Cardiovascular risk in Rheumatoid Arthritis and other inflammatory disorders

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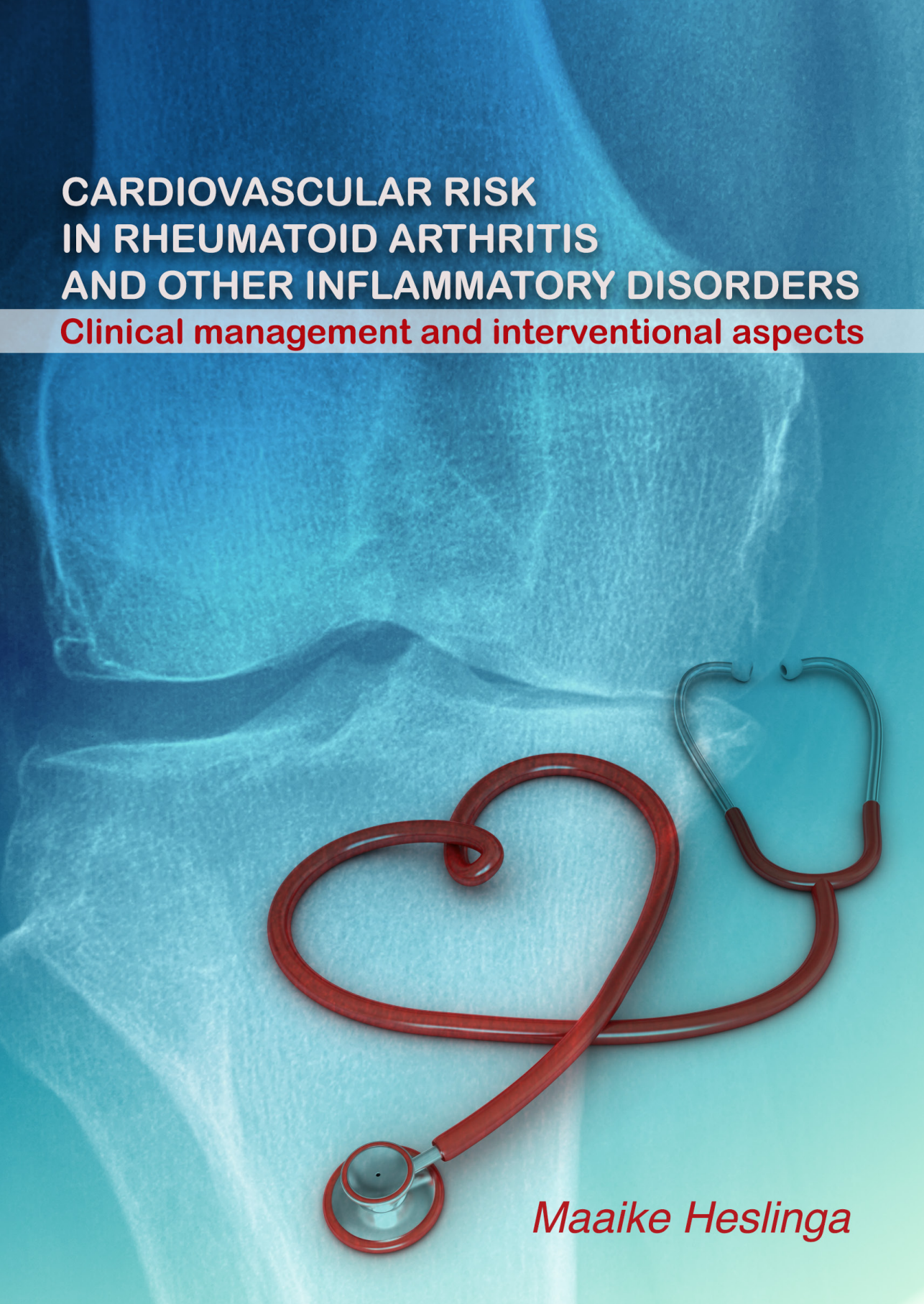
Clinical management and interventional aspects



Maaike Heslinga

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Clinical management and interventional aspects

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General introduction and thesis outline

Nurmohamed MT, Heslinga M, Kitas GD

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GENERAL INTRODUCTION

Compared with the general population, patients with rheumatic diseases are at increased risk of developing several comorbid conditions, of which cardiovascular comorbidities are the most common and have the greatest effect on mortality(1). The epidemiology and pathogenesis of cardiovascular comorbidities in inflammatory joint diseases (IJDs) are particularly well-studied for rheumatoid arthritis (RA), but have also been investigated for rheumatic diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE). Growing awareness of this increased cardiovascular risk has led to several efforts to unravel the underlying mechanisms, especially in RA. The elevated risk is only partly explained by increased prevalence of traditional cardiovascular risk factors such as age, gender, dyslipidaemia, hypertension, smoking, obesity and diabetes mellitus; systemic inflammation, genetic factors and treatment effects might also have important roles (Figure 1). Pathogenic mechanisms and clinical expression of cardiovascular comorbidities vary greatly between different rheumatic diseases, but atherosclerosis seems to be a shared factor in all IJDs.

A logical consequence of the increased awareness of cardiovascular comorbidity in rheumatic disease is a shift from its recognition towards prevention and treatment. Development of cardiovascular risk assessment models in patients with IJD has been attempted, and more evidence is emerging of the effects of rheumatological and cardiovascular treatments on cardiovascular risk and outcomes. However, despite these advances, much remains to be learned in this field.

Rheumatoid arthritis and cardiovascular disease burden

Patients with RA have an increased risk of premature death compared with the general population(2). The main cause for this increase in mortality is cardiovascular disease. Several observational cohort studies have examined the magnitude of the increased risk by studying the occurrence of cardiovascular events in patients with rheumatic diseases. In a meta-analysis (1), an overall 48% (pooled RR 1.48, 95% CI 1.36–1.62) increased risk for incident cardiovascular disease was observed in patients with RA, compared with the general population. The results of a prospective study of a Dutch RA cohort suggested that the magnitude of the cardiovascular risk increase in RA (around twofold) is similar to that observed in patients with type 2 diabetes (3). This finding was corroborated by the results of a Danish nationwide study (4) and attributed to a similar rate of acceleration of atherosclerosis in these two conditions (5). In patients with RA the increased risk of myocardial infarction

(MI) is greater (around 68%) than that of cerebrovascular accident (around 41%), compared to persons without RA (6-8). In addition, an 87% increased risk of congestive heart failure in RA was observed, mostly in rheumatoid-factor-positive patients, but whether this level of risk would exist in contemporary RA cohorts is unclear. Evidence derived from observational studies suggests that effective control of inflammation - either with biologic or nonbiologic DMARDs, particularly anti-TNF agents and methotrexate - is associated with reduction of cardiovascular disease risk (9). Although developments in therapeutic strategies in the past decades are reflected by a decline in mortality rates, the mortality gap between patients with RA and the general population has not improved, demonstrating that cardiovascular disease is still a major issue in these patients (10).

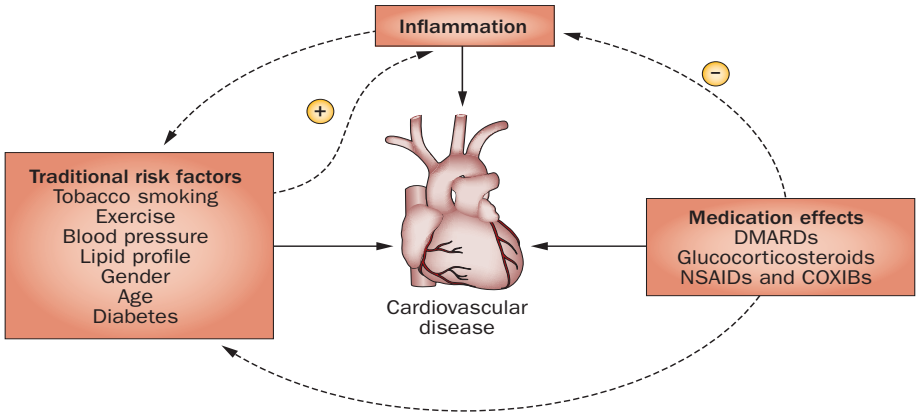

Figure 1 | Contributors to cardiovascular risk in IJDs. Patients with IJDs have increased risk of cardiovascular disease compared with the general population, mainly resulting from traditional risk factors and inflammation. Traditional cardiovascular risk factors include age, gender, dyslipidaemia, hypertension, smoking, obesity, lack of exercise and diabetes mellitus. Medication can affect cardiovascular risk by targeting inflammation, but can also have undesired effects—glucocorticosteroids, for example, are associated with dyslipidaemia, hypertension, hyperglycaemia, and osteoporosis. Inflammation can modify some traditional risk factors, the best-known example being the influence on lipid profile. Abbreviations: COXIB, cyclooxygenase-2 selective inhibitor; IJD, inflammatory joint disease.

Contributions of known risk factors

Traditional risk factors are important contributors to the cardiovascular risk in the general population as well as in patients with IJD. Despite this fact, when

adjusting for traditional risk factors, the absolute cardiovascular risk for patients with RA is still increased when compared with the general population. As such, RA (and possibly other IJDs) is an independent risk factor for cardiovascular disease. Traditional cardiovascular risk factors contribute to the excess cardiovascular disease seen in IJD, albeit in a different way than in the general population.

Cholesterol

Cholesterol is an example of a risk factor with specific characteristics in patients with RA. Hypercholesterolaemia is an important risk factor for cardiovascular disease in the general population. However, assessment of cholesterol is complicated in patients with RA. Several studies have evaluated lipid profiles in patients with IJDs, especially RA (11), and the overall consensus is that active inflammation in RA leads to a decline in levels of total cholesterol, LDL cholesterol, and HDL cholesterol compared with individuals without RA (12). The greatest suppression occurs in levels of HDL cholesterol, leading to an unfavourable lipid profile. This 'lipid paradox', where lower lipid levels are associated with higher cardiovascular risk, has also been reported in other inflammatory diseases (13). The lipid paradox in RA could be explained by modification of lipids by inflammation, which not only lowers lipid levels, but also alters lipid structure and function, changing the usual antiatherogenic effects of HDL cholesterol into proatherogenic effects (14). In the context of cardiovascular risk assessment in patients with RA, measurement of the ratio of total cholesterol to HDL cholesterol is recommended in clinical practice, and it might be reasonable to suggest that lipid measurements during inactive stages of the disease are the most representative of the overall situation in a given patient. Evidence suggests that lipid-lowering (statin) therapy is substantially underutilized in patients with RA who fulfil the general population thresholds for this treatment and could have adverse consequences in terms of cardiovascular outcome (15).

Cigarette smoking

Smoking is a known environmental risk factor for RA, and a higher prevalence of smokers has been observed in patients with RA than in matched controls without RA (16). In RA, smoking is associated with both inflammation (17) and factors that are predictive of cardiovascular outcome, such as rheumatoid factor and anti-citrullinated protein antibody (ACPA) positivity, rheumatoid nodules, lower response to anti-TNF treatment and rheumatoid cachexia (18-22). These interacting mechanisms make it difficult to determine the contribution of smoking to cardiovascular risk in this population, raising the question of whether population-

based risk-prediction models are also applicable to patients with IJD.

Hypertension

The reported prevalence of hypertension in patients with RA ranges between 4 and 73% (23). In a meta-analysis no difference was found in the prevalence of hypertension between 2,956 patients with RA and 3,713 matched controls (OR 1.09, 95% CI 0.91–1.31) (24). In contrast, in a study designed to evaluate hypertension associated with RA, the prevalence of hypertension was substantially higher in individuals with RA than in matched controls (25). The results of the international, cross-sectional COMORA study showed that hypertension is prevalent in 40% of patients with RA, although interpretation of this value is hampered by the lack of a control population (26). Nowadays, mean asleep systolic blood pressure and sleep-time relative systolic blood pressure decline are the most significant predictors of CVD events (27), and some studies have performed 24-hour ambulatory blood pressure monitoring in RA patients. One of these studies found no difference in 24-hour blood pressure patterns, including nocturnal blood pressure decline (28), but there is evidence that this is outcome is related to disease activity and use of anti-rheumatic medication. Nevertheless, hypertension is both underdiagnosed and undertreated in patients with RA.

Diabetes and insulin resistance

The association between RA and insulin resistance is strongly supported by the results of many studies (29-31), and is most likely mediated by inflammation, because insulin resistance correlates with levels of markers of inflammation and disease activity. Insulin resistance often precedes diabetes, and diabetes is more prevalent in RA compared to controls (32). Control of inflammation with potent anti-inflammatory therapies, such as anti-TNF agents, seems to reverse insulin resistance (33). Anti-inflammatory agents can also be effective in preventing diabetes, and in a study of patients with RA or psoriasis, the risk of new diabetes was lower for individuals initiating therapy with a TNF inhibitor or hydroxychloroquine compared with other (nonbiologic) DMARDs (34).

Thyroid disease

Coexistence of autoimmune hypothyroidism with RA can affect cardiovascular risk. Among patients with RA, those with hypothyroidism have an increased cardiovascular risk compared with those having normal thyroid function (35). This effect of hypothyroidism has traditionally been attributed to impaired vascular endothelial function, hypertension and adverse effects on lipid profiles.

In patients with RA, the presence of thyroid peroxidase (TPO) antibodies, which is strongly predictive of autoimmune hypothyroidism, is associated with greater cIMT progression (36). This association suggests that assessment of thyroid function and the TPO antibodies is important in the context of cardiovascular risk management in patients with IJD.

Inflammation and cardiovascular risk

In addition to traditional risk factors, inflammation is an important, independent, contributor to cardiovascular risk. The link was first established in the general population, where C-reactive protein (CRP) levels are associated with cardiovascular risk (37). In patients with IJD, markers of active inflammation, including levels of CRP, erythrocyte sedimentation rates, numbers of affected joints and disease activity scores, as well as disease severity or cumulative inflammation (estimated by radio graphic scores), have all been linked to cardiovascular risk (38-43). IJDs and atherosclerosis are considered to have an inflammatory pathogenesis, in which the mechanisms of formation, progression, instability and rupture of the atherosclerotic plaque resemble the mechanisms observed in synovitis (44) (Figure 2). Although high-grade systemic inflammation seems to be central to the cardiovascular risk in patients with IJD (Figure 3), the interaction between inflammation, traditional risk factors, genetic factors and medication effects has not yet been fully elucidated.

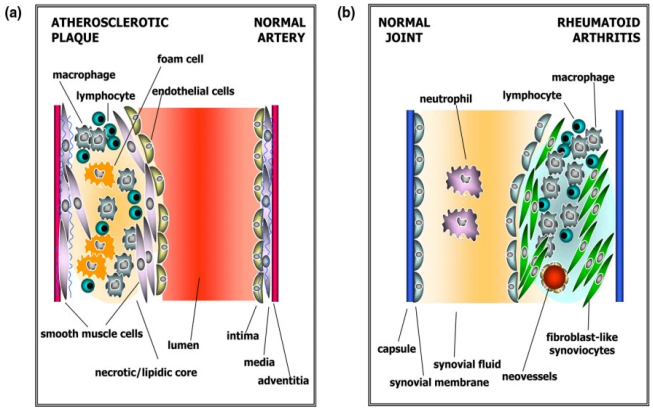

Figure 2 | Similarities between the atherosclerotic plaque and rheumatoid arthritis joint. The (a) atherosclerotic plaque has many features in common with (b) rheumatoid arthritic synovium. First, in both diseases, blood-borne mononuclear cells are recruited to sites that are devoid of any significant inflammation in physiological conditions. Second, upregulation of cytokines and matrix-degrading enzymes is central to the pathogenesis of both diseases.

Third, both in rheumatoid arthritis and atherosclerosis, immune cells do not target resident cells in the same way that diabetogenic T cells directly destroy pancreatic islets. Instead, immune cells begin complex interactions with the resident cell types, which proliferate, change their properties and phenotype, and contribute to the inflammatory process and tissue destruction. *Adapted from: Full, L.E., Ruisanchez, C. & Monaco, C. The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther 11, 217 (2009).* https://doi.org/10.1186/ar2631

Effects on prothrombotic phenomena

The immune and coagulation systems are closely linked: inflammatory cytokines induce expression of tissue factor, inhibit the protein C system and act as inhibitors of fibrinolysis, promoting a hypercoagulable state (45). Platelets are important factors in normal homeostasis and also have a role in inflammation with the release of a range of thrombotic and inflammatory molecules; the adhesion and aggregation of platelets are key to the processes that occur at the onset of MI after plaque rupture (46). Although data relating to venous thrombotic events in IJDs are scarce, it seems that the risks of pulmonary embolism and deep-vein thrombosis are increased in patients with RA when compared with the general population (47).

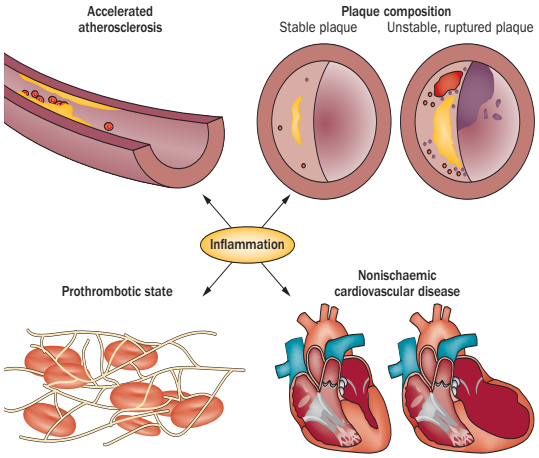

Figure 3 | Contribution of inflammation to cardiovascular disease. Rheumatic inflammation is thought to be a major contributor to accelerated atherosclerosis. IJD is associated with frequency, severity and vulnerability of coronary plaques. Patients with IJD have higher risk of infarction after plaque rupture than individuals without IJD, because of a hypercoagulable state induced by inflammation. Nonischaemic heart disease like myocarditis, heart failure

and myocardial dysfunction also contributes to the burden of cardiovascular disease in IJD. Abbreviation: IJD, inflammatory joint disease.

Predicting cardiovascular risk in IJD

Risk-prediction models

The well-established cardiovascular risk in patients with RA, and to a lesser extent in other IJDs, implies that cardiovascular risk assessment should be part of routine care in these patients. Clinicians should be able to identify those patients at highest risk, to adapt their management accordingly. Unfortunately, cardiovascular risk in patients with RA is still underestimated in clinical practice (48), and despite improvements in the understanding of the risk and the recommendations given by the European League Against Rheumatism (EULAR) Task Force, the management of cardiovascular risk remains unsatisfactory (49). In the past 12 years, several algorithms have been developed to aid the prediction of risk for cardiovascular disease, such as the Framingham Risk Score, the Reynolds Risk Score, QRISK®3 and SCORE (50-54). These risk models are largely based on longitudinal cohort studies performed in the general population, raising the question of whether they can also be of use in patients with IJD. QRISK®3 was developed in a population that included patients with RA, and RA is an independent risk factor in the algorithm. The Reynolds Risk score incorporates CRP levels, but not within the range seen in high-grade inflammatory diseases. None of these risk models takes into account the influence of inflammation and antirheumatic medication on lipids and other classic risk factors, nor considers systematic differences between IJD populations (which are predominantly female, with restricted age ranges) and the general population. Some attempts have been made to address these problems. For instance, the EULAR Task Force has recommended adapting risk models when calculating cardiovascular risk in patients with RA by incorporating a multiplication factor of 1.5 (55). The 2012 ESC guidelines (56), as well as QRISK®3, incorporate RA as an independent cardiovascular risk factor in their models, although in the ESC recommendations presence of RA has no influence on clinical management, in contrast to QRISK®3. However, neither of these approaches seems to improve accuracy in estimates of cardiovascular risk in patients with IJD relative to models that do not include RA (57, 58), and risk-stratification models for this group of patients require improvement. The 2013 guidelines of the joint task force of the American College of Cardiology (ACC) and American Heart Association (AHA) used the novel Pooled Cohort Equations to calculate the 10-year risk of atherosclerotic cardiovascular disease (59). Compared with previous

guidelines, in patients with RA, this calculation considerably increased the number who would be recommended for cholesterol-lowering statin treatment, but did not improve prediction of cardiovascular risk (60, 61). Patients with RA often suffer from asymptomatic atherosclerosis and silent ischaemic disease in the presence of an unstable plaque, which can lead to sudden death (62). An early diagnosis of atherosclerosis, before the onset of clinically evident cardiovascular disease, can enable earlier and more aggressive primary prevention measures. Imaging studies and specific biomarkers could potentially help with early diagnosis. Alternatively, IJD-specific risk-prediction models might not be necessary if an approach of 'blanket primary prevention' of specific lipid and blood-pressure targets was taken in all patients with IJD, similar to the practice associated with diabetes (56). Whereas such an approach would be simpler than developing specific models, its safety, effectiveness and cost-effectiveness in these populations would need to be formally assessed.

Biomarkers

In addition to imaging techniques, the value of a number of biomarkers in cardiovascular-risk prediction has been investigated, at least in the general population. These biomarkers include genetic factors, markers of inflammation, immunological markers and markers of endothelial function (5). Serum uric acid levels have associations with hypertension, renal dysfunction and cardiovascular disease in patients with RA, in the general population and in other at-risk populations, but it remains unclear whether they reflect specific pathogenic pathways or are epiphenomena (63). Researchers have evaluated the utility of B-type natriuretic peptide as a marker for cardiovascular risk in the presence of rheumatic disease (64). The use of biomarkers in risk-prediction models to improve cardiovascular risk stratification was demonstrated in a large European population wherein additional measurement of the combination of N-terminal pro-brain natriuretic peptide, CRP and troponin I led to an improved 10-year-risk estimation, compared with a conventional-risk-factor model alone (65). The value of these biomarkers for risk prediction in the presence of IJDs is not known. A difficulty in the assessment of this value is that the influence of IJD activity and treatment on biomarker levels has not yet been determined. Another issue is that, whereas in the general population large sample sizes are available, IJD cohorts are much smaller, making it more difficult to validate biomarkers against specific end points (such as MI), meaning that international collaborations are likely to be required in this field.

Cardiovascular risk management

Cardiovascular risk assessment provides opportunities for disease prevention. From the perspective of the rheumatologist, management of cardiovascular comorbidity of patients with IJD has three main principles: pharmacological management and nonpharmacological management of cardiovascular risk factors, and tight control of disease activity (Figure 4). Unfortunately, the risk of cardiovascular disease in patients with RA is still not fully recognized, and these patients receive preventive measures less often than the general population.

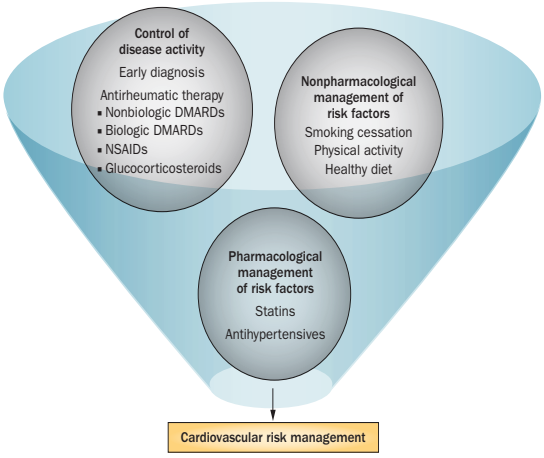

Figure 4 | Principles of cardiovascular risk management by rheumatologists. From the perspective of the rheumatologist, the management of cardiovascular comorbidity of patients with IJD has three main principles. Pharmacological management of cardiovascular risk factors includes medication to control blood pressure and lipid levels. Nonpharmacological management of cardiovascular risk factors includes lifestyle interventions such as cessation of tobacco smoking and engagement in regular physical activity. Control of disease activity consists of strategies to control the chronic systemic inflammation in IJD, by means of DMARDs, NSAIDs, cyclooxygenase-2 selective inhibitors and glucocorticosteroids. Abbreviations: IJD, inflammatory joint disease.

Lifestyle interventions

Lifestyle interventions should be the first steps in cardiovascular risk management, and patients should be advised to quit tobacco smoking and to engage in regular physical activity. Evidence pertaining to lifestyle interventions demonstrates that exercise has several cardiovascular benefits in patients with RA. Structured

exercise therapy improves microvascular and macrovascular function and cardiorespiratory fitness, and decreases cardiovascular risk (66). Although data on exercise are emerging, data on dietary interventions are still sparse.

Pharmacological interventions

In the general population, and also in patients with diabetes, preventive measures such as lowering blood pressure and lipid levels are effective in reducing the burden of cardiovascular disease (67). Whether these measures are also beneficial for patients with IJD has not yet been studied sufficiently, although, notably, it seems that statins have a moderate anti-inflammatory effect in RA (68). Large, randomized, controlled trials are necessary to compare the effects of preventive measures, with cardiovascular disease outcomes as end points. Such trials require large numbers of patients and several years of follow-up observation, and are very difficult to conduct in populations of patients with IJDs. Despite the limited availability of evidence relating to the management of traditional risk factors in patients with rheumatic diseases, wide-ranging support exists for the practice of offering cardiovascular risk management to all patients meeting the criteria set for risk reduction in the general population. This strategy would require that all patients with IJD are screened regularly, and when an increase in risk is identified, patients should be managed accordingly. However, the key question remains who is responsible for the preventive care of this group of patients. In most countries, primary-care physicians carry out cardiovascular risk management. Currently, awareness of the high risk in this group of patients is inadequate among all health-care professionals, from primary-care physicians to cardiologists and even rheumatologists. Therefore, achieving adequate awareness is an important objective, which should lead to appropriate cardiovascular risk screening and preventive measures.

Control of disease activity

Tight disease control is thought to improve all outcomes in IJDs, including cardiovascular outcomes, although randomized trials investigating cardiovascular outcomes in this disease management approach are lacking. Chronic systemic inflammation contributes substantially to the cardiovascular risk associated with IJDs, and adequate suppression of disease activity is necessary to reduce this risk. This goal can be achieved by early diagnosis and treatment of IJDs. However, from the cardiovascular point of view, the best way to control inflammation is unknown. Several DMARDs are available for treatment of IJDs, and although they might all decrease cardiovascular risk by reducing inflammation, other possible

cardioprotective or deleterious properties are also important to consider. The influence of antirheumatic therapies on lipid levels has received particular attention because of the interaction between lipids and inflammation, although the clinical relevance of this influence is uncertain. Notably, all the available evidence relating to the effects of antirheumatic therapy on cardiovascular disease is derived from observational studies, and caution is required when making conclusions on the basis of this evidence, due to potential bias.

