EDITOR'S CHOICE

EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis

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Accepted 3 September 2009
Published Online First 22 September 2009

ABSTRACT

Objectives: To develop evidence-based EULAR recommendations for cardiovascular (CV) risk management in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: A multidisciplinary expert committee was convened as a task force of the EULAR Standing Committee for Clinical Affairs (ESCCA), comprising 18 members including rheumatologists, cardiologists, internists and epidemiologists, representing nine European countries. Problem areas and related keywords for systematic literature research were identified. A systematic literature research was performed using MedLine, Embase and the Cochrane library through to May 2008. Based on this literature review and in accordance with the EULAR's ''standardised operating procedures'', the multidisciplinary steering committee formulated evidence-based and expert opinion-based recommendations for CV risk screening and management in patients with inflammatory arthritis.

Results: Annual CV risk assessment using national guidelines is recommended for all patients with RA and should be considered for all patients with AS and PsA. Any CV risk factors identified should be managed according to local guidelines. If no local guidelines are available, CV risk management should be carried out according to the SCORE function. In addition to appropriate CV risk management, aggressive suppression of the inflammatory process is recommended to further lower the CV risk.

Conclusions: Ten recommendations were made for CV risk management in patients with RA, AS and PsA. The strength of the recommendations differed between RA on the one hand, and AS and PsA, on the other, as evidence for an increased CV risk is most compelling for RA.

Providing recommendations for monitoring and/or management and/or treatment of musculoskeletal disorders is one of the goals of the EULAR Standing Committee for Clinical Affairs (ESCCA).[1] Obviously, management of patients with inflammatory arthritis focuses not on cardiovascular (CV) morbidity and mortality. However, standardised mortality ratios (SMRs) are raised and the majority of premature deaths are attributable to CV disease.[2–4] CV morbidity is also enhanced and there is an increased prevalence of all stages of atherogenesis, from endothelial dysfunction to increased thickness and plaque in carotid arteries, to fatal and non-fatal myocardial infarction and stroke.[5–10] Moreover, the excess CV burden persists after adjustment for traditional CV risk factors.[11 12] Evidence is best documented for rheumatoid arthritis (RA), but patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) also appear to be at increased CV risk. Accordingly, available evidence supports inflammatory arthritis as an independent CV risk factor, and CV risk screening and management is therefore needed.

CV risk screening and management strategies have been developed for the general population and are based on CV risk score calculators, such as the Framingham score (often used in the United States) and the Systematic Coronary Risk Evaluation (SCORE) model (often used in Europe).[13 14] Traditional risk factors integrated in these models are age, gender, smoking, blood pressure and lipid (cholesterol and high-density lipoprotein-cholesterol (HDL-c)) levels. Risk estimates are based on information from the general population but the accuracy of these models has not been adequately evaluated in inflammatory arthritis, such as RA, AS and PsA.[15] Hence, we summarised and evaluated currently available literature according to the EULAR standardised operating procedures, to provide evidence-based EULAR recommendations for CV risk management in patients with inflammatory arthritis.

Participants and objectives

A multidisciplinary guideline development committee was commissioned by ESCCA. The steering committee comprised 18 members including rheumatologists, cardiologists, internists and epidemiologists, representing nine European countries. The objectives were (*a*) to identify and critically appraise evidence for specific CV interventions aimed at lowering the CV risk in RA; (*b*) to develop EULAR recommendations on the basis of the presented literature search for CV risk assessment in patients with RA, AS and PsA; (*c*) to determine future research goals.

Systematic literature search

A systematic search of literature published between January 1966 and May 2008 was undertaken using

Medline, Embase and the Cochrane library databases (Appendix 1, supplementary online file). The search consisted of two or three components: (*a*) the rheumatic disease in Medical Subject Headings (MeSH) or title abstract terms; (*b*) MeSH or title abstract terms for each CV traditional risk factor—that is, age, gender, cholesterol, blood pressure and smoking; (*c*) the MeSH or title abstract term "cardiovascular disease" was added to the search with age and gender in order to increase specificity. We only included key articles supporting issued recommendations. Selected articles were screened for eligibility by two investigators (MJLP and MTN).

