

EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update

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ABSTRACT

Patients with rheumatoid arthritis (RA) and other inflammatory joint disorders (IJD) have increased cardiovascular disease (CVD) risk compared with the general population. In 2009, the European League Against Rheumatism (EULAR) taskforce recommended screening, identification of CVD risk factors and CVD risk management largely based on expert opinion. In view of substantial new evidence, an update was conducted with the aim of producing CVD risk management recommendations for patients with IJD that now incorporates an increasing evidence base. A multidisciplinary steering committee (representing 13 European countries) comprised 26 members including patient representatives, rheumatologists, cardiologists, internists, epidemiologists, a health professional and fellows. Systematic literature searches were performed and evidence was categorised according to standard guidelines. The evidence was discussed and summarised by the experts in the course of a consensus finding and voting process. Three overarching principles were defined. First, there is a higher risk for CVD in patients with RA, and this may also apply to ankylosing spondylitis and psoriatic arthritis. Second, the rheumatologist is responsible for CVD risk management in patients with IJD. Third, the use of non-steroidal anti-inflammatory drugs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and Assessment of Spondyloarthritis International Society. Ten recommendations were defined, of which one is new and six were changed compared with the 2009 recommendations. Each designated an appropriate evidence support level. The present update extends on the evidence that CVD risk in the whole spectrum of IJD is increased. This underscores the need for CVD risk management in these patients. These recommendations are defined to provide assistance in CVD risk management in IJD, based on expert opinion and scientific evidence.

INTRODUCTION

Cardiovascular disease (CVD) risk in patients with rheumatoid arthritis (RA) and other inflammatory joint disorders (IJD), in particular ankylosing spondylitis (AS) and psoriatic arthritis (PsA), is

substantially elevated compared with the general population. For RA, the magnitude of this excess risk appears comparable to that reported for patients with diabetes mellitus,^{1–3} necessitating aggressive and targeted CVD risk management. In 2009, the European League Against Rheumatism (EULAR) task force was convened to critically appraise existing evidence on CVD risk in patients with IJD. This EULAR task force formulated 10 recommendations for the screening and identification of CVD risk factors and the implementation of CVD risk management in IJD (see online supplementary file 1).⁴ In view of substantial new evidence, an update of the CVD risk management recommendations was performed.

In general, CVD risk management involves the determination of a cardiovascular risk profile of an individual patient by using values including gender, age, smoking status, blood pressure, lipid values and diabetes mellitus status. These variables are used in risk prediction algorithms such as Framingham⁵ and the Systematic Coronary Risk Evaluation (SCORE)⁶ to calculate a 10-year risk of CVD events. When this CVD risk exceeds a certain value, that is, a 10-year risk of 10% for a fatal or non-fatal CVD event (Framingham) or a 10-year risk of 5% for fatal CVD events (SCORE), lifestyle changes and treatment with lipid-lowering agents is recommended. The importance of a healthy lifestyle is emphasised for all persons, including patients at low and intermediate cardiovascular risk. Additionally, the European Society of Cardiology (ESC) guideline on CVD prevention in clinical practice also recommends CVD risk stratification for patients with hypertension.⁷ The initiation of antihypertensives depends on the grade of hypertension and total cardiovascular risk. Drug treatment is recommended for patients with grade 3 hypertension, but also grade 2 and grade 1 hypertension with a high CVD risk.⁷ Validated RA-specific CVD risk prediction models with a proven superiority over general population CVD risk prediction algorithms are currently lacking.⁷ Furthermore, the existing general population risk prediction models that aid the identification of patients who would benefit from primary prevention of CVD have been shown to inaccurately

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estimate the CVD risk in RA.^{8,9} Therefore, in 2009 the EULAR task force advocated the use of a 1.5 multiplication factor for these risk prediction models when certain RA disease characteristics were present.⁴ In addition, certain commonly used variables in existing CVD risk prediction algorithms are influenced by inflammation and anti-inflammatory therapy. These risk factors behave differently in patients with IJD than in the general population, necessitating clarification and practical guidelines for rheumatologists in daily clinical practice.

For this update, a new EULAR task force reviewed all the previous recommendations from 2009 on CVD risk management in IJD. New areas were addressed, including the value of imaging in the routine assessment of CVD risk.

METHODS

Task force

With the approval of the EULAR Executive Committee, the convenor (MTN) and methodologist (DPMS) who guided the task force in 2009 formed a new task force with the aim of reviewing and updating the 2009 EULAR recommendations for CVD risk management in RA and other IJD (see online supplementary file 1).⁴ The task force comprised 26 members from 13 European countries, including 2 patient representatives, 14 rheumatologists, 2 cardiologists, 3 internists, 1 healthcare professional and 4 fellows. The entire process was conducted in accordance with the 2014 EULAR standardised operating procedures.¹⁰

Literature search

The convenor (MTN) started by formulating a list of potential research questions. These were discussed and refined during a teleconference with other members of the task force. Thereafter, the fellows (RA, SCH, SR, MH) under guidance of the convenor (MTN) and the methodologist (DPMS) compiled the search terms for a comprehensive systematic literature review to cover all the research questions. The protocol for the literature search was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (<http://www.prisma-statement.org>). The Wiley/Cochrane Library, Pubmed/Medline and Embase were searched from inception (by RA, SCH, MH and librarians LJS and JCFK). The Wiley/Cochrane Library was searched up to 9 February 2015, PubMed up to 10 February 2015 and Embase up to 13 February 2015. A single search was conducted embracing all aspects of the different research questions. The following search terms were used (including synonyms and closely related words) as index terms or free-text words: ‘rheumatoid arthritis’ or ‘spondyloarthritis’ and ‘cardiovascular disease’ and ‘cholesterol’ or ‘blood pressure’ or ‘smoking’ or ‘diabetes’ or ‘chronic kidney insufficiency’ or ‘sex factors’ or ‘vitamin D’ or ‘adrenal cortex hormones’ or ‘tumor necrosis factor’ or ‘anti-inflammatory agents’ or ‘inflammation’ or ‘carotid intima media’. The full search strategies for the Wiley/Cochrane Library, PubMed and Embase are shown in online supplementary file 2.

All duplicates were removed from the results of the first search (figure 1). The remaining studies were screened by title

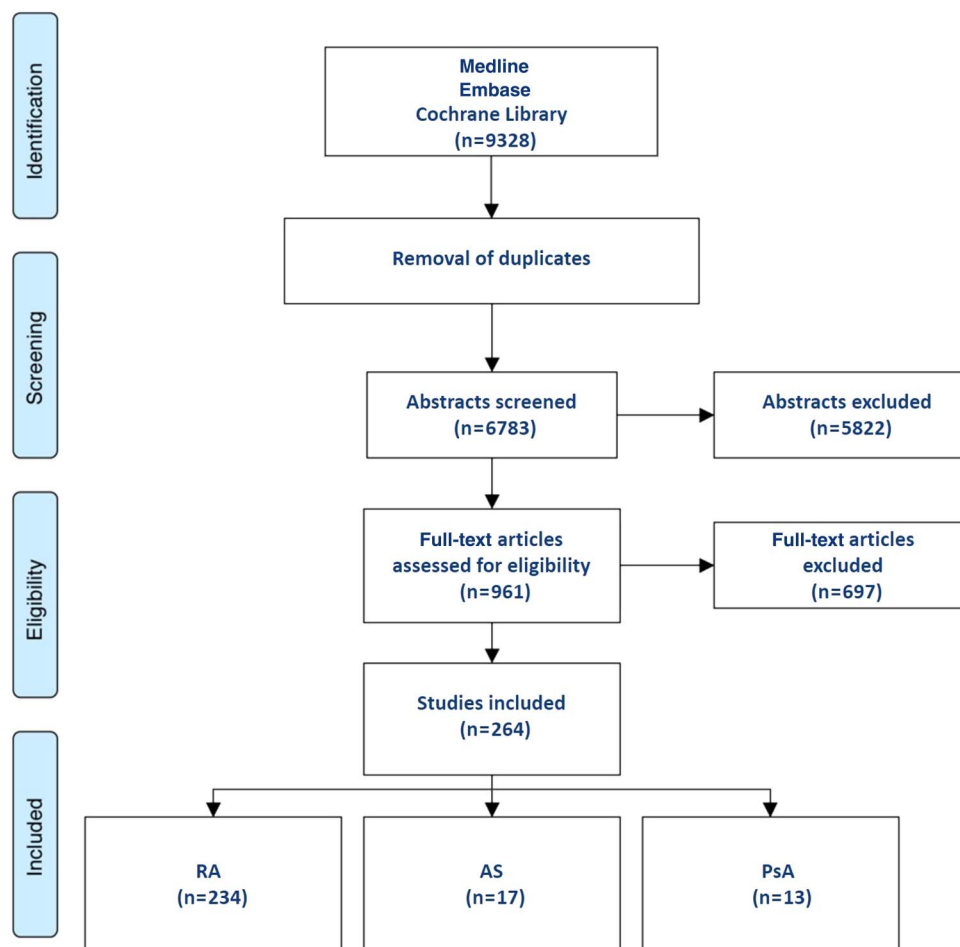


Figure 1 Flow chart of the search and selection process. RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis.