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THESIS OUTLINE

The focus of part I of this thesis is on cardiovascular risk and its management. **Chapter two** consists of recommendations on cardiovascular risk management from the European League Against Rheumatism (EULAR) taskforce. In these recommendations are defined to provide assistance in CVD risk management in IJD, based on expert opinion and scientific evidence. **Chapter three and four** contain the results from the I-CaRe study in with the cardiovascular risk profile of patients with rheumatoid arthritis was assessed in order to optimize cardiovascular risk management in these patients. In **chapter five** we examined the differences in cardiovascular risk when calculated with different risk models at different times in the course of the disease; that is before and after treatment with anti-rheumatic drugs. Not only patients with RA suffer from a higher cardiovascular burden, but also patients with other inflammatory autoimmune disorders, such as psoriasis and IBDs (e.g. Crohn's disease and ulcerative colitis), especially when more autoimmune disorders co-exist. Therefore, in **chapter six** we assessed the prevalence proportion and incidence rate of cardiovascular morbidity in patients with inflammatory arthritis and co-existent autoimmune disorders. As autoimmune thyroid disease often coexists with rheumatoid arthritis, we investigated in **chapter seven** whether RA patients with thyroid dysfunction have an increased risk of new cardiovascular disease compared to euthyroid RA patients.

Part II outlines the effects of different treatment regiments on cardiovascular outcomes or markers. **Chapter eight** describes the associations between the biomarkers NT-proBNP and sRAGE with disease activity in early RA patients before and during antirheumatic treatment.. In **chapter nine** the effects of etanercept on lipid metabolism and other cardiovascular risk factors in patients with psoriatic arthritis are investigated in an observational cohort. **Chapter ten** describes the changes that occur in markers of coagulation and fibrinolysis in patients with AS starting golimumab treatment. **Chapter eleven** summarizes the findings of the different chapters and offers implications for further research.

PART 1
CARDIOVASCULAR RISK AND MANAGEMENT

CHAPTER 2
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 Framingham (5) 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 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 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).

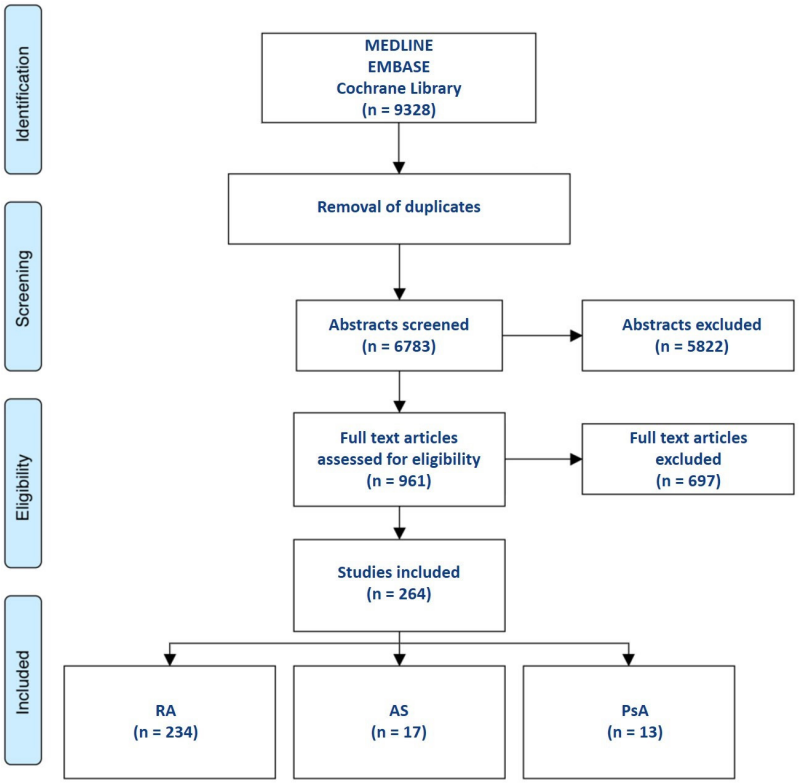

Figure 1 | Flow chart of the search process. RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis.

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 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), diabetes mellitus (19) 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 (36–38) on stroke are more conflicting (34). 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.

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–D	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)

table continues

		Level of evidence	Strength of recommendation	Level of agreement (SD)
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.

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 (63–65), and CVD risk in a limited number of studies (54). 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 ≥5% and <10%) and very high risk (eg, SCORE ≥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 (133–139) when compared with non-RA controls (77). 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 (89). 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 years (163) 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 extraarticular 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 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?

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CHAPTER 3
Cardiovascular risk management in rheumatoid arthritis patients still suboptimal: the Implementation of Cardiovascular Risk Management in Rheumatoid Arthritis project

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ABSTRACT

Objective
To assess the 10-year cardiovascular (CV) risk score and to identify treatment and undertreatment of CV risk factors in patients with established RA.

Methods
Demographics, CV risk factors and prevalence of cardiovascular disease (CVD) were assessed by questionnaire. To calculate the 10-year CV risk score according to the Dutch CV risk management guideline, systolic blood pressure was measured and cholesterol levels were determined from fasting blood samples. Patients were categorized into four groups: indication for treatment but not treated; inadequately treated, so not meeting goals (systolic blood pressure 4140mmHg and/or low-density lipoprotein 42.5 mmol/l); adequately treated; or no treatment necessary.

Results
A total of 720 consecutive RA patients were included, 375 from Reade and 345 from the Antonius Hospital. The mean age of patients was 59 years (S.D. 12) and 73% were female. Seventeen per cent of the patients had a low 10-year CV risk (<10%), 21% had an intermediate risk (1019%), 53% a high risk (520%) and 9% had CVD. In total, 69% had an indication for preventive treatment (cholesterollowering or antihypertensive drugs). Of those, 42% received inadequate treatment and 40% received no treatment at all.

Conclusion
Optimal CV risk management remains a major challenge and better awareness and management are urgently needed to reduce the high risk of CVD in the RA population.

INTRODUCTION

Patients with RA have an increased risk of premature death compared with the general population, mainly because of the risk of cardiovascular disease (CVD) [1, 2]. The CV risk of patients with RA is comparable to the risk of patients with type 2 diabetes mellitus (DM) [3, 4]. In addition to CV mortality, non-fatal CVD, such as myocardial infarction, cerebrovascular accidents and heart failure (HF) are more common in RA [5]. Several determinants contribute to this increased risk, including traditional CV risk factors such as age, gender, dyslipidaemia, hypertension, smoking, obesity and DM, however, these factors only partially explain the excess CV risk [6, 7]. In addition to traditional risk factors, systemic inflammation is an important independent contributor to CV risk in RA [8, 9]. Another explanation for the increased CV risk is that in RA (traditional), CV risk factors are undertreated, as comorbidity in patients with a chronic disease is often undertreated [10]. However, details of undertreatment in RA are sparse. In light of the strong evidence that the CV risk in RA is of the same order of magnitude as that in type 2 DM, the Dutch cardiovascular risk management (CV-RM) guideline considers RA, like type 2 DM, an independent risk factor for CVD, for which CV-RM is necessary [11]. Evidence on (pharmacological) management of traditional CV risk factors in patients with rheumatic diseases is limited, but there are no indications that the effects of statins or antihypertensives in RA would be different than in the general population [1216], thus CV-RM should be offered to all patients meeting the criteria set for risk reduction in the general population [17]. However, implementation of CV risk screening is still a challenge [18]. This strategy requires that all patients with RA, like patients with type 2 DM and/or CVD, are screened regularly (yearly) and CV risk managed accordingly. Since 2011, Implementation of Cardiovascular Risk Management in Rheumatoid Arthritis (I-CaRe) has offered CV risk screening to RA patients visiting Reade, a rheumatology and rehabilitation centre in Amsterdam or Antonius Hospital in Sneek, a small city in the northern rural area of The Netherlands. The goal of this project was to assess the 10-year CV risk score and to identify treatment and undertreatment of CV risk factors in RA patients.

METHODS

Study population and design

For this prospective cross-sectional cohort study, consecutive RA patients visiting the outpatient rheumatology clinic of Reade or Antonius Hospital were included. All patients were 518 years of age and diagnosed by a rheumatologist according to the

1987 ACR criteria for RA [19]. There were no other exclusion criteria. All patients were asked to sign an informed consent according to the Declaration of Helsinki before study participation and the study was approved by the local ethics committees of Slotervaart Hospital/Reade and Antonius Hospital. CV risk screening comprised a questionnaire, physical examination, laboratory investigations and assessment of the 10-year CV risk according to the Dutch CV-RM guideline.

Patient characteristics

Information on age, gender, smoking, disease history (with a special focus on CVD), CV risk factors and CV preventive medication use (including antihypertensive medication, statins, antidiabetic medication and anticoagulants), RA-related factors, disease duration, RF and ACPA positivity and the presence of erosive disease were collected from the medical files. Assessment of current anti-inflammatory medication included use of NSAIDs, DMARDs and corticosteroids.

CV risk and disease definitions

CVD history was defined as a history of coronary heart disease (including angina pectoris, myocardial infarction, percutaneous coronary intervention and coronary artery bypass surgery), HF, cerebral vascular disease [including ischaemic stroke (cerebrovascular accidents), transient ischaemic attack and carotid endarterectomy] and peripheral arterial disease. This was asked by questionnaire but also checked afterwards in the medical files to verify that the diagnosis was confirmed by a specialist (cardiologist, neurologist or vascular specialist). CV risk factors included self-reported DM, self-reported hypertension and/or the use of antihypertensives, self-reported hypercholesterolaemia and/or the use of statin therapy and smoking status assessed by the questionnaire or the presence of high blood pressure [systolic blood pressure (SBP) >140mmHg] or high cholesterol [low-density lipoprotein (LDL) >2.5 or total cholesterol (TC):high-density lipoprotein (HDL) ratio >8] measured during the physical examination. Overweight was defined as a BMI 525 kg/m2 and obesity as a BMI 530 kg/m2.

Physical examination

Specially trained and experienced research nurses performed a physical examination, including blood pressure, waist and hip circumference, height and weight. Blood pressure was measured twice (left and right) in a sitting position after 5 min of rest. Waist circumference was measured at the level of the navel and hip circumference at the level of the trochanter major of the hip bone (widest circumference). The waist:hip ratio comprised the ratio of these two circumference

measurements. BMI was calculated from height and weight (clothed without shoes). RA was assessed by the 28-joint DAS (DAS28) [20] and physical functioning by the HAQ [21].

Laboratory tests

The glucose and lipid profile, including TC, triglycerides, HDL and LDL, were assessed in fasting blood samples using the standard techniques and the atherogenic index (TC:HDL ratio) was calculated. All the above tests were performed the same day that blood was drawn.

10-year CV risk calculation

The 10-year CV risk was calculated with the Dutch SCORE table, which uses gender, age, smoking status, SBP and the TC:HDL ratio [11]. To account for RA as a risk factor, the Dutch CV-RM guideline adds 15 years to the actual age in order to calculate 10-year CV risk. This is the same strategy that is used for the risk factor DM, since a large population-based cohort study showed that the vascular age of DM patients is 15 years greater than the vascular age of patients without DM [22] and other studies have shown that the CV risk of RA patients resembles that of DM patients [3, 5, 23, 24]. According to the Dutch CVRM guideline, we classified a risk of <10% as low, 10-20% as intermediate and 520% as high. Patients with a history of CVD were assessed separately, as a secondary prevention group. In high-risk patients and in intermediate-risk patients with a BMI 535 kg/m2, antihypertensive therapy is recommended when SBP is >140mmHg and/or statin therapy is recommended when LDL is >2.5 mmol/l. In patients with an intermediate or low 10-year CV risk the criteria are SPB >180 mmHg or TC:HDL ratio >8. After we calculated the 10-year CV risk, we categorized patients into four groups: untreated patients with an indication for treatment, inadequately treated patients (i.e. not meeting treatment goals, e.g. SBP 4140mmHg or LDL 42.5 mmol/l), adequately treated patients and untreated patients without an indication for treatment (i.e. no increased CV risk).

Statistical analysis

For the statistical analysis, SPSS version 22.0 (IBM, Armonk, NY, USA) was used. Patient characteristics were expressed as number and percentage [mean (S.D.)] when normally distributed or median (interquartile range) when not normally distributed. Independent t-tests were used to compare variables with a normal distribution. The Pearson chi-square test was performed on dichotomous variables. The threshold for significance was set at $P<0.05$ (two-sided).

RESULTS

Patient characteristics

From 2011 to 2015 a total of 720 consecutive RA patients underwent CV risk screening: 375 from Reade and 345 from Antonius Hospital. Patients from Antonius Hospital were more often male, older, had more prevalent CVD and more frequently were on statins and anticoagulant drugs (Table 1). In contrast, patients from Reade had longer RA disease duration, were more often RF and ACPA positive and had more active and erosive disease. In the Reade patients, biologic treatment was more frequent and glucocorticoid treatment less frequent.

Prevalence of CVD

A history of CVD was present in 61 (8%) patients, with a slightly higher prevalence in those from Antonius Hospital compared with Reade (10 vs 7%). The following conditions were present: coronary heart disease (n = 29), HF (n = 4), cerebrovascular disease (n = 29) and peripheral artery disease (n = 6). Of the men, 13% had a history of CVD vs 7% of women. Patients with a history of CVD were significantly older; more often diagnosed with DM, hypertension and hypercholesterolaemia and more often used antidiabetic drugs, antihypertensives, statins and anticoagulants, but less often NSAIDs compared with patients without CVD. They also had a higher waist:hip ratio, lower TC, lower HDL, lower LDL and higher fasting glucose levels versus patients without CVD (Table 1).

10-year CV risk assessment

The presence of high blood pressure and high cholesterol as measured during the CV risk screening as well as the mean 10-year CV risk score are shown in Table 2. A total of 125 (17%) patients had a low 10-year CV risk, 153 (21%) patients had an intermediate risk and 381 (53%) patients had a high risk (Fig. 1).

CV risk preventive treatment

In total, 500 patients (69%) had an indication to receive antihypertensives, statins or both (Fig. 2). Of those, 199 (40%) did not receive treatment at all and 212 (42%) were inadequately treated; the other 18% were adequately treated. A total of 419 patients had an indication for statin treatment; 270 patients (64%) did not use statins despite having an indication and 149 received treatment. Fifty per cent of them reached an LDL of <2.5. A total of 378 patients had an indication for antihypertensive treatment; 123 patients (33%) did not receive treatment, while 255 used antihypertensives. Fifty per cent of them reached an SBP <140 mmHg. Fig. 3 shows the numbers and percentages per CV risk group.

Table 1 | Characteristics of rheumatoid arthritis patients in Reade, Amsterdam and Antonius hospital, Sneek, with and without CVD

	All patients (n=720)	Amsterdam (n=375)	Sneek (n=345)	CVD (n=61)	no CVD (n=659)
Demographics					
Females, %	73	77	69*	59	74#
Age, years, mean (SD)	59±12	58±11	61±12*	68±8.5	59±11.7#
Cardiovascular disease history, %	8	7	10*	100	0
Cardiovascular risk factors, %					
Currently smoking	22	22	21	20	22
Hypercholesterolemia (self-reported)	33	38	28	54	32#
Hypertension (self-reported)	43	47	38	67	42#
Diabetes mellitus (self-reported)	6	6	6	18	5#
Cardiovascular preventive medication use, %					
Antihypertensives use	36	33	39	77	32#
Statins use	21	15	27*	66	17#
Anti-diabetics use	5	4	5	13	4#
Anticoagulants use	11	8	14*	77	5#
Disease characteristics					
Disease duration, years, mean (SD)	7 (2-14)	10 (5-18)	4 (2-9)*	9 (4-16)	7 (2-14)
RF positive, %	61	67	55*	60	63
ACPA positive, %	61	64	58*	64	66
Erosive disease, %	46	53	39*	58	46
Anti-inflammatory medication use, %					
NSAID use	36	36	37	21	38
Methotrexate use	68	70	65	73	68
Other DMARD use	24	20	28*	18	25
Biological use	36	59	12*	45	36
Corticosteroid use	24	18	30*	33	24
Physical examination					
Systolic blood pressure, mm/Hg	138±19	135±18	140±19*	141±19	137±19
Waist Hip Ratio, mean (SD)	0.91±0.09	0.91±0.09	0.91±0.09	0.93±0.07	0.91±0.09#
Body Mass Index, kg/m2	26.8±4.9	26.7±5.1	26.9±4.6	27.1±4.6	26.8±4.9
Disease activity score of 28 joints	2.44±1.15	2.65±1.22	2.20±1.02*	2.72±1.18	2.41±1.15
Laboratory tests, mean (SD)					

table continues

	All patients (n=720)	Amsterdam (n=375)	Sneek (n=345)	CVD (n=61)	no CVD (n=659)
Lipid profile					
Total cholesterol, mmol/l	5.3±1.0	5.5±1.0	5.1±1.1*	4.7±1.0	5.4±1.0#
Triglycerides, mmol/L	1.4±0.7	1.4±0.8	1.3±0.7*	1.5±1.0	1.3±0.7
LDL-cholesterol, mmol/l	3.1±0.9	3.2±0.9	3.0±0.9*	2.5±0.8	3.2±0.9#
HDL-cholesterol, mmol/l	1.6±0.5	1.6±0.5	1.6±0.4	1.5±0.4	1.6±0.5#
Total cholesterol/HDL-ratio	3.6±1.2	3.7±1.3	3.4±1.1*	3.4±1.1	3.6±1.2
Fasting glucose, mmol/l	5.5±1.5	5.6±1.7	5.5±1.2	6.0±1.9	5.5±1.4#

Results are presented as mean and standard deviation (SD), median and interquartile range (IQR) or percentage (%).
*p<0.05 between Amsterdam and Sneek #p<0.05 between patients with cardiovascular disease (CVD) and patients without cardiovascular disease (no CVD)
ACPA=Anti-citrullinated protein antibodies, DMARD= Disease Modifying Anti-Rheumatic Drugs, HDL=High-densitity lipoproteïn, LDL= Low-densitity lipoproteïn, NSAID= Non-Steroidal Anti-Inflammatory drugs, RF=Rheumatoid factor.

Table 2 | Cardiovascular risk score of rheumatoid arthritis patients in Reade, Amsterdam and Antonius hospital, Sneek

	All patients (n=720)	Amsterdam (n=375)	Sneek (n=345)
10-year cardiovascular risk score	22±13	21±12	23±13
Systolic bloodpressure >140 mm/Hg	40	36	45*
Systolic bloodpressure >180 mm/Hg	3	1	4*
LDL > 2,5 mmol/l	73	79	68*
Total cholesterol/HDL-ratio≥8	1	1	0
Total cholesterol ≥ 6.5 mmol/l	12	15	9*

Results are presented as mean and standard deviation (SD) or percentage (%). *p<0.05 between Amsterdam and Sneek. LDL= Low-densitity lipoproteïn, HDL=High-densitity lipoproteïn.

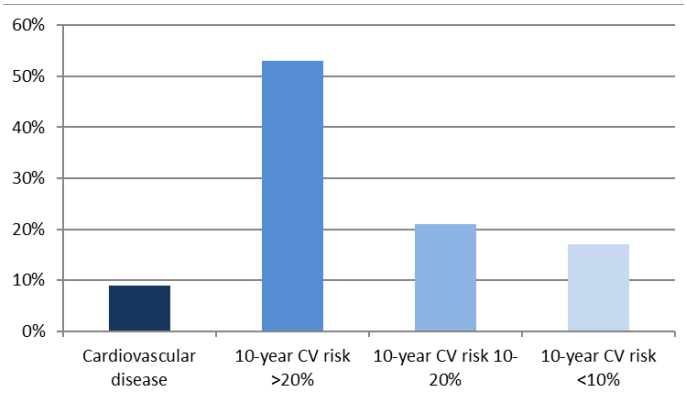

Figure 1 | Percentages of rheumatoid arthritis patients with cardiovascular disease, high, intermediate or low 10-year cardiovascular risk

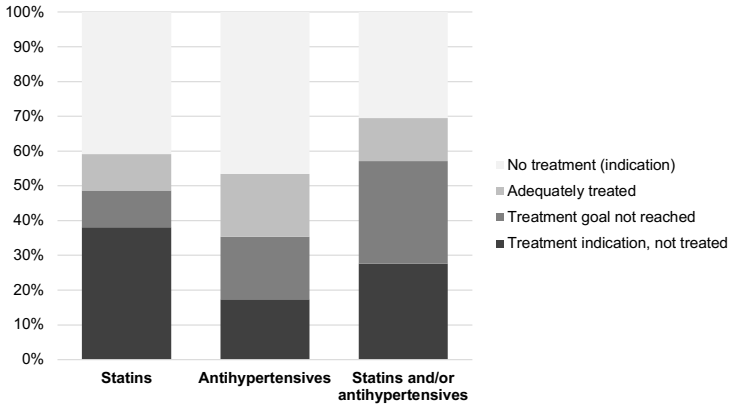

Figure 2 | Percentages of rheumatoid arthritis patients receiving (adequate) cardiovascular risk preventive treatment

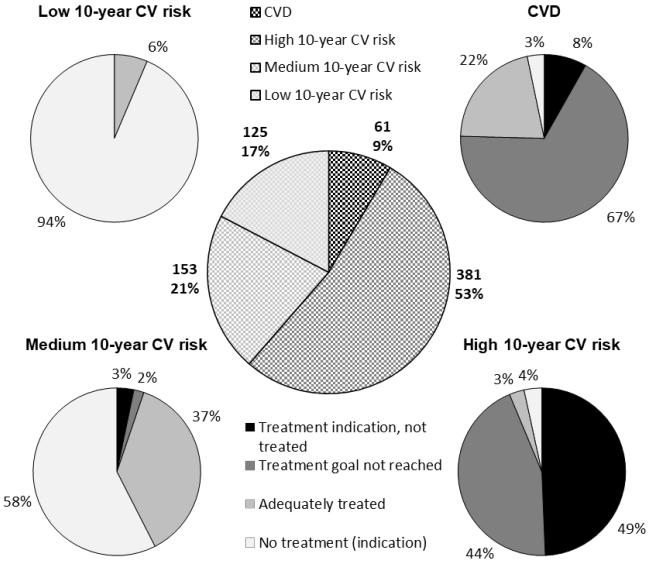

Figure 3 | Preventive medication per risk group

DISCUSSION

The results of this study confirm both a high prevalence of CVD risk and a very low prevalence of (adequate) preventive treatment in RA patients, not only in patients with a high CV risk (primary prevention), but also in patients who have already experienced CVD (secondary prevention). Our finding that 80% of RA patients are inadequately treated for CV risk is equal to that of another recently published Dutch study [25]. However, that cohort was established in 2006 and thus at a time when RA was not considered an independent CV risk factor. It is therefore worrisome that

CV-RM implementation has not improved since then. Previously a study to establish whether lipidlowering therapy was used appropriately or not in RA patients revealed that of the 115 patients who were at 'high risk' of CVD, only 8 were receiving statins [26]. In accordance with this, a cohort study using Medicare data reported that in RA patients with indications for annual lipid testing, this was not performed in one-third of patients [27]. There are several factors that might explain this lack of improvement. First, the current CV-RM guideline was published very shortly before the present study actually started. This could explain why CV-RM has not yet been implemented in all RA patients. Second, a potential weakness of the current Dutch CV-RM guideline is the addition of 15 years to account for the additive CV risk that comes with RA. This addition is not based on level A evidence and thus may hamper implementation, especially in young persons, knowing that they have to start a lifetime treatment. Moreover, RA patients often use many drugs to control disease activity and perhaps are reluctant to take additional drugs, particularly those that do not treat actual symptoms. Also, potential side effects, such as muscle and joint pain with statin use, could limit use in RA patients since they often already have muscle or joint pain due to active disease. Strengths of this study include the size of the study population and the fact that it is a two-centre study, including patients from rural and urban areas, making it a diverse RA population. Active disease can interfere with CV risk estimation, particularly because of interference with lipid levels. In our study population, the mean disease duration was 10 years and only 2% of patients had active disease (defined as a DAS28 >5.1), therefore it is likely that CV risk was stable for most of the patients. A limitation of this study is that we could not take into account some secondary CV risk factors, such as family history of CVD, physical activity and kidney function. These factors are, like BMI, considered CV risk increasing, which can serve as an additional reason to give CV risk prevention treatment. Thus the lack of this information could have underestimated our results. Ideally, blood pressure should be measured twice and the average used to calculate CV risk, but for practical reasons only one assessment was done. However, when blood pressure was too high we recommended reassessment by the general practitioner. Unfortunately, in this study we did not determine the reasons why RA patients were not treated or treated inadequately. This will be addressed in a followup implementation project that will be started shortly. Another study that we are currently undertaking is to investigate if yearly CV risk screening initiated by the rheumatologist improves CV-RM implementation. Two strategies will be tested: one strategy is to send high CV risk patients to their general practitioner to implement and control CV-RM, the second strategy is to send RA patients with a high CV risk to an internal specialist who implements CV-RM in the context of

a specialty CV-RM clinic. Ideally the effects of statins or antihypertensives on CV disease prevention in RA should be investigated in a large randomized trial; however, thus far no intervention trials with statins or antihypertensives and CV disease prevention in RA have been published. The TRACE RA trial was a placebo-controlled study investigating the efficacy of atorvastatin in patients with RA that was terminated early because of a low overall event rate [28]. Nevertheless, a reduction of 34% in CVD events in the statin group was demonstrated, although this did not reach statistical significance. Furthermore, data from epidemiological studies and post hoc subgroup analyses of large, secondary CV prevention trials show that the effects of statins on cholesterol levels in RA patients appear to be at least equivalent to the effects of statins in the general population [15, 29, 30]. Other studies have shown beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on CV risk in RA [12]. Moreover, the effects of cardioprotective agents might be even more pronounced in RA, as the pleiotropic effects of statins, ACE inhibitors and angiotensin blockers include anti-inflammatory properties [14, 31-35]. In the future, randomized controlled intervention trials are necessary to assess the actual effect of statins, ACE inhibitors and other lifestyle intervention strategies on CV risk in RA. In conclusion, our results indicate that effective strategies for adequate CV-RM are urgently needed to reduce CV risk in the RA population.

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Disclosure statement

The authors have declared no conflicts of interest.

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CHAPTER 4
Suboptimal cardiovascular risk management in rheumatoid arthritis patients despite an explicit cardiovascular risk screening program

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ABSTRACT

Objective

In 2011, we started to offer cardiovascular (CV) risk screening to rheumatoid arthritis (RA) patients with a high CV risk. After 1 year, we assessed whether patients labelled as high CV risk had started preventive treatment when indicated, and whether the CV risk score had changed.

Methods

CV risk screening was performed in both a large outpatient rheumatology clinic and a general hospital in the Netherlands, and the general practitioner or the internist was informed about the results of the CV screening, including specific advice on the initiation or adjustment of cardiopreventive drugs. National guidelines were used to assess how many patients were eligible for preventive treatment. After 1 year, CV risk, lifestyle, and treatment were re-evaluated. Patients with a history of CV disease at baseline or who experienced a CV event during follow-up were excluded from the analyses.

