologics. Full details are given in Table I.

Presence of cardiovascular events

Patients were considered to have had CV events if they had documented diagnoses in their hospital records of myocardial infarction (MI), angina, stroke, transient ischaemic attack (TIA), peripheral vascular disease (PVD), carotid artery stenosis, coronary artery bypass grafting (CABG) or angioplasty. The last 3 diagnoses/procedures were included as they are almost exclusively present in patients with CV events. Primary/other secondary care provider records were not examined.

Patient demographics and RA characteristics

Information was collected on demographics (age, sex, ethnicity), RA characteristics (disease duration, disease activity score 28 (DAS28), presence of rheumatoid factor or erosions) and medications.

Cardiovascular risk factor assessment – definitions, screening and treatment

Information was collected on 5 CV risk factors: hypertension, hyperlipidaemia, diabetes mellitus, smoking and obesity. These were chosen because of their substantial evidence base linking them to atherosclerosis alongside their treatability. In patients without recent fasting lipid/glucose profiling these were undertaken in keeping with national guidance (3). CV risk factor presence, screening and treatment definitions are outlined in Table II.

Local approval

Data collection was undertaken as an audit of CV risk factor assessment against National Institute of Clinical Excellence (NICE) guidance (3). Ethical approval and consent were therefore not required, in keeping with UK National Research Ethics Service guidelines. Local research and development approval was gained prior to data collection.

Statistical analysis

Statistical analysis used the Statistical Package for the Social Sciences (SPSS) version 18.0. Distributional/normality plots were examined for abnormal distributions and the Kolmogorov-Smirnov/Shapiro-Wilk tests applied. Values were expressed as means and standard deviations (SD), median (25^{th}–75^{th} per-

Table I. Characteristics of 309 patients with rheumatoid arthritis grouped by the presence or absence of previous cardiovascular events.

	Patient characteristics		no CV event n=282	CV event n=27
Demographic features	Mean age in years (95% CI)		58 (57, 60)	69 (65, 72)
	Gender	Women	231 (82)	18 (67)
		Men	51 (18)	9 (33)
	Ethnicity	Caucasian	188 (67)	22 (82)
		Black	55 (20)	3 (11)
		Other	39 (14)	1 (4)
	Median disease duration in years (IQR)		8 (3–12)	20 (11–32)
RA Characteristics	Rheumatoid factor positive		224 (79)	23 (85)
	Erosions		153 (54)	19 (70)
	Extra-articular features		44 (16)	7 (26)
	Median swollen joint count (IQR)		2 (0–4)	1 (0–4)
	Median tender joint count (IQR)		2 (0–5)	1 (0–5)
	Median patient global assessment (IQR)		40 (20–55)	35 (20–73)
	Median ESR (IQR)		21 (9–36)	28 (20–35)
	Mean DAS28 (95% CI)		3.78 (3.60, 3.95)	3.73 (3.05, 4.40)
Cardiovascular Risk Factors	*Hypertension*	Hypertension present	150 (53)	23 (85)
		Median systolic BP (IQR)	130 (116–140)	135 (120–144)
		Median diastolic BP (IQR)	78 (70–83)	70 (67–80)
	Lipids	Hyperlipidaemia present	105 (37)	24 (89)
		Median Cholesterol (IQR)	4.9 (4.4–5.6)	5.7 (4.3–7.1)
	Diabetes	Diabetes Mellitus present	30 (11)	4 (15)
	Smoking	Smoker/Ex-smoker	141 (51)	19 (71)
		Never smoked	139 (49)	7 (26)
	Obesity	Obesity present	77 (27)	4 (15)
		Median BMI (IQR)	27 (24-32)	25 (22–29)

Except where otherwise indicated values are number (%); CI: confidence interval; IQR: interquartile range.

Table II. Diagnosis, screening and treatment of cardiovascular risk factor definitions.