and abstract by six investigators (RA, SCH, SR, MH, DPMS and MTN) for suitability. Titles and abstracts were eligible if the abstract contained clear information about the aims and objectives of the study. From this selection of abstracts, full-text articles were assessed for eligibility by the fellows (RA, SCH, SR and MH). References of included articles were manually scanned for other relevant studies. The included articles were evenly divided among the four fellows, based on their area of expertise. Each fellow read the full texts and distilled and summarised the most important results. From these results, also taking into account the ten 2009 recommendations, 10 concept recommendations were derived.

Consensus finding

The EULAR task force held a 1-day meeting with all members on 31 March 2015. During this meeting, the 10 concept recommendations were presented by the four fellows. All 10 concept recommendations were discussed and subsequently adapted or dropped, and new recommendations were formulated. The principles guiding the consensus meeting were: (1) all of the 2009 recommendations were reconsidered on the basis of new evidence, (2) any of the 2009 recommendations could be kept unchanged, be modified or be totally abandoned, (3) new recommendations could be added. After the meeting, the updated and new recommendations were graded based on the methodological strength of the underlying literature and were categorised according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system.¹¹ Thereafter, the 10 concept recommendations

were sent out by email for anonymous voting. All members of the task force were asked to indicate their level of agreement (LOA) for each recommendation on a 0–10 scale (0, no agreement at all; 10, full agreement). The results on agreement were averaged and are hence presented as mean (SD).

RESULTS

Literature search

In total, 9328 articles were identified. After removal of duplicates, 6783 articles were screened by title and abstract. In total, 961 full-text articles were assessed for eligibility by the fellows (RA, SCH, SR and MH). Ultimately, 264 articles were included (figure 1).

Overarching principles

The task force defined three overarching principles of CVD risk management in RA and other IJD (table 1).

- A. *Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA*

Acknowledging the increased CVD risk in IJD was included as a recommendation in our previous guideline of 2009. However, in view of its generic nature, this ‘recommendation’ was moved to the Overarching principles section of this paper. Since the publication of the 2009 EULAR recommendations, the evidence for an enhanced CVD risk in IJD has increased. For example, it was shown in a large Danish cohort study that the risk of myocardial infarction (MI) in patients with RA is comparable to that in patients

Table 1 Overarching principles and recommendations

	Level of evidence	Strength of recommendation	Level of agreement (SD)
Overarching principles			
A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA.			
B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD.			
C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS			
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; CVD, cardiovascular disease; EULAR, European League against Rheumatism; HDLc, high-density lipoprotein cholesterol; IJD, inflammatory joint disorder; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; TC, total cholesterol.

with diabetes mellitus.² Furthermore, in the same study the risk of MI in RA was found to be approximately 70% higher than in the general population, which corresponds with the risk of non-RA subjects who are 10 years older.² Regarding mortality in RA, a meta-analysis including eight studies with follow-up ranging from the year 1955 to 1995 concluded that the standardised mortality rates (SMRs) in RA were elevated compared with the general population (ie, pooled SMR 1.47, 95% CI 1.19 to 1.83) and that these SMRs did not change over time.¹² Data from the Norfolk Arthritis Register with follow-up until 2012 revealed comparable results with increased all-cause mortality in patients with RA compared with the general population along with stable SMRs over the past 20 years.¹³ New evidence strengthens the notion that the excess risk of CVD morbidity and mortality in patients with RA is related to both traditional and novel CVD risk factors. Novel risk factors include inflammation, presence of carotid plaques, anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) positivity, extra-articular RA manifestations, functional disability and hypothyroidism.^{14 15}

Recent studies reveal increased SMRs in AS, ranging from 1.6 to 1.9.^{16–18} These studies report either death of circulatory origin or infection as the main cause of death in these patients.^{16–18} Compared with controls, patients with AS have an increased risk of vascular death and CVD events.^{19–27} Dyslipidaemia,²⁷ increased prevalence of hypertension,^{19 21 22 28} diabetes mellitus^{19 22 25} and increased carotid intima media thickness (cIMT) or atherosclerotic plaques^{29–31} have all been reported in AS. Furthermore, an increased prevalence of (non-) atherosclerotic cardiac disease is reported in AS, such as aortic valve dysfunction and conduction disorders, but it is currently unknown whether and to what extent this affects CVD risk.^{32 33} In PsA, reported SMRs range from 0.8 to 1.6.^{17 34 35} Overall, patients with PsA are at an increased risk of CVD events; however, data on stroke are more conflicting.^{34 36–38} Likewise, in PsA CVD risk seems to be influenced by an increased prevalence of CVD risk factors such as hypertension^{37–40} and increased arterial stiffness.^{41–43}

B. The rheumatologist should ensure that CVD risk management is performed in patients with RA and other IJD.

The responsibility for CVD risk management should be defined locally due to different healthcare systems and economic priorities in each country. Therefore, CVD risk management may include healthcare professionals other than rheumatologists. In clinical practice, it is not always clear who is taking responsibility for CVD risk assessment and management in patients with IJD and the task force therefore recommends that the treating rheumatologist should ensure that CVD risk assessment and management is being performed regularly, should record who is performing it and should make sure that the patient is aware of the need for regular risk assessment.

C. The use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and the Assessment of Spondyloarthritis International Society (ASAS).^{44 45}

NSAIDs and corticosteroids are commonly used for the treatment of IJD and these agents effectively lower disease activity and inflammation. However, both treatment options have been associated with an increased CVD risk.^{46–48} As these medications are often indispensable in tackling disease activity in patients with IJD, the task force feels that their

use should be evaluated on an individual patient level. Furthermore, lowering disease activity may have beneficial effects on the CVD risk. Therefore, the task force recommends to use NSAIDs and corticosteroids according to treatment-specific guidelines.

Recommendations

In line with the 2009 guidelines, we opted to give again 10 recommendations for CVD risk management. In total, three recommendations remained unchanged, six recommendations were altered and there is one new recommendation. One of the 2009 recommendations (#1) was moved to the overarching principles as described previously. A list of the updated recommendations, including the levels of evidence with the strength of recommendation and the LOA based on voting by the task force, is shown in [table 1](#). The recommendations follow a logical sequence, and they are not listed in sequence of importance. All recommendations are discussed in detail below.

1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA (unchanged, LOA 9.1 (1.3)).