Results

A high 10 year CV risk (> 20%) was present in 58%, and 55% had an indication for anti-hypertensives, statins, or both. At follow-up, cardiopreventive drug treatment had been started or adjusted in only one-third of patients with an indication for treatment. After screening, 42% of patients reported having changed their lifestyle, through more exercise (24%), diet adaption (20%), and weight loss (11%).

Conclusion

Despite clear guidelines to improve CV risk, the results of a programme comprising active screening, targeted advice, and referral to the general practitioner or internist prove that primary prevention remains a major challenge in high-risk RA patients.

INDRODUCTION

Cardiovascular disease (CVD) is the main cause of death in patients with rheumatoid arthritis (RA) (1). Compared with the general population, in patients with RA the risk for incident CVD is doubled, comparable to that of patients with diabetes mellitus (2, 3). Both systemic inflammation and increased prevalence of traditional cardiovascular (CV) risk factors (including age, male gender, hypercholesterolaemia, hypertension, smoking, obesity, and diabetes mellitus) contribute to this increased CV risk. Therefore, the Dutch CV risk management guideline acknowledges RA as an independent risk factor for CVD, requiring CV riskmanagement (4). In addition, undertreatment of traditional CV risk factors may further increase the CV risk, but details on this subject are scarce. In 2011, Implementation of Cardiovascular Risk Management in Rheumatoid Arthritis (I-CaRe) started to offer CV risk screening to RA patients visiting Reade, a large rheumatology and rehabilitation centre inAmsterdam, and the Department of Rheumatology in the Antonius Hospital, Sneek, in the Netherlands. Previous results of the I-CaRe project demonstrated that an indication for preventive treatment (cholesterol-lowering or antihypertensive drugs) was present in over two-thirds of RA patients in whom the 10 year CV risk score was assessed (5). However, only 42%of those received (inadequate) treatment and 40% received no treatment at all. Thus, optimization of CV risk management remains a challenge, and better awareness and management are indispensable to reduce the high risk of CVD. The goal of this follow-up study was to assess whether patients labelled as high CV risk started preventive treatment if indicated, and whether their CV risk score changed after 1 year.

METHOD

Study population and design

For this prospective cohort study, patients included in the I-Care project between 2011 and 2016 were considered. The I-Care project, which started in 2011, aimed to assess the 10 year CV risk score and identify (under)treatment of CV risk factors in RA patients (5). For this follow-up study we aimed to assess whether patients labelled as high CV risk during the initial screening had indeed started preventive treatment, if indicated. All patients were aged 18 years or older and diagnosed by a rheumatologist, according to the American College of Rheumatology (ACR) criteria of 1987 for RA (6). In Reade, patients were included in the analyses if they had a baseline visit and a follow-up visit. Data were collected at baseline and again after 1 year of follow-up. Patients from the Antonius Hospital had a baseline visit and

a follow-up visit with the internist shortly thereafter. These different strategies were chosen because each clinic adapted the strategy that best fitted their local practice. All patients signed informed consent before study participation and the study was approved by the local ethics committees of Slotervaart Hospital & Reade and Antonius Hospital Sneek (number P1042).

Patient characteristics

Information on demographic factors, including age, gender, smoking, disease history, with a special focus on CVD, CV risk factors, and CV-preventive medication use, including anti-hypertensive medication, statins, and anti-diabetic medication, RA-related factors, disease duration, rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positivity, and presence of erosive disease, were collected from the medical files. Patients with a history of CVD were excluded from the analyses. Assessment of current anti-inflammatory medication included use of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and corticosteroids.

CV risk and disease definitions

CVD history was defined as a history of coronary heart disease (including angina pectoris, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery), heart failure, cerebral vascular disease (including ischemic stroke, transient ischaemic attack, and carotid endarterectomy), and peripheral arterial disease and atherosclerosis of major arteries. This was first asked about by a questionnaire, and if a CVD was reported or the patient's reply was positive for a history of CVD, this was checked in the medical files, to verify that the diagnosis had been confirmed by a specialist (cardiologist, neurologist, or vascular specialist). CV risk factors included self-reported diabetes mellitus, self-reported hypertension and/or the use of anti-hypertensives, self-reported hypercholesterolaemia and/or the use of statin therapy, and smoking status assessed by the questionnaire or the presence of high blood pressure [systolic blood pressure (SBP) > 140 mmHg] or high cholesterol [low-density lipoprotein (LDL) > 2.5 mmol/L or total cholesterol/high-density lipoprotein (TC/HDL) ratio > 4] measured during the physical examination. Overweight was defined as a body mass index (BMI) ≥ 25 kg/m2 and obesity as a BMI ≥ 30 kg/m2.

Physical examination

A physical examination, including blood pressure, waist and hip circumference, length and weight, was performed. Blood pressure was measured twice (left and

right) in a sitting position after 5 min of rest. Waist circumference was measured at the level of the umbilicus, and hip circumference at the level of the trochanter major of the hip bone (widest circumference). The waist-to-hip ratio comprised the ratio of these two measurements. BMI was calculated from height and weight (clothed without shoes). RA activity was assessed by the Disease Activity Score based on 28- joint count (DAS28) (7) and physical functioning by the Health Assessment Questionnaire.

Laboratory tests

Glucose and lipid profiles, including TC, triglycerides, HDL, and LDL, were assessed in fasting blood samples using standard techniques, and the TC/HDL ratio was calculated. All of the above tests were performed on the same day that blood was drawn.

Calculation of 10 year CV risk

The Dutch CV risk calculator is based on the European SCORE risk model, and uses gender, age, smoking status, SBP, and the TC/HDL ratio to calculate the 10 year risk of both fatal and non-fatal CV events. To account for RA (or diabetes) as a risk factor, 15 years is added to the actual age to calculate the 10 year CV risk (4). According to the Dutch CV risk management guideline, we classified a risk < 10% as low, between 10% and 20% as intermediate, and a ≥ 20% as high. Patients with a history of CVD at baseline or who experienced a CV event during follow-up were excluded from the analyses, because in the Dutch SCORE model for primary prevention, patients usually already receive cardiopreventive drugs in the case of pre-existing CVD. For Reade patients, the results of the CV screening were reported to the general practitioner (GP), who decided whether to start preventive medication. GPs in and around Amsterdam were involved in the project and were educated about CV risk in RA through an interactive training session. When one of their patients was screened, they received the results by letter. In case of a high CV risk, the advice was to treat the patient according to the Dutch CV risk management guideline. CV risk screening was repeated after 1 year and the 10 year CV risk at follow-up was calculated using age at baseline. For the patients from the Antonius Hospital, the internist was informed about the CV risk results and all patients were referred to the internist for further follow-up. This method was chosen for this location because shortly before the initiation of the I-CaRe project, this collaboration between the departments of Rheumatology and Vascular Medicine of the Antonius Hospital was established.

Cardiopreventive treatment

Based on the Dutch CV risk management guideline, in high-risk patients, and in intermediate-risk patients with a BMI ≥ 35 kg/m2, anti-hypertensive therapy is recommended when SBP is > 140 mmHg and/or statin therapy is recommended when LDL > 2.5 mmol/L. In patients with an intermediate or low 10 year CV risk, the criteria are SBP > 180 mmHg or TC/HDL ratio > 8. After calculation of the 10 year CV risk, we categorized patients into four groups: group 1, untreated patients with an indication for treatment; group 2, inadequately treated patients (i.e. not meeting treatment goals; SBP ≤ 140 mmHg or LDL ≤ 2.5 mmol/L); group 3, adequately treated patients; and group 4, untreated patients without an indication for treatment (i.e. no increased CV risk).

Follow-up

In Reade, CV risk screening was repeated after 1 year and the 10 year CV risk at follow-up was calculated using age at baseline. Patients were asked to complete a questionnaire about the actions that were taken following the results of the initial screening. All Reade patients were evaluated after 1 year, and in patients with high CV risk at baseline and receiving inadequate or no treatment (groups 1 and 2), we assessed whether they really started preventive treatment. For patients from the Antonius Hospital, we assessed whether the internist had started treatment after referral.

Statistical analysis

For the statistical analysis, SPSS version 23.0 (IBMCorp., Armonk, NY, USA) was used. Patient characteristics are expressed as number and percentage, means ± sd, when normally distributed, or median and interquartile range when not normally distributed. To test for differences between baseline and follow-up, the paired t-test and McNemar test were used. The threshold for significance was set at $p < 0.05$ (two-sided).

RESULTS

Patient and disease characteristics

For this study, 720 patients were included: 375 patients from Reade and 345 patients from the Antonius Hospital. A history of CVD was present in 61 patients at baseline and 12 new cases of CVD occurred after 1 year. These 73 patients were excluded from the analyses. In Reade, 47 patients were lost to follow-up after 1 year for various reasons, such as refusal or inability to contact. Baseline characteristics

of those 47 patients were similar to those of the whole group (data not shown). In the Antonius Hospital, seven patients did not make an appointment with the internist. We tried to retrospectively collect data on CV risk factors from the patients from the Antonius Hospital, but this was not possible in the majority of patients since data on blood pressure and cholesterol were not available. Baseline patient characteristics are shown in Table 1. Patients in the study had longstanding stable disease, with mean DAS28 at baseline and after 1 year of follow-up of 2.41 and 2.55, and 77% and 70% of the patients had low disease activity at baseline and after 1 year of followup, respectively.

Table 1 | Patient characteristics at baseline

	All patients		Reade		Antonius Hospital	
	647		346		301	
Demographics						
Females	482	(75)	267	(77)	215	(71)
Age, years	58	± 12	58	± 11	59	± 12
Disease duration, years	7	(2-14)	10	(5-18)	4	(1-9)
RF positive	400	(63)	233	(70)	167	(56)
ACPA positive	396	(66)	221	(73)	175	(58)
Erosive disease	293	(46)	184	(55)	109	(36)
Disease activity score of 28 joints	2.41	± 1.14	2.62	± 1.20	2.17	± 1.02
Anti-inflammatory medication use						
NSAID	245	(38)	127	(37)	118	(41)
Methotrexate	435	(68)	243	(70)	192	(66)
Other DMARD	160	(25)	73	(21)	87	(30)
Biological	232	(36)	196	(57)	36	(12)
Glucocorticoid	146	(23)	61	(18)	85	(29)

Results are presented as mean and standard deviation (SD), median and interquartile range (IQR) or number and percentage (%)
ACPA: Anti-citrullinated protein antibodies, DAS28: Disease activity score 28 joint count, DMARD: Disease Modifying Anti-Rheumatic Drug, HAQ: Health Assessment Questionnaire NSAID: Non-Steroidal Anti-Inflammatory drugs, RF=Rheumatoid factor.

CV risk and indication for cardiopreventive treatment

In Table 2, CV risk factors at baseline and after 1 year (only Reade) are shown separately for both centres. In Reade, mean 10 year CV did not change and the majority of patients remained in the same risk category. There was a significant decrease in TC, LDL-cholesterol, and the TC/HDL ratio. The proportion of patients

with high LDL and TC decreased, but no significant change in the presence of SBP > 140 mmHg was found. Finally, a higher percentage of patients used statins or anti-hypertensives after 1 year. There was a significant difference in 10 year CV risk score between baseline and 1 year assessment, but this was not clinically relevant.

Table 2 | Cardiovascular risk factors at baseline and after one year in patients without CV disease

	Reade					Antonius Hospital	
	Baseline		Follow-up			Baseline	
N	346		299			301	
Cardiovascular risk							
10-year CV risk score	21	± 12	21	± 12	*	23	± 13
CV risk: <10%	65	(19)	61	(21)	*	60	(20)
10-20%	86	(25)	81	(27)		63	(21)
>20%	195	(56)	155	(52)	*	178	(59)
Physical examination							
Systolic blood pressure (mm/Hg)	135	± 18	135	± 18		140	± 19
Waist Hip Ratio	0.91	± 0.09	0.90	± 0.07		0.91	± 0.09
Body Mass Index (kg/m^2)	26.6	± 5.0	26.3	± 4.8		27.0	± 4.8
Laboratory tests (mmol/L or ratio)							
Total cholesterol	5.5	± 1.0	5.2	± 1.0	*	5.2	± 1.1
Triglycerides	1.4	± 0.8	1.4	± 0.8		1.3	± 0.6
LDL-cholesterol	3.3	± 0.9	3.1	± 0.9	*	3.0	± 0.9
HDL-cholesterol	1.6	± 0.5	1.6	± 0.5		1.6	± 0.5
Total cholesterol/HDL	3.7	± 1.3	3.5	± 1.2	*	3.7	± 1.3
Fasting glucose	5.5	± 1.7	5.5	± 1.5		5.5	± 1.7
Cardiovascular risk factors							
Currently smoking	76	(22)	60	(20)		68	(23)
Diabetes mellitus (self-reported)	20	(6)	13	(5)		13	(4)
Systolic blood pressure >140 mm/Hg	119	(34)	102	(34)		134	(45)
LDL > 2.5 mmol/L	275	(80)	220	(74)	*	212	(71)
Total cholesterol ≥ 6.5 mmol/L	52	(15)	30	(10)		30	(10)
Cardiopreventive medication use							
Antihypertensives	99	(29)	94	(31)	*	101	(35)
Statins	40	(12)	56	(19)	*	65	(22)
Anti-diabetics	14	(4)	10	(3)		11	(4)

Results are presented as mean ± standard deviation (SD) or number and percentage (%).
CV: Cardiovascular, HDL: High-density lipoprotein, LDL: Low-density lipoprotein
* p <0.05 between baseline and follow up

Of all patients, at baseline 357 patients (55%) had an indication for the use of anti-hypertensives, statins, or both. Because follow-up assessments differed between Reade and the Antonius Hospital, the results are described separately. In Figure 1, percentages of patients receiving preventive treatment at baseline and follow-up in Reade are shown. In Reade, 192 patients had an indication for statin treatment but only 40 of them (21%) used a statin; of those, 18 patients (9%) reached an LDL < 2.5 mmol/L. Of 160 patients with an indication for anti-hypertensive treatment, 99 (62%) used anti-hypertensives and 61 (37%) did not. Of the patients who used anti-hypertensives, 55 (34%) reached an SBP < 140 mmHg. After 1 year of follow-up, 105 out of 173 patients (61%) who received inadequate or no treatment at baseline were still untreated or undertreated after 1 year. Of the 105 patients with an indication for antihypertensives without adequate treatment at baseline, 53 (50%) received no or inadequate treatment after 1 year.

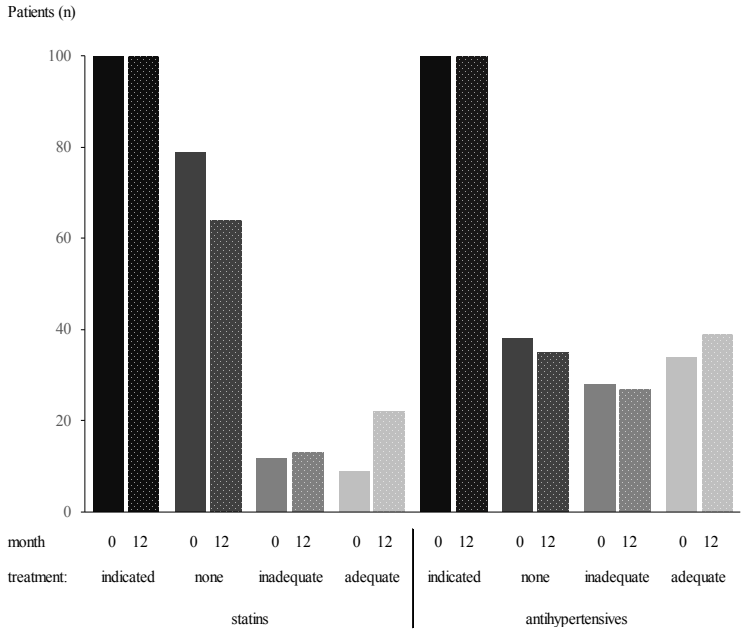

Figure 1 | Percentage of rheumatoid arthritis patients receiving (adequate) preventive treatment at baseline and after one year of follow-up in Reade

Figure 2 shows the number of patients with an indication for treatment who started or adjusted cardiopreventive therapy and the number reaching treatment goals (only for Reade). In the Antonius Hospital, after initial screening all patients were referred to an internist. As a result of those referrals, 27 (23%) of the 109 patients

with an indication for anti-hypertensives without adequate treatment at baseline started or adjusted anti-hypertensive therapy. Fifty-four of the 134 patients (40%) who received no statin or had not yet reached their LDL goal started with a statin or adjusted the dose.

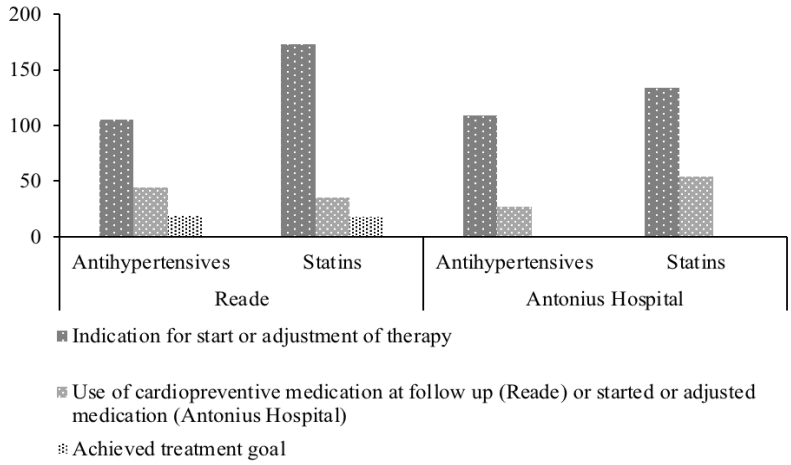

Figure 2 | Number of patients with an indication for treatment who started or adjusted cardiopreventive therapy and the number reaching treatment goals

Follow-up by the GP in Reade

Of all patients in Reade without a history of CVD, 48 (16%) were contacted by their GP for a visit, and 37 patients (12%) made an appointment with their GP themselves. In total, 83 patients (24%) visited their GP after our screening. In those patients, monitoring of cholesterol and blood pressure was performed in 44 (53%) and 52 patients (63%), respectively. Of the patients who visited their GP, 26 (31%) were prescribed statins, and 25 (30%) received a prescription for anti-hypertensives. Nine were referred to another specialist, mostly a cardiologist, for further follow-up. Of the patients who visited the GP, nine had a low CV risk, 17 intermediate, and 57 high. In the patients with an indication for starting or adjusting cardiopreventive medication (n = 191) at baseline, 63 (33%) visited their GP. Change in CV risk 1 year after the start of the CV risk management programme Analyses were performed only for Reade. In Reade, the majority of patients remained in the same risk category, regardless of whether they visited their GP. However, we did find differences in CV risk score in the patients who started cardiopreventive therapy. In patients with an indication for statin treatment at baseline (n = 174) but inadequate or no treatment,

mean CV risk was 29%. As shown in Table 3, at 1 year follow-up, this risk decreased to 24% for the patients who were on statin therapy and reached treatment goals. In those who used statins without reaching treatment goals, or in patients who did not use statins after baseline, the 10 year CV risk score remained high. Patients with no treatment indication had a CV risk of 13% at baseline and follow-up. Similar results were seen for patients with an indication for anti-hypertensives.

Table 3 | Change in 10-year Dutch CV risk score after one year sorted by treatment status

	Mean 10-year Dutch CV risk score	
	Baseline	Follow-up
Reade		
Statins; no or inadequate treatment at baseline		
Follow-up adequately treated	29%	24%
Follow-up treatment goal not reached	29%	32%
Follow-up treatment indication, not treated	29%	31%
No treatment indication or adequately treated at baseline	13%	13%
Antihypertensives; no or inadequate treatment at baseline		
Follow-up adequately treated	33%	23%
Follow-up treatment goal not reached	33%	35%
Follow-up treatment indication, not treated	33%	33%
No treatment indication or adequately treated at baseline	16%	17%

Lifestyle factors (only available for Reade)

One year after the initial screening, patients in Reade were asked whether they had made any lifestyle changes as a result of the screening. In total, 42% of patients reported that they had adapted their lifestyle; 24% of the patients exercised more, 20% had adapted their diet, and 11% reported that they had lost weight. Nine patients had stopped smoking (3%) and two reported that they smoked less. However, 54% reported that they had not adopted a healthier lifestyle. The main reason for this was that patients reported that they already had a healthy lifestyle (28%); in addition, 14% did not want to make lifestyle changes, because they did not consider themselves to be at high CV risk, 8% felt that a lifestyle change was not necessary, and some patients (3%) did not know how to adopt a healthier lifestyle. Of the patients without cardiopreventive medication at baseline, 37% reported having made lifestyle changes; these percentages were 44%in the group that used either a statin or anti-hypertensive therapy and 40% of the patients who used both a statin and a antihypertensive.

DISCUSSION

This cohort study in the Netherlands illustrates that, despite clear recommendations to improve CVD risk management, adherence to guidelines in high-risk RA patients for primary prevention of CVD remains a major challenge. Cardiopreventive drug treatment was started or adjusted in only one-third of patients with an indication for treatment. CV risk declined after 1 year, from 29% to 24%, in the patients who used cardiopreventive therapy. This signals an important issue, namely the need for better implementation strategies to reduce and control the increased CV risk associated with RA. As the increased CV risk in RA is due to both the disease activity and increased prevalences of the 'traditional' CV risk factors, CV risk management should receive more attention. Previous studies have sent a similar message: a study in UK primary care patients demonstrated that although anti-hypertensive prescription rates were higher in patients with RA than in controls, CV risk assessment was often incomplete and thus suboptimal. In a French cohort of early arthritis patients, 58% of patients at high CV risk did not reach the recommended LDL-cholesterol target. On the other hand, in a study in a US managed care setting, the measurement of blood pressure and LDL-cholesterol, as well as treatment with cardiopreventive medication, was higher in patients with RA compared with general controls, but this difference may be explained by the dissimilar setting. One year after the implementation of our CV risk management programme, we found a reduction in CV risk in the patients who started medication, reflecting the importance of adequate CV risk management. Moreover, some individual CV risk factors such as cholesterol and smoking status improved. However, we did not find a clinically relevant decrease in 10 year CV risk in the whole group. This is not surprising, as only a small proportion of patients contacted their GP. Our results demonstrate undertreatment of both hypertension and dyslipidaemia, as many patients who had an indication to use preventive medications did not receive adequate treatment and were still untreated or undertreated after 1 year of follow-up, despite instructions to both patients and GPs. However, it is encouraging that the intervention of screening for CV risk factors prompted a reasonable proportion of patients to adapt their lifestyle, including taking more exercise, making dietary changes, and losing weight. Unfortunately, we could not assess the reasons why patients did not visit their GP or why therapy was not initiated. This may partly be due to non-adherence by either patients or physicians, and since patients visited different GPs in the Amsterdam region, there may also be differences between physicians. However, even if the pros and cons of medication are well discussed by the physician, a large proportion

of patients still prefers not to use medication (8). Non-adherence to guidelines is an often reported phenomenon (9, 10). A Dutch cohort study reported that in 66% of statin users from the general population, statin treatment was inconsistent with the Dutch CV risk management guideline, especially in patients with low 10 year risk (8). We checked whether patients without adequate preventive therapy were different from those with preventive therapy, but we found no differences in age, gender, or RA activity between patients who started cardiopreventive therapy and those who did not. The issue of clinical inertia probably also contributes to undertreatment of CV risk factors, and is regarded as a major cause of uncontrolled hypertension and dyslipidaemia. This may be a particular problem in the RA population, where therapeutic inertia is reflected by the presence of non-adherence to the current ACR treatment recommendations. We expected that as a result of our screening, patients in Amsterdam (especially those with high 10 year CVD risk) would be motivated to visit their GP for follow-up. However, cardiopreventive treatment was started in only a small proportion of patients with an indication for treatment. In the Antonius Hospital, this was about the same: 23% and 40% of patients with an indication for preventive therapy started anti-hypertensives and statins, respectively, despite referral to the internist. Differences in GPs' personal and professional attitudes may also play a role in their adherence to CV risk management guidelines (11). Because we used different protocols at the two sites, we could not compare these outcomes side by side. For both sites, we left the decision of whether to start medication to the GP or internist, without giving strict advice on this. This method was chosen in consultation with the GPs involved in the protocol design. Lifestyle modifications are often the first step in CV risk management, and although some patients adjusted their lifestyle, there is also room for improvement in this area. Finally, risk perception by patients needs to be considered. Previous studies have shown that changing one's behaviour is a difficult challenge (12). This may be due to the fact that risk communication does not always fit within the reference framework of an individual patient, and patients may not fully understand themagnitude of the risk that is explained to them. Improving the effectiveness of health risk communications would therefore improve the effectiveness of risk management counselling. There are some limitations of our study. First, the addition of 15 years to the age of RA patients for the CV risk calculation is only used in the Netherlands, and therefore our results are difficult to compare with other studies using other calculators. For example, the Heart- SCORE, which calculates the 10 year risk of a fatal CV event and multiplies this by 1.5 for RA patients, is commonly used in Europe (13, 14). We specifically chose to use the Dutch SCORE method because it is widely applied in the

Netherlands, particularly by Dutch GPs. Furthermore, the addition of 15 years to the CV risk resulted, in comparison to the unadjusted (without 15 years) CV risk score, in reclassification of 25% and 56% of patients to the intermediate- and high-risk categories, respectively. When not using the 15 year addition, 26% of patients would be in the intermediate-risk and 22% in the high-risk category. Another potential limitation could be that the risk was communicated to patients differently in Reade and the Sneek Hospital. In Reade, we used a standard model for this and all staff involved received the same training, whereas in the Antonius Hospital, the results of the CV risk screening were also communicated to patients by the vascular internist. Finally, patients who had an indication for cardiopreventive treatment may not have been candidates for cardiopreventive therapy after a second evaluation by their GP or internist. However, it is unlikely that this potential issue fully explains the undertreatment found in this group. Furthermore, in some cases, the GP may have initiated a CV-preventive treatment, but the patient may have stopped or not have taken the medication because of an adverse effect or unwillingness to use it. We collected data on this issue in our questionnaire after 1 year. However, since such a small proportion of patients visited the GP in the first place, and medication was not started in most of those patients, the non-adherence issue was present in only a very small number of patients, and we did not report these data in detail. Conclusion Our results show that when screening indicates the need for cardiopreventive treatment, this is generally not done, despite information being provided to patients and their primary care physicians or internists, resulting in suboptimal CVriskmanagement. Although both patients and GPs received information on CV risk, only a small proportion of patients at high CVD risk visited their GP. Increasing this percentage is an important first step towards improved CV risk management. This could be solved by more intensive counselling (e.g. by motivational interviewing) as well as an immediate follow-up to check whether appropriate therapy has been initiated. This is an implementation project that will be initiated shortly at our centres.

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No potential conflict of interest was reported by the authors.