Risk Factor	Diagnosis	Screening	Treatment
Hypertension	Present if: • Documented diagnosis in hospital records or • Anti-hypertensive use or • Systolic BP ≥140mmHg or • Diastolic BP ≥90mmHg*	Screened if BP ever measured (in medical records or from patient recollection)	Adequately treated if systolic BP <140mmHg and diastolic BP <90mmHg**
Hyperlipidaemia	Present if: • Documented diagnosis in hospital records or • Lipid lowering agent use or • Fasting total cholesterol ≥5.2mmol/L†	Screened if: • Diagnosis definition met or • Previous fasting lipid levels recorded on hospital laboratory system or taken from patient recollection	Treatment assessment restricted to patients without known hyperlipidaemia who agreed to fasting lipid profiles. Total cholesterol ≥5.2 considered threshold for treatment†
Diabetes Mellitus	Present if: • Documented diagnosis in hospital records or • Diabetic medication use‡	Screened if: • Diagnosis definition met or • Previous fasting glucose/oral glucose tolerance tests recorded on hospital laboratory system or taken from patient recollection	Treatment efficacy not assessed
Obesity	Present if BMI ≥30¥	Screened if height and weight previously measured by health professional (documented in hospital records or from patient recollection)	Considered treated if obese and previous weight loss advice given by health professional (documented in hospital records or from patient recollection)
Smoking	Patients grouped as current, ex- or life-long non-smokers	Screened if previous smoking history taken (in hospital records or from patient recollection)	Treated if smoking cessation advice given by health professional (documented in hospital records or from patient recollection)

*BP values for hypertension derived from the British Hypertension Society guidelines (5); **BP treatment targets from NICE guidelines for the treatment of hypertension (6); †total cholesterol level for hyperlipidaemia derived from the American National Cholesterol Education Program Expert Panel programme (7); ‡fasting glucose levels not used to define diabetes as seldom done on more than one occasion; ¥BMI value for obesity derived from NICE guidelines on obesity management in adults (8).

centile values) or percentages as appropriate. Binary logistic regression evaluated the association between individual factors and CV events. *P*-values <0.05 were considered significant.

Results

Prevalence of cardiovascular events and risk factors

Twenty-seven (9%) patients had previous CV events, comprising MI (9 patients), angina (13), PVD (3), previous angioplasty/CABG (7), carotid artery stenosis (2) and TIA/stroke (7). Ten had multiple events.

Many patients had CV risk factors, comprising hypertension in 173 (56%), hyperlipidaemia in 129 (42%), diabetes in 34 (11%), obesity in 81 (26%) and ex/current-smoking in 160 (52%).

Risk factors for cardiovascular events

Univariate analysis (Table III) showed several factors were associated with CV events. These comprised a demographic factor (age), RA factors (disease duration and erosions) and CV risks (hypertension, hyperlipidaemia and smoking status).

Two multivariate logistic regression models were developed. The first included all significant associations (age, disease duration, erosions, hypertension, hyperlipidaemia and smoking status). This showed hyperlipidaemia (OR 29; 95% CI 3.4, 243; p=0.002) and disease duration (OR 1.10; 95% CI 1.04, 1.16; p=0.001) remained significant factors and were therefore independently associated with CV events. The second model excluded hyperlipidaemia, as patients with CV events may receive statin therapy regardless of serum lipid levels. In this analysis hypertension (OR 6.8; 95% CI 1.4, 34.0; p=0.019) and disease duration (OR 1.09; 95% CI 1.04, 1.14; p=<0.001) remained significant.

Screening and treatment of cardiovascular risk factors

– hypertension

Median systolic and diastolic BP readings were 130mmHg (IQR 117–140) and 77mmHg (IQR 70–83). The mean time since last BP measurement was 10 months (95% CI 8, 12). 111 patients received anti-hypertensive agents, of which 52 (47%) had ongoing hypertension and were thus under treated (6). Fifty-four (28%) of 190 patients without documented hypertension had elevated BP measurements indicating possible undiagnosed hypertension.

