

Cardiovascular risk in rheumatoid arthritis and diabetes: how does it compare and when does it start?

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There is a substantial amount of evidence for an increased cardiovascular risk in rheumatoid arthritis (RA), 1.5–2-fold in comparison with the general population,^{1,2} but large-scale studies are still lacking. The majority of the evidence originates from several decades ago, a different era of natural history and management of RA, and thus there is still an unmet need for contemporary large epidemiological studies addressing the magnitude of the cardiovascular risk in RA. These studies should also address if and to what extent the cardiovascular risk in RA is comparable to that of diabetes, an established paradigm for a doubled cardiovascular risk,³ as recent studies have pointed towards this direction.^{4,5} If confirmed, then this may underpin the need for cardiovascular risk prevention and management in patients with RA, and a possible approach towards achieving this in everyday practice.

CARDIOVASCULAR RISK IN RA VERSUS DIABETES: CARRÉ STUDY

In a prospective Dutch study, the magnitude of the enhanced cardiovascular risk in RA was investigated by comparing prevalent cardiovascular disease (CVD) with that of diabetes.⁵ The study comprised 353 RA patients (diagnosed between 1989 and 2001, aged between 50 and 75 years; the CARDiovascular research in Rheumatoid arthritis (CARRÉ) study), and participants of a population-based cohort study on CVD and its risk factors (Hoorn study). Prevalent CVD was

observed in 13% patients with RA, 5% in individuals without diabetes and 12% in individuals with type 2 diabetes (n=194), respectively. The OR for CVD, adjusted for age and sex, were 3.1 in RA patients and 2.3 in individuals with type 2 diabetes in comparison with individuals without diabetes. Adjustment for (other) cardiovascular risk factors only slightly attenuated the OR, indicating that RA itself is an independent CVD risk factor. The prospective part of the investigation showed cardiovascular events in 9% of the RA patients and in 4% of the individuals without diabetes from the general population.⁶ The incidence rates were 3.1 per 100 patient-years for RA patients, and 1.5 per 100 person-years for individuals from the general population. The age and sex-adjusted relative risk was 2.0 with almost no change after adjusting for cardiovascular risk factors. Altogether, the CARRÉ study suggests that the cardiovascular risk in RA is increased to an extent that is comparable to that of diabetes, but confirmatory data from larger groups of patients are clearly needed.

CARDIOVASCULAR RISK IN RA VERSUS DIABETES: NATIONWIDE DANISH STUDY

In this issue of the journal, Lindhardsen *et al*⁷ conducted a nationwide study to investigate whether the risk of myocardial infarction (MI) in patients with RA is comparable to the risk in patients with diabetes (*see page 929*). The study comprised the whole Danish population older than 16 years and this cohort was followed during a 10-year period until 31 December 2006. By coupling nationwide registers, subjects with new-onset RA, new-onset diabetes and subjects developing a new (first) MI were identified. The cohort included more than 4 300 000 persons, of whom approximately 10 500 developed RA and 130 000 diabetes. The overall, fully adjusted, incidence rate ratio (IRR) of MI in RA was 1.7 (95% CI 1.5 to 1.9), which was completely comparable to the risk in diabetes: IRR

1.7 (95% CI 1.6 to 1.8). The IRR was age dependent, particularly in women younger than 50 years, who had a 5.5-fold increased risk. At the start of the study, 19 377 patients with an RA diagnosis were excluded indicating a prevalence of approximately 0.045%, and this appears low in comparison with other European countries, where it is approximately 1%. This could be due to either underreporting or a true lower prevalence in Denmark. Moreover, RA diagnosis was defined according to International Classification of Diseases codes in combination with prescription of disease-modifying antirheumatic drugs. Therefore, the observed results most likely do not apply to mild cases of RA, treated with non-steroidal anti-inflammatory drugs only. Similarly, the prevalence of diabetes appears low in comparison with the incidence of diabetes (1.8% and 3.0%, respectively) lower than the overall diabetes prevalence of 4.2% in Denmark.⁸ However, as argued by the authors, at present an earlier diagnosis of diabetes and more intensive antidiabetic therapy are plausible explanations for this apparent discrepancy between prevalence and incidence. Nevertheless, these results are clearly relevant, as the RA patients encountered in our daily rheumatological practice resemble the RA population studied by Lindhardsen *et al*.⁷