In the previous recommendations from 2009, the importance of control of disease activity to lower CVD risk was emphasised. New evidence still portrays an association between higher cumulative inflammatory burden and increased CVD risk in RA.^{49–54} Disease duration does not seem to affect CVD risk independently.⁵⁰ However, disease activity as well as the number and duration of flares over time do contribute to the risk of CVD.^{49–52} There is now additional evidence showing a reduction of CVD risk in patients treated with disease-modifying antirheumatic drugs (DMARDs). Reducing inflammation is important in RA for CVD risk management, but the type of treatment may be less important. Conventional synthetic DMARDs (csDMARDs), in particular methotrexate (MTX), as well as biological DMARDs (bDMARDs), such as the TNF inhibitors (TNFi), are often associated with a significant reduction in CVD risk in patients with RA.^{46 49 51 53 55–62} The CVD risk appears to decrease even further after long-term use.^{53 56} Reduction of disease activity after treatment with tocilizumab or rituximab (RTX) shows a beneficial effect on cIMT, a surrogate marker for CVD, and CVD risk in a limited number of studies.^{54 63–65} Beneficial effects of TNFi and MTX on arterial stiffness have also been described.^{43 66–71} One study described a reduction in aortic inflammation and stiffness measured by ¹⁸F-FDG positron emission tomography-CT after TNFi treatment in patients with RA.⁷²

For both AS and PsA, evidence for the association between inflammation and an enhanced CVD risk is less abundant compared with RA. In view of shared pathogenic mechanisms, it is plausible that decreasing the inflammatory burden in AS and PsA will also have favourable effects on the CVD risk in these patients. Therefore, control of disease activity, as is routinely recommended, is expected to lower CVD risk for both AS and PsA.

2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy (changed, LOA 8.8 (1.1)).

CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years, so that lifestyle advice and CVD preventive treatment can be initiated when indicated. The advice to screen patients with IJD for CVD risk on a yearly basis has been changed to screening every 5 years, which is in line with the latest ESC guidelines.⁷ Currently, there is no

evidence that annual CVD risk assessment compared with 5-year risk assessment leads to a more significant reduction in CVD mortality or morbidity in patients with IJD. Depending on the CVD risk algorithm that is used for screening, patients can be categorised as having low to moderate risk (eg, SCORE <5%), high risk (eg, SCORE \geq 5% and <10%) and very high risk (eg, SCORE \geq 10%).⁷ Once screened, patients with a low risk can be routinely screened again after 5 years. However, if the risk is intermediate rescreening may be done sooner, especially if disease progression is more rapid. Patients with a high risk or established CVD should be treated for all present CVD risk factors according to existing guidelines. A healthy lifestyle should be recommended to all persons, including patients with low and intermediate cardiovascular risk.⁷ CVD risk evaluation should be reconsidered after major changes in antirheumatic therapy, that is, the initiation of bDMARDs or other drugs that may cause pronounced increases in low-density lipoprotein cholesterol (LDLc) or alter other CVD risk factors, so that doctors can act accordingly.^{73 74}

3. CVD risk assessment for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available (unchanged, LOA 8.7 (2.1)).

Evidence is scarce with regard to the validity of disease-specific CVD risk prediction models to accurately predict risk in individual patients with RA, and it is therefore currently recommended to perform risk evaluation according to general population guidelines. Several novel and RA disease-specific factors have been associated with an increased risk of CVD, but at present it is uncertain if these factors will meaningfully and cost-effectively improve CVD risk prediction in patients with RA.

4. Total cholesterol (TC) and high-density lipoprotein cholesterol (HDLc) should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids are perfectly acceptable (changed, LOA 8.8 (1.2)).

The relationship between serum lipid levels and CVD risk is non-linear and potentially paradoxical in RA. Patients with RA with highly active disease generally have lower serum TC and LDLc levels compared with the general population, while their CVD risk is elevated.^{73 75-78} As described in the 2009 recommendations, these patients also have reduced serum levels of HDLc and higher levels of triglycerides as compared with healthy controls.⁷⁸⁻⁸¹ In general, controlling disease activity has widespread effects on the lipid profile. Treatment with TNFi and/or csDMARDs (mainly MTX) results in an overall increase of lipid components, but mostly HDLc, which improves the TC/HDLc ratio.⁷⁹⁻⁹³ A limited number of studies have reported beneficial effects of RTX and tocilizumab on individual lipid components.^{64 94 95} However, the net effect of treatment with these agents is an overall increase of individual lipid components without changes in TC/HDLc ratio.^{54 96-101} The same appears to be true for tofacitinib.¹⁰⁰ Still, statins are effective at reducing lipid levels in tocilizumab or tofacitinib-treated patients with sustained elevations of TC and LDLc.^{99 100} As described in the 2009 recommendations, the TC/HDLc ratio is a better CVD risk predictor in RA than individual lipid components.^{78 102} From a practical point of view, both TC and HDLc can be used when using online calculators. As lipid components appear to be modifiable by disease activity and anti-inflammatory therapy, assessment of the lipid profile should preferably be done when a patient has stable disease or is in remission. Finally, measurement of TC and HDLc are perfectly acceptable in non-fasting state, as noted in the recent

2016 European Guidelines on CVD prevention in clinical practice: prevention guidelines.⁷

5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the risk algorithm (changed, LOA 7.5 (2.2)).

The SCORE risk calculator is recommended for CVD risk prediction in the general population by the ESC guidelines.¹⁰³ However, CVD risk prediction models developed for the general population do not include non-traditional CVD risk factors and hence there is a possibility of underestimation of future CVD if these models are applied in patients with RA. It is indeed reported that several CVD prediction models inaccurately predict the risk of CVD in patients with RA.^{8 104 105} The 2009 EULAR recommendations for CVD risk management suggested a multiplication factor of 1.5 to the calculated total CVD risk if the patient fulfilled certain disease-specific criteria (ie, disease duration of >10 years, RF or ACPA positivity and the presence of certain extra-articular manifestations).⁴ It has been argued that the application of this multiplication factor does not reclassify as many patients as was expected into a more appropriate risk category.^{9 106} In addition, QRESEARCH Cardiovascular Risk Algorithm (QRisk) 2, a CVD risk prediction model that includes RA as a risk factor with a multiplication factor of 1.4 for all patients with RA,¹⁰⁷ tended to overestimate the CVD risk in patients with RA. QRISK 2 estimates the risk of fatal and non-fatal CVD combined.⁸ Currently, there are no alternative CVD risk prediction models with a proven accuracy and superiority for patients with IJD. Based on all recent epidemiology, this multiplication factor is still the most evidence-based way of estimating CVD risk in patients with RA. Therefore, the use of an RA-adapted risk prediction model is recommended over the use of an unadapted general population model, since there is a higher level of evidence on their predictive value. Based on this, the EULAR task force still recommends to adapt general population CVD risk algorithms (except for QRISK 2, in which the multiplication factor is intrinsic to the algorithm) with a 1.5 multiplication factor for all patients with RA. In contrast to the 2009 recommendations, the presence of certain RA-specific criteria is not mandatory anymore for the application of this multiplication factor, as evidence on the increased CVD risk in patients who are in the early stages of RA, patients with a recent RA diagnosis and patients without extra-articular manifestations.^{108 109}

6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA (new, LOA 5.7 (3.9)).

The presence of carotid plaques is associated with poor CVD-free survival and is strongly linked to future acute coronary syndrome (ACS) in patients with RA, with a rate of ACS of 1.1 (95% CI 0.6 to 1.7) per 100 person-years (pyrs) for patients with RA with no carotid plaques and 4.3 (95% CI 2.9 to 6.3) per 100 pyrs for those with bilateral plaques.^{66 110} RA-specific factors contribute to the presence of carotid atherosclerosis in addition to traditional CVD risk factors.¹¹¹ Disease duration and disease activity have been shown to be associated with plaque size and vulnerability in patients with RA.^{112 113} The most recent ESC Guidelines on CVD prevention in clinical practice recommend considering screening for carotid artery atherosclerosis in patients with moderate CVD risk (class: IIa, level of evidence: B, GRADE: strong).⁷ Autoimmune diseases like RA, systemic lupus erythematosus and psoriasis were acknowledged as diseases with increased CVD risk.⁷ Due to the high pretest probability for detection of carotid artery plaques by use of ultrasound in patients with RA, and the clinical consequence of

indication for statin treatment if a carotid plaque is present, this procedure could be of additional value for CVD risk evaluation. Ultrasound of the carotid arteries to identify atherosclerosis has been shown to reclassify a considerable proportion of patients with RA into a more appropriate CVD risk group in accordance with current guidelines.¹¹⁴

7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation (changed, LOA 9.8 (0.3)).