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CHAPTER 5
Change in cardiovascular risk after initiation of anti-rheumatic treatment in early rheumatoid arthritis

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ABSTRACT

Objectives

To determine if cardiovascular (CV) risk scores, traditional risk factors and the resulting indication for preventive treatment change after initiation of anti-rheumatic treatment in early rheumatoid arthritis (RA) patients.

Methods

Disease activity, blood pressure, acute phase proteins and lipid profile were evaluated in early RA patients at baseline and after four weeks of anti-rheumatic treatment. CV risk scores (Dutch Systematic Coronary Risk Evaluation (SCORE) and European Heart SCORE) and indication for preventive CV treatment (according to the Dutch CV risk management guidelines) were determined.

Results

One hundred and four consecutive RA patients were included, 7% had a history of CV disease. At baseline, 29.9% and 3.1% were classified as high risk according to the Dutch SCORE and Heart SCORE, respectively. According to the Dutch CV-risk management guidelines that use the Dutch SCORE, all high risk patients had at baseline an indication for (adaptations of) preventive treatment. From the CV risk score the components blood pressure and TC:HDL ratio decreased during anti-rheumatic treatment and 9% of the patients switched their CV risk category. In total 13% of the patients had a change in advice for preventive CV treatment after one month of anti-rheumatic treatment.

Conclusion

CV risk management is important in RA patients, however the timing of assessment, as well as the use of a particular CV risk model, influences the advice about the need for CV preventive treatment. Further research is needed to determine which risk model is optimal and when in the course of RA it should be applied.

INTRODUCTION

Ischemic heart diseases and strokes are the most common causes of death, accounting together for 15 million deaths in 2015 (1). Different cardiovascular (CV) risk models exist, which estimate the 10-year risk of fatal and non-fatal CV diseases (CVD), and indicate if an antihypertensive and/or statin is necessary to lower the chance of a future CV event (2-5). Rheumatoid arthritis (RA) is associated with an increased risk of CVD, with atherosclerotic diseases being the leading cause of death (6;7). CV risk models were developed for the general population and do not perform well in the RA population(4). Therefore, the European League Against Rheumatism (EULAR) recommends to use a modified risk score for RA patients, by applying a multiplication factor of 1.5 to the CV risk scores (8). In the Dutch Systematic COronary Risk Evaluation (SCORE) a correction for RA patients is already taken into account (2;4;5).

The increased risk in RA patients for CVD has multiple causes. RA and CVD are both multifactorial disorders, with some shared risk factors (smoking, metabolic syndrome), common susceptibility genes and they might even have a shared etiology (6;9-13). However, most interesting is the influence of inflammation on CVD. Current evidence supports an important role of inflammation in the formation of an atherosclerotic plaque (14;15). Previous literature showed that improvement in RA disease activity is associated with an increase in cholesterol levels, and a decrease in TC:HDL ratio; an important CV risk predictor (16). However, all previous studies assessed the change in lipid profile six months or later after initiation of anti-rheumatic treatment (16-19). It is unclear whether this effect is already present early after initiating treatment and what effect this would have on CV risk and optimal CV risk management. Therefore, different CV risk scores (Dutch SCORE and European Heart SCORE), the traditional risk factors and indication for preventive treatment were determined in early RA patients before and after the first four weeks of anti-rheumatic treatment. Exploratory analysis were performed to determine the effect of inflammation on CV risk score, as well as the relation between inflammation, CV risk scores and the different components of the risk score.

METHODS

Study population

The 'Early Arthritis Cohort' at Reade in Amsterdam, the Netherlands, includes

patients aged 18 years and older, with no prior treatment with disease-modifying antirheumatic drugs (DMARDs). Patients in this cohort who fulfilled the ACR/EULAR 2010 criteria for RA (20) and started treatment with methotrexate and glucocorticoids, between June 2014 and March 2017, were included in this study. Patients with insulin-dependent diabetes mellitus were excluded. All patients gave written informed consent according to the Declaration of Helsinki and approval was obtained from the local ethics committee (Ethics Committee of the Slotervaart Hospital and Reade, Amsterdam, The Netherlands).

Measurements

At baseline, patients were interviewed to record details about symptom history, disease history (special focus on CVD), clinical characteristics, demographics and medication use (including antihypertensives and statins).

At baseline and after four weeks, disease activity was measured with the Disease Activity Score of 44 joints (DAS44) and physical functioning by the Health Assessment Questionnaire (HAQ). Body mass index (BMI) was calculated from height and weight and blood pressure was measured manually according to the standard hospital procedures. Blood sample measurements at baseline were rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), and at baseline and four weeks: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and lipid profile, consisting of total cholesterol (TC), triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.

Cardiovascular risk

CVD history was defined as an objectively confirmed by specialists history of coronary heart disease (myocardial infarction, angina pectoris, percutaneous coronary intervention and coronary artery bypass surgery, cerebral vascular disease and peripheral arterial disease). Patients with a CVD history were excluded from CV risk analyses. CV risk at baseline and after four weeks of treatment was retrospectively determined using the official online sites, according to two different risk scores: Dutch Systematic COronary Risk Evaluation (SCORE) and the European Heart SCORE (2;3). The Dutch SCORE risk model uses gender, age, smoking status, systolic blood pressure (SBP) and the TC:HDL ratio. To account for RA (or diabetes) as risk factor the Dutch CV-risk management (CV-RM) guideline adds 15 years to the actual age in order to calculate the 10-year CV risk. A risk<10% is classified as low, between 10% and 20% intermediate and a risk ≥20% as high risk. According to the Dutch CV-RM guideline, preventive treatment with an antihypertensive or

statin is indicated in high risk patients with a SBP >140 mmHg or a LDL> 2.5 mmol/l, respectively (21). The European Heart SCORE risk model predicts the 10-year risk of a fatal heart attack, stroke or other circulatory problems in low risk regions of Europe by gender, age, SBP, TC:HDL ratio and smoking status. To calculate this Heart SCORE risk the results were multiplied with 1.5, which is suggested for RA patients in the updated EULAR 2015/2016 recommendations (8). The Heart SCORE considers a risk of <5% as low/medium, between 5 and 10% as high and ≥10% as very high. To be able to compare the Heart SCORE with the Dutch SCORE, we considered a Heart SCORE risk of <5% as low, a risk between 5 and 10% as medium and a risk ≥10% as high.

Statistical analyses

Patient characteristics were expressed as number (percentage), means ± standard deviation (SD), when normally distributed or median [interquartile range], when skewed distributed.

Changes in inflammation markers and (components of) the risk scores over four weeks of treatment were analyzed with a paired t-test (normal distributed) or Wilcoxon test (skewed distributed). The relation between the two CV risk scores was determined with a Spearman correlation coefficient, the percentage of agreement, as well as a weighted kappa. Kappa can be interpreted as the percentage of agreement after correcting for chance(<0 indicates no agreement, 0 to 0.2 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial and 0.81 to 1.0 as almost perfect agreement)(22;23). The numbers of patients that were reassigned to another CV risk group (low, medium or high) after four weeks of treatment, according to the two risk scores were calculated, and Stuart-Maxwell analyses were applied.

To analyse the association between CV risk score and disease activity, tobit mixed model analyses were performed. Tobit mixed model analysis can be used when the outcome is either left- or right censored (like the maximum risk score in de CVD models)(24). The individual components of the CV risk scores were compared with disease activity, by linear mixed model analyses and excluded patients who used antihypertensive drugs or statins in analysis which involved blood pressure or cholesterol, respectively. In the mixed model analyses time and the interaction between time and the independent variable were added to assess the relationship at the different time points and all analyses were performed separately for males and females and were adjusted for age and smoking. The tobit and Stuart-Maxwell

analyses were performed with Stata (version 14), all other statistical analyses were performed using SPSS (version 21.0).

RESULTS

In total 153 patients were eligible to participate, of which 104 were included in the current analyses. Reasons not to include patients for analyses were: three patients did not reach week four, 37 patients did not start on methotrexate in combination with prednisolone, four patients dropped out before week four, three patients had no complete data at baseline and two patients did not fulfil the ACR/EULAR 2010 criteria for RA. The mean age of the included patients was 49 years and 67% was female. The mean DAS44 was 3.5 which decreased after one month of anti-rheumatic treatment to 1.6. A history of CVD was present in seven patients (7%). The following conditions were present: one patient with a myocardial infarction, one patient with a percutaneous coronary intervention, one patient with a coronary artery bypass surgery, three patients with a cerebral vascular disease and one patient with peripheral arterial disease. No patients experienced a CV event during the first four weeks of anti-rheumatic treatment. Twenty-six (25.0%) patients smoked at baseline, and one quit smoking during these four weeks. Five patients used a statin and 16 patients used antihypertensive drugs, which did not change during follow-up (Table 1).

Table 1 | Demographics and outcomes at baseline and after four weeks of anti-rheumatic treatment

	Baseline		After 4 weeks	
Demographics				
Age	48.5	(12.4)		
Gender (females)	70	(67.3%)		
Symptom duration (months)	7.0	[3.0-21.0]		
RF positive	82	(78.8%)		
ACPA positive	86	(82.7%)		
RF or ACPA positive	89	(86%)		
RA disease				
DAS44	3.5	(3.3)	1.6	(0.9)*
VAS44	61.4	(27.2)	22.3	(22.6)*
SJC44	8.0	[3.0-13.0]	2.0	[0.0-3.3]*
TJC44	8.0	[4.0-16.0]	1.5	[1.5-5.0]*

table continues

	Baseline		After 4 weeks	
ESR	20.5	[9.0-32.8]	7.0	[5.0-12.0]*
CRP	7.2	[3.8-25.0]	2.0	[0.9-4.1]*
HAQ	1.0	[0.5-1.6]	0.3	[0.0-0.6]*
CV risk components				
History of CV events	7	(6.7%)	7	(6.7%)
Current smoking	26	(25.0%)	25	(24%)
Statin use	5	(4.8%)	5	(4.8%)
Antihypertensive use	16	(15.4%)	16	(15.4%)
BMI	26.1	(5.3)	26.3	(5.4)
Syst RR‡	130.8	(22.5)	127.8	(17.7)
Dia RR‡	80.5	(11.5)	78.4	(10.0)*
TC†	5.0	(0.9)	5.7	(1.1)*
HDL†	1.4	(0.4)	1.9	(0.5)*
LDL†	3.2	(0.8)	3.3	(0.9)*
Trigly†	1.3	(0.6)	1.5	(0.8)*
TC:HDL ratio†	3.9	(1.3)	3.2	(1.0)*
CV risk scores				
Dutch SCORE linear risk score Δ	11.0	[3.5-23.5]	10.0	[3.0-22.0]*
Dutch SCORE low risk scoreΔ	43	(44.3%)	46	(47.4%)
Dutch SCORE medium risk scoreΔ	25	(25.8%)	20	(20.6%)
Dutch SCORE high risk scoreΔ	29	(29.9%)	31	(32.0%)
Heart SCORE linear risk scoreΔ	0.0	[0.0-1.5]	0.0	[0.0-1.5]*
Heart SCORE low risk scoreΔ	90	(92.8%)	94	(96.9%)
Heart SCORE medium risk scoreΔ	4	(4.1%)	1	(1.0%)
Heart SCORE high risk scoreΔ	3	(3.1%)	2	(2.1%)

Numbers are presented as frequency (percentage), mean (SD) or median [IQR].
Δ Patients without cardiovascular events, n=97
‡ Patients without antihypertensives, n=88
† Patients without statins, n=99
** Statistical difference (p<0.05) between baseline and after four weeks*
ACPA: anti-citrullinated protein antibody, BMI: body mass index, CRP: C-reactive protein, CV: cardiovascular, DAS: disease activity score, Dia RR: diastolic blood pressure, ESR: erythrocyte sedimentation rate, HAQ: health assessment questionnaire, HDL: high-density lipoprotein, IQR: interquartile range, LDL: low-density lipoprotein, RA: rheumatoid arthritis, RF: rheumatoid factor, SCORE: Systematic Coronary Risk Evaluation, SD: standard deviation, SJC: swollen joint count, Syst RR: systolic blood pressure, TC: total cholesterol, TJC: tender joint count, trigly: triglycerides, VAS: visual analogue scale

Cardiovascular risk score at baseline

At baseline median Dutch SCORE and Heart SCORE were 11.0% [3.5-23.5] and 0.0%

[0.0-1.5], respectively, see table 1. The correlation between absolute values of the Dutch SCORE and Heart SCORE gave a spearman coefficient of 0.79 with a p-value of <0.01. The agreement between the different risk categories (low, medium, high) was 62.4%, and gave a slight correlation (K=0.13, p<0.01). The Dutch risk model classified 29.9% of the patients as high risk, were the Heart SCORE risk model classified 3.1% of the patients as high risk. Three patients (3.1%) had a high risk according to both the CV risk models.

Of the 29 (29.9%) high CV risk patients according to the Dutch SCORE, 28 patients had an increased LDL and, according to the CV-RM guidelines, a statin indication. One patient already used a statin and thus needed dose optimization. Nineteen of the 29 patients had an increased SBP and therefore needed antihypertensive treatment, of those patients seven already had an antihypertensive, but needed dose optimization. In total all 29 high risk patients (29.9%) had an indication for (adaptations of) preventive treatment.

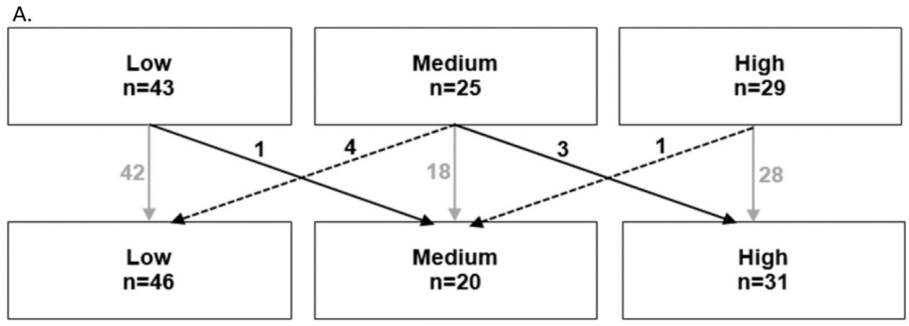
The change in cardiovascular risk score after four weeks

The number of patients that changed in CV risk category (low, medium, high) was not significantly different in both calculators. According to the Dutch SCORE nine (9.3%) patients switched from risk category, of which five patients went to a lower category and four patients to a higher category. In the Heart SCORE four (4.1%) patients changed from category, see figure 1.

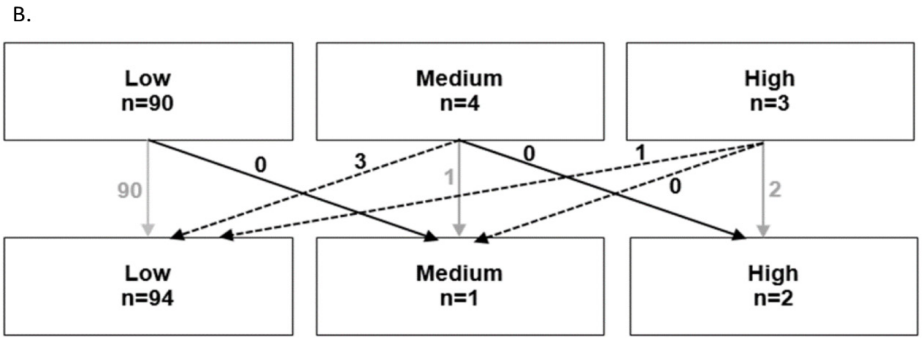
The Dutch SCORE risk model showed that 31 (32.0%) patients were at high risk after four weeks. Twenty-seven (27.8%) patients had an increased LDL, thus an indication for statin treatment. Of the 27 patients, one already used a statin. Of the 31 patients, 13 (13.4%) patients had an increased blood pressure, thus in need of antihypertensive treatment of which five needed dose optimization.

In total three patients were indicated for a statin at baseline, but not anymore after four weeks and two patients did not need statins at baseline, but did after four weeks. Six patients had an antihypertensive indication at baseline and two doses optimization, but not at four weeks and two patients needed antihypertensives based at the values of four weeks, but not at baseline. This included one patient who was indicated for a statin and an antihypertensive at baseline, but not after four weeks, and one patient the other way around. In conclusion, in 13 (13.4%) patients the advice for (adaptations of) preventive treatment changed during the first four weeks of anti-rheumatic treatment.

Figure 1 | Number of patients that changed from cardiovascular risk score category, during the first month of anti-rheumatic treatment, according to the Dutch SCORE (A) and European Heart SCORE (B), n=97



Stuart-maxwell analyses for Dutch SCORE, p=0.247.



Stuart-maxwell analyses for Heart SCORE risk score, p=0.135.

(Components of) Cardiovascular risk scores and the association with disease activity

The DAS44 of all patients improved during follow-up. Lipid levels increased during treatment, especially HDL, which resulted in a decrease in TC:HDL ratio from 3.9 (1.3) at baseline to 3.2 (1.0) after four weeks of anti-rheumatic treatment. The mean blood pressure decreased with 3 mmHg for systolic and 2 mmHg for diastolic blood pressure (Table 1).

The results of the tobit mixed model analyses relating disease activity with CV risk scores were inconclusive. A higher DAS44 was associated with a lower CV risk score, which showed a stronger effect after four weeks. However, the presence of

a higher ESR and CRP had no effect at baseline and were after four weeks related with higher CV risk scores (Table 2).

The linear mixed model analyses relating disease activity with the separated components of the CV risk scores showed that a higher DAS44 was associated with lower lipid levels, and an increase in TC:HDL ratio, especially at baseline. For ESR and CRP comparable results were observed. The association between disease activity and blood pressure gave inconclusive results (Table 3).

Table 2 | Mean effect over time for baseline and week four values, between disease activity and cardiovascular risk scores (with interaction with the time)

	Dutch SCORE		HeartSCORE	
	Beta (CI)	**p-value**	**Beta (CI)**	**p-value**
DAS44	-0.09 (-0.90-0.71) -0.91 (-1.93-0.12)	0.819* 0.084	-0.32 (-0.77-0.13) -0.70 (-1.38- -0.02)	0.158 0.041
SJC	0.01 (-0.13-0.15) -0.04 (-0.35-0.27)	0.887 0.802	-0.01 (-0.08-0.07) -0.07 (-0.27-0.13)	0.873 0.488
ESR	(-0.02-0.05) -0.02 (-0.12-0.09)	0.364 0.769	0.00 (-0.01-0.02) 0.02 (-0.01-0.05)	0.656 0.244
CRP	0.00 (-0.03-0.04) 0.09 (-0.04-0.21)	0.852 0.184	0.00 (-0.02-0.02) 0.02 (-0.01-0.05)	0.858 0.232

CI: confidence interval, CRP: C-reactive protein, DAS: disease activity score, ESR: erythrocyte sedimentation rate, SJC: swollen joint count
Grey values: values after four weeks of treatment
** interaction with time p<0.10*

Table 3 | Mixed model between components of the cardiovascular risk score and disease activity, at baseline and after four weeks of anti-rheumatic treatment, corrected for age, smoking status, interaction over time and separated for gender

Males	TC† Beta (CI) and p-value	HDL† Beta (CI) and p-value	LDL† Beta (CI) and p-value	Trigly† Beta (CI) and p-value	TC:HDL ratio† Beta (CI) and p-value	Syst RR‡ Beta (CI) and p-value	Dia RR‡ Beta (CI) and p-value
DAS44	-0.28 (-0.49- -0.06) 0.013 -0.10 (-0.48-0.28) 0.608	-0.13 (-0.20- -0.05) 0.001* 0.02 (-0.11-0.15) 0.764	-0.15 (-0.35-0.04) 0.119 -0.11 (-0.46-0.23) 0.511	-0.01 (-0.18-0.16) 0.926 -0.05 (-0.25-0.25) 0.755	0.20 (-0.06-0.46) 0.135 -0.04 (-0.50-0.42) 0.878	0.36 (-4.03-4.74) 0.871* -5.79 (-13.65-2.07) 0.144	1.37 (-1.09-3.84) 0.266 -0.78 (-5.19-3.63) 0.723
ESR	-0.01 (-0.02-0.00) 0.011 0.00 (-0.05-0.03) 0.888	-0.01 (-0.01-0.00) 0.001 0.00 (-0.01-0.02) 0.656	-0.01 (-0.02-0.00) 0.210 0.00 (-0.04-0.04) 0.832	<0.01 (-0.01-0.01) 0.536 -0.01 (-0.05-0.02) 0.426	0.01 (-0.01-0.02) 0.277 0.01 (-0.05-0.06) 0.825	0.05 (-0.15-0.25) 0.617 0.56 (-0.51-1.62) 0.296	0.09 (-0.02-0.20) 0.107 0.47 (-0.10-1.04) 0.104
CRP	-0.02 (-0.03- -0.01) 0.002 -0.03 (-0.09-0.04) 0.431	-0.01 (-0.01-0.00) 0.000 0.00 (-0.02-0.03) 0.730	-0.01 (-0.02-0.00) 0.032 -0.02 (-0.09-0.04) 0.465	<0.01 (-0.01-0.01) 0.734* -0.06 (-0.12- -0.01) 0.026	0.01 (-0.01-0.02) 0.280 -0.02 (-0.10-0.07) 0.648	0.09 (-0.12-0.29) 0.402 0.98 (-0.48-2.44) 0.182	0.08 (-0.03-0.19) 0.161 0.16 (-0.65-0.98) 0.687
Females	TC† Beta (CI) and p-value	HDL† Beta (CI) and p-value	LDL† Beta (CI) and p-value	Trigly† Beta (CI) and p-value	TC:HDL ratio† Beta (CI) and p-value	Syst RR‡ Beta (CI) and p-value	Dia RR‡ Beta (CI) and p-value
DAS44	-0.02 (-0.19-0.14) 0.761* 0.25 (0.06-0.44) 0.011	-0.04 (-0.13-0.05) 0.352 0.04 (-0.07-0.14) 0.490	-0.02 (-0.15-0.12) 0.794* 0.15 (-0.01-0.31) 0.070	-0.02 (-0.15-0.10) 0.742 0.07 (-0.07-0.22) 0.327	0.16 (-0.02-0.33) 0.085 0.11 (-0.09-0.32) 0.281	-0.82 (-4.39-2.74) 0.648 -1.29 (-5.66-3.08) 0.558	-0.16 (-2.32-1.99) 0.882 -0.61 (-3.25-2.02) 0.645
ESR	-0.01 (-0.02-0.00) 0.067* 0.02 (-0.01-0.04) 0.156	<0.01 (-0.01-0.00) 0.160 -0.01 (-0.02-0.01) 0.417	-0.01 (-0.01-0.00) 0.115* 0.02 (0.00-0.04) 0.063	<0.01 (-0.01-0.01) 0.802 0.01 (-0.01-0.03) 0.465	<0.01 (-0.01-0.01) 0.757 0.02 (-0.01-0.04) 0.250	<0.01 (-0.17-0.18) 0.975 -0.25 (-0.34-0.84) 0.449	<0.01 (-0.10-0.11) 0.979 0.12 (-0.26-0.51) 0.522
CRP	-0.01 (-0.02-0.00) 0.015 -0.03 (-0.06-0.01) 0.145	-0.004 (-0.01-0.00) 0.044 -0.02 (-0.033-0.00) 0.098	-0.01 (-0.01-0.00) 0.022 -0.01 (-0.04-0.01) 0.340	<0.01 (-0.01-0.00) 0.283 -0.01 (-0.04-0.02) 0.435	<0.01 (-0.01-0.01) 0.944 0.01 (-0.02-0.05) 0.728	<0.01 (-0.17-0.18) 0.958 0.16 (-0.60-0.92) 0.677	-0.02 (-0.13-0.08) 0.691 0.10 (-0.35-0.55) 0.656

CI: confidence interval, CRP: C-reactive protein, CV: cardiovascular, DAS: disease activity score, Dia RR: diastolic blood pressure, ESR: erythrocyte sedimentation rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, Syst RR: systolic blood pressure, TC: total cholesterol, trigly: triglycerides Grey values: values after four weeks of treatment

** interaction with time p<0.10, †without statins, ‡without antihypertensives*

DISCUSSION

Comparison between the Dutch SCORE and Heart SCORE CV risk models revealed a slight agreement between low, medium and high CV risk categories.

According to the Dutch CV-RM guidelines, 30% of the early RA patients had an indication for (adaptations of) preventive treatment at baseline. However, 13% of all the patients had a different indication after four weeks of anti-rheumatic treatment. If baseline CV risk assessment would be applied, this would lead to potential overtreatment in 10% of all the patients.

The risk estimation of the two different CV risk calculators resulted in a significant difference in CV risk score. Clinically this will have an impact on the therapy and prevention strategies chosen, as a patient who is regarded as low risk by one calculator could be classified as high risk by another, and vice versa(7). The Dutch SCORE estimates more patients as high risk, 10 times more often than the Heart SCORE. Overestimating the CV risk can lead to unnecessary treatment, while underestimating may result in CV diseases which could have been prevented. This is partly explained as the Dutch SCORE measures the 10-year risk on CV morbidity and mortality, and the Heart SCORE only assesses the risk on mortality and does not take non-fatal CV events into account (5). However, morbidity can cause functional limitations, therefore it is important for patients and society, and should be taken into account in a CV risk model. In conclusion, it is important to know the limitations of the CV risk calculator which estimated the CV risk of your patient.

CV preventive treatment is proven to be effective, therefore it is important to assess CV risk (25-27). As an increased CV risk is already present in early RA, and might even be present in the preclinical phase, CV risk management should be applied early in the disease course (5;28-32). In the present study, we found that, according to the Dutch SCORE, already 30% of the patients were classified as high CV risk at the onset of RA. However, many patients were classified in a different risk category after the first month of anti-rheumatic treatment. In 13% of the patients, this led to a change in preventive treatment advice. This percentage would probably be lower when applying Heart SCORE, as more patients were calculated as low risk according to this risk model, and so less patients switched from risk category during follow-up. Still, both at baseline and after four weeks of anti-rheumatic treatment many patients needed CV preventive treatment according to the Dutch CV-RM guidelines and did not receive this, reflecting under-treatment, confirming

previous reports (33-35).

A higher disease activity was associated with an increased TC:HDL ratio, however the effect of disease activity on the Dutch CV risk SCORE gave inconclusive results. On the one hand, an increase in DAS44 was associated with lower CV risk, but on the other hand, higher ESR and CRP were associated with higher CV risk scores. Because inflammation generally leads to an increased TC:HDL ratio, a higher CV risk is expected if markers of inflammation are high (18;19). This association was opposite for DAS44, a possibility is that other components of the DAS like the visual analogue scale and/or tender joint count disturb this association. The association between measures of inflammation and cholesterol levels, especially TC:HDL ratio was strongest at baseline, when all patients had a high disease activity. At four weeks, nearly all patients had low disease activity, which explains why this association was not present anymore after four weeks. Although there was no unambiguous association between disease activity and CV risk score, we do think that it is important to calculate CV risk during a time of low disease activity.