Table III. Univariate analysis of factors associated with CV events in 309 RA patients.

Characteristic			Univariate Logistic Regression Odds ratio (95% CI)	*p*-value
Demographics	Age		1.06 (1.03, 1.10)	0.001
	Gender		–	0.061
	Ethnicity	Caucasian	–	0.188
		Black	–	0.229
		Other	–	0.143
RA specific factors	Sero-positive		–	0.221
	Erosions		2.96 (1.07, 8.15)	0.036
	Extra-articular features		–	0.153
	28 SJC		–	0.906
	28 TJC		–	0.693
	Disease global VAS		–	0.694
	ESR		–	0.130
	DAS28		–	0.884
	Disease duration		1.09 (1.06, 1.13)	<0.001
Cardiovascular risk factors	Hypertension		6.44 (1.89, 21.9)	0.003
	Systolic BP		–	0.353
	Diastolic BP		–	0.166
	Hyperlipidaemia		13.5 (3.96, 45.9)	<0.001
	Fasting cholesterol		–	0.357
	Diabetes Mellitus		–	0.510
	Ever smoked		2.66 (1.08, 6.52)	0.033
	Obesity		–	0.260

– Hyperlipidaemia

Only 43 of 218 patients (20%) without known hyperlipidaemia had fasting lipid levels measured in the preceding 12 months; 117 patients (38%) had not previously had lipid status assessments. Fasting lipid levels were performed in 102 patients without diagnosed hyperlipidaemia, of whom 38 (37%) had undiagnosed hyperlipidaemia with total cholesterol levels ≥5.2mmol/L (7).

– Smoking

Information on whether a smoking history had been taken was captured in 193 patients; 164 (85%) had previously had their smoking status assessed. 43% of current/ex-smokers had received smoking cessation advice.

– Diabetes Mellitus

Two hundred and seventy-five patients were not known to have diabetes mellitus, while one hundred and sixty-seven (54%) patients had never had their glucose status evaluated.

– Obesity

Information on BMI measurement had been captured in 207 patients, of which 157 (76%) had been screened for obesity. 49% of obese patients had received weight loss advice from a health professional.

Discussion

CV events were prevalent in our cohort. They had occurred in 9% of patients, which is higher than in the general population, estimated at 1.7% (9), but similar to the 9.3% previously reported in RA (10). Many patients had CV risk factors, which despite this excess CV burden were incompletely managed.

CV risk assessments were often not performed, suggesting incomplete guideline implementation (3). Hyperlipidaemia and diabetes mellitus had not been screened for in one third and one half of our cohort respectively. We also found evidence of under treatment of CV risk factors with BP values exceeding target levels in 47% of hypertensive patients on anti-hypertensives (6) and one third of patients without diagnosed hyperlipidaemia having total cholesterol levels ≥5.2mmol/L (7).

Comorbidities are often poorly managed in long-term diseases. This is particularly relevant in RA, where concurrent illnesses are common and contribute to disease outcomes. We consider that the main restrictions on CV risk assessment in RA are clinical time constraints, uncertainties as to who is responsible for undertaking this process, limited primary care involvement and reduced patient adherence. This latter factor seemed particularly relevant with many patients not attending organised fasting blood tests for lipid/glucose evaluation. Incomplete CV risk management is not unique to RA – the EUROASPIRE study found deficiencies in CV risk factor treatment in coronary artery disease, further highlighting guideline implementation inadequacies (11).

We consider that CV risk assessment in RA could be improved by two strategies- firstly using annual reviews for CV risk assessment and secondly improving patient screening adherence through education. Current guidelines advocate incorporating CV risk assessment into annual reviews (shown to reduce cholesterol and BP in diabetic individuals (12)). We advocate their use and suggest they should be undertaken by primary care health professionals, who have more experience of treating CV risks. However rheumatologists, who better appreciate RA comorbidites, should ensure they occur through forming close collaborative relationships with general practitioners involving education and local guideline formation. It is known that adherence in RA is limited, with medication adherence rates of 30–80% (13). These are improved by patient education programs (14). Adherence to CV risk screening and treatment may thus be improved by educating patients regarding CV morbidity in RA. This could be included in the annual review, using supportive educational material.