Since the 2009 recommendations, no new strong evidence has emerged on the role of smoking on CVD risk in IJD and hence this recommendation remains unchanged. Thus, patients should be advised to stop smoking and directed towards the locally defined evidence-based smoking cessation programmes, even if they have failed previously. The 2009 recommendations did not discuss diet or exercise, but it was mentioned in the research agenda.⁴ Research on the role of exercise in RA management has advanced considerably since 2009. Physical inactivity is common in patients with RA, and has been associated with an adverse CVD risk profile.^{115–117} There is accumulating data that structured exercise therapy has beneficial CVD effects in patients with RA, at least in the short and medium term.^{118–120} Exercise has been shown to reduce long-term inflammation in epidemiological studies conducted in the general population and increased physical activity was associated with lower levels of C reactive protein (CRP).¹²¹ This has also been demonstrated in a study with patients with RA in which a 6-month exercise programme lowered CRP levels, probably related to a reduction in body fat.¹¹⁸ Moreover, improvements in both microvascular and macrovascular function were found after 3 months of exercise in RA.¹²⁰ To date, no studies have shown any adverse effects as a result of exercise.¹¹⁹ Hence, in RA, high-intensity exercise is not contraindicated and should be encouraged in those already accustomed to activity. Physical activity that is enjoyable is more likely to be sustained.

A Mediterranean diet is characterised by a high consumption of fruit, vegetables, legumes and cereals, and contains less red meat and more fish compared with common Western diets. Olive oil or vegetable oil is the primary source of fat intake. This diet has been shown to be associated with a reduced incidence of major CVD events in the general population.¹²² In RA, the positive effect of a Mediterranean diet may be mediated by the effect of this diet on disease activity.¹²³ However, there is no specific evidence available on the effect of dietary modifications on CVD risk in patients with IJD. Therefore, we recommend national guidelines regarding a healthy diet as part of a healthy lifestyle as discussed below.

An important issue remaining is how lifestyle interventions should be advocated to patients with IJD. Studies in this field demonstrate that if information is provided, this should be linked to behavioural education.¹²⁴ A randomised controlled trial in patients with RA evaluated the effect of cognitive behavioural patient education with regard to modifiable CVD risk factors in people with RA: patients receiving this intervention had more knowledge, and improved behavioural intentions, however, actual behaviour did not differ between groups.¹²⁵ Obviously, this area is in need of more research.

8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population (changed, LOA 9.2 (1.3)).

Hypertension is a major modifiable risk factor contributing to increased CVD risk in IJD.^{126–128} Several mechanisms may lead to the development of hypertension, including the use of

certain antirheumatic drugs such as corticosteroids, NSAIDs, ciclosporin and leflunomide.^{129–132} It is important to realise that hypertension seems to be both underdiagnosed and undertreated in patients with RA.¹²⁷ For the management of hypertension and hyperlipidaemia, there is no evidence that treatment thresholds should differ in patients with IJD compared with the general population. In the past years, no new evidence has emerged that ACE inhibitors and angiotensin II (ATII) receptor blockers should be the preferred treatment choice for hypertension in patients with RA. Therefore, the previous treatment preferences for ACE inhibitors and ATII receptor blockers have been omitted.

Since the 2009 recommendations, several studies have assessed the efficacy of statins in patients with RA. Statins appeared to be at least as effective in reducing cholesterol levels, atherosclerotic burden and CVD morbidity and mortality, and they do not have more adverse reactions in patients with RA when compared with non-RA controls.^{77 133–139} In addition, statins have anti-inflammatory properties that may result in an even greater CVD risk reduction when combined with anti-inflammatory therapy in RA, but studies on this effect are scarce.^{140–142} A few preclinical studies found unfavourable effects of statins on RTX efficacy in patients with haematological malignancies.^{143 144} However, several clinical studies showed no significant differences in outcome between statin users and non-users receiving RTX treatment for a haematological malignancy.^{145–148} Clinical trials investigating this issue in RA are scarce. Three clinical studies in RA found no adverse effect of statins on RTX efficacy.^{149–151} Only one observational study reported a significant difference in disease activity 6 months after first RTX treatment in statin users as compared with non-users, but this finding was borderline significant ($p=0.049$) in a small sample size of statin-exposed patients ($n=23$ exposed vs $n=164$ non-exposed).¹⁵² Obviously, further research is necessary to address this issue properly.

9. Prescription of NSAIDs in RA and PsA should be given with caution, especially for patients with documented CVD or in the presence of CVD risk factors (changed, LOA 8.9 (2.1)).

The 2009 recommendations advocate that NSAIDs should be used with caution in this population or may even be contraindicated.^{4 153 154} Since the publication of the former recommendations, new evidence has emerged on the role of cyclooxygenase-2 inhibitors (COXIBs) and non-selective NSAIDs in CVD risk. A recent meta-analysis concluded that, overall, both non-selective NSAIDs and COXIBs have adverse effects on CVD outcomes in patients with RA and PsA.⁴⁶ However, the increased CVD risk was mainly observed for rofecoxib, which was withdrawn from the market in 2004. There is evidence that NSAIDs might increase CVD risk in RA to a lesser extent in comparison to the general population than was previously thought.⁴⁸ Hence, there is no evidence to be stricter with NSAID treatment in patients with RA than what is recommended in the national guidelines for patients with no RA. Safety data regarding the use of NSAIDs in patients with IJD and prevalent CVD comorbidities are lacking. Naproxen seems to have the safest CVD risk profile.^{46 48} In general, diclofenac is contraindicated in patients with established congestive heart failure (NYHA class II–IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease, and new evidence supports similar restrictions for ibuprofen use.^{153 154}

For patients with AS, NSAIDs are recommended as first-line drug treatment by the ASAS/EULAR group in the recommendations for the management of pain and stiffness in patients with

AS, and an individual clinical evaluation regarding NSAIDs use in patients with AS with established CVD is therefore needed.¹⁵⁵

10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum, and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked (unchanged, LOA 9.5 (0.7)).

Corticosteroids rapidly and effectively reduce inflammation in RA, but they have also been associated with an increased CVD risk, although the literature shows conflicting results. Since the 2009 recommendations, new studies have found a dose-dependent and duration-dependent increase in CVD risk associated with corticosteroid use in RA.^{47 156 157} A relatively high daily dose (ie, already starting from 8 to 15 mg/day), a high cumulative dose and a longer exposure to corticosteroids (in years) appear to be associated with a higher CVD risk.^{47 156–158} Some authors argued that this increased CVD risk was confounded by indication, as it was no longer significant after correction for disease activity.^{53 159–161} On the contrary, other studies that had corrected for disease activity still found a (cumulative) dose-dependent and duration-dependent increase in CVD-related morbidity and mortality in patients with RA.^{47 156} However, this does not mean that confounding by indication has been completely addressed and this is a major limitation of all safety studies on corticosteroids. There is no conclusive evidence about the long-term effects of corticosteroids, particularly in low daily dosage, on safety outcomes including CVD events in RA. In patients with active disease, the benefit of reducing high-grade inflammation may counteract the adverse CVD effects of corticosteroid use by reduction of inflammation and by improving mobility. In other words, steroids may help to abrogate the harmful effect of inflammation on the cardiovascular system, but they will still carry their own adverse effects on CVD risk. Altogether, from a CVD prevention point of view, the lowest effective dose of corticosteroids should be prescribed for the shortest possible duration in the treatment of active IJD. This recommendation is in line with the EULAR recommendations on management of glucocorticoid therapy.⁴⁴

DISCUSSION

The 2015 update of the 2009 EULAR recommendations for CVD risk management in IJD comprises 3 overarching principles and 10 recommendations. The first overarching principle reinforces and extends the evidence of an increased CVD risk in IJD. The second principle indicates the responsibility of the rheumatologist for coordinating CVD risk management in patients with IJD, whereas the last principle aims to put this recommendation update more in line with other (EULAR) recommendations.