When comparing the MI rates between the two studies then there is a striking difference: the incidence of MI was approximately 0.6/100 patient-years in the Danish study versus approximately 2.3/100 patient-years in the CARRÉ study. Moreover, another recently published study revealed a rate of approximately 0.2/100 patient-years.⁹ Methodological issues might (partly) explain these striking differences, but also that MI rates differs across populations. Obviously, these findings will have power implications for cardiovascular intervention trials in RA.

WHEN DOES THE INCREASED CARDIOVASCULAR RISK IN RA START?

Carotid artery intima media thickness (IMT) is an important marker for early, preclinical, atherosclerosis and a predictor of future cardiovascular events in the general population,¹⁰ but this has not yet been shown in RA. However, several investigations have studied IMT in patients with RA, and a recent meta-analysis of 22 studies, encompassing 1384 RA patients and 1147 controls, revealed an overall greater carotid IMT in RA of 0.09 mm (95% CI 0.07 to 0.11 mm).¹¹ As

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disease characteristics, such as disease duration, were not related to carotid IMT this would imply that there was already an increased IMT early in the disease. However, the number of studies with early RA patients was small and comprised a limited number of patients. Moreover, a more recent study in 79 early RA patients did not demonstrate an increased IMT.¹²

Using general population norms, the observed carotid IMT difference of 0.09 mm of the meta-analysis of RA studies would indicate an approximately 15% increased cardiovascular risk,¹³ and this is significantly less than expected, compared with the approximately doubled cardiovascular risk in RA indicated by the hard endpoint epidemiological studies. As the majority of cardiovascular events are caused by plaque instability and rupture this may imply that, in a 'high-grade' inflammatory state, such as this of RA, plaques may rupture more easily and earlier than in a non-inflammatory situation.¹⁴

It is important to note that dyslipidaemia is already present in the preclinical phase of RA. In a recent controlled study of 79 subjects who later developed RA, the lipid profile over time and its relationship with inflammation and serological markers was studied.¹⁵ The lipid profile displayed, on average, 4% higher total cholesterol, 9% lower high-density lipoprotein cholesterol and 17% higher triglyceride levels compared with matched controls ($p \leq 0.05$), at least 10 years before the onset of RA symptoms, indicating an approximately 15–20% increased risk, which is remarkably similar to the increased risk extrapolated from the meta-analysis.

Altogether there appears to be an increased cardiovascular risk already at disease onset of RA, that is further substantiated by the findings of Lindhardtsen *et al*⁷ and others.¹⁶ In contrast, several other reports indicate that a clear excess of cardiovascular risk is only observed after approximately 10 years of RA disease duration.^{17,18} One of the reasons for this discrepancy might be that at disease onset there is a limited increased risk that is further amplified by clinically overt RA, leading to an increased slope of cardiovascular events against time. This widening difference with the general population may differ between investigations, resulting in an earlier or later detection of the enhanced cardiovascular burden in comparison with the general population. This could explain why some epidemiological studies of incident

(early) RA have not demonstrated a markedly increased cardiovascular risk, whereas the majority of studies of prevalent (established) RA have clearly shown such an excess.¹⁹

CARDIOVASCULAR RISK MANAGEMENT IN RA: WHEN AND HOW?

There is currently little doubt that the cardiovascular risk in RA is substantially elevated in comparison with the general population, and that it is comparable to patients with diabetes. There are several suggestions, including the study of Lindhardtsen *et al*,⁷ that the RR is higher in younger age groups, but as the absolute risk is much higher in older age groups, preventive cardiovascular strategies should not be restricted to a particular age group.