The change in CV risk score and so the advice about preventive treatment is probably correlated with the reduction of disease activity or the initiation of anti-rheumatic treatment. Previous literature described a reduction in acute myocardial infarction with the use of methotrexate (RR 0.81), but a dose-dependent increase with glucocorticoid use (RR 1.32) (36-38). An improvement in TC:HDL ratio was found after one and two years of COBRA-light treatment, however this did not had a favorable effect on CV risk prediction (18;19). Furthermore, lower disease activity (obtained with anti-rheumatic treatment) was associated with a lower blood pressure (39;40).

Unfortunately, we could not take into account some additional CV risk factors, such as renal function, physical activity and family history of CVD. These factors are considered as CV risk modifying factors which can be an additional reason to give CV risk prevention treatment. Therefore, the lack of these factors may have influenced our results.

In addition to the Dutch SCORE and Heart SCORE, different CV risk scores are available. For example, the Framingham risk score is commonly used in the United States. However, this score is not generally applied in Europe and is limited to estimating the 10-year risk of a myocardial infarction and coronary heart disease-related death, thus underestimating the total atherosclerotic vascular disease

risk(31;41). Especially, risk calculators that correct for the Systematic inflammation are interesting. For example, the QRISK-2 and QRISK-3 calculators are used to predict CV risk in the United Kingdom, these calculators take RA into account as a separate CV risk factor. As a zip code is also a component of these algorithms, these calculators are not feasible in other countries (5;42). The Reynolds Risk score includes high-sensitivity CRP levels into the risk model, however this risk score is not recommended for patients with a Systematic inflammatory disease, as CRP levels will be increased due to the inflammatory disease (5). Further efforts were already performed to develop a RA-specific risk calculator, however, a new calculator (including DAS or HAQ) did not demonstrate an improvement compared to the current CV risk models which are used in the general population (43;44). The influence of fluctuations in disease activity over time in RA patients is difficult to incorporate in risk prediction models; single disease activity measurements (as DAS, CRP and ESR) are maybe not good enough, a biomarker that measures cumulative RA disease activity might fulfill this unmet need (44).

In conclusion, CV risk management is important early in the course of RA, as preventive CV treatment is proven to be effective and should be applied as early as possible (5;25-27;31). However, the timing of CV risk assessment, as well as the availability of different CV risk models, influences the advice on the need for (adaptations of) CV preventive treatment. Further research is needed to determine which risk model is optimal and when in the course of RA it should be applied.

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Competing interests

Non declared for this study.

Contributorship

All authors have substantially contributed to the conception or design of the work; the acquisition, analysis, and interpretation of data for the work. The authors revised the article critically and approved to the final version to be published. All agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethical approval
Medical Ethics Committee of the Slotervaart Hospital and Reade approved the protocol; patients gave written informed consent before inclusion, and the study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice

Provenance and peer review
Not commissioned, externally peer reviewed

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CHAPTER 6
Amplified prevalence and incidence of cardiovascular disease in patients with inflammatory arthritis and coexistent auto-immune disorders

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ABSTRACT

Objective

This study aims to assess the prevalence proportion and incidence rate of cardiovascular morbidity in patients with inflammatory arthritis compared with that in controls, and to determine whether the co-existence of multiple autoimmune disorders is associated with an amplified risk of cardiovascular disease.

Methods

Data from the Nivel Primary Care Database were used to assess prevalence proportion and incidence rate of cardiovascular disease in patients with inflammatory arthritis only, patients with inflammatory arthritis coexistent with another autoimmune disorder, and controls. Hazard ratios were calculated using Cox regression models.

Results

The prevalence proportions in inflammatory arthritis patients were increased for type 1 diabetes [odds ratio (OR) 1.80, 95% CI: 1.27, 2.55], hypothyroidism (OR 1.49, 95% CI: 1.37, 1.61), psoriasis (OR 2.72, 95% CI: 2.49, 2.97) and IBD (OR 2.64, 95% CI: 2.28, 3.07) compared with that in controls. Cardiovascular disease prevalence (OR 1.34, 95% CI: 1.28, 1.41) and incidence rates (incidence rate ratio 1.3, 95% CI: 1.23, 1.41) were higher in inflammatory arthritis patients compared with that in controls, and were further increased in the presence of a second autoimmune disorder. The hazard ratio for cardiovascular disease was 1.32 (95% CI: 1.23, 1.41) for patients with inflammatory arthritis only, and 1.49 (95% CI: 1.31, 1.68) for patients with inflammatory arthritis co-existent with another autoimmune disorder.

Conclusion

The amplification of cardiovascular disease risk in inflammatory arthritis patients with multiple autoimmune disorders warrants greater awareness, and since autoimmune disorders often co-exist, the need for cardiovascular risk management in these patients is once again emphasized.

INTRODUCTION

Inflammatory arthritis (IA) is an overarching term used to describe a group of conditions defined by inflammation of the joints. These diseases include, among others, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. IA is associated with an excessive risk of cardiovascular mortality and morbidity (1-3). Traditional and non-traditional cardiovascular risk factors, such as hypertension, dyslipidemia, smoking and obesity, inflammation, use of medication, e.g. NSAIDs and glucocorticoids, and also genetic factors contribute to this increased risk for cardiovascular disease (CVD)(3). A higher cardiovascular burden is not only found in inflammatory arthritis (IA) patients, but also in other inflammatory auto-immune disorders, such as psoriasis and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (5, 6). Diabetes mellitus is a well-known risk factor for CVD, both type 1 and 2 have been associated with increased CVD risk (7,8). Raterman et al demonstrated that the co-existence of hypothyroidism and rheumatoid arthritis is associated with an amplified CVD prevalence (9). In all of these disorders, it is considered that chronic (low grade) inflammation has a role in the pathogenesis of the accelerated atherosclerosis (10). This raises the question if cardiovascular risk is amplified in IA patients with co-existent auto-immune disorder.

This study aims to assess the prevalence proportion and incidence rate of cardiovascular morbidity in patients with inflammatory arthritis compared to controls, and to determine if the co-existence of multiple autoimmune disorders is associated with amplified risk of CVD. An increased CVD risk for IA patients has been demonstrated by many studies; however it is yet unknown if other auto-immune disorders are more common in IA patients and how this affects CVD risk. Thus far, the vast majority of studies is performed on a selected group of arthritis patients from academic clinics. Data from a representative IA population, consisting of patients with both high and low disease activity, are sparse. It's important to investigate CVD incidence rate and prevalence proportion in primary care patients, since data from a secondary setting might overestimate the magnitude of cardiovascular risk as patients with more severe disease exaggerate CVD rates. For this study, we used data originating from Dutch general practitioners (GP) electronic health records, in which GPs record medical information using recorded International Classification of Primary Care (ICPC) diagnoses (11).

METHODS

Study population

Data from Nivel Primary Care Database (Nivel-PCD) were used (12). Data were retrieved from EHRs from a sample of approximately 500 general practices with more than 1.5 million registered patients spread throughout the Netherlands. The International Classification of Primary Care (ICPC) is used to record medical diagnoses (11). The EHRs contain information on consultations, morbidity, prescriptions and diagnostic measures. When a prescription is issued, a diagnostic code is recorded and the selected drug is automatically linked to the Anatomical Therapeutic Chemical (ATC) Classification System (13). The patients and general practices are representative of the Dutch population. Since almost all Dutch citizens are registered at a primary care practice, Nivel-PCD does also contain patients who do not visit their GP on a regular basis. Furthermore, it is possible to estimate an epidemiological denominator. This study has been approved according to the governance code of Nivel-PCD, under number NZR-00317.041. Dutch law allows the use of electronic health records for research purposes under certain conditions. According to this legislation, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (Dutch Civil Law, Article 7:458). Our study database spanned the period January 1, 2010 through January 1, 2017. The start of follow up was defined as the date of cohort entry or in the case of incident IA, controls became cases with a start of follow up from the moment of the diagnosis. Patients and the public were not involved in the design, conduct or reporting of the research.

Selection of IA patients and controls

All patients who were recorded as having inflammatory arthritis (IA), based on ICPC-code L88 – 'Rheumatoid arthritis and related disorders', were selected for this study (11). The date of diagnosis is recorded in the database, this holds true for both incident and prevalent cases in whom the diagnosis was made before 1 January 2010. Selection based on this code might include some non-IA patients, and therefore we also performed our analysis using only subjects with an ICPC-code L88 in combination with specific anti-rheumatic drug prescriptions. Since this yielded similar results (a stronger effect size but less power), we only show the analyses using the larger group (selection on code L88 only). We matched all IA patients (cases) with controls (patients without ICPC code L88) in a 1:1 ratio, by age and sex in the same general practice. If a control subject received a diagnosis of IA during follow up, they became a case subject, and were subsequently matched.

Classification of auto-immune diseases

This study used a combination of recorded diagnoses and prescribed medication to determine whether the patient was diagnosed as having type 1 diabetes (ICPC code T90 and the start of insulin within the first year after recording the diagnostic code), hypothyroidism (ICPC code T86), psoriasis (ICPC code S91), multiple sclerosis (ICPC code N86), Crohn's disease and ulcerative colitis (ICPC code D94). The incidence rate and prevalence proportion of cardiovascular disease (CVD) were determined by recorded ICPC codes angina pectoris (K74), acute myocardial infarction (K75), other ischemic heart disease (K76), transient ischemic attack (TIA) (K89), stroke (K90), peripheral arterial disease (K92), decompensatio cordis (K77) and cor pulmonale (K82). In the tables we have used the term heart failure to include the diseases documented as decompensatio cordis and cor pulmonale. The composite variable CVD was composed of angina pectoris , acute myocardial infarction and other ischemic heart disease, cerebrovascular disease was composed of TIA and stroke, and heart failure of decompensatio cordis and cor pulmonale. When the outcome all CVD is used, this consist of all the above mentioned CVD diagnoses.

Statistical analyses

First, we determined the prevalence proportion of CVD and risk factors in IA patients compared to controls using logistic regression techniques. We assessed the prevalence proportion of CVD in three groups: controls, patients with only IA, and patients with IA with another coexistent auto-immune disorder. We regarded patients with IA and any other auto-immune disorder, but also calculated risks for the individual other auto-immune disorders separately. Incidence rate of CVD was assessed in patients without CVD at baseline by calculating incidence rates and incidence rate ratio's. Hazard ratios were calculated using cox regression models. All statistical analyses were performed with Stata/SE 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Prevalence rate of auto-immune disorders

We identified 28,345 IA cases with 28,249 matched controls. Two-thirds of the patients were female, the mean age was 60 years. We found an increased prevalence proportion of type 1 diabetes mellitus, hypothyroidism, psoriasis and Crohn's disease and ulcerative colitis in the IA population. On the other side, the prevalence proportion of multiple sclerosis was lower in cases compared to controls, but the absolute prevalence of multiple sclerosis in this cohort was very

small, only 5 cases, limiting the clinical significance of this finding. IA patients had an increased risk for other auto-immune diseases, with highest odds ratio for psoriasis [2.72 (2.49 - 2.97)] (table 1). However, the odds for prevalent multiple sclerosis was decreased in IA patients. Furthermore, patients with IA more often had one or more concomitant auto-immune disorders: in 13.5% of IA patients one auto-immune disorder other than IA was present vs in 7.3% of non-IA controls.

Table 1 | Prevalence proportion (%) of auto-immune disease

	Inflammatory arthritis (n=28345)	Controls (n=28249)	Odds ratio (95% CI)
Type 1 diabetes	0.31	0.17*	1.80 (1.27 – 2.55)*
Hypothyroidism	5.76	3.97*	1.49 (1.37 – 1.61)
Psoriasis	6.43	2.46*	2.72 (2.49 - 2.97)
Multiple sclerosis	0.15	0.24	0.64 (0.44 – 0.94)
Crohn's disease and ulcerative colitis	2.22	0.85*	2.64 (2.28 – 3.07)
1 other auto-immune disorder	13.45	7.31	1.97 (1.86 – 2.09)*
2 other auto-immune disorders	0.70	0.19	3.76 (2.77 – 5.09)*

*=p<0.001, CI = confidence interval, odds ratios are corrected for age and sex
Prevalence proportion is displayed as absolute percentage

Prevalence proportion of cardiovascular disease

Compared with controls, patients with IA had an increased prevalence proportion of all cardiovascular disease (corrected OR 1.34, 95% CI 1.28 – 1.41), as well as an increased prevalence proportion of hypertension (OR 1.23, 95% CI 1.18 – 1.27) and hypercholesterolemia (OR 1.09, 95% CI 1.03 – 1.15) (table 2). Correction for hypertension, hypercholesterolemia and diabetes yielded similar data (data not shown).

Table 2 | Prevalence proportion (%) of cardiovascular disease and risk factors

	Inflammatory arthritis	Controls	Odds ratio (95% CI)
Prevalence proportion of total CVD	18.84	15.5	1.34 (1.28 – 1.41)*
Coronary artery disease	9.9	7.98	1.27 (1.20 – 1.35)*
Cerebrovascular disease	4.9	4.55	1.07 (0.99 – 1.15)
Heart failure	4.15	2.92	1.43 (1.31 – 1.58)*
Peripheral vascular disease	3.9	2.69	1.46 (1.33 – 1.61)*

table continues

	Inflammatory arthritis	Controls	Odds ratio (95% CI)
Prevalence proportion of CV risk factors			
Hypertension	32.84	28.94	1.23 (1.18 – 1.27)*
Hypercholesterolemia	12.16	11.23	1.09 (1.03 – 1.15)*
Use of cardiopreventive medication			
Anticoagulants	29.57	26.65	1.39 (1.34 – 1.45)*
Antihypertensive medication	47.57	40.7	1.40 (1.35 – 1.45)*
Statin	3.9	2.69	1.22 (1.18 – 1.27)*

Prevalence proportion is displayed as percentage
*=p<0.001, CI = confidence interval, CVD = cardiovascular disease
Odds ratios are corrected for age and sex

Next, we examined if the risk for prevalent CVD was increased if there was a co-existent other autoimmune disorder. We found that for all outcomes, the risk increased for IA patients and this was further amplified if another auto-immune disorder was present (table 3). Correction for hypertension, hypocholesteremia and diabetes yielded similar data (data not shown).

Table 3 | Risk for prevalent CVD for IA patients with and without a co-existent other autoimmune disorder

	Controls (reference)	Inflammatory arthritis only	Inflammatory arthritis + any other autoimmune disorder
Odds ratio (95% CI)			
All CVD	1	1.34 (1.27 – 1.41)*	1.72 (1.57 – 1.89)*
Coronary heart disease	1	1.26 (1.18 – 1.35)*	1.72 (1.54 – 1.92)*
Cerebrovascular disease	1	1.07 (0.99 – 1.17)	1.22 (1.04 – 1.42)
Heart failure	1	1.44 (1.30 – 1.59)*	1.88 (1.59 – 2.22)*
Peripheral vascular disease	1	1.45 (1.31 – 1.61)*	1.70 (1.43 – 2.01)*
Prevalence proportion of CV risk factors	1	1.21 (1.16 – 1.26)*	1.60 (1.49 – 1.73)*
Use of cardioprotective medication	1	1.43 (1.37 – 1.49)*	1.81 (1.68 – 1.96)*

*=p<0.001, CI = confidence interval, CVD = cardiovascular disease
Odds ratios are corrected for age and sex

The risk amplification was also found when we looked separately at the addition of individual auto-immune disorders. The risk increase was largest if there was co-

existent type 1 diabetes (OR 3.55, 95% CI 2.08 – 6.06, p<0.001), but was also present for the co-existence of hypothyroidism (1.81 (1.59 – 2.07), p<0.001), psoriasis (1.66 (1.45 – 1.90), p<0.001) and Crohn's disease and ulcerative colitis (1.50 (1.16 – 1.95), p=0.002) and MS (2.15 (0.88 – 5.28)), although the last did not reach statistical significance (supplementary table 1).

Incidence rate of cardiovascular disease

In addition to prevalence proportions, we also examined the incidence rate of CVD. The median duration of follow up was 3.2 years, 3.1 for IA patients and 3.7 in controls. In IA patients, 1,969 new cases of CVD occurred in 69,195 person years, resulting in an incidence rate of 28.5. In controls, 1,555 new cases of CVD occurred in 72,013 person years, resulting in an incidence rate of 21.6 (table 4). Incidence ratios and hazard ratios were increased for all types of CVD for IA patients compared to controls (table 4) and remained significant after correction for diabetes, hypertension and hypercholesterolemia (data not shown). In addition to an increased prevalence proportion of CVD in the presence of other autoimmune disorders, we also found an increased incidence rate (table 5).

Table 4 | Inncidence rate of cardiovascular disease in cases and controls

	Inflammatory arthritis			Controls			IR ratio (95% CI)	Hazard ratio (95% CI)
	#	PY	Rate	#	PY	Rate		
All CVD	1969	69195	28.5	1555	72013	21.6	1.3 (1.23 - 1.41)*	1.32 (1.24 – 1.41)*
Coronary heart disease	782	71584	10.9	640	73814	8.7	1.3 (1.13 – 1. 40)*	1.26 (1.13 – 1.39)*
Cerebrovascular disease	645	72160	8.9	575	74163	7.8	1.2 (1.03 – 1.29)*	1.14 (1.02 – 1.28) (p 0.018)
Heart failure	442	72671	6.1	260	74840	3.5	1.8 (1.50 –2.05)*	1.75 (1.50 – 2.04)*
Peripheral vascular disease	338	72705	4.6	237	74833	3.2	1.5 (1.24 – 1.74)*	1.46 (1.24 – 1.73)*

*=p<0.001, CI = confidence interval, hazard ratios are corrected for age and sex

Table 5 | Risk of incident CVD (hazard ratio and 95% CI) for IA patients with and without a co-existent other autoimmune disorder

	Controls (reference)	Inflammatory arthritis only	Inflammatory arthritis + any other autoimmune disorder
All CVD	1	1.32 (1.23 – 1.41)*	1.49 (1.31 – 1.68)*
Coronary heart disease	1	1.29 (1.16 – 1.45)*	1.25 (1.01 – 1.54) (p 0.038)
Cerebrovascular disease	1	1.13 (1.0 – 1.27) (p 0.05)	1.44 (1.17 – 1.77) (p 0.001)
Heart failure	1	1.71 (1.45 – 2.01)*	1.90 (1.44 – 2.50)*
Peripheral vascular disease	1	1.41 (1.18 – 1.68)*	1.81 (1.35 – 2.43)*

*=p<0.001, CI = confidence interval, CVD = cardiovascular disease, odds ratios are corrected for age and sex

DISCUSSION

This study demonstrates an increased prevalence proportion of type 1 diabetes, hypothyroidism, psoriasis and Crohn's disease/ulcerative colitis in patients with IA compared to controls. Moreover,, patients with IA more often had one or more concomitant auto-immune disorders.

The clustering of auto-immune disorders has been described previously for RA, especially the co-occurrence of type 1 diabetes and hypothyroidism, and may be explained by involvement of shared cytokine pathways, like the interleukin and tumor necrosis factor (TNF) pathways and genetic pathways like the major histocompatibility complex (MHC) (14-18). For example, a polymorphism in the protein tyrosine phosphatase non-receptor type 22 (PTPN22) pathway is associated with RA, diabetes and autoimmune thyroid disease, and might contribute to auto-immunity by altering the thresholds for T and B cell receptor signaling(19, 20). Furthermore, predisposing factors to autoimmunity interact with environmental triggers such as exposure to certain infectious agents, drugs and smoking. And last, the presence of one autoimmune disease might render an individual at increased risk of other auto-immune disease by the body's altered immunologic mechanisms or exposure to immunosuppressive drugs. Our data support that clustering of auto- immune diseases in IA patients is common and physicians should be alert on this phenomenon when treating patients with IA.

Moreover, the prevalence proportion and incidence rate of CVD, with the exception of cerebrovascular disease, were increased for patients with IA, independent of the cardiovascular risk factors hypertension, hypercholesteremia and diabetes. As cerebrovascular disease includes both ischemia and bleeding, a possible explanation for this exception could be that IA patients have only an increased risk of one of the types of CVA, most likely ischemic CVA.

An increased CVD incidence rate in IA patients was already demonstrated by several studies, mostly hospital based, whereas our present cohort comprises primary care patients from the general population (21). While a large proportion of IA patients visits both the general practitioner and a rheumatologist, there are patients that are only treated in primary care, i.e. patients with low disease activity. It is likely that our database contains patients with lesser disease activity compared to secondary care cohorts, and thus better estimates CVD risk for the IA population. Furthermore, we were able to show a longitudinal effect, since data used for this study are collected in a longitudinal matter, registering all occurring disease episodes, prescriptions and primary care visits.

In addition, we found that the risk for prevalent and incident cardiovascular disease was increased in IA patients and that this was further amplified if another auto-immune disorder was present. Given the already high cardiovascular burden in IA patients, it is relevant to detect any risk enhancing factors in these patients. Previously, Raterman et al showed that the co-existence of hypothyroidism and inflammatory arthritis is associated with an amplified CVD risk (9). An increased cardiovascular risk has also been reported in psoriasis and psoriatic arthritis (3). For Crohn's disease and ulcerative colitis, and increased CV risk has been previously reported (5). There are several explanatory mechanisms behind the increased risk in the different auto-immune disorders, but a common denominator might be the chronic inflammatory state leading to accelerated atherosclerosis (10, 22). Currently, several guidelines for cardiovascular risk management incorporate RA as an additional CVD risk factor, although the exact risk increase for RA patients is not yet determined. Our data show that when more than one autoimmune disease is present, CVD risk is even further amplified, and should be taken into account when estimating CVD risk in IA patients.

Some limitations need to be considered. First, the use of ICPC-code L88 consists of different diagnoses, including for example spondyloarthropathy. Therefore, misclassification is possible, also because GPs are not always able to establish the

exact diagnosis the first time. However, this would only mean that the observed effects are underestimated and the true effect is even larger. Furthermore, the diagnosis of IA is usually made by a rheumatologist, and primary care physicians then register the diagnosis mentioned in the medical correspondence. Second, data on smoking status and certain other cardiovascular risk factors were unavailable, and our analysis could not be adjusted for these variables. Furthermore, we could not take into account all possible auto-immune disorders, since not all diseases have an individual ICPC-code. Nevertheless, we demonstrated that the presence of co-existent auto-immune disorder in IA patients increased CV risk in a longitudinal primary care dataset consisting of a large amount of patients and controls representative of the general population. Working with large datasets has some limitations, but these do not outweigh the benefits of analyzing longitudinal data over a period of 6 years with detailed registration of disease episodes.

In conclusion, because of the increased risk of a second autoimmune disorder in IA patients, physicians should screen for signs or symptoms of those diseases. Second, the amplification of CV risk in IA patients with multiple auto-immune disorders warrants awareness of this phenomenon and since auto-immune disorders often co-exists, the need for cardiovascular risk management in not only RA, but all IA patients especially with co-occurrent auto-immune disorder is once again emphasized.

Competing interest

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Authorship statement

All authors made substantial contributions to the conception of the work; the acquisition, analysis, and interpretation of data for the work, drafting the article or revising it. All authors approved of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. M. Heslinga is the guarantor for this work.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study

have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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CHAPTER 7
Co-existent subclinical hypothyroidism is associated with an increased risk of new cardiovascular events in rheumatoid arthritis - an explorative study

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Submitted

ABSTRACT

Objective
Autoimmune thyroid disease often coexists with rheumatoid arthritis (RA) and is associated with an elevated cardiovascular(CV) risk. However, studies in RA are scarce. To investigate whether autoimmune thyroid disease increases the risk of new CV disease (CVD) in RA.

Methods
Thyroid-stimulating hormone (TSH) and serum free thyroxine(FT4) were assessed in 323 RA patients participating in an ongoing prospective cohort study designed to assess CV risk factors, morbidity and mortality. Cox proportional hazard models were used to calculate hazard rates (HR) for new CVD and adjusted for age, sex, smoking, prevalent CVD, thyroxine replacement therapy and RA duration.

Results
Of the 323 participants, 65.3% were females aged 63 ± 7 years. At baseline 8.1% was hypothyroid (n=26, 16 clinical, 10 subclinical), 6.8% was hyperthyroid (n = 22, 13 clinical, 9 subclinical) and 85.1% (n=275) was euthyroid. 94 patients (29.1%) developed a new CV event during follow up. Compared to the euthyroid patients, age, sex and prevalent CVD adjusted HR was 2.83 (95% CI 1.13-7.09 P=0.026) for subclinical hypothyroidism. Further adjustment for smoking, thyroxine replacement therapy and RA duration resulted in a HR of 3.0 (95% CI 1.19–7.54; P=0.02) for CV events in patients with subclinical hypothyroidism.

Conclusion
There was no difference in CVD between RA patients with hypothyroidism and hyperthyroidism vs. euthyroid patients. Coexistence of subclinical hypothyroidism with RA was associated with a higher occurrence of new CV events. Treatment trials are needed to determine whether thyroxine supplementation can further improve cardiovascular outcome in these patients.

Keywords
rheumatoid arthritis, subclinical hypothyroidism, cardiovascular disease, thyroid disease

INTRODUCTION

In patients with rheumatoid arthritis (RA) the cardiovascular (CV) disease (CVD) risk is doubled, leading to an excess mortality (1-3). Several factors contribute to this amplified risk, such as traditional CV risk factors, inflammatory burden and the use of certain anti-rheumatic medications (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids) (4). It is unclear which (combination of) factors eventually lead to, and fully explain the increased CVD risk in RA. Hence, investigating novel pathogenic mechanisms and pathways is relevant.

Coexistence of autoimmune thyroid disease with RA has been associated with an elevated CVD risk, especially in hypothyroid patients, with Raterman et al. reporting an odds ratio (OR) of 4.1 and McCoy et al. a hazard ratio (HR) of 2.0 for new CV events (5, 6). For subclinical hypothyroidism (defined as normal free thyroxine concentrations with an elevated thyroid-stimulating hormone level), this association is much less consistent (7, 8). In the general population, the same is observed in hypothyroid patients, with relative risks (RR) of 1.15 for myocardial infarction (MI) and 1.96 for cardiac death when compared with euthyroid persons (7, 9-11). In addition, Ning et al. described an increased CV risk in subclinical hypothyroidism, especially in those with TSH levels of 10 mU/L or higher (9). Several other studies report an increased CVD risk in persons with subclinical hypothyroidism in the general population (10-12), but not all studies have found this association (13, 14).

Thyroid hormones exert a variety of positive effects on the cardiovascular system, such as a positive inotropic effect on the heart and a decrease in vascular resistance due to increased production of nitric oxide (15). In contrast, hypothyroidism is associated with lipid abnormalities that might contribute to accelerated atherosclerosis (8, 16). In line with this, we previously reported a fourfold higher risk of CVD in female RA patients with clinical hypothyroidism compared with euthyroid RA patients (17). Since the existing literature is mostly of cross-sectional origin (i.e. reporting prevalence of CVD in RA patients with thyroid dysfunction instead of incidence), we have assessed the relationship between thyroid abnormalities and new CV events in a previously described cohort of RA patients (5), now with long term follow up.