CVD risk assessment in IJD

Presently, the enhanced CVD risk in RA, but also in AS and PsA, is widely acknowledged. Thus far, fully validated RA-specific CVD risk prediction models that both improve on general population models and are cost-effective are lacking, although multiple attempts have been made.^{8 105 162} Some even question the need for a disease-specific CVD risk prediction model for RA, although existing models inaccurately estimate the CVD risk in these patients.^{8 9} In 2009, this led to the addition of a 1.5 multiplication factor for the calculated CVD risk in patients with RA if certain disease characteristics were

present.⁴ Meanwhile, alternative approaches have also been advocated, for example, to increase the age of a patient with RA by 15 years¹⁶³ or adding a multiplication factor of 1.4.³ Currently, it is unknown what approach would be most appropriate. In the light of this, the task force opted to retain the 1.5 multiplication factor to correct for the increased CVD risk in patients with RA compared with the general population. However, considering that the CVD risk is already increased in early disease or at disease onset and in patients without extra-articular manifestations, the three disease-specific criteria for the application of this multiplication factor were removed. This makes the estimation of CVD risk in patients with RA easier and therefore more feasible for daily clinical practice. As no conclusive evidence has emerged regarding the precise CVD risk in patients with AS and PsA, the task force opted not to include a multiplication factor for these diseases. In line with the ESC Guidelines, the recommendation to perform CVD risk assessment was extended to once every 5 years for patients found to be at low-to-moderate cardiovascular risk as there is no evidence that CVD risk assessment every year for IJD reduces CVD risk more than screening every 5 years.¹⁶⁴ In patients with an intermediate risk for CVD, screening should be performed more often. Patients at high to very high cardiovascular risk should promptly be treated for existing CVD risk factors. The new recommendation (#6) includes the option of screening for carotid plaques in patients with RA as a tool for CVD risk assessment, because carotid plaques are associated with future ACS in patients with RA. Whether routine screening of the carotid arteries is possible in daily clinical practice will depend on local availability. The LOA of 5.7 (3.9) for recommendation #6 possibly indicates the absence of evidence for routine screening of the carotid arteries in general.

CVD risk reduction in IJD

Just as in the 2009 recommendations, the importance of optimal anti-inflammatory therapy for CVD risk reduction in RA is emphasised in this update. There is accumulating evidence that decreasing the inflammatory burden in RA translates into a lower CVD risk. As inflammation is related to CVD risk in all IJD, we extrapolated this recommendation to AS and PsA, although further evidence for these types of IJD would be valuable. Equally important is the treatment of traditional CVD risk factors that are present in these patients according to national guidelines.¹²⁸ However, awareness of some issues when performing risk estimation and management in patients with IJD is important. Active disease of IJD is associated with reduced lipid levels that increase (ie, normalise) during effective anti-inflammatory treatment. Biologics have the most pronounced lipid increasing effect, which has led to mandatory lipid assessment during treatment with tocilizumab.¹⁰⁰ However, it is also important to realise that the anti-atherogenic properties of HDLc improve during biologic treatment.^{94 95} Therefore, it is important to assess the net effect of lipid modulation by biologics. Currently, the effect of these changes on CVD outcomes is not known. In addition, awareness of possible adverse effects of certain medications such as NSAIDs and corticosteroids has been emphasised. Except for smoking cessation, lifestyle recommendations were not given in our previous guideline. Since then accumulating data demonstrate that regular physical activity has beneficial CVD effects in patients with RA and hence this has been incorporated in the updated recommendations. In addition, favourable CVD effects have also been observed with a Mediterranean diet, although a formal study in patients with IJD has not yet been conducted. As it is not likely that the effect

Recommendation

of diet would be different in patients with IJD than in the general population, we also added this in our lifestyle recommendation.

Conclusion

In general, the LOA for the recommendations was (very) high, except for recommendations #5 (LOA 7.5) and #6 (LOA 5.7). As in 2009, the level of evidence was moderate for most of the recommendations. Several important questions which arose during the development of these recommendations remain unanswered. These questions have been put on the

research agenda (box 1). The 2015/2016 update of the EULAR recommendations for CVD risk management in patients with RA and other forms of IJD confirms and further extends the evidence of an increased CVD risk in the whole spectrum of IJD and reinforces the need for proper CVD risk management in these patients. As these updated recommendations are based on a pan-European consensus, it is hoped that they will facilitate CVD risk management in daily clinical practice, ultimately leading to a decreased CVD burden in our patients.

Box 1 Research agenda

1. Can we make adjustments to the current CVD risk models to improve estimation of CVD risk in patients with IJD?
2. How high is the CVD risk in patients with spondyloarthropathies or non-radiographic axial SpA compared with the general population?
3. What is the benefit/risk ratio of intensive anti-inflammatory therapy on CVD risk in patients with IJD?
4. Is the increased CVD risk in patients with spondyloarthropathies independent of traditional risk factors and what is the association between CVD risk and inflammation in spondyloarthropathies?
5. Is there an increased prevalence of cardiac abnormalities, including aortic valve dysfunction and conduction disorders in patients with spondyloarthropathies and how does this affect overall CVD risk?
6. How does treatment with NSAIDs affect the CVD risk in patients with IJD, in particular patients with AS?
7. Should we treat patients with AS continuously or intermittently with NSAIDs from a CVD point of view?
8. Should treatment targets for blood pressure and lipids be different in patients with IJD from the general population?
9. What is the effect of different modes of action of antirheumatic drugs on CVD risk?
10. What is the relationship between residual disease activity and CVD risk in patients with RA on stable DMARD therapy?
11. Is there additional value in measuring lipid subparticles in patients with IJD for estimation of CVD risk?
12. What is the added value of ultrasound of the carotid arteries to measure cIMT and reveal presence of atherosclerotic plaques in patients with IJD regarding CVD risk estimation and in which (sub) population should we conduct this?
13. What is the additional value of novel biomarkers for CVD risk prediction?
14. What is the best technique for implementing lifestyle changes and education in patients with IJD?
15. Health economics. Are interventions cost-effective in terms of reducing the number of fatal and non-fatal CVD events?
16. Is the prevalence of venous thrombotic events in patients with IJD increased? If so, what are the underlying mechanisms?

AS, ankylosing spondylitis; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatoid drug; IJD, inflammatory joint disorder; cIMT, carotid intima media thickness; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathy.