Experts' consensus

When the literature search was completed, 10 concept recommendations were formulated. These were discussed within the steering committee until consensus was reached.

Categorising evidence

The grading of the recommendations was based on the methodological strength of the underlying literature, which was categorised according to standard guidelines (supplementary online tables). Obviously, the level of evidence is far greater for RA than for AS and PsA and therefore, the strength of recommendations is higher for patients with RA. Hence, for AS and PsA our recommendations should be seen as points to consider rather than definitive recommendations.

RESULTS

Recommendations

Table 1 lists the recommendations for CV management in RA, PsA and AS.

1. RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden

The overall SMR for RA is approximately two and numerous reports have demonstrated that the excess mortality is mostly due to CV disease.[1 2] It is unclear whether survival for patients with RA has improved over recent years as conflicting observations have been published.[16–19] The absolute risk of CV death is highest for elderly, male patients with RA, whereas the relative risk is highest for young female patients with RA.[20 21] CV morbidity is also enhanced and the magnitude of CV risk in RA may equal the CV risk in patients with type 2 diabetes.[22] Traditional CV risk factors—that is, hypertension, dyslipidaemia and smoking, probably occur more frequently, but the evidence is not uniform and adequate studies are lacking.[23–27] Traditional CV risk factors, however, only account partially for the excess CV risk. The key feature explaining the increased CV risk seems to be inflammation, as it, on the one hand, has an important role in different stages of atherogenesis, and, on the other, accentuates established CV risk factors.[28–31] Moreover, there is strong evidence showing that chronic inflammatory markers are independently associated with CV mortality and morbidity in RA.[31–35] Information about mortality rates in AS or PsA compared with the general population is limited, but reported SMRs are increased and range from 1.5 to 1.9, and similar to RA, the excess mortality is predominantly due to CV disease.[4] Presently, evidence for an increased CV risk in these patients is emerging and therefore AS and PsA should also be considered as CV risk factors.

2. Adequate control of disease activity is necessary to lower the CV risk (best evidence for anti-tumour necrosis factor treatment and methotrexate treatment)

Studies investigating the association between inflammation and atherosclerosis, using surrogate markers for CV disease, such as

Table 1 The 10 recommendations for cardiovascular (CV) risk management in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

Recommendations	Level of evidence	Strength of recommendation
1. RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden	2b–3	B
2. Adequate control of disease activity is necessary to lower the CV risk	2b–3	B
3. CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed	3–4	C
4. Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: – Disease duration of more than 10 years – RF or anti-CCP positivity – Presence of certain extra-articular manifestations	3–4	C
5. TC/HDL cholesterol ratio should be used when the SCORE model is used	3	C
6. Intervention should be carried out according to national guidelines	3	C
7. Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options	2a–3	C-D
8. The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors	2a–3	C
9. Corticosteroids: use the lowest dose possible	3	C
10. Recommend smoking cessation	3	C

ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AT-II, angiotensin II; coxibs, cyclo-oxygenase-2 inhibitors; HDL, high-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

intima medial thickness, confirm the important role of inflammation in accelerating atherosclerosis.[36–38] These results illustrate the interplay between inflammation and atherosclerosis in inflammatory arthritis and underline the importance of a more aggressive approach for treatment of inflammatory arthritis. Early and effective antirheumatic treatment, such as tumour necrosis factor blockers and methotrexate (MTX), has been shown to be independently associated with a lower CV risk.[39–45] Effective treatment may also result in improved physical activity, subsequently leading to a decreased risk of hypertension, obesity and diabetes, all important determinants of CV disease. Moreover, MTX may induce hyperhomocysteinaemia through a depletion of folic acid levels.[46] Hyperhomocysteinaemia has toxic effects on the endothelium, is procoagulant and therefore a CV risk factor.[47–49] Hence, folic acid is advised as it prevents MTX-induced hyperhomocysteinaemia, albeit the ultimate effect on CV risk in RA is unknown.[50 51]

3. CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed (in absence of national guidelines the SCORE function model is recommended)