METHODS

Study population

The CARRÉ (CARdiovascular research and RhEumatoid arthritis) observational cohort study (n=353) was initiated to investigate the incidence of CVD and its risk factors in patients with longstanding RA. Study enrollment was between June 2000 and January 2002. As previously described (1), patients were eligible if they fulfilled the 1987 American College of Rheumatology classification criteria, were diagnosed with RA between 1989 and 2001, and were aged between 50 and 75 years. The participants were followed for 15 years, with study visits at baseline, 3 years, 10 years and a CV disease questionnaire in 2015 at 15 years. Study participants who were lost to follow up before the first study visit at 3 years were excluded from the analyses. All CV events were confirmed in medical records.

RA-related and thyroid function data

Demographic data, medical history, medication use, family history, and Disease Activity Score of 28 joints (DAS28) were assessed. C-reactive protein, erythrocyte sedimentation rate and (radiographic) erosions in hands and feet were assessed at all visits. Rheumatoid factor (RF), anti–citrullinated protein antibody (ACPA), TSH, serum free thyroxine (FT4), and thyroid peroxidase antibodies (anti-TPO) were only assessed at baseline and thyroid function was only available for 323 patients. Patients were classified into groups by their thyroid function as euthyroid, hyperthyroid (known diagnosis of hyperthyroidism or TSH <0.3 mU/L and FT4 >24 pmol/L), hypothyroid (known diagnosis of hypothyroidism or TSH >4.0 mU/L and FT4 <10 pmol/L), subclinical hypothyroid (TSH>4.0 mU/L and normal FT4) and subclinical hyperthyroid (TSH<0.3 mU/L and normal FT4).

CV risk factor assessments

Smoking status, blood pressure, body mass index (weight/height^2 in kg/m^2), total cholesterol (TC), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), triglycerides, TC/HDLc ratio, glucose, and HbA1c were assessed.

CV disease assessment

Fatal and non-fatal CV events verified in medical records were registered according to the International Statistical Classification of Diseases and Related Health Problems 9th revision (ICD-9 codes, 410.0 – 410.9, 435.9, 436, 443.9 and 798) as described previously (1). Sudden deaths were registered as CV mortality if this

was confirmed by autopsy. CV events were classified into prevalent CV disease at baseline and new CV events during follow up. Patients were censored after the first fatal or non-fatal CV event or death due to other reasons. The last (event-free) follow up visit was used as censor date for the participants who were lost to follow up. At 15 years, the remaining participants were censored at study cessation time: March 1, 2015. Medical records of the patients lost to follow up were searched in order to extract data on the occurrence of CV events.

Statistical analysis

All data has been analysed with IBM SPSS statistics version 23. Data are presented as mean ± standard deviation, median with an interquartile range or numbers and percentages. Cox proportional hazard models were used to calculate hazard rates (HR) for new CV events in patients with RA subdivided into patients who are euthyroid, hyperthyroid, hypothyroid, subclinical hyperthyroid or subclinical hypothyroid. These models were corrected for the following confounders based on literature: age, sex, prevalent CVD, smoking, thyroxine replacement therapy, and RA duration. A p-value of below 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of all patients are shown in table 1. Patients with missing thyroid function data, patients who were lost to follow up before the first study visit and non-caucasians (n= 30) were excluded. At baseline 8.1% of the patients had hypothyroidism (n=26, 16 clinical and 10 subclinical hypothyroidism), 6.8% had hyperthyroidism (n = 22, 13 clinical and 9 subclinical hyperthyroidism) and 85.1% (n=275) was euthyroid. 12 patients with clinical hypothyroidism, 1 patient with hyperthyroidism and 1 patient with subclinical hyperthyroidism were receiving thyroxine replacement therapy (RT) and they were all female. For 13 patients the duration of hypothyroidism was available, which was 23 (15 – 36) years. Systolic and diastolic blood pressure, sex, anti-TPO levels and thyroxine replacement therapy differed between the different thyroid function groups at baseline (supplementary table 1).

Development of new CV events

94 patients with RA (29%) developed a CV event during a median follow up of 11 years and 2916 patient years, resulting in an incidence rate of 3.22 CV events per 100 patient years. 36% (n=9) of the hypothyroid, 30.4% (n=7) of the hyperthyroid

Table 1 | Baseline characteristics of all participants

	N= 323
Demographics	
Age, years	63 ± 7
Females, no. (%)	211 (65.3)
Cardiovascular risk factors	
Previous CVD, no. (%)	47 (14.6)
Hypertension, no. (%)	197 (61)
Systolic BP, mmHg	142 ± 20
Diastolic BP, mmHg	81 ± 8
TC/HDLc ratio	4.4 ± 1.5
TC, mmol/L	5.8 ± 1.1
HDLc, mmol/L	1.5 ± 0.5
LDLc, mmol/L	3.7 ± 1.0
Triglycerides, mmol/L	1.32 (0.96 – 1.82)
Currently smoking, no (%)	94 (29.1)
Pack years	19 (2-38)
Body mass index, kg/m^2	26.7 ± 4.8
Diabetes, no. (%)	14 (4.3)
Thyroid function absolute	
TSH, mU/l	1.30 (0.91 – 1.90)
Anti-TPO positive, no. (%)	36 (11.1)
Anti-TPO, U/mL	102 (65 – 295)
Thyroid function groups	
Euthyroid	275 (85.1)
Hyperthyroid	22 (6.8)
Hypothyroid	26 (8.1)
Medication	
Antihypertensive drugs	82 (25.4)
Statins	37 (11.5)
Aspirin	54 (16.7)
Thyroxine replacement therapy, no. (%)	13 (4)
RA variables	
IgM-RF ≥30 U/mL	235 (72.8)
ACPA ≥50 kU/L	167 (51.7)
DAS28	3.9 ± 1.3
Disease duration	7 (4 – 10)
Erosion on radiographs	260 (80.5)

Continuous variables are presented as mean ± SD or median (IQR). Categorical and dichotomous variables are presented as numbers and percentages (%). CVD = cardiovascular disease; BP = blood pressure; TC = total cholesterol; LDLc = low-density lipoprotein; HDLc = high-density lipoprotein; pack years = (packs smoked per day)(years as a smoker); DM = type 2 diabetes mellitus; RA = rheumatoid arthritis; IgM-RF = immunoglobulin M rheumatoid factor; ACPA = Anti-citrullinated protein antibody; DAS28 = Disease Activity Score; TSH= thyroid-stimulating hormone; FT4= free thyroxine; anti-TPO= anti-thyroid peroxidase antibodies.*

and 28.2% (n=78) of the euthyroid RA patients developed a new CV event over time. Compared to the euthyroid persons, age and sex adjusted HR were 1.08 (95% CI 0.50-2.36; P=0.84) for hyperthyroid patients and 1,48 (95% CI 0.72-3.04; P=0.28) for hypothyroid patients. A closer look at the subclinical hypothyroid patients revealed a significantly higher incidence of new CV events, with an age, sex and prevalent CVD adjusted HR of 2.83 (95% CI 1.13-7.09 P=0.03) (table 2, figure 1). Further adjustment for smoking, thyroxine replacement therapy and RA duration resulted in a HR of 3.0 (95% CI 1.19–7.54; P=0.02) for CV events in patients with subclinical hypothyroidism (figure 1).

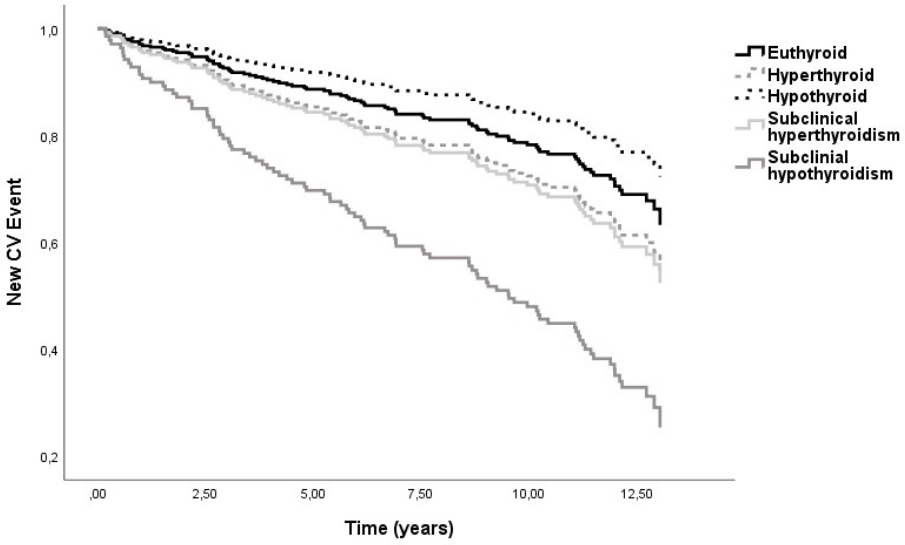

Figure 1 | Estimated survival probability stratified by thyroid function based on the multivariate Cox analysis

Table 2 | CV risk in thyroid dysfunction groups compared to euthyroid patients

	*HR**	*95%CI*	*P*
Hyperthyroid	1.09	0.34-3.55	0.88
Hypothyroid	0.70	0.25-1.97	0.50
Subclinical hyperthyroidism	1.36	0.50-3.72	0.55
Subclinical hypothyroidism	2.83	1.13-7.09	0.03

*adjusted for age, sex and prevalent CVD

DISCUSSION

In this explorative study, the prevalence of thyroid disorders is twice as high in RA patients when compared with numbers reported for the general population (18, 19). More importantly, coexistence of subclinical hypothyroidism in RA is associated with an increased risk of new CV events when compared with euthyroid RA patients. This is an important finding, as coexistence of subclinical hypothyroidism amplifies the already high CVD risk in RA patients. Interestingly, none of the patients with subclinical hypothyroidism was receiving thyroxine replacement therapy, in contrast to the majority of the patients with hypothyroidism. All patients on thyroxine replacement therapy were female. As patients with clinically overt hypothyroidism are generally treated with thyroxine supplements, this may decrease CVD risk, although this warrants further confirmation in treatment trials. Regarding CVD risk factors, a significantly higher systolic blood pressure was present in RA patients with hypothyroidism, compared with the other groups. There were no significant differences in the other traditional CVD risk factors.

Several limitations need mentioning. First, although the prevalence of thyroid disorders was higher in our RA population, the total number of patients was still small. However, the findings of this explorative study are in line with existing literature and underscore the necessity of further research. Second, some patients with subclinical hypothyroidism spontaneously convert to euthyroidism. Unfortunately, there was insufficient data available to investigate this further. Lastly, we did not have any information about therapy in the hyperthyroidism group and the duration of the thyroid disorder in a large number of patients, which could have influenced the results.

Despite these limitations, our results show that subclinical hypothyroidism may further amplify CVD risk in RA patients. Whether there is a direct relationship

between subclinical hypothyroidism (and high anti-TPO levels) and the increased CVD risk we identified, needs to be elucidated in treatment trials. If external validation can confirm this amplified CVD risk, cardiovascular risk management is warranted in this subgroup of patients, and the next question is whether thyroxine supplementation can further improve cardiovascular outcome in subclinical hypothyroid RA patients.

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Supplementary table 1 | Baseline characteristics of the different thyroid function groups

	Euthyroid (n= 275)	Hypothyroidism (n= 16)	Subclinical hypothyroidism (n=10)	Hyperthyroidism (n=13)	Subclinical hyperthyroidism (n=9)
Demographics					
Age, years	63 ± 7	67 ± 7	61 ± 6	65 ± 8	64 ± 6
Females, no. (%)*	171	16	6	13	5
Cardiovascular risk factors					
Previous CVD, no. (%)	42	3	0	0	2
Hypertension, no. (%)	161 (58.5)	14 (87.5)	6 (60)	9 (69.2)	7 (71.8)
Systolic BP, mmHg*	141 ± 16	157 ± 29	143 ± 18	145 ± 21	152 ± 20
Diastolic BP, mmHg*	80 ± 8	86 ± 10	81 ± 15	83 ± 8	85 ± 7
TC/HDLc ratio	4.38 ± 1.57	4.47 ± 1.71	4.44 ± 1.46	4.16 ± 1.13	4.23 ± 1.29
TC, mmol/L	5.82 ± 1.13	5.56 ± 1.01	5.92 ± 1.67	5.99 ± 0.85	5.01 ± 0.63
HDLc, mmol/L	1.46 ± 0.49	1.42 ± 0.55	1.45 ± 0.63	1.51 ± 0.30	1.27 ± 0.35
LDLc, mmol/L	3.72 ± 1.05	3.49 ± 1.13	3.97 ± 1.18	3.95 ± 0.86	2.97 ± 0.53
Triglycerides, mmol/L	1.32 (0.96 – 1.80)	1.46 (1.00 – 2.01)	1.21 (0.91 – 1.64)	1.25 (1.01 – 1.58)	1.59 (1.12 – 2.22)
Currently smoking, no (%)	83 (30.2)	3 (18.8)	3 (30)	1 (7.7)	4 (44.4)
Pack years	19 (2 – 40)	22 (0 – 40)	12 (0 – 18)	8 (0 – 26)	15 (2 – 24)
Body mass index, kg/m^2	27 ± 5	28 ± 4	27 ± 6.36	28 ± 6	29 ± 5
Diabetes, no. (%)	13 (14.7)	1 (6.3)	-	-	-
Thyroid function absolute					
TSH, mU/l	1.32 (0.95 – 1.84)	1.07 (0.33 – 3.75)	4.85 (4.3 – 9.02)	0.82 (0.52 – 1.32)	0.27 (0.11 – 0.35)
Anti-TPO positive, no. (%)*	25	3	5	1	1
Anti-TPO, U/mL*	10 (10 – 17)	10 (10 – 62)	82 (14 – 346)	10 (10 – 15)	10 (10 – 18)
Medication					
Antihypertensive drugs	68 (24.7)	6 (37.5)	1(10)	4 (30.8)	3(33.3)
Statins	32 (11.6)	2 (12.5)		1(7.7)	2 (12.2)
Aspirin	45 (16.4)	4 (25)	1(10)	1(7.7)	3 (3.33)
Thyroxine replacement therapy, no. (%)*	-	12 (75)	-	1(7.7)	1(11.1)

*Continuous variables are presented as mean ± SD or median (IQR). Categorical and dichotomous variables are presented as numbers and percentages (%). *Statistically significant difference. CVD = cardiovascular disease; BP = blood pressure; TC = total cholesterol; LDLc = low-density lipoprotein; HDLc = high-density lipoprotein; pack years = (packs smoked per day)*(years as a smoker); DM = type 2 diabetes mellitus; RA = rheumatoid arthritis; IgM-RF = immunoglobulin M rheumatoid factor; ACPA = Anti–citrullinated protein antibody; DAS28 = Disease Activity Score; TSH= thyroid-stimulating hormone; FT4= free thyroxine; anti-TPO= anti-thyroid peroxidase antibodies.*

PART 2
INTERVENTIONAL ASPECTS

CHAPTER 8
Changes in NT-proBNP and sRAGE levels in early arthritis after start of treatment

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Submitted

ABSTRACT

Objective

Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality, mostly caused by cardiovascular (CV) disease. Several biomarkers of CV function were found to be increased in RA with some suggesting a relationship with disease activity and improvement upon adequate antirheumatic treatment. Promising biomarkers include N-terminal pro-brain natriuretic peptide (NT-proBNP) and the soluble receptor form of advanced glycation end products (sRAGE). The objective of this study was to investigate associations between NT-proBNP and sRAGE levels with markers of inflammation and disease activity in early RA patients and their changes during (effective) antirheumatic treatment.

Methods

Data from 342 consecutive early RA patients participating in the "Parelsnoer" cohort were used. At baseline and after 6 months disease activity, NT-proBNP and sRAGE levels were assessed.

Results

After 6 months, NT-proBNP decreased from 83 pmol/l (mean) at baseline to 69 pmol/l at follow up, sRAGE increased from 997 pg/mL to 1125 pg/mL. A larger decrease in ESR or CRP was associated with larger changes in NT-proBNP and sRAGE. For every point decrease in ESR, there was a 1.7 point decrease in NT-proBNP and a 2.2 increase in sRAGE. For CRP this was 1.7 and 2.7 respectively ($P < 0.001$).

Conclusion

Suppressing disease activity, independent of achieving remission, increases sRAGE levels and decreases NT-proBNP levels. Whether this translates in a decrease of incident cardiovascular disease remains to be elucidated.

Significance and innovation

In early arthritis patients, disease activity (DAS28) is significantly associated with both NT-proBNP and sRAGE.

Initiation of treatment decreases NT-proBNP and increases sRAGE, and its magnitude is associated with change in markers of inflammation.

Suppressing disease activity, independent of achieving remission, increases sRAGE levels and decreases NT-proBNP levels.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality, mostly caused by cardiovascular disease (CVD), including myocardial infarction, cerebrovascular accident and heart failure.(1, 2) Previously , we demonstrated that the risk of developing CVD in RA was even higher than in diabetes.(3) This excess morbidity and mortality cannot be explained by traditional risk factors alone, as inflammation and medication effects also contribute.

Several markers for RA disease activity, including levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), numbers of affected joints and disease activity scores, are associated with CVD risk. (4-6) In the last decade, several biomarkers of CV function emerged that were increased in RA and related to disease activity. (7-9) Some of these CV function biomarkers improved upon optimal antirheumatic treatment. (10, 11) Thus far, data on these CV biomarkers in (very) early RA are sparse, particularly in this era of treat-to-target strategies.

Promising biomarkers include brain natriuretic peptide (BNP), its inactive metabolite N-terminal pro-brain natriuretic peptide (NT-proBNP) and advanced glycation end products (AGEs) and its soluble receptor form (sRAGE). BNP is a hormone primarily produced in atrial cardiomyocytes in the healthy heart, but in case of heart failure, the ventricular myocardium becomes the main site of BNP production. (12) NT-proBNP, the inactive N-terminal fragment of BNP, is used as a biomarker in CVD, mostly for heart failure (13-15). In RA patients, levels of CRP are correlated with levels of NT-proBNP (16, 17) and in the general population NT-proBNP has been shown to be a predictor of cardiovascular mortality (18).

AGEs are formed via non-enzymatic glycation of proteins and lipids in the aging process, but their formation is accelerated in various disorders including diabetes, renal disease and inflammatory diseases (19-21), such as RA. (22) AGEs elicit a pro-inflammatory state and are involved in numerous pathologic situations through interacting with their receptor RAGE. The soluble receptor form (i.e. sRAGE) prevents AGE/RAGE interaction, and in RA, sRAGE levels are lower compared to controls. (8) AGEs are involved in the pathogenesis of atherosclerosis through various mechanisms (23), such as the promotion of oxidized LDL formation, increase in vascular wall permeability and creation of reactive oxygen species and are observed in atherosclerotic lesions. (24)

This study aimed to investigate both cross-sectional and longitudinal associations between RA disease activity and NT-proBNP levels and sRAGE in early arthritis patients and study changes in these markers during (optimal) antirheumatic treatment, using data from the the Parelsnoer Institute (PSI) biobanking project. (25)

METHODS

Study setting and patients

The Parelsnoer Institute (PSI) is a collaborative biobanking project of all eight University Medical Centers in the Netherlands which was launched in 2007 includes fifteen large disease specific cohorts in 2020 (the so-called 'Parels' or 'Pearls'). Clinical and biochemical data collected as part of the Rheumatoid arthritis Pearl offers the possibility to investigate this in a cohort of early arthritis patients. (25) It aims to facilitate medical research, by providing an infrastructure and standard procedures for the establishment, expansion and optimization of clinical biobanks for scientific research. Fifteen 'Pearls' are identified within PSI, and for each Pearl a specific clinical dataset is established. The data in PSI are collected both via electronic and manual methods and are hosted in a web based application (ProMISe). Biomaterials are stored in UMCs according to the PSI biobanking protocol. All data are registered in a central database. For this study, data from patients included in the 'Rheumatoid arthritis and osteoarthritis' pearl were used. Patients were included in this Pearl with a non-traumatic arthritis (excluding septic arthritis or crystal arthritis), confirmed by a physician, and arthritis complaints less than two years. Diagnosis was then specified during the baseline visit: if patients fulfilled the *2010* ACR/EULAR Classification criteria, patients were diagnosed as having early RA. Data were collected at baseline, after 3, 6, 12, 18 and 24 months and yearly thereafter. For the purpose of this study, we used data from patients with early RA, i.e fulfilling the 2010 ACR/EULAR criteria. We used biobank data from the first 6 months of the study period. We included early RA patients if they had a baseline and 6 month visit, and if a DAS28-ESR score was done during both visits. Patients were excluded if there was no biomaterial available at baseline.

Study outcomes

At baseline, duration of arthritis and demographic data including age, gender, ethnicity, height, weight and smoking status were collected. Comorbidities were recorded by a trained study nurse. Disease activity was assessed at every study visit by the disease activity score of 28 joints (DAS28-ESR). (26) Laboratory parameters

were assessed, including include CRP and ESR, and biomaterial including serum, plasma and DNA was collected and biobanked at each visit. Rheumatoid factor (IgM-RF) and anti-citrullinated protein antibodies (ACPA) were only assessed at baseline. Medication use was recorded at each visit. Improvement of disease or response to therapy after 6 months was defined according to the EULAR response criteria. (27) To establish if remission was achieved after 6 months, the criterion DAS28-ESR <2.6 was used.

NT-proBNP en sRAGE assessment

Serum sRAGE concentrations were measured using an ELISA based technology that uses electrochemiluminescence for detection on a Meso Scale Discovery Quickplex SQ 120 Imager (cat. # F214Q, Meso Scale Discovery, Rockville MD; *intra-assay CV, 1,4% ; inter-assay CV: 8,8%).* Plasma levels of NT-proBNP were analysed using the Elecsys 1010 electrochemiluminescence immunoassay (Roche Diagnostics, Almere, the Netherlands). NT-proBNP values were compared to reference levels according to the PRIDE study guidelines (< 50 years of age, NT-proBNP ≤ 450 pmol/L; 50 to 75 years of age, ≤ 900 pmol/L and > 75 years of age, ≤ 1800 pmol/L). (28)

Statistical analyses

Patient characteristics are described as number and percentage, means ± standard deviation (SD), when normally distributed, or median and interquartile range (IQR) when not normally distributed.

Linear regression analyses were performed to assess univariate associations between disease activity as independent variable and NT-proBNP and sRAGE as dependent variable at baseline. Linear mixed model analyses were used to assess longitudinal associations between disease activity and NT-probBNP and sRAGE. All analyses were adjusted for age, gender, smoking status, BMI, history of diabetes, hypertension and previous CVD. Furthermore, we calculated the changes in DAS28, CRP, ESR, NT-proBNP and sRAGE after 6 months. We tested associations between magnitude of change in markers of disease activity (e.g. DAS28-ESR, CRP and ESR) after 6 months and magnitude of change in NT-proBNP and sRAGE levels after 6 months using linear regression. We also used linear regression to detect a difference in change in NT-proBNP and sRAGE levels between the group in remission and the group not in remission at six months. For the statistical analysis SPSS version 25.0 (SPSS IBM software, USA) was used. The threshold for significance was set at p <0.05 (two-sided), with no correction for multiple testing.

RESULTS

Patient characteristics

For this study, data from 342 consecutive patients from 4 centers was used. Patients had a mean disease duration at baseline of 5.3 months. Baseline characteristics are shown in table 1.

Table 1 | Baseline characteristics of the early RA patients

Demographics		
Gender, female, n (%)	227	(66.4%)
Age, mean ± SD	57	(14)
Etnicity, Caucasian, n (%)	313	(94.8%)
Disease characteristics		
Symptom duration in months, mean ± SD	5.3	± 8.5
RF positive, n (%)	130	(40.6%)
ACPA positive, n (%)	97	(32.1%)
DAS28-ESR, mean ± SD	4.1	± 1.0
ESR, median (IQR)	22	(11-36)
CRP, median (IQR)	9	(3-21)
BMI, kg/m^2, mean ± SD	26.9	± 4.9
Smoking status, n (%)		
Never	111	(33.9%)
Former > 6 months	133	(40.7%)
Former < 6 months	2	(0.6%)
Current smoker	81	(24.8%)
Comorbidity, n (%)		
History of CVD	12	(3.5%)
Hypertension	84	(24.6%)
Diabetes	5	(1.5%)
Use of medication, n (%)		
NSAIDs	184	(84.8%)
Hydroxychloroquine	5	(3.2%)
Prednisolone	37	(23.6%)
Methotrexate	63	(40.1%)
Other nbDMARD	5	(2.1%)
Biologic DMARD	4	(1.7%)
Biomarkers		
NT-proBNP (pmol/ml), median (IQR)	83.4	(43.3-158.3)
sRAGE (pg/ml), mean ± SD	997	± 483

ACPA: anti citrullinated protein antibodies, BMI: body mass index, CRP: C-reactive protein, CVD: cardiovascular disease, DAS28: disease activity score of 28 joints, DMARD: disease modifying anti rheumatic drug, ESR: erythrocyte sedimentation rate, IQR: interquartile range, nbDMARD: non-biologic DMARD, NT-proBNP: N-terminal pro-brain natriuretic peptide, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor, SD: standard deviation, sRAGE: soluble receptor advanced glycation end product

Disease activity

At baseline, 64% of the patients had moderate disease activity (DAS28-ESR between 3.2 and 5.1), 20% had low disease activity (DAS28-ESR between 2.6 and 3.1) and 15% of patients had highly active disease (DAS28-ESR above 5.1). At 6 months , 99 (29.3%) of the patients were non-responders, 89 (26.3%) were moderate responders and 150 (44.4% were good responders. After 6 months, 162 (47.6%) achieved remission (DAS28-ESR <2.6) (table 2).

Table 2 | Disease activity

	Baseline	6 Months
Mean DAS28-ESR	4.10 ± 1.02	2.77 ± 1.13
< 2.6	5 (1.5%)	162 (48.1%)
< 3.2	68 (20.2%)	66 (19.6%)
< 5.1	214 (63.5%)	99 (29.4%)
> 5.1	50 (14.8%)	10 (3.0%)
EULAR response		
Non-responder	na	99 (29.3%)
Moderate responder	na	89 (26.3%)
Good responder	na	150 (44.4%)

DAS28-ESR: disease activity score of 28 joints

Correlation of markers of disease activity with NT-proBNP and sRAGE

NT-proBNP and sRAGE were correlated with variables of disease activity, both at baseline and over time (table 3 and 4). A rise in DAS28-ESR, ESR and CRP was associated with increased NTproBNP levels values and decreased sRAGE levels. Remarkably, only 7 patients had a NT-proBNP value above threshold for their age. (28)

Changes in NT-proBNP and sRAGE after 6 months

After 6 months of treatment, the median value of NT-proBNP decreased from 83

pmol/ml at baseline to 69 pmol/ml at follow up, the mean change in NT-proBNP was -28.94 (p<0.001) for all patients. sRAGE increased from 997 pg/ml at baseline to 1125 pg/ml after 6 months of treatment, the mean increase was 127.59 (p<0.001). We found no significant associations between change in DAS28 and change in NT-proBNP or sRAGE, or between responders and non-responders after 6 months of treatment. However, a larger decrease in ESR or CRP levels was associated with a larger decrease in NT-proBNP and greater increase in sRAGE levels. For every point change in ESR, there was a 1.7 point decrease in NT-proBNP and a 2.2 increase in sRAGE. For CRP this was 1.7 and 2.7 respectively (table 4).