Our study has several limitations. In cross-sectional evaluations the impact of dynamic markers like the ESR is not assessable. The fatal nature of atherosclerosis makes censoring bias inevitable. We did not examine primary care records; although most GP practices have pathology results processed by the hospital important data may have been overlooked. BP measurements were performed once; as a dynamic measure increasing in stress we probably overestimated hypertension. We evaluated total cholesterol, which may be unsuitable to decide lipid status in RA, falling in active disease. As our sample size was relatively small it is possible associations with CV events were overlooked. There was a short time period of 12 months between NICE guidance publication and patient evaluation; we may have found superior CV risk assessments if patients were evaluated later. Finally we did not include a control group; however previous research has confirmed excess CV events in RA compared with age matched controls adjusted for CV risk factors (15).

We conclude that atherogenesis in RA is multifactorial with contributions from RA specific and CV risk factors. These risks are inadequately managed. Annual reviews, in which CV risk assessment and patient education occur, should become routine practice.

References

1. VAN HALM VP, PETERS MJL, VOSKUYL AE *et al*.: Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRÉ Investigation. *Ann Rheum Dis* 2009; 68: 1395-400.
2. DEL RINCON I, FREEMAN GL, HAAS RW, O'LEARY DH, ESCALANTE A: Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. *Arthritis Rheum* 2005; 52: 3413-23.
3. MANAGEMENT OF RHEUMATOID ARTHRITIS IN ADULTS. [INTERNET]: [Cited 2011 January 18]. Available from http://www.nice.org.uk/nicemedia/live/12131/43329/43329.pdf
4. PANOULAS VF, DOUGLAS KMJ, MILIONIS HJ *et al*.: Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology* 2007; 46: 1477-82.
5. WILLIAMS B, POULTER NR, BROWN MJ *et al*.: Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; 18: 139-85.
6. MANAGEMENT OF HYPERTENSION IN ADULTS IN PRIMARY CARE. [INTERNET]: [Cited 2010 September 12]. Available from http://www.nice.org.uk/nicemedia/pdf/CG034NICEguideline.pdf.
7. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The Expert Panel. *Arch Intern Med* 1988; 148: 36-69.
8. Obesity – guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. [Internet]. [Cited 2010 June 3]. Available from http://www.nice.org.uk/nicemedia/pdf/CG43NICEGuideline.pdf.
9. Series 10, No 229. Summary Health Statistics for the U.S. Population: National Health Interview Survey, 2004. [Internet]. [Cited 2010 September 12]. Available from http://www.cdc.gov/nchs/nhis/nhis_series.htm#08reports.
10. NARANJO A, SOKKA T, DESCALZO MA *et al*.: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008; 10: R30.
11. EUROASPIRE II STUDY GROUP: Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; 22: 554-72.
12. SMITH R, KREBS J, WEATHERALL M, MCBAIN L, HULLAH M, SHAPLESKI M: Analysis of a primary care led diabetes annual review programme in a multi ethnic cohort in Wellington, New Zealand. *Diabetes Res Clin Pract* 2011; 91: 164-70 [Epub 2010 Dec 30].
13. VAN DEN BEMT BJ, VAN LANKVELD WG: How can we improve adherence to therapy by patients with rheumatoid arthritis? *Nat Clin Pract Rheumatol* 2007; 3: 681.
14. BRUS HL, VAN DE LAAR MA, TAAL E, RASKER JJ, WIEGMAN O: Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis. *Ann Rheum Dis* 1998; 57: 146-51.
15. DEL RINCÓN ID, WILLIAMS K, STERN MP, FREEMAN GL, ESCALANTE A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44: 2737-45.