As noticed earlier, CV risk assessment is recommended for all patients with RA and should be considered for all patients with AS and PsA. In this regard, to ensure sufficient take up of CV risk assessment, we have recommended that all patients receive an annual CV risk assessment but we recognise that in patients with low CV risk and inactive disease a lower frequency of assessment—for example, every 2 or 3 years, could be adopted. Additionally, CV risk assessment should be reconsidered during the disease course, as inflammation as well as antirheumatic treatment may alter CV risk factors, but again this is only necessary in patients already at increased CV risk. Hence, the treatment and follow-up plan should be determined on an individual basis and with regard to risk profile, morbidity, comorbidity and the patient's preferences. It should also be noted that CV risk assessment can be easily incorporated into a routine visit to monitor RA by addition of the determination of non-fasting lipids (cholesterol and HDL-c) to routine laboratory tests and by measurement of blood pressure.

4. Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria:

►Disease duration of more than 10 years
►RF or anti-CCP positivity
►Presence of certain extra-articular manifestations

Since traditional CV risk factors are already included in existing CV risk score models, it is important to identify other factors associated with an increased CV risk in RA. One important predictor is disease duration, which is illustrated by numerous reports observing that excess mortality increases with a longer disease duration.[16 52] A meta-analysis showed a mean SMR of 1.2 for inception cohorts (<2 years' disease duration) compared with a mean SMR of 1.9 for established disease.[53] Other prognostic CV disease markers are rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) positivity.[33 54–58] Finally, patients with severe disease (eg, those with extra-articular manifestations) have an increased risk for CV disease.[56 58–60] Therefore, it is recommended that the derived CV risk estimate should be multiplied by 1.5 if at least two of the following criteria are present: disease duration of more than 10 years, RF and/or anti-CCP positivity, presence of severe extra-articular manifestations.[61] Since available comparative studies did not adequately adjust for important confounders (social class, physical activity and others), and in addition, few, if any, adjusted for all established CV risk factors using continuous data, it is possible that the excess CV risk in inflammatory arthritis, over and above traditional risk factors, has been overestimated. Hence, a conservative approach—that is, a multiplication factor of 1.5 (rather than 2.0), has been chosen on the basis of the evidence from observational SMR reporting studies as well as expert opinion. At present, this multiplication factor should only be used for patients with RA.

5. Total cholesterol/HDL cholesterol ratio should be used when the SCORE model is used

Dyslipidaemia, particularly low levels of HDL-c, and high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and triglycerides are associated with an increased CV risk in the general population.[62–64] Particularly, the TC/HDL-c ratio is an important prognostic indicator for future CV disease.[64] Patients with inflammatory arthritis, particularly those with active disease, have low HDL-c levels resulting in a higher—that is, unfavourable, TC/HDL-c ratio, and high triglyceride levels.[65–67] Moreover, it appears that these unfavourable lipid changes may already be present at least 10 years before the onset of RA.[68] Hence, an unfavourable lipid profile may contribute to the increased CV risk in patients with inflammatory arthritis. By contrast, disease-modifying antirheumatic drugs (including initial corticosteroids) appear to have beneficial effects on the lipid profile in patients with early active RA—that is, an increase of TC but a more pronounced increase of HDL-c resulting in a lower (more favourable) TC/HDL-c ratio.[69–71] Tumour necrosis factor blockers are also associated with a transient increase of TC and HDL-c, mostly accompanied with improvement of the TC/HDL-c ratio, during the first few months of the treatment.[72–74] Thereafter the results become divergent and this might be due to differences in disease activity, (changes of) co-medication, particularly corticosteroids, dietary intake and physical activity.[75–77] Hence, future studies should appropriately examine these potential confounders to reach valid conclusions. In the meantime, it appears that the ratio of TC to HDL-c is the most stable marker of lipid-associated risk in RA.