Table 3 | Correlation between NT-proBNP, sRAGE and markers of disease activity at baseline

	DAS28-ESR	ESR	CRP
NT-proBNP			
Unadjusted	1.19 (1.06-1.33) P = 0.003	1.01 (1.01-1.02) p <0.001	1.02 (1.01-1.02) p <0.001
Model 2	1.21 (1.03-1.43) p = 0.022	1.01 (1.00-1.01) p <0.001	1.02 (1.01-1.02) p <0.001
Model 3	1.21 (1.03-1.42) p = 0.020	1.01 (1.00-1.01) p = 0.001	1.02 (1.01-1.02) p <0.001
sRAGE			
Unadjusted	-73.58 (-123.50- -23.66) P = 0.004	-3.54 (-5.71- -1.38) P = 0.001	-6.12 (-8.68- -3.56) p <0.001
Model 2	-54.76 (-123.480-13.97) P = 0.118	-2.93 (-5.15- -0.71) P = 0.010	-5.28 (-7.87- -2.70) p <0.001
Model 3	-68.02 (-136.76-0.72) P = 0.052	-2.83 (-5.17- -0.49) P = 0.018	-5.32 (-7.98- 2.67) p <0.001

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, smoking status, BMI and history of diabetes, hypertension and CVD

After 6 months, 162 (47.6%) achieved remission (DAS28 <2.6). In these patients, mean Δ NT-proNBP was 39, versus 29 in the patients not in remission. Changes in sRAGE were 168 and 122 respectively. These differences reached no statistical significance.

Table 4 | Longitudinal correlations between disease activity and NT-proBNP and sRAGE

	DAS28-ESR	ESR	CRP
NT-proBNP			
Unadjusted	1.16 (1.09-1.23) p <0.001	1.01 (1.01-1.01) p <0.001	1.01 (1.01-1.02) p <0.001
Model 2	1.16 (1.09-1.23) p <0.001	1.01 (1.01-1.01) p <0.001	1.01 (1.01-1.02) p <0.001
Model 3	1.16 (1.09-1.24) p <0.001	1.01 (1.01-1.01) p <0.001	1.01 (1.01-1.02) p <0.001
sRAGE			
Unadjusted	-78.60 (-103.56- -53.60) P <0.001	-4.16 (-5.56- -2.76) P <0.001	-4.94 (-6.52- -3.36) p <0.001
Model 2	-81.31 (-106.12- -56.49) P <0.001	-4.29 (-5.71- -2.86) P <0.001	-5.21 (-6.81- -3.62) p <0.001
Model 3	-82.97 (-107.49- -58.45) P <0.001	-4.33 (-5.71- -2.95) P <0.001	-5.11 (-6.64- -3.58) P <0.001

Model 2: adjusted for age and gender

Model 3: adjusted for age, gender, smoking status, BMI and history of diabetes, hypertension and CVD

Table 5 | Associations between change in disease activity and change in NT-proBNP and sRAGE after 6 months

	Δ NT-proBNP	Δ sRAGE
Δ DAS28	-11.0 (-23.9 - 1.8)	4.5 (-23.5 - 32.4)
Δ ESR	1.7 (0.8 - 2.6)	2.2 (-4.4 - -0.3)
Δ CRP	1.7 (0.8 - 2.6)	2.7 (-4.5 - -0.7)

DISCUSSION

In our cohort of very early RA patients, we demonstrated associations between NT-proBNP and sRAGE and CRP, ESR and DAS28, both at baseline and during follow-up. During 6 months of treatment with anti-inflammatory medication, NT-proBNP decreased and sRAGE increased. There was an association between the magnitude of change in inflammatory markers (ESR and CRP) and change in NT-proBNP and sRAGE. Also, mean NT-proBNP was lower and mean sRAGE higher in patients in remission. To our knowledge this is the first study that found these longitudinal associations in very early RA patients.

A recently published study described a higher serum sRAGE in RA patients compared to healthy controls; serum sRAGE positively correlated with DAS28. (30) In this study, only cross sectional correlations were investigated. A relation between CRP and NT-proBNP has previously been described in a cohort of 238 RA patients. However, these patients had a substantially longer disease duration (16), Moreover, the investigators analyzed their data in a dichotomous way, rather than with a continuous analysis, thereby limiting the interpretation. Another study demonstrated a higher level of BNP in RA patients, similar to our cohort, compared to healthy controls, and RA patients with active RA having higher BNP levels than RA patients with moderately active or inactive disease (17), but this was not studied prospectively. In the IDEA study, researchers demonstrated that NT-proBNP values in RA patients decreased after treatment with infliximab and methotrexate. (31). Thus far there have been no longitudinal studies investigating AGEs in very early RA.

Several limitations need to be considered. Although we did demonstrate a decrease in NT-proBNP, all values were within normal limits for age and gender. Therefore, the clinical significance remains unknown. However, based on the mechanisms behind the production of NT-proBNP and sRAGE, we hypothesize that suppression of inflammation benefits the myocardium and endothelium. In heart failure patients, a greater decrease in NT-proBNP declines morbidity and mortality. (31) A prospective study on the effects of sacubitril-valsartan on cardiac outcomes demonstrated that reduction in NT-proBNP concentrations over 12 months correlated with improvements in markers of cardiac volume and function. (32)

Results from the ECHOES (Echocardiographic Heart of England Screening study) cohort demonstrated that an increased NT-proBNP level, even still within normal limits, increased the risk of developing heart failure over time. (33) Another limitation of this study is that we had no information on some of the possible confounders, for example cholesterol levels. However, correction for other CV confounders that are correlated with cholesterol levels, such as smoking, BMI and hypertension did not influence our results.

In conclusion, suppressing disease activity, independent of achieving remission, increases sRAGE levels and decreases NT-proBNP levels. Both of these markers have been associated with CVD in the general population. Our results imply that RA treatment might positively affect these markers, independently of whether or not remission is achieved. The strength of this study is that we were able to examine these markers over time in a cohort of very early arthritis patients. It provides yet

more evidence that prompt suppression of inflammatory activity, maybe even particularly in early RA is essential not only to preserve synovium and cartilage, but also endothelium and myocardium. Obviously, the association with 'hard' cardiovascular endpoints needs to be further investigated.

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Contributors

Study design: MH, RA, DW, TH, JL, AB, WL, MN. Data collection: TH, JL, AB, WL, MN. Data analysis: MH, RA, MN. Interpretation of findings: MH, CT, RA, DW, TH, JL, AB, WL, MN. Preparation of manuscript: MH, CT, RA, DW, TH, JL, AB, WL, MN. All authors read and approved the final manuscript.

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CHAPTER 9
The Effects of 5-year Etanercept Therapy on Cardiovascular Risk Factors in Patients with Psoriatic Arthritis

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ABSTRACT

Objectives
To investigate the effects of etanercept on lipid metabolism and other known CVD risk factors in patients with PsA.

Methods
In an observational cohort of 118 consecutive patients with PsA, CVD risk factors were assessed over a period of 5 years. Mixed model analyses were performed to investigate the effects of etanercept therapy on CVD risk factors over time.

Results
Disease Activity Score (DAS28), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) decreased during therapy with etanercept. There was an increase in total cholesterol (TC), high density lipoprotein cholesterol (HDLc) and low density lipoprotein cholesterol (LDLc). The TC/HDLc ratio remained unaltered. The apolipoprotein B to apolipoprotein A-I (apoB/apoA1) ratio decreased significantly. An increase in CRP was associated with an increase in the apoB/apoA1 ratio.

Conclusions
Serum lipid concentrations showed small changes over a 5 year period of etanercept therapy and were inversely associated with inflammatory markers. Other CVD risk factors remained stable. The apoB/apoA1 ratio decreased over time and an increase in disease activity was associated with an increase in this ratio. However, this modest lipid modulation cannot explain the observed beneficial cardiovascular effects of etanercept and etanercept likely exerts its favourable cardiovascular effects through inflammation-related mechanisms.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory joint disorder (IJD) that occurs in approximately 14 to 30 percent of patients who are affected by the skin condition psoriasis. (1;2) In the last decade, severe psoriasis, but also rheumatic diseases such as rheumatoid arthritis (RA), have been associated with an increased risk of developing cardiovascular disease (CVD).(3) There is accumulating evidence that PsA should also be considered a disease that is accompanied by a heightened CVD risk (4;5). However, literature about the underlying mechanisms that generate this increased risk is scarce. In all inflammatory arthropathies, including PsA, accelerated atherosclerosis is observed as a consequence of inflammatory mediators that also play an important role in the development and progression of these disorders, such as tumor necrosis factor alpha (TNF-α). TNF-α is a powerful pro-inflammatory cytokine that induces inflammation in skin and joints, but also in vascular endothelium, by which it directly influences vascular morphology. (6) Additionally, TNF-α is known to modify traditional risk factors for CVD, such as the lipid metabolism, insulin resistance and body weight, presumably further increasing CVD risk.(7) Indeed, an increased prevalence of lipid disorders, hypertension and obesity have been reported in both psoriasis (8) and PsA. (3;9;10) Yet, hyperlipidemia, an important and modifiable CVD risk factor, is rarely observed in its 'classic' form in IJD (11). Generally, inflammation induces a decrease in all serum lipids and this is usually reversed by effective anti-inflammatory therapy, though conflicting literature exists. It is suggested that other lipid measurements, such as apolipoprotein B (apo B) and the ratio between apolipoprotein B and apolipoprotein A-I (apo B/apo A1 ratio) might be better predictors of CVD risk in these patients, as conventional lipid profiles are difficult to interpret in the context of high-grade inflammation. (12;13) Optimal anti-inflammatory therapy is thought to reduce CVD risk in all IJD and this might be mediated by favorable changes in cardiovascular risk factors (e.g. the lipid profile). (14) However, the long term effects of anti-inflammatory treatment, especially of biological agents, on CVD risk and CVD risk factors in patients with PsA have not yet been adequately investigated. Etanercept, a potent inhibitor of TNF-α, has beneficial effects on CVD risk in patients with RA, an effect thought to be partially mediated by favourable effects on the lipid profile.(15) For PsA, literature on the association between disease activity and lipid levels is limited, although it is assumed that lipids are also modified by inflammation in PsA. (16) Thus far, long-term effects of etanercept on lipid levels and other CVD risk factors in PsA are unknown. Therefore, we investigated the effects of etanercept therapy on cardiovascular risk factors, with special

focus on lipid profiles, in a cohort of patients with PsA with extended follow up.

METHODS

Study population

118 consecutive patients who were diagnosed with PsA and scheduled to receive their first ever prescription of etanercept were recruited for an observational cohort at the department of Rheumatology in the Jan van Breemen Institute in Amsterdam between April 2004 and February 2014. The diagnosis of PsA was made by a rheumatologist. All patients started etanercept according to the consensus statement on initiation of treatment with biologicals . Treatment was with subcutaneous administration of etanercept alone, either 50 mg once a week or 25 mg twice a week, or with concomitant methotrexate and/or prednisone. The study was conducted in compliance with the declaration of Helsinki and approved by the local Medical Ethics Committee of Slotervaart Hospital, approval number P0538 was provided. Written informed consent was obtained from all patients.

Study design

Patients visited the Rheumatology outpatient clinic at the Jan van Breemen Institute for study assessments at baseline, 1, 3, 6 and 12 months and every following year up to 5 years of etanercept therapy. Disease activity was measured with the Disease Activity Score (DAS28), the Psoriasis Area and Severity Index (PASI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Prior and current medication use, systolic and diastolic blood pressure and body mass index (BMI = weight / height2, in kg/m2) were recorded at each visit. Triglycerides (TG) and total cholesterol (TC) were assessed using an enzymatic colorimetric test. High density lipoprotein cholesterol (HDLc) was measured using polyethylene glycol (PEG) modified enzymes. Low density lipoprotein cholesterol (LDLc) was calculated using the Friedewald formula when triglycerides were lower than 4.5 mmol/l. TC/HDLc ratios were calculated. Apolipoprotein A1 (apo A) and apolipoprotein B (apo B) were measured in a subpopulation of 81 patients with an immunoturbidimetric assay. All blood samples were determined batch wise.

Statistical analysis

Data are presented as mean ± standard deviation (SD) in case of normal distribution and otherwise as median and interquartile range (IQR) or numbers and percentages. Log transformations were done if necessary. Mixed models analyses were performed to assess the changes in CV risk factors over time and their relation to

disease activity parameters such as DAS28, CRP and ESR, because this method is designed for analyzing cohort data with missing values. The unstructured random covariance type was used. Patients were only included in the analysis if study assessments were performed at baseline and at least at one other visit during follow up. The univariate models were adjusted for potential confounders age, gender, disease duration, concomitant MTX, prednisone, NSAIDs, antihypertensives and statin use. A P-value less than 0.05 was considered statistically significant. All data were analyzed with SPSS version 20.0.

RESULTS

The study population consisted of 118 patients with a mean age of 47 ± 13 years and a nearly equal proportion of men (n=58) and women (n=60). The baseline characteristics are presented in table 1. Patients had a median psoriasis duration of 13 (5 – 22) years and a median arthritis duration of 6 (2 – 13) years. 12 patients had previously been treated with adalimumab and 1 with infliximab. 53 patients were using methotrexate (MTX) and 9 patients were using prednisone concomitantly with etanercept. The median duration of etanercept treatment was 4 (2 – 5) years.

Table 1 | Baseline characteristics

	n=118
Demographics	
Age, years	47±13
Females	60 (50.8)
PsA related factors	
Psoriasis duration, years	13 (5-22)
Arthritis duration, years	6 (2-13)
Psoriasis Area Severity Index	0 (0-2)
Disease Assessment Score 28	4.36±1.39
Swollen joint count	5 (2-10)
Tender joint count	7 (3-15)
ESR, mm/h	16 (6-28)
CRP, mg/L	6 (2-14)
VAS disease activity	59±24
Health assessment questionnaire	1.0 (0.5-1.6)
Anti-inflammatory medication use	
Use of previous biologics	13 (11.0)

table continues

	n=118
Concomitant methotrexate use	53 (44.9)
Methotrexate dose, mg/wk	19.0±7.5
Concomitant prednisone use	9 (7.6)
Prednosine dose, mg/day	7.2±3.6
Use of other DMARDs	11 (9.3)
NSAIDs use	58 (49.2)
CVD-related factors	
Current smoking	15 (12.7)
Body mass index, kg/m^2	27±6
Obesity	67 (56.8)
Systolic blood pressure, mmHg	130±22
Diastolic blood pressure, mmHg	81±10
Hypertension	47 (39.8)
Diabetes mellitus	8 (6.8)
Antihypertensive use	28 (23.7)
Statin use	11 (9.3)
Creatinine, umol/L	75±18
Lipid profile	
Total cholesterol, mmol/L	5.31±1.24
HDL cholesterol, mmol/L	1.43±0.43
LDL cholesterol, mmol/L	3.21±1.05
LDL ≥ 2.5*	88 (74.6)
Triglycerides, mmol/L	1.29 (0.85-1.87)
Total cholesterol/HDLc ratio	3.99±1.37
Apolipoprotein A1, g/L**	1.55±0.42
Apolipoprotein B, g/L**	0.89±0.27
ApoB/Apo A1 ratio**	0.6±0.2

Values are presented as mean ± SD, median (IQR) or numbers (percentages). VAS= visual analogue scale, NSAIDs= nonsteroidal anti-inflammatory drugs, HDL= high density lipoprotein, LDL = low density lipoprotein.

*sulfasalazine, hydroxychloroquine, leflunomide, *dyslipidemia, **Apolipoproteins were available for a subgroup of 81 patients

Changes in inflammatory parameters

Study assessments were performed at baseline, 4, 16, 28, 52, 104, 156, 208 and 260 weeks. ESR, CRP and DAS28 decreased significantly over time, with the greatest decrease in the first month after the start of etanercept treatment (figure 1).

DAS28 remained high in patients who discontinued therapy after 28 (3.13±1.65 vs. 1.98±1.08; p=0.003) and 52 weeks (2.86±1.45 vs. 1.62±0.94; p=0.001). CRP and ESR were significantly elevated in the patients who discontinued therapy after 28 (ESR 9 (3-30) vs. 4 (2-8); p=0.028 and CRP 2 (1-12) vs. 2 (1-3); p=0.049) and 52 weeks (ESR 19 (5-39) vs. 4 (2-7); p=0.009 and CRP 5 (2-10) vs 1(1-2); p=0.003). In the mixed models analysis patients who discontinued therapy had higher DAS28 in comparison to patients who continued etanercept treatment over 5 years (RC 0.56 95%CI 0.12-0.99; p=0.013). The PASI did not differ between these patients (data not shown). The reasons for discontinuing therapy were remission (n=8), failure (n=11), adverse events (n=10), migration or non-response (n=9), pregnancy wish (n=1), and other unknown reasons (n=3).

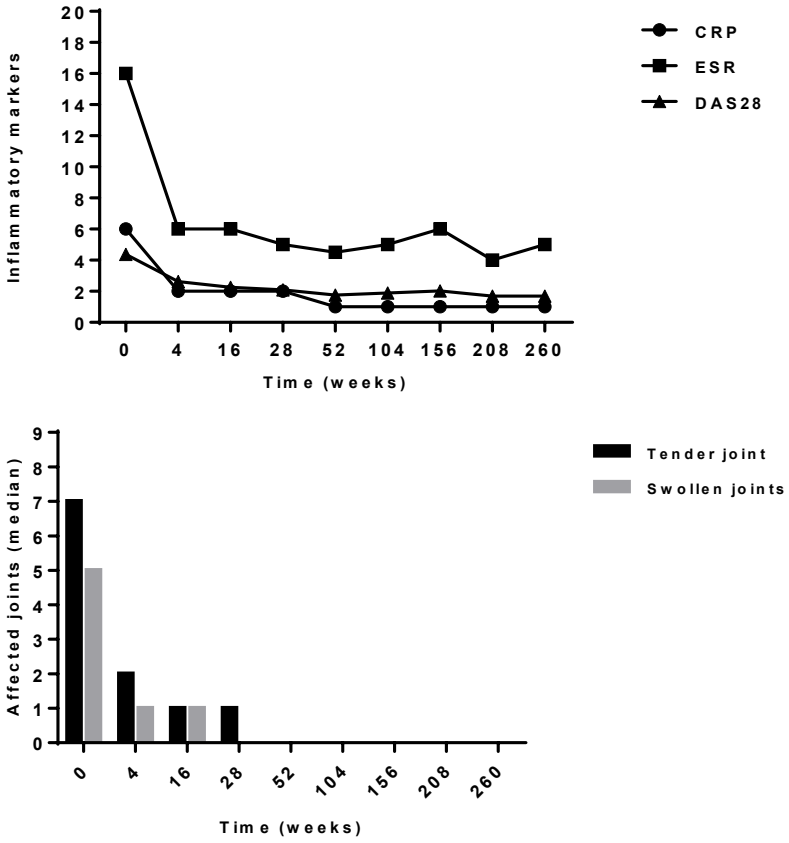

Figure 1 | Disease activity parameters *CRP= C-reactive protein, ESR= erythrocyte sedimentation rate, DAS28= disease assessment score 28.*
CRP and ESR are presented as median (IQR), DAS28 is presented as mean ± SD.

Changes in CVD risk factors over time during etanercept therapy

At baseline 39.8% of the patients had hypertension, 74.6% had dyslipidemia and 56.8% was overweight. TC/HDLc ratio was above 3.5 in 56.4% of the patients and 6.8% had diabetes.

The mixed models analysis showed a significant increase in TC, HDLc and LDLc over 5 years after correction for age, gender, disease duration, concomitant MTX, prednisone and statin use. Apo A1 and Apo B measurements were available in a subpopulation of 81 patients. The ApoB/ApoA1 ratio decreased significantly over 5 years, while the TC/HDLc-ratio remained stable (table 2). Blood pressure, BMI, creatinine, and triglycerides remained stable over the years (table 2). The mean lipid levels per visit are shown in figure 2.

Table 2 | Mixed models analysis of changes in CVD related factors over 5 years

	Mean	*RC*	*95% CI*	*P-value*
Systolic blood pressure	130 ± 20	-0.001	-0.02 – 0.02	0.92
Diastolic blood pressure	81 ± 11	0.002	-0.01 – 0.01	0.66
BMI	27 ± 5	0.002	-0.0001 – 0.004	0.07
Creatinine	75 ± 17	-0.003	-0.01 – 0.01	0.55
Total cholesterol	5.38 ± 1.12	0.0008	0.0001 – 0.001	0.03
*Adjusted**		*0.0008*	*-0.0001– 0.002*	*0.02*
HDLc	1.34 ± 0.45	0.0005	0.0001 – 0.001	<0.01
*Adjusted**		*0.0005*	*0.0002 – 0.001*	*<0.01*
LDLc	3.19 ± 0.98	0.0008	-0.0001 – 0.002	0.03
*Adjusted**		*0.0009*	*-0.0001 – 0.002*	*0.02*
Triglycerides	1.37 (0.96 – 2.00	-0.00003	-0.0005 – 0.0005	0.99
TC/HDLc-ratio	4.01 ± 1.30	0.0006	-0.0006 – 0.002	0.31
Apo A1^	1.59 ± 0.34	0.00001	-0.0005 – 0.0005	0.98
Apo B^	0.89 ± 0.24	-0.0001	-0.0004 – 0.0001	0.34
ApoB/apoA1 ratio^	0.58 ± 0.20	-0.0002	-0.0005 – 0.00001	0.06
*Adjusted**		*-0.0003*	*-0.0005 - -0.00005*	*0.02*

BMI=body mass index, HDLc= high density lipoprotein cholesterol, LDLc= low density lipoprotein cholesterol, TC/HDLc- ratio = total cholesterol to high density lipoprotein cholesterol ratio, Apo A1= apolipoprotein A1, Apo B = apolipoprotein B, ApoB/ApoA1 ratio = apolipoprotein B to apolipoprotein A1 ratio.

**adjusted for age, gender, disease duration, concomitant MTX, prednisone and statin use.*

^subanalysis of 81 patients at baseline with apo a1 and apo b measurements available.

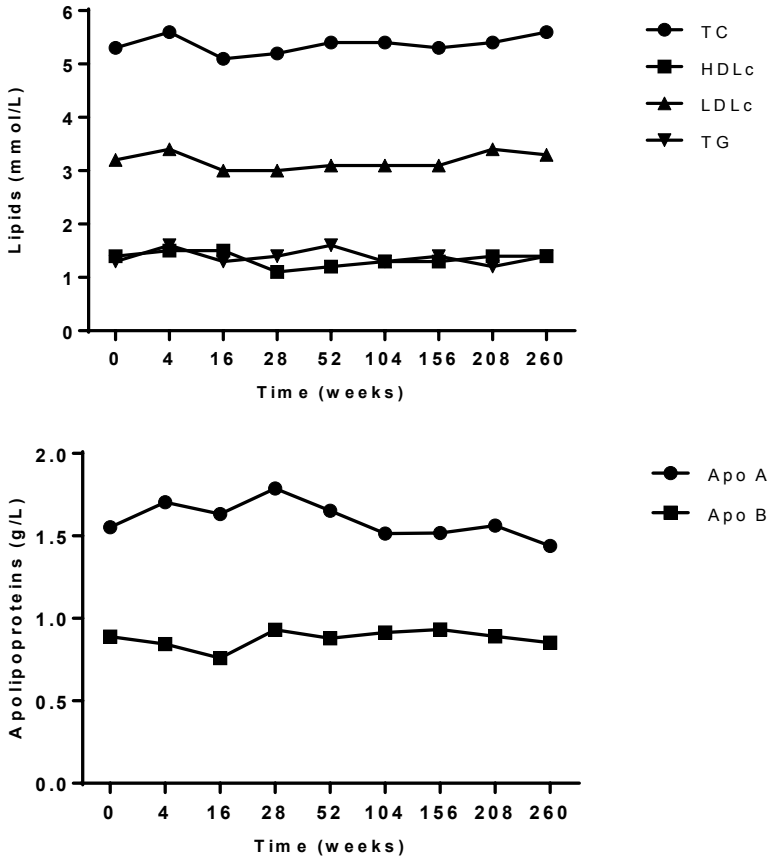

Figure 2 | Changes in lipids over a 5-year period.

Relationship between CVD risk factors and disease activity

In the mixed models analyses changes in DAS28 were associated with changes in diastolic blood pressure, TC, HDLc and triglycerides (table 3). One point increase in DAS28 was associated with an increase in diastolic blood pressure, a decrease in TC and triglycerides. This association was still significant after adjustment for age, gender, disease duration and concomitant medication use (table 3). There was a trend for an increased apo B/ apo A1 ratio with one point increase in DAS28 (p=0.057). A point increase in DAS28 was associated with an increase in HDLc. However, this was not significant after correction for above mentioned variables. The TC/HDLc ratio did not change significantly with changes in DAS28. When patients were split into responders vs. nonresponders, patients with a DAS28 above 2.6 as opposed to patients with a DAS28 under 2.6 had lower TC and triglycerides, while the HDLc was

increased (table 4). An increase in CRP was associated with a decrease in TC (RC -0.09, 95%CI -0.16 – -0.02, P= 0.02) and an increase in the apo B/Apo A1 ratio (RC 0.03 95%CI 0.004 – 0.05, P=0.02). There was a trend for a decrease in triglycerides (RC-0.04, 95%CI -0.08 – 0.003, P=0.07) and in apo A1 (RC -0.05, 95%CI -0.09 – 0.01, P= 0.077) after adjustment for above mentioned confounders.