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REFERENCES

- van Halm VP, Peters MJ, Voskuyl AE, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis* 2009;68:1395–400.
- Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis* 2011;70:929–34.
- Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336:1475–82.
- Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
- D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743–53.
- 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;24:987–1003.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37:2315–81.
- Arts EE, Poppa C, den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2015;74:668–74.
- Gómez-Vaquero C, Corrales A, Zacarias A, et al. SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis. *Arthritis Res Ther* 2013;15:R91.
- van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Dadoun S, Zeboulon-Ktorza N, Combescure C, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine* 2013;80:29–33.
- Humphreys JH, Warner A, Chipping J, et al. Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. *Arthritis Care Res (Hoboken)* 2014;66:1296–301.
- Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. *Rheumatology (Oxford)* 2013;52:45–52.
- Solomon DH, Kremer J, Curtis JR, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. *Ann Rheum Dis* 2010;69:1920–5.
- Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Ann Rheum Dis* 2011;70:1921–5.
- Mok CC, Kwok CL, Ho LY, et al. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. *Arthritis Rheum* 2011;63:1182–9.
- Exarchou S, Lie E, Lindström U, et al. Mortality in ankylosing spondylitis: results from a nationwide population-based study. *Ann Rheum Dis* 2016;75:1466–72.
- Bremander A, Petersson IF, Bergman S, et al. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care Res (Hoboken)* 2011;63:550–6.
- Zöller B, Li X, Sundquist J, et al. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol* 2012;12:41.
- Brophy S, Cooksey R, Atkinson M, et al. No increased rate of acute myocardial infarction or stroke among patients with ankylosing spondylitis: a retrospective cohort study using routine data. *Semin Arthritis Rheum* 2012;42:140–5.
- Chou CH, Lin MC, Peng CL, et al. A nationwide population-based retrospective cohort study: increased risk of acute coronary syndrome in patients with ankylosing spondylitis. *Scand J Rheumatol* 2014;43:132–6.
- Essers I, Stolwijk C, Boonen A, et al. Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study. *Ann Rheum Dis* 2016;75:203–9.
- Haroon NN, Paterson JM, Li P, et al. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. *Ann Intern Med* 2015;163:409–16.
- Keller JJ, Hsu JL, Lin SM, et al. Increased risk of stroke among patients with ankylosing spondylitis: a population-based matched-cohort study. *Rheumatol Int* 2014;34:255–63.
- Mathieu S, Pereira B, Soubrier M. Cardiovascular events in ankylosing spondylitis: an updated meta-analysis. *Semin Arthritis Rheum* 2015;44:551–5.
- Peters MJ, Visman I, Nielen MM, et al. Ankylosing spondylitis: a risk factor for myocardial infarction? *Ann Rheum Dis* 2010;69:579–81.
- Kang JH, Chen YH, Lin HC. Comorbidity profiles among patients with ankylosing spondylitis: a nationwide population-based study. *Ann Rheum Dis* 2010;69:1165–8.
- Peters MJ, van Eijk IC, Smulders YM, et al. Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2010;37:161–6.
- Resorlu H, Akbal A, Resorlu M, et al. Epicardial adipose tissue thickness in patients with ankylosing spondylitis. *Clin Rheumatol* 2015;34:295–9.
- Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, et al. The high prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis without clinically evident cardiovascular disease. *Medicine (Baltimore)* 2009;88:358–65.
- Dik VK, Peters MJ, Dijkmans PA, et al. The relationship between disease-related characteristics and conduction disturbances in ankylosing spondylitis. *Scand J Rheumatol* 2010;39:38–41.
- Forsblad-d'Elia H, Wallberg H, Klingberg E, et al. Cardiac conduction system abnormalities in ankylosing spondylitis: a cross-sectional study. *BMC Musculoskelet Disord* 2013;14:237.
- Horreau C, Pouplard C, Brenaut E, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2013;27(Suppl 3):12–29.
- Buckley C, Cavill C, Taylor G, et al. Mortality in psoriatic arthritis—a single-center study from the UK. *J Rheumatol* 2010;37:2141–4.
- Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;74:326–32.
- Gladman DD, Ang M, Su L, et al. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009;68:1131–5.
- Ernste FC, Sánchez-Menéndez M, Wilton KM, et al. Cardiovascular risk profile at the onset of psoriatic arthritis: a population-based cohort study. *Arthritis Care Res (Hoboken)* 2015;67:1015–21.
- Gulati AM, Semb AG, Rollefstad S, et al. On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population-based data from the Nord-Trøndelag Health Study. *Ann Rheum Dis* 2016;75:819–24.
- Edson-Heredia E, Zhu B, Lefevre C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. *J Eur Acad Dermatol Venereol* 2015;29:955–63.
- Shang Q, Tam LS, Sanderson JE, et al. Increase in ventricular-arterial stiffness in patients with psoriatic arthritis. *Rheumatology (Oxford)* 2012;51:2215–23.
- Costa L, Caso F, D'Elia L, et al. Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. *Clin Rheumatol* 2012;31:711–15.
- Angel K, Provan SA, Gulseth HL, et al. Tumor necrosis factor-alpha antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. *Hypertension* 2010;55:333–8.
- Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;72:1905–13.
- Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896–904.
- Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
- del Rincón I, Battafarano DF, Restrepo JF, et al. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Ann Rheum Dis* 2014;66:264–72.
- Lindhardsen J, Gislason GH, Jacobsen S, et al. Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a

- nationwide cohort study. *Ann Rheum Dis* 2013; Published Online First 8 June 2013.
- 49 Ajejanova S, Andersson ML, Frostegård J, *et al.* Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. *J Rheumatol* 2013;40:1958–66.
- 50 Arts EE, Fransen J, den Broeder AA, *et al.* The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. *Ann Rheum Dis* 2015;74:998–1003.
- 51 Myasoedova E, Chandran A, Ilhan B, *et al.* The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. *Ann Rheum Dis* 2016;75:560–5.
- 52 Zhang J, Chen L, Delzell E, *et al.* The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:1301–8.
- 53 Innala L, Möller B, Ljung L, *et al.* Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. *Arthritis Res Ther* 2011;13:R131.
- 54 Rao VU, Pavlov A, Kleaman M, *et al.* An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. *Arthritis Rheumatol* 2015;67:372–80.
- 55 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;63:522–9.
- 56 Bili A, Tang X, Pranesh S, *et al.* Tumor necrosis factor α inhibitor use and decreased risk for incident coronary events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2014;66:355–63.
- 57 Chatterjee S, Sarkate P, Ghosh S, *et al.* Early, structured disease modifying anti-rheumatic drug (DMARD) therapy reduces cardiovascular risk in rheumatoid arthritis—a single centre study using non-biologic drugs. *J Assoc Physicians India* 2013;61:531–4.
- 58 Desai RJ, Rao JK, Hansen RA, *et al.* Tumor necrosis factor- α inhibitor treatment and the risk of incident cardiovascular events in patients with early rheumatoid arthritis: a nested case-control study. *J Rheumatol* 2014;41:2129–36.
- 59 Ljung L, Askling J, Rantapää-Dahlqvist S, *et al.* The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour necrosis factor inhibitors and the risk in the general population: a national cohort study. *Arthritis Res Ther* 2014;16:R127.
- 60 Micha R, Imamura F, Wyler von Ballmoos M, *et al.* Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. *Am J Cardiol* 2011;108:1362–70.
- 61 Morgan CL, Emery P, Porter D, *et al.* Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. *Rheumatology (Oxford)* 2014;53:186–94.
- 62 Solomon DH, Curtis JR, Saag KG, *et al.* Cardiovascular risk in rheumatoid arthritis: comparing TNF- α blockade with nonbiologic DMARDs. *Am J Med* 2013;126:730.e9–17.
- 63 Benucci M, Saviola G, Manfredi M, *et al.* Factors correlated with improvement of endothelial dysfunction during rituximab therapy in patients with rheumatoid arthritis. *Biologics* 2013;7:69–75.
- 64 Kerekes G, Soltész P, Dér H, *et al.* Effects of rituximab treatment on endothelial dysfunction, carotid atherosclerosis, and lipid profile in rheumatoid arthritis. *Clin Rheumatol* 2009;28:705–10.
- 65 Kume K, Amano K, Yamada S, *et al.* Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. *J Rheumatol* 2011;38:2169–71.
- 66 Ajejanova S, de Faire U, Jogestrand T, *et al.* Carotid atherosclerosis, disease measures, oxidized low-density lipoproteins, and atheroprotective natural antibodies for cardiovascular disease in early rheumatoid arthritis—an inception cohort study. *J Rheumatol* 2012;39:1146–54.
- 67 Galarra B, Khan F, Kumar P, *et al.* Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. *Rheumatology (Oxford)* 2009;48:1418–23.
- 68 Kerekes G, Soltész P, Szucs G, *et al.* Effects of adalimumab treatment on vascular disease associated with early rheumatoid arthritis. *Isr Med Assoc J* 2011;13:147–52.
- 69 Ristić GG, Lepić T, Glisić B, *et al.* Rheumatoid arthritis is an independent risk factor for increased carotid intima-media thickness: impact of anti-inflammatory treatment. *Rheumatology (Oxford)* 2010;49:1076–81.
- 70 Vassilopoulos D, Gravos A, Vlachopoulos C, *et al.* Adalimumab decreases aortic stiffness independently of its effect in disease activity in patients with rheumatoid arthritis. *Clin Rheumatol* 2015;34:359–64.
- 71 Vizzardi E, Cavazzana I, Sciatti E, *et al.* Evaluation of ascending aorta wall in rheumatoid arthritis by tissue and strain Doppler imaging during anti-tumor necrosis factor- α therapy. *Clin Cardiol* 2014;37:738–43.
- 72 Mäki-Petäjä KM, Elkhawad M, Cheriyan J, *et al.* Anti-tumor necrosis factor-alpha therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. *Circulation* 2012;126:2473–80.
- 73 Myasoedova E, Crowson CS, Kremers HM, *et al.* Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011;70:482–7.
- 74 van Sijl AM, Peters MJ, Knol DL, *et al.* The effect of TNF-alpha blocking therapy on lipid levels in rheumatoid arthritis: a meta-analysis. *Semin Arthritis Rheum* 2011;41:393–400.
- 75 Boyer JF, Bongard V, Cantagrel A, *et al.* Link between traditional cardiovascular risk factors and inflammation in patients with early arthritis: results from a French multicenter cohort. *Arthritis Care Res (Hoboken)* 2012;64:872–80.
- 76 Liao KP, Cai T, Gainer VS, *et al.* Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. *Arthritis Care Res (Hoboken)* 2013;65:2046–50.
- 77 Semb AG, Holme I, Kvien TK, *et al.* Intensive lipid lowering in patients with rheumatoid arthritis and previous myocardial infarction: an explorative analysis from the incremental decrease in endpoints through aggressive lipid lowering (IDEAL) trial. *Rheumatology (Oxford)* 2011;50:324–9.
- 78 Toms TE, Panoulas VF, Douglas KJM, *et al.* Are lipid ratios less susceptible to change with systemic inflammation than individual lipid components in patients with rheumatoid arthritis? *Angiology* 2011;62:167–75.
- 79 de Groot L, Jager NA, Westra J, *et al.* Does reduction of disease activity improve early markers of cardiovascular disease in newly diagnosed rheumatoid arthritis patients? *Rheumatology (Oxford)* 2015;54:1257–61.
- 80 Filippatos TD, Derdemezis CS, Voulgari PV, *et al.* Effects of 12 months of treatment with disease-modifying anti-rheumatic drugs on low and high density lipoprotein subclass distribution in patients with early rheumatoid arthritis: a pilot study. *Scand J Rheumatol* 2013;42:169–75.
- 81 Georgiadis AN, Voulgari PV, Argyropoulou MI, *et al.* Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients. *Semin Arthritis Rheum* 2008;38:13–19.
- 82 Curtis JR, John A, Baser O. Dyslipidemia and changes in lipid profiles associated with rheumatoid arthritis and initiation of anti-tumor necrosis factor therapy. *Arthritis Care Res (Hoboken)* 2012;64:1282–91.
- 83 Daien CI, Duny Y, Barnette T, *et al.* Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta-analysis. *Ann Rheum Dis* 2012;71:862–8.
- 84 Kerr G, Aujero M, Richards J, *et al.* Associations of hydroxychloroquine use with lipid profiles in rheumatoid arthritis: pharmacologic implications. *Arthritis Care Res (Hoboken)* 2014;66:1619–26.
- 85 Kirkham BW, Wasko MC, Hsia EC, *et al.* Effects of golimumab, an anti-tumour necrosis factor- α human monoclonal antibody, on lipids and markers of inflammation. *Ann Rheum Dis* 2014;73:161–9.
- 86 Liao KP, Playford MP, Frits M, *et al.* The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. *J Am Heart Assoc* 2015;4:pii: e001588.
- 87 Morris SJ, Wasko MC, Antohe JL, *et al.* Hydroxychloroquine use associated with improvement in lipid profiles in rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 2011;63:530–4.
- 88 Navarro-Millán I, Charles-Schoeman C, Yang S, *et al.* Changes in lipoproteins associated with methotrexate or combination therapy in early rheumatoid arthritis: results from the treatment of early rheumatoid arthritis trial. *Arthritis Rheum* 2013;65:1430–8.
- 89 Rho YH, Oeser A, Chung CP, *et al.* Drugs used in the treatment of rheumatoid arthritis: relationship between current use and cardiovascular risk factors. *Arch Drug Inf* 2009;2:34–40.
- 90 Ronda N, Greco D, Adorni M, *et al.* New anti-atherosclerotic activity of methotrexate and adalimumab: complementary effects on lipoprotein function and macrophage cholesterol metabolism. *Arch Drug Inf* 2015;67:1155–64.
- 91 Sandoo A, van Zanten JJCS, Toms TE, *et al.* Anti-TNFalpha therapy transiently improves high density lipoprotein cholesterol levels and microvascular endothelial function in patients with rheumatoid arthritis: a pilot study. *BMC Musculoskelet Disord* 2012;13:127.
- 92 Soubrier M, Jouanel P, Mathieu S, *et al.* Effects of anti-tumor necrosis factor therapy on lipid profile in patients with rheumatoid arthritis. *Joint Bone Spine* 2008;75:22–4.
- 93 Arts E, Fransen J, Lemmers H, *et al.* High-density lipoprotein cholesterol subfractions HDL2 and HDL3 are reduced in women with rheumatoid arthritis and may augment the cardiovascular risk of women with RA: a cross-sectional study. *Arthritis Res Ther* 2012;14:R116.
- 94 McInnes IB, Thompson L, Giles JT, *et al.* Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 2015;74:694–702.
- 95 Raterman HG, Levels H, Voskuyl AE, *et al.* HDL protein composition alters from proatherogenic into less atherogenic and proinflammatory in rheumatoid arthritis patients responding to rituximab. *Ann Rheum Dis* 2013;72:560–5.