6. Intervention should be carried out according to national guidelines.

CV risk assessment differs from country to country. The SCORE model is used in some countries, whereas in other countries the Framingham or no model is used. In addition, risk factors included in the models as well as treatment thresholds for initiation of cardioprotective agents or treatment goals may differ. As there is no evidence to indicate preference of one model above the other (and likewise treatment thresholds), risk assessment and management should be carried out according to national guidelines. If there are no local guidelines on the risk model to use then, the use of SCORE (see ''Example'' below) is advised. Commonly used treatment thresholds are a systolic blood pressure of 140 mm Hg and an LDL-c level of 2.5 mmol/l.

As evidence describing the effect of cardioprotective agents on CV end points in inflammatory arthritis is lacking, we have to extrapolate evidence from the general population in order to guide clinicians in their decision on the use of cardioprotective

agents in inflammatory arthritis. This means that modification and or specific intervention, such as antihypertensive agents or statins, should be the same as in the general population and should be initiated according to national guidelines. This statement is supported by a great number of observational studies as well as expert consensus.

7. Statins, ACE-inhibitors and/or angiotensin II blockers are preferred treatment options due to their potential anti-inflammatory effects

Intervention trials with statins and/or antihypertensive agents and CV end points in RA have not been published thus far. However, it is very unlikely that the effect of statins and/or antihypertensive agents would be attenuated. The effect might be more pronounced as statins and ACE inhibitors possess potential anti-inflammatory properties, which may be clinically significant in the context of inflammatory disorders. A randomised controlled trial of atorvastatin in RA demonstrated,[78] in addition to a moderate decrease in disease activity, a significant reduction in TC and LDL-c in statin-treated patients with RA. The observed changes were at least equivalent to expected reductions in TC and LDL-c in non-RA subjects given atorvastatin.[79] Since reduction in LDL-c is the best simple predictor of relative CV risk reduction, it is conceivable that at least an equivalent risk reduction will be achieved.[80–84] Similarly to statins, ACE inhibitors and angiotensin II (AT-II) blockers may also have a favourable effect on inflammatory markers and endothelial function in RA.[83 85–87] Hence, these agents are preferred, when antihypertensive agents are indicated. Nevertheless, future research with CV end points is needed to examine these questions more profoundly.

8. The role of cyclo-oxygenase-2 inhibitors and most non-steroidal anti-inflammatory drugs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors

Non-steroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase-2 inhibitors (coxibs) are associated with an increased CV risk.[88 89] The overall effects of NSAIDs and coxibs on CV risk are difficult to ascertain, as on the one hand, most of them, but not all, have prothrombotic effects due cyclo-oxygenase 2 inhibition, and on the other hand, these agents improve mobility of patients with RA, which might counterbalance the prothrombotic effects.[90 91] Moreover, a possible interaction between some NSAIDs and aspirin has been reported as some NSAIDs may impair aspirin's antiplatelet function.[92–96] Conclusive evidence is not yet available and therefore the potential atherothrombotic risk of any NSAID or COXIB must be taken into account when prescribing these drugs according to recommendations from the European Medicines Agency, especially in patients with documented CV disease or in the presence of CV risk factors.

9. Corticosteroids: use the lowest dose possible

Corticosteroids are commonly used in rheumatic patients and may influence the CV risk in two competing ways. On the one hand, corticosteroids could enhance CV risk owing to their potentially deleterious effects on lipids, glucose tolerance, insulin production and resistance, blood pressure and obesity.[95–97] On the other hand, corticosteroids may actually decrease the risk of atherosclerosis and CV disease by suppressing inflammation, which paradoxically may improve glucose intolerance and dyslipidaemia.[98 99] Owing to these opposing effects of corticosteroids on CV risk, it is important to take into account rheumatic disease features as well as traditional CV risk factors when considering the net effects of corticosteroids on CV risk.[100] Furthermore, CV risk is higher in patients treated with long-term high doses compared with low doses of corticosteroids.[101]

Altogether, there is no clear evidence that low-dose corticosteroids contribute significantly to the enhanced CV risk in inflammatory arthritis, in contrast to high-dose corticosteroids. Corticosteroids rapidly and effectively suppress inflammation in RA and their use might be justified for short-term treatment—for example, for "bridging therapy" in the period between initiation and response to disease-modifying antirheumatic drug treatment, although the debate appears not to be settled yet. Therefore, a conservative approach was chosen, recommending the use of the lowest dose for the shortest period possible.