There are several pivotal steps in cardiovascular risk management in RA. The first is acknowledging that this risk exists, and unfortunately it does not appear that this realisation has been consistently translated into routine clinical practice in many parts of the world. The second step involves the determination of the cardiovascular risk profile (including at least an assessment of blood pressure, smoking status and lipid profile) at regular intervals. On the basis of these and other easily accessible data (eg, age, sex, family history of premature coronary heart disease etc.) and the aid of calculators such as Framingham and SCORE, the 10-year cardiovascular risk of a particular person can be calculated. Primary prevention involving treatment with statins and/or antihypertensive agents is only indicated in the general population when this 10-year risk is above a certain value. For instance, in The Netherlands this would be a 10-year cardiovascular mortality risk of 10% or more, whereas in the UK this would be a 10-year cardiovascular morbidity risk of 20% or more. The third step is to make sure that such primary prevention therapy is successfully implemented, ie, that predetermined targets of blood pressure and cholesterol are achieved (although it is still uncertain what exactly these targets should be for RA patients, those accepted in the general population should be aimed for at the least)—there is much evidence that this is not happening, either in the management of blood pressure²⁰ or dyslipidaemia²¹ in patients with RA. Finally, tight RA disease control is likely to decrease cardiovascular risk, but the effects of antirheumatic medications on individual cardiovascular risk factors need to be regularly assessed.²² The task force of the European League Against

Rheumatism (EULAR) has recently issued 10 recommendations regarding cardiovascular risk management in patients with RA and other types of inflammatory arthritis,²³ several aspects of which warrant comment. First, as the cardiovascular risk appears to be increased even before disease onset it is necessary to screen all patients with RA. Second, the existing risk models applied to the general population underestimate the true cardiovascular risk in RA. Therefore, the EULAR task force advocated the use of a 1.5 multiplication factor when two out of three of the following characteristics are present: disease duration of 10 years or more, the presence of extra-articular manifestations or the presence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies. This recommendation was based on the existing literature until May 2008, and since then there have been some reports advocating alternative approaches, for example, to increase the age of an RA patient by 10 years to get a more precise cardiovascular risk estimate, to use other risk scores, such as the Reynold's risk score, which incorporates C-reactive protein in the risk algorithm or the QRISK2 algorithm, which includes RA (like diabetes) as an independent risk factor.^{24,25} Obviously, any of these approaches (including the EULAR recommendations) should be fully validated, and the discussion will only be solved by the development of an RA-specific cardiovascular risk prediction model through specifically designed prospective studies, which will take several years to complete. The EULAR task force clearly underscored the need for further research in this field, including the development of RA-specific cardiovascular risk algorithms as well as the need for hard cardiovascular endpoint trials with statins and/or antihypertensive agents in RA.

CONCLUSIONS

If there was any doubt or debate about an enhanced cardiovascular risk in RA, the findings of Lindhardtsen *et al*⁷ clearly settles this. Importantly, they also provide further evidence that the cardiovascular risk in RA is broadly similar to that of contemporarily managed diabetes. In this respect is important to note that the cardiovascular risk in diabetes has decreased during recent decades probably as a result of cardiovascular risk management with statins and antihypertensive agents.²⁶

The results of the study by Lindhardtsen *et al*⁷ as well as the success of cardiovascular risk management in diabetes provides a clear incentive to identify and actively

manage, if necessary, cardiovascular risk in all RA patients as part of quality routine rheumatological practice. This is particularly important, as, for instance, the need for cardiovascular risk management is hardly acknowledged in primary care.²⁷ The EULAR recommendations provide a useful framework towards achieving cardiovascular risk management, but they also clearly acknowledge the need for further research, including hard cardiovascular endpoint primary prevention trials specifically in patients with RA.

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