- 96 Hsue PY, Scherzer R, Grunfeld C, *et al.* Depletion of B-cells with rituximab improves endothelial function and reduces inflammation among individuals with rheumatoid arthritis. *J Am Heart Assoc* 2014;3:e001267.
- 97 Makrilakis K, Fragiadaki K, Smith J, *et al.* Interrelated reduction of chemerin and plasminogen activator inhibitor-1 serum levels in rheumatoid arthritis after interleukin-6 receptor blockade. *Clin Rheumatol* 2015;34:419–27.
- 98 Mathieu S, Pereira B, Dubost JJ, *et al.* No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. *Rheumatology (Oxford)* 2012;51:1107–11.
- 99 Navarro G, Taroumian S, Barroso N, *et al.* Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected clinical conundrums. *Semin Arthritis Rheum* 2014;43:458–69.
- 100 Souto A, Salgado E, Maneiro JR, *et al.* Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. *Arthritis Rheumatol* 2015;67:117–27.
- 101 Strang AC, Bisoendial RJ, Kootte RS, *et al.* Pro-atherogenic lipid changes and decreased hepatic LDL receptor expression by tocilizumab in rheumatoid arthritis. *Atherosclerosis* 2013;229:174–81.
- 102 Peters MJL, Voskuyl AE, Sattar N, *et al.* The interplay between inflammation, lipids and cardiovascular risk in rheumatoid arthritis: why ratios may be better. *Int J Clin Pract* 2010;64:1440–3.
- 103 Perk J, De Backer G, Gohlke H, *et al.* European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Int J Behav Med* 2012;19:403–88.
- 104 Crowson CS, Matteson EL, Roger VL, *et al.* Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. *Am J Cardiol* 2012;110:420–4.
- 105 Arts EE, Popa CD, den Broeder AA, *et al.* Prediction of cardiovascular risk in rheumatoid arthritis: performance of original and adapted SCORE algorithms. *Ann Rheum Dis* 2016;75:674–80.
- 106 Corrales A, Parra JA, González-Juanatey C, *et al.* Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1764–70.
- 107 Hippisley-Cox J, Coupland C, Robson J, *et al.* Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QRresearch database. *BMJ* 2010;341:c6624.
- 108 Goodson NJ, Wiles NJ, Lunt M, *et al.* Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum* 2002;46:2010–19.
- 109 Hannawi S, Haluska B, Marwick TH, *et al.* Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. *Arthritis Res Ther* 2007;9:R116.
- 110 Evans MR, Escalante A, Battafarano DF, *et al.* Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2011;63:1211–20.
- 111 del Rincón I, Freeman GL, Haas RW, *et al.* Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. *Arthritis Rheum* 2005;52:3413–23.
- 112 Semb AG, Rollefstad S, Provan SA, *et al.* Carotid plaque characteristics and disease activity in rheumatoid arthritis. *J Rheumatol* 2013;40:359–68.
- 113 Wällberg-Jonsson S, Ohman M, Rantapää-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid arthritis? *Scand J Rheumatol* 2004;33:373–9.
- 114 Corrales A, González-Juanatey C, Peiró ME, *et al.* Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis* 2014;73:722–7.
- 115 van den Berg MH, de Boer IG, le Cessie S, *et al.* Are patients with rheumatoid arthritis less physically active than the general population? *J Clin Rheumatol* 2007;13:181–6.
- 116 Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, *et al.* Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *Eur J Cardiovasc Prev Rehabil* 2009;16:188–94.
- 117 Hernández-Hernández V, Ferraz-Amaro I, Díaz-González F. Influence of disease activity on the physical activity of rheumatoid arthritis patients. *Rheumatology (Oxford)* 2014;53:722–31.
- 118 Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, *et al.* Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:748–51.
- 119 Lemmey AB, Marcora SM, Chester K, *et al.* Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. *Arthritis Rheum* 2009;61:1726–34.
- 120 Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, *et al.* Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1819–25.
- 121 Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002;13:561–8.
- 122 Estruch R, Ros E, Salas-Salvado J, *et al.* Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
- 123 Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis* 2003;62:208–14.
- 124 Iversen MD, Hammond A, Betteridge N. Self-management of rheumatic diseases: state of the art and future perspectives. *Ann Rheum Dis* 2010;69:955–63.
- 125 John H, Hale ED, Trehan GJ, *et al.* A randomized controlled trial of a cognitive behavioural patient education intervention vs a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease. *Rheumatology (Oxford)* 2013;52:81–90.
- 126 Chung CP, Giles JT, Petri M, *et al.* Prevalence of traditional modifiable cardiovascular risk factors in patients with rheumatoid arthritis: comparison with control subjects from the multi-ethnic study of atherosclerosis. *Semin Arthritis Rheum* 2012;41:535–44.
- 127 Protogerou AD, Panagiotakos DB, Zampeli E, *et al.* Arterial hypertension assessed “out-of-office” in a contemporary cohort of rheumatoid arthritis patients free of cardiovascular disease is characterized by high prevalence, low awareness, poor control and increased vascular damage-associated “white coat” phenomenon. *Arthritis Res Ther* 2013;15:R142.
- 128 Baghdadi LR, Woodman RJ, Shanahan EM, *et al.* The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLoS ONE* 2015;10:e0117952.
- 129 Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, *et al.* Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2008;47:72–5.
- 130 Kellner H, Bornholdt K, Hein G. Leflunomide in the treatment of patients with early rheumatoid arthritis—results of a prospective non-interventional study. *Clin Rheumatol* 2010;29:913–20.
- 131 Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. *Cardiol Rev* 2011;19:184–91.
- 132 Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. *Cochrane Database Syst Rev* 2010;(1):CD007893.
- 133 De Vera MA, Choi H, Abrahamowicz M, *et al.* Impact of statin discontinuation on mortality in patients with rheumatoid arthritis: a population-based study. *Arthritis Care Res (Hoboken)* 2012;64:809–16.
- 134 Rollefstad S, Ik Dahl E, Hisdal J, *et al.* Systemic inflammation in patients with inflammatory joint diseases does not influence statin dose needed to obtain LDL cholesterol goal in cardiovascular prevention. *Ann Rheum Dis* 2015;74:1544–50.
- 135 Semb AG, Kvien TK, DeMicco DA, *et al.* Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis Rheum* 2012;64:2836–46.
- 136 Sheng X, Murphy MJ, MacDonald TM, *et al.* The comparative effectiveness of statin therapy in selected chronic diseases compared with the remaining population. *BMC Public Health* 2012;12:712.
- 137 Rollefstad S, Kvien TK, Holme I, *et al.* Treatment to lipid targets in patients with inflammatory joint diseases in a preventive cardio-rheuma clinic. *Ann Rheum Dis* 2013;72:1968–74.
- 138 Rollefstad S, Ik Dahl E, Hisdal J, *et al.* Rosuvastatin-induced carotid plaque regression in patients with inflammatory joint diseases: the rosuvastatin in rheumatoid arthritis, ankylosing spondylitis and other inflammatory joint diseases study. *Ann Rheum Dis* 2015;74:1718–28.
- 139 McCarey DW, McInnes IB, Madhok R, *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet* 2004;363:2015–21.
- 140 Cojocararu L, Rusali AC, Suta C, *et al.* The role of simvastatin in the therapeutic approach of rheumatoid arthritis. *Autoimmune Dis* 2013;2013:326258.
- 141 Lv S, Liu Y, Zou Z, *et al.* The impact of statins therapy on disease activity and inflammatory factor in patients with rheumatoid arthritis: a meta-analysis. *Clin Exp Rheumatol* 2015;33:69–76.
- 142 Mäki-Petäjä KM, Booth AD, Hall FC, *et al.* Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. *J Am Coll Cardiol* 2007;50:852–8.
- 143 Cragg MS. The potential effect of statins on rituximab immunotherapy. *PLoS Med* 2008;5:e77.
- 144 Winiarska M, Bil J, Wilczek E, *et al.* Statins impair antitumor effects of rituximab by inducing conformational changes of CD20. *PLoS Med* 2008;5:e64.
- 145 Ennishi D, Asai H, Maeda Y, *et al.* Statin-independent prognosis of patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP therapy. *Ann Oncol* 2010;21:1217–21.