10. Recommend smoking cessation

At present, although there is no strong evidence that smoking has a key role in the excess CV risk in RA, it clearly contributes to a higher absolute risk in individual patients. Hence,

Box 1 Research agenda

- Information about the effects of lipid-lowering and antihypertensive agents on cardiovascular (CV) risk in inflammatory arthritis is lacking. Randomised controlled trials are needed to examine this question and some long-term trials are currently being conducted. Additional information is needed about the number needed to harm and the number needed to treat with respect to interaction between lipid-lowering agents and/or antihypertensive agents and antirheumatic treatment in inflammatory arthritis.
- The search strategy did not include information about lifestyle modification—for example, weight control and physical activity. Lifestyle should be considered as a major CV risk factor. Modest reduction in weight or improvement in physical activity may significantly reduce the CV risk. Hence, lifestyle modification should be given to all patients. Briefly, smoking cessation, weight reduction and exercise are pivotal (evaluating the effect of lifestyle modification on the CV risk in inflammatory arthritis was added to the future research agenda).
- The contribution of other CV risk factors like stress, educational and social background towards excess CV disease in inflammatory rheumatic conditions is presently unknown and needs to be established.
- Accurate CV risk assessment may be more difficult in inflammatory arthritis as the relative role of traditional risk factors contributing to the increased CV risk is unclear. Therefore, studies evaluating the efficacy and applicability of different CV risk scores are needed in inflammatory arthritis.
- Probably, existing risk score models underestimate risk in women. This may be important particularly in rheumatoid arthritis, where there is a female sex preponderance, and warrants further investigation.
- As evidence for ankylosing spondylitis and psoriatic arthritis is emerging we will revise the guidelines accordingly within 3 years.
- Our recommendation for the multiplication factor of 1.5 is derived mainly from relevant standardised mortality ratios and, because information from large-scale prospective cohort studies is lacking. Obviously, this value should be re-examined in due course when better evidence emerges.