- 146 Koo YX, Tan DS, Tan IB, *et al.* Effect of concomitant statin, metformin, or aspirin on rituximab treatment for diffuse large B-cell lymphoma. *Leuk Lymphoma* 2011;52:1509–16.
- 147 Nowakowski GS, Maurer MJ, Habermann TM, *et al.* Statin use and prognosis in patients with diffuse large B-cell lymphoma and follicular lymphoma in the rituximab era. *J Clin Oncol* 2010;28:412–17.
- 148 Samaras P, Heider H, Haile SR, *et al.* Concomitant statin use does not impair the clinical outcome of patients with diffuse large B cell lymphoma treated with rituximab-CHOP. *Ann Hematol* 2010;89:783–7.
- 149 Das S, Fernandez Matilla M, Dass S, *et al.* Statins do not influence clinical response and B cell depletion after rituximab treatment in rheumatoid arthritis. *Ann Rheum Dis* 2013;72:463–4.
- 150 Lehane PB, Lacey S, Hessey EW, *et al.* Effect of concomitant statins on rituximab efficacy in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:1906–8.
- 151 Mazilu D, Gudu T, Ionescu R, *et al.* Statins do not influence long-term rituximab clinical efficiency in rheumatoid arthritis patients. *Biomed Res Int* 2014;2014:689426.
- 152 Arts EE, Jansen TL, Den Broeder A, *et al.* Statins inhibit the antirheumatic effects of rituximab in rheumatoid arthritis: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Ann Rheum Dis* 2011;70:877–8.
- 153 Pharmacovigilance Risk Assessment Committee (PRAC). New safety advice for diclofenac—CMDh endorses PRAC recommendation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001830.jsp&mid=WC0b01ac058004d5c1.
- 154 Pharmacovigilance Risk Assessment Committee (PRAC). PRAC recommends updating advice on use of high-dose ibuprofen. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002306.jsp&mid=WC0b01ac058004d5c1
- 155 van den Berg R, Baraliakos X, Braun J, *et al.* First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Rheumatology (Oxford)* 2012;51:1388–96.
- 156 Ajeganova S, Svensson B, Hafström I. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. *BMJ Open* 2014;4:e004259.
- 157 Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, *et al.* Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. *Rheumatology (Oxford)* 2013;52:68–75.
- 158 Greenberg JD, Kremer JM, Curtis JR, *et al.* Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:576–82.
- 159 Aviña-Zubieta JA, Abrahamowicz M, Choi HK, *et al.* Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study. *Ann Rheum Dis* 2011;70:990–5.
- 160 Nadareishvili Z, Michaud K, Hallenbeck JM, *et al.* Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. *Arthritis Rheum* 2008;59:1090–6.
- 161 van Sijl AM, Boers M, Voskuyl AE, *et al.* Confounding by indication probably distorts the relationship between steroid use and cardiovascular disease in rheumatoid arthritis: results from a prospective cohort study. *PLoS ONE* 2014;9:e87965.
- 162 Solomon DH, Greenberg J, Curtis JR, *et al.* Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. *Arthritis Rheumatol* 2015;67:1995–2003.
- 163 Wiersma T, Smulders YM, Stehouwer CD, *et al.* [Summary of the multidisciplinary guideline on cardiovascular risk management (revision 2011)]. *Ned Tijdschr Geneesk* 2012;156:A5104.
- 164 Ray KK, Kastelein JJ, Boekholdt SM, *et al.* The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J* 2014;35:960–8.