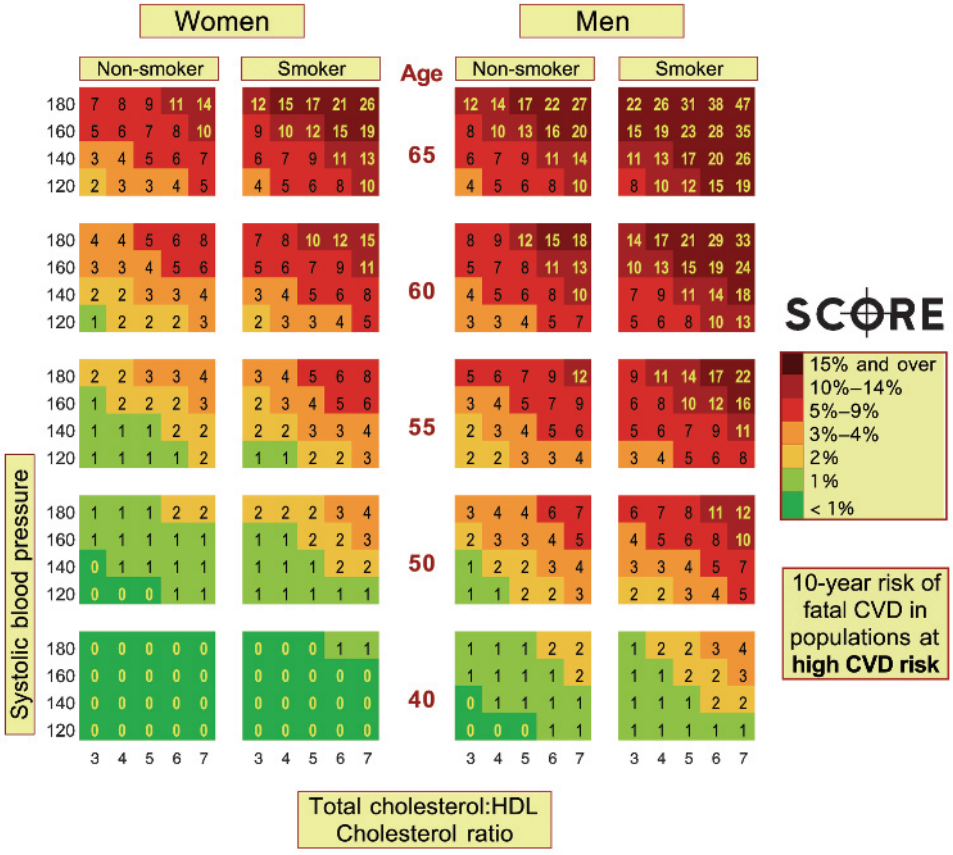

Figure 1 Ten-year risk of fatal cardiovascular disease (CVD) in patients at high CVD risk. Chart based on total cholesterol:high-density lipoprotein (HDL) cholesterol. Reproduced from Conroy RM, Pyorala K, Fitzgerald AP, *et al*. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**(11):987–1003, by permission of Oxford University Press.

rheumatologists are strongly recommended to advise and help their patients to stop smoking, wherever possible, using best evidence-based methods.

RESEARCH AGENDA

The committee composed a research agenda to further optimise CV risk management (box 1). As evidence for AS and PsA is emerging, we will re-evaluate the evidence for AS and PsA and aim to revise the guidelines within 3 years. We acknowledge that our recommendations for the multiplication factor of 1.5 are derived mainly from relevant SMRs, which strictly speaking is not ideal. However, there is a scarcity of prospective cohorts to enable the more usual approach in defining multiplication factors. Therefore, the arbitrary but conservative threshold of 1.5 has been chosen. Interestingly, data from a recent UK general practitioner study provides additional support for a multiplication factor of around 1.5.[102] Obviously, this value can be re-examined in due course when better evidence emerges.

CLINICAL IMPLICATIONS AND IMPLEMENTATION OF RECOMMENDATIONS

This guideline is aimed primarily at rheumatologists but also at a broad spectrum of other healthcare providers and reflect "best practice" for patients with inflammatory arthritis.

Although the greater CV risk is increasingly acknowledged, limited attention is paid to detecting and managing CV comorbid conditions such as hypertension and dyslipidaemia. Early identification, adequate CV risk management and ongoing monitoring of risk factors are mandatory to reduce the (excess) CV risk. The first principle of management is to assess and control all components of total CV risk. This includes appropriate evidenced-based advice with regard to smoking, physical activity, nutrition, weight and blood pressure. Cardioprotective treatment should be initiated when the estimated 10-year CV risk is above the risk threshold for each country, whether 10% or 20%. Finally, the clear relationship between disease activity and CV disease underlines the importance of tight disease control. Overall, this document provides evidence-based and expert opinion-based recommendations on the steps that should be followed to lower the CV risk in patients with inflammatory arthritis.

EXAMPLE

Figure 1 shows the 10-year risk of fatal cardiovascular disease in patients at high risk. Consider a 63-year-old female patient with RA with total cholesterol of 7.5 mmol/l and HDL-c of 1.5 mmol/l, a systolic blood pressure of 165 mm Hg, who smokes. In this instance, according to the SCORE model, the 10-year CV risk is 7% risk of fatal CV disease within 10 years. If this patient is IgM-RF positive and has disease duration of more than 10 years, we need to multiply this risk by 1.5, resulting in a 10.5% chance of fatal CV disease within 10 years. According to current "Dutch" guidelines, treatment with statins and/or hypertensive agents will be started when the CV risk score is above 10%, provided that the systolic blood pressure is ⩾140 mm Hg and/or the LDL-c is ⩾2.5 mmol/l. Hence, treatment with a statin and an antihypertensive agent will be started.

Acknowledgements: We thank Hans Ket, medical information specialist (VU University Medical Center) for his contribution to the systematic literature search.

Funding: This project was financially supported by the European League Against Rheumatism (EULAR).

Competing interests: Hans Bijlsma was the Handling Editor for this article.

Provenance and peer review: Not commissioned; externally peer reviewed.

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