Table 3 | Association between DAS28 and CVD related factors over 5 years

	Mean	*RC*	*95% CI*	*P-value*
Systolic blood pressure	130 ± 20	0.43	-0.41 – 1.28	0.31
Diastolic blood pressure	81 ± 11	0.64	0.12 – 1.17	0.02
*Adjusted**		*0.56*	*0.03 – 1.09*	*0.04*
BMI	27 ± 5	-0.001	-0.099 – 0.097	0.98
Creatinine	75 ± 17	-0.18	-0.76 – 0.39	0.53
Total cholesterol	5.38 ± 1.12	-0.05	-0.09 – -0.007	0.02
*Adjusted**		*-0.05*	*-0.09– -0.01*	*0.02*
HDLc	1.34 ± 0.45	0.04	0.01 – 0.06	0.007
*Adjusted**		*0.03*	*0.000001 – 0.05*	*0.05*
LDLc	3.19 ± 0.98	-0.02	-0.06 – 0.03	0.47
Triglycerides#	1.37 (0.96 – 2.00)	-0.03	-0.05 – -0.01	0.006
*Adjusted**		-0.03	-0.06 – -0.01	0.008
TC/HDLc-ratio	4.01 ± 1.30	-0.04	-0.11 – 0.02	0.21
Apo A1^	1.59 ± 0.34	-0.0008	-0.03 – 0.03	0.96
Apo B^	0.89 ± 0.24	0.009	-0.008 – 0.03	0.29
ApoB/apoA1 ratio^	0.58 ± 0.20	0.01	-0.003 – 0.03	0.11
*Adjusted**		*0.014*	*-0.0004 – 0.03*	*0.057*

BMI=body mass index, HDLc= high density lipoprotein cholesterol, LDLc= low density lipoprotein cholesterol, TC/HDLc- ratio = total cholesterol to high density lipoprotein cholesterol ratio, Apo A1= apolipoprotein A1, Apo B = apolipoprotein B, ApoB/ApoA1 ratio = apolipoprotein B to apolipoprotein A1 ratio.

^subanalysis of 81 patients at baseline with apo a1 and apo b measurements available.

**adjusted for age, gender, disease duration, concomitant MTX, prednisone, nsaids, antihypertensives and statin use. #log transformed*

Table 4 | CV risk factors in DAS28>2.6 vs. DAS28<2.6 over 5 years

	Responder	*Nonresponder*	*RC*	*95% CI*	*P-value*
Systolic blood pressure	128 ± 19	133 ± 20	2.01	-0.65 – 4.67	0.14
Diastolic blood pressure	80 ± 10	82 ± 12	1.27	-0.37 – 2.92	0.13
BMI	25.9 ± 3.8	28.7 ± 5.8	-0.27	-0.55 – 0.004	0.05
Creatinine	76 ± 14	74 ± 21	-0.80	-2.26 – 0.66	0.28
Total cholesterol	5.45 ± 1.02	5.29 ± 1.25	-0.16	-0.29 – -0.02	0.03
*Adjusted**			*-0.017*	*-0.31– -0.03*	*0.02*
HDLc	1.31 ± 0.45	1.38 ± 0.45	0.11	0.04 – 0.18	0.004
*Adjusted**			*0.08*	*0.009 – 0.16*	*0.03*
LDLc	3.23 ± 0.92	3.15 ± 1.07	-0.06	-0.20 – 0.07	0.35
Triglycerides#	1.37 (0.99 – 2.04)	1.38 (0.95 – 1.90)	-0.09	-0.16 – -0.01	0.02
*Adjusted**			-0.09	-0.16 – -0.01	0.02
TC/HDLc-ratio	4.01 ± 1.26	4.03 ± 1.34	-0.08	-0.27 – 0.11	0.41

*BMI=body mass index, HDLc= high density lipoprotein cholesterol, LDLc= low density lipoprotein cholesterol, TC/HDLc- ratio = total cholesterol to high density lipoprotein cholesterol ratio. *adjusted for age, gender, disease duration, concomitant MTX, prednisone, antihypertensives and statin use. #log transformed*

DISCUSSION

Etanercept therapy effectively reduced DAS28, CRP and ESR, as markers of disease activity, in patients with PsA, with the greatest reduction of disease activity at six months. This reduction persisted until five years of therapy in those who continued treatment. At baseline a substantial proportion of the patients had hypertension (39.8%), dyslipidemia (74.6%) and was overweight (56.8%). In addition, 56.4% of the patients had an elevated TC/HDLc ratio and 6.8% had diabetes. This is consistent with previous reports of an increased prevalence of traditional CVD risk factors in PsA patients.(3;9) Interestingly, the majority of patients showed nearly normal TC, HDLc and TG values at baseline. Over a five year period of etanercept therapy, patients with PsA showed a significant increase in TC, HDLc and LDLc. Similarly as in RA, where it has been reported that during times of active inflammation, LDLc and HDLc decrease, while anti-inflammatory treatment, for example with TNF inhibitors, can reverse this. There is a non-linear relationship between lipid levels and CVD risk in inflammatory joint disorders (most data is available for RA). A decrease in lipid levels (i.e. total cholesterol, LDL cholesterol and triglycerides), is often seen in patients with active inflammation, while their CVD risk is increased.

During treatment with anti-inflammatory agents lipid levels increase in these patients, which is considered to be a normalization of lipid levels. In this study, we demonstrated that this phenomenon also holds true for PsA, i.e. treatment with etanercept increases lipid levels. This increase in lipids should probably be considered as a normalization of serum lipid levels and a reflection of effective anti-inflammatory therapy, rather than an adverse effect of etanercept. To avoid misinterpretation of cardiovascular risk status in these patients, measurement of lipid levels for the purpose of cardiovascular risk estimation should preferably be performed when disease activity is stable or in remission. The other CVD risk factors, i.e. blood pressure, BMI, creatinine, and TG remained stable over the years, although there was a trend for an increase in BMI in these patients (p=0.07). Increases in BMI with TNFi treatment has been described previously in patients with psoriasis (16-18) and PsA.(18) Furthermore, the TC/HDLc-ratio remained stable over 5 years, which is to be expected as these lipid values generally change in the same direction during inflammation and suppression of inflammation with therapy. (17) Normally, this would indicate that the CVD risk remains stable over 5 years. However, there was a significant decrease in the apoB/apoA1 ratio over time, which could reflect a decrease in CVD risk. A previous study showed that the ApoB/ApoA1 ratio is associated with an increased risk of fatal myocardial infarction in men and in women (RR 1.23, 95%CI 1.18-1.27 and 1.38, 95%CI 1.25-1.52 respectively).(18) Intriguingly, elevated disease activity markers, i.e. DAS28 and CRP, were associated with an unfavorable lipid profile, i.e. lower TC and triglycerides but an increase in the apo B/apo A1 ratio (RC 0.03 95%CI 0.004 – 0.05), a possible reflection of an increase in CVD risk. Also, there was a trend for a decrease in apo A1, the cardio protective component of HDLc, with one point increase in CRP. In line with this, over time an increase in DAS28 was associated with a small increase in diastolic blood pressure (0.56 mmHg per point increase in DAS28) and there was a trend for an increased HDLc and apoB/apoA1 ratio per point increase in DAS28 (p=0.057). This might seem surprising, as HDLc is known as cardio protective and most studies report a decrease in HDLc during inflammation, although these studies have focused on RA and not on PsA. These 'conflicting' results may indicate that a raise in HDLc does not necessarily translate into a favorable lipid and CVD risk profile in patients with high disease activity, as HDL composition rather than its levels determine its function.(19)

HDLc which is normally considered anti-atherogenic, could change into a pro-atherogenic molecule due to modification of HDLc subcomponents under inflammatory conditions. In our study, the decrease in apo A-I (trend) and the

increase in apoB/apoA1 ratio, with elevation of inflammatory markers, suggest a change in the HDLc molecule to a more pro-atherogenic HDLc under high-grade inflammation. Thus, we consider the higher TC and TG in patients with low DAS28 scores in this study a normalization of serum lipid levels and a reflection of effective anti-inflammatory therapy. Conversely, the patients with high DAS28 who had lower total cholesterol and triglycerides, and higher HDL cholesterol are considered to have a worse CVD risk profile, also in accordance to existing literature on this subject.

Several limitations should be considered. The changes in lipid levels were small in this study and the clinical relevance of such small changes is probably limited. Additionally, apolipoprotein values were only available in a subpopulation of patients. Therefore, mixed models was used as it is designed to analyse this type of data. However, we expect that these findings will be even more significant in a larger group of patients, as we have already found significant differences in apolipoproteins in this small group of patients with PsA.

Nevertheless, our study demonstrates stable CVD risk factors, especially a stable lipid profile in a heterogeneous population of patients with PsA over a five year period of etanercept therapy. To our knowledge, no other study has described changes in CVD risk factors over an extended period of time in patients with PsA receiving TNFi therapy, although a beneficial effect of TNFi on surrogate markers of atherosclerosis (i.e. carotid intima media thickness) in PsA has been reported. (20) Furthermore, significant changes in apoB/apoA1 ratio, BMI and diastolic blood pressure were found over time during etanercept therapy, reflecting a possible beneficial effect on lipid subcomponents, blood pressure, body composition, and consequently CVD risk in these patients. However, these changes were only small and require further study. Modulation of lipids and other known CVD risk factors probably only partially explains the favourable effects of anti-TNF therapy on CVD risk. Hence, the presumed beneficial effects of TNFi on CVD risk in PsA appears to be mediated by other mechanisms, likely related to inflammation.

Acknowledgements
None

Competing interests
The authors declare that they have no competing interests.

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CHAPTER 10
Favorable effects on the hemostatic system in ankylosing spondylitis patients treated with golimumab

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ABSTRACT

Objectives

Ankylosing spondylitis (AS) patients with active disease have an increased cardiovascular risk. Tumor necrosis factor alpha (TNF), an important mediator in the inflammatory pathway, induces an imbalance between clotting and fibrinolysis, resulting in a hypercoagulable state, thus amplifying not only the arterial cardiovascular risk, but also the risk for venous thromboembolism (VTE).

Methods

In this study on the effects of starting golimumab on the coagulation and fibrinolytic systems in AS patients inflammation markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were compared to coagulation and fibrinolytic parameters Prothrombin fragment 1+2 (F1+2), Thrombin-antithrombin complex (TAT), Plasmin-alpha 2-antiplasmin complex (PAP), von Willebrand factor (VWF) and D-Dimer, at baseline and after 4 weeks of golimumab therapy.

Results

Thirty-five patients were included. Both median (IQR) CRP and ESR decreased after one month of treatment (from 5.5 (2.1-15.5) to 2.0 (1.0-5.0) and from 13 (6-25) to 4 (2-11) respectively). All coagulation markers also decreased, F1+2 from 436 (351-508) to 324 (178-484), TAT from 4.7 (3.2-6.0) to 3.6 (3.0-4.9) , VWF from 151 (61) to 132 (41) , PAP from 671 (459-988) to 440 (386-650) and D-Dimer from 0.28 (0.19-0.38) to 0.23 (0.17-0.30).

Conclusions

AS patients with active disease have signs of an activated coagulation system. During treatment, a larger decrease of inflammation markers induced by golimumab therapy was associated with a larger decrease in coagulation parameters. Whether the decreased coagulation status results in a lower risk for VTE remains to be established in long-term clinical studies.

INTRODUCTION

Inflammatory joint diseases are associated with increased cardiovascular risk; there are many studies reporting on the incidence of arterial thrombosis in clinical manifestations like myocardial infarction and stroke.(1) An important mediator in the inflammatory pathway is tumor necrosis factor alpha (TNF)(2). In the general population, TNF induces an imbalance between clotting and fibrinolysis resulting in a hypercoagulable state, thus amplifying not only the arterial cardiovascular risk, but also the risk for venous thromboembolism (VTE)(3-5). It is known that TNF-inhibitors (TNFi) decrease the arterial CV risk, but the effect on risk factors for VTE is not known(6). Moreover, there are only sparse data indicating that coagulation activation may be increased in AS patients and that suggests a relationship with inflammation and disease activity(7). Therefore, we investigated the effect of golimumab on the coagulation and fibrinolytic systems in consecutive AS patients treated with golimumab.

The immune and coagulation systems are closely linked by a shared origin, and current literature points to increased activity of both the coagulation and fibrinolytic systems in patients with inflammatory joint diseases(7). TNF is a key player in several inflammatory joint diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). For this study, we used AS as a 'human model' to study the interplay between inflammation, anti-inflammatory medication and coagulation. Our objective was to examine the effect of TNFi therapy on coagulation and fibrinolysis makers.

MATERIALS AND METHODS

Study protocol

Patient data from our observational cohort 'Golimumab and AS' were used for this study. This cohort included patients between March, 30th 2012 and February 12th 2016 at the Amsterdam Rheumatology and Immunology Center (locations Reade and VU University Medical Center) in the Netherlands.

All consecutive AS patients who initiated golimumab therapy, as prescribed by a rheumatologist in routine daily practice, were asked to participate in this longitudinal cohort. In this cohort, study variables including demographic variables, disease related outcomes and blood samples were collected at baseline (before the start of golimumab) and after 1 month of golimumab use. Inclusion criteria for

this cohort were a previous diagnosis of AS according to the 1984 modified New York criteria for AS, prescription of golimumab in accordance with the international consensus of the Assessment of Spondyloarthritis international Society (ASAS) for initiating TNFi in AS, age of 18 years or older and exclusion criteria were the prior use of golimumab or language barrier(8, 9). All patients were treated with golimumab 50 mg through subcutaneous injection once a month.

This study was performed in compliance with the declaration of Helsinki and approved on July 23th 2012 by the local Medical Ethics Committee of Slotervaart and Reade Hospital (NL 39155.048.11, METC P1166.) All patients gave written informed consent.

Outcome measures

At baseline and after 4 weeks of treatment, the patients were assessed by a physician or research nurse, evaluating the disease status, concomitant medication and adverse events. Physical examination, including height, weight, and blood pressure, was performed at every visit according to standard hospital procedures. Laboratory measurements included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Prothrombin fragment 1+2 (F1+2), Thrombin-antithrombin complex (TAT), Plasmin-alpha 2-antiplasmin complex (PAP), von Willebrand factor (VWF) and D-Dimer. AS-specific variables included the Ankylosing Spondylitis Disease Activity Score–CRP (ASDAS-CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Statistical analysis

Data are presented as mean (± SD), median (with first and third quartile), or percentages.

All laboratory analyses were performed in the Department of Experimental Vascular Medicine of the Amsterdam University Medical Centers. D-dimer levels were determined with a particle-enhanced immunoturbidimetric assay (Innovance D-Dimer, Siemens Healthcare Diagnostics, Marburg, Germany). Prothrombin fragment F1+2 and Thrombin-antithrombin complex were determined by Enzygnost monoclonal ELISAs from Siemens Healthcare Diagnostics.PAP was analyzed by ELISA from DRG Diagnostica. VWF antigen levels were determined with an ELISA developed in our laboratory using antibodies from Dako (Glostrup, Denmark).

RESULTS

Patient characteristics

Thirty-five patients were included in the cohort, 22 (63%) male, 13 (37%) female, with a median disease duration of 8 years. Of all patients who started golimumab, 17 were TNFi-naïve and 18 had previously used one or more other TNFi. Baseline characteristics are shown in table 1.

Seventeen TNFi switchers switched because of failure of the previous TNFi, 1 person switched because remission was achieved during treatment with the first TNFi but a flare occurred later on.

Table 1 | Baseline characteristics

N=35		
Age, years (±SD)	45	(± 12)
Male, no (%)	22	(63 %)
Disease duration, years, median (IQR)	8	(3-19)
TNFi-naïve, no (%)	17	(49 %)
Switcher, failure on 1 TNFi, no (%)	9	(26 %)
Switcher, failure on 2 TNFi, no (%)	9	(26 %)
BASDAI, mean (±SD)	6.1	(± 1.4)
ASDAS-CRP, mean (±SD)	3.5	(± 0.9)
ESR, mm/h, median (IQR)	13	(6-25)
CRP, mg/L, median (IQR)	5.5	(2.1-15.5)
NSAID use, no (%)	27	(77 %)
Prednisone use, no (%)	4	(11 %)
History of CVD, no (%)	2	(6 %)
Smoking status		
None, no (%)	24	(69 %)
Current, no (%)	9	(26 %)
Past, no (%)	2	(6 %)

Continuous variables are presented as means ± SD or as medians (IQR). Categorical and dichotomous variables are presented as numbers and/or percentages. ASDAS = Ankylosing Spondylitis Disease Activity Score; TNFi = Tumor Necrosis Factor inhibitor; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; CVD = cardiovascular disease; ESR = erythrocyte sedimentation rate; NSAID = non-steroidal anti-inflammatory drug

Association between disease activity and markers of coagulation

In comparison to historical controls, AS patients had, at baseline, higher levels of coagulation activation markers (10). First, we examined the association of markers of disease activity (ASDAS, BASDAI, CRP and ESR) at baseline with markers of coagulation and fibrinolysis. Results are displayed in table 2A and table 2B. We found that, at baseline, higher values of CRP and ESR were significantly associated with higher levels of PAP and D-Dimer: higher inflammatory markers means an increase in PAP and D-Dimer. This was also the trend for the other coagulation markers, although this was not statistically significant. However, we could not find an association between the more subjective markers ASDAS and BASDAI after 4 weeks of treatment. Nevertheless, we found that higher CRP and ESR were associated with increased coagulation markers, although this association was no longer statistically significant.

Table 2A | Association between disease activity and coagulation-markers at baseline

	F1+2	TAT	PAP	VWF	D-Dimer
ASDAS	-106 (-386-174)	-1.0 (-2.3-0.2)	116 (-59-290)	-3.2 (-30.1-23.7)	0.16 (-0.03 – 0.36)
BASDAI	-0.18 (-144.96-144.6)	-0.19 (-1.25-0.88)	34 (-64-132)	-3.2 (-16.7-10.3)	0.047 (-0.057-0.150)
CRP	-4.0 (-16.8 – 8.8)	0.046 (-0.049 – 0.141)	10 (2 – 18)	0.78 (-0.74-2.29)	0.10 (0.02 – 0.19)
ESR	-3.5 (-11.8-4.7)	0.046 (-0.013-0.106)	6.1 (0.5-11.6)	0.48 (-0.50-1.5)	0.006 (0.000-0.012)

ASDAS: AS Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, F1+2 = prothrombin fragment 1+2, TAT: thrombin-antithrombin complex, PAP: Plasmin-antiplasmin complex, VWF: von Willebrand factor

Table 2B | Association between disease activity and coagulation-markers at 4 weeks

	F1+2	TAT	PAP	VWF	D-Dimer
BASDAI	10 (-35-55)	0.19 (-0.19-0.57)	-5.6 (-48.9-37.7)	-0.70 (-12.3-10.9)	0.012 (-0.010-0.033)
CRP	-4.0 (-10.6-2.6)	0.003 (-0.103-0.108)	4.0 (-6.9-14.9)	-0.24 (-1.81-1.33)	0.002 (-0.002-0.005)
BSE	1.4 (-7.7-10.4)	0.001 (-0.138-0.140)	6.5 (-7.7-20.7)	1.8 (-0.1-3.6)	0.003 (-0.001-0.007)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, F1+2 = prothrombin fragment 1+2, TAT: thrombin-

antithrombin complex, PAP: Plasmin-antiplasmin complex, VWF: von Willebrand factor
NB Association between ASDAS and markers of coagulation was not performed due to missing values

Change in markers of disease activity and markers of coagulation after 1 month of treatment

Second, we assessed how markers of inflammation, coagulation and fibrinolysis changed over time. We found a decrease in ESR and CRP after one month of treatment, and a decrease in all markers of coagulation. (Table 3)

Table 3 | Values of markers of inflammation and coagulation at baseline and after 4 weeks

	Baseline	Week 4
ASDAS-CRP, mean (±SD)	3.5 ± 0.9	2.6 ± 1.1
BASDAI, mean (±SD)	6.1 ± 1.4	4.9 ± 2.4
ESR, mm/h, median (IQR)	13 (6-25)	4 (2-11)
CRP, mg/L, median (IQR)	5.5 (2.1-15.5)	2.0 (1.0-5.0)
F1+2, pmol/L , median (IQR)	436 (351-508)	324 (178-484)
TAT, µg/L, median (IQR)	4.7 (3.2-6.0)	3.6 (3.0-4.9)
PAP, µg/L, median (IQR)	671 (459-988)	440 (386-650)
VWF, %, median (IQR)	141 (109-187)	127 (107-155)
D-Dimer, mg/L, median (IQR)	0.28 (0.19-0.38)	0.23 (0.17-0.30)

ASDAS: AS Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, F1+2 = prothrombin fragment 1+2, TAT: thrombin-antithrombin complex, PAP: Plasmin-antiplasmin complex, VWF: von Willebrand factor

Overall, we found that coagulation markers decreased to a larger extent in patients with a greater decrease in disease activity, as represented by a greater decrease in CRP and ESR (Table 4).

Table 4 | Association between change in CRP and ESR and markers of coagulation at week 4

	ΔF1+2	ΔTAT	ΔPAP	ΔVWF	ΔD-Dimer
ΔCRP	0.7 (-3.3 – 4.8)	0.1 (-0.1 – 0.3)	3.0 (-4.7 – 10.7)	1.0 (0.2 – 1.9)	0.01 (-0.01 – 0.02)
ΔESR	0.3 (-3.8 – 4.5)	0.2 (0.01 – 0.3)	5.5 (-2.0 – 12.9)	0.9 (-0.01 – 1.8)	0.01 (-0.01 – 0.02)

DISCUSSION

In this cohort of patients that started golimumab, we found that after 4 weeks of treatment, markers of disease activity decreased, as well as all markers of coagulation.

At baseline, CRP and ESR were significantly associated with PAP and D-Dimer levels: thus a higher inflammatory load might induce coagulation activation. This is underscored by increased levels of the other coagulation markers albeit that this did not reach statistical significance. Overall, markers of coagulation decreased to a larger extent in patients with a greater decrease in CRP and ESR.

As far as we know, this effect has not been described in AS patients. However, studies in RA patients have been performed. One study in RA patients using infliximab suggested that TNFi therapy is accompanied with normalization of the prothrombotic biomarkers D-dimer and F1+2(11). Another study, which included patients on TNFi therapy or methotrexate, found that after 6 weeks of therapy, levels of fibrinogen and D-dimer decreased in the TNFi therapy group(12). This exploratory study shows that there is an effect, albeit small, on coagulation markers after the initiation of TNFi in AS patients. As AS patients have increased risk for VTE, anti-inflammatory therapy might not only be relevant in reducing back pain and spinal deformity, but may reduce VTE incidence as well. Because of the exploratory nature of this study, there are some limitations, like the small sample size and short duration of follow up. Furthermore, a control group was lacking. Nevertheless, AS patients with active disease appear to have an increased procoagulant state in comparison to healthy controls. This might have consequences for drug tapering as this might induce increased coagulation activation in some patients. A future challenge is therefore to identify these patients.

Finally, whether or not the favourable effects of TNFi therapy on the coagulation system persist and ultimately result in a lower risk for VTE remains to be established in prospective clinical studies.

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None

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CHAPTER 11
SUMMARY AND DISCUSSION

SUMMARY

The risk for cardiovascular disease in rheumatoid arthritis (RA) patients has been a concern for the last two decades; since research showed that this risk is increased compared to the general population. In 2009, the European League Against Rheumatism (EULAR) task force recommended screening, identification of CVD risk factors and CVD risk management in RA patients. Since then, substantial new insights in this field has been published, largely based on expert opinion. In **chapter two** the updated recommendations on cardiovascular risk management from the European League Against Rheumatism (EULAR) task force are discussed. In these recommendations, three overarching principles and 10 recommendations were formulated. The first overarching principle is that clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This was already known in 2009, but now with extended evidence. Secondly, the rheumatologist is responsible for the initiation of risk management in patients with RA and other IJD, but can/should of course involve other healthcare professionals other than rheumatologists, depending on the local organization of healthcare. Third, the use of NSAIDs and corticosteroids, which have potentially adverse cardiovascular effects, should be in accordance with treatment-specific recommendations from EULAR and ASAS. Ten recommendations were defined, based on a pan-European consensus. These recommendations, are meant to facilitate CVD risk management in daily clinical practice, ultimately leading to a decreased CVD burden in RA patients.

We conducted the I-CaRe Project in Reade, Amsterdam, and Antonius Hospital, Sneek to investigate and optimize cardiovascular risk management. In **chapter three**, we performed a cardiovascular risk screening and calculated the 10-year cardiovascular (CV) risk score in 720 patients from Reade and the Antonius Hospital, using the Dutch cardiovascular risk guideline. Over half of these patients (53%) were found to have a high cardiovascular risk. Furthermore, we identified (under) treatment of CV risk factors in these patients. In total, 69% had an indication to use cholesterol lowering or antihypertensive drugs. Of those, 42% received inadequate treatment and 40% received no treatment at all. In **chapter four the results** of this project after one year are described. The results from the baseline screening as described in chapter three were communicated to the general practitioner, including specific advice on the initiation or adjustment of cardio preventive drugs, whereas in the Antonius Hospital all patients were referred to the internist. The decision to start or adjust preventive medication was at the discretion of the

general practitioner or internist. After one year, we re-evaluated CV risk, lifestyle and treatment. After this year, cardio preventive drug treatment was only started or adjusted in one third of patients with an indication for treatment. However, we did find lifestyle changes; 42% of patients reported to have changed their lifestyles including more exercise, diet adaption and weight loss. Despite clear guidelines, both local (Dutch guideline) and international, like the EUAR guideline, and the active implementation of a screening program, we have to conclude that optimal CV risk management remains a major challenge in the RA population.

Not only cardiovascular risk management, but also the prediction of cardiovascular risk itself remains a challenge in the RA population. In **chapter five** it is shown that different CV risk scores are calculated, dependent on which risk prediction tool was used and when, in the course of the disease, the risk was calculated. This inevitably leads to differences in advices on preventive medication dependent on the stage of disease activity. It appears to make most sense to calculate cardiovascular risk during the period that RA patients are in a state of low or stable disease activity. This of course needs to be further investigated by studies using longer follow up. As stated in de EULAR recommendations, patients with RA not only suffer from a higher cardiovascular burden, but also demonstrate increased prevalence of other inflammatory autoimmune disorders. In **chapter six** we assessed the prevalence proportion and incidence rate of cardiovascular morbidity in patients with inflammatory arthritis and co-existent autoimmune disorders. We demonstrated an increased prevalence proportion of type 1 diabetes, hypothyroidism, psoriasis and Crohn's disease/ulcerative colitis in patients with inflammatory arthritis compared with controls. Moreover, patients with inflammatory arthritis more often had one or more concomitant autoimmune disorders. We confirmed once again the increased cardiovascular risk for patients with inflammatory arthritis, and found that this risk was further amplified in the presence of another coexistent autoimmune disorder. The amplification of cardiovascular disease risk in inflammatory arthritis patients with multiple autoimmune disorders warrants greater awareness for this phenomenon, and since autoimmune disorders often co-exist, the need for cardiovascular risk management in these patients is once again emphasized.

Although there are a few randomized trials investigating cardiovascular outcomes in RA disease management, it is accepted that suppression of inflammation is beneficial for cardiovascular risk, and tight disease control is thought to improve cardiovascular outcomes. Part II of this thesis puts focus on effects of treatment on different outcomes and markers of CVD.

As described in chapter six, the coexistence of inflammatory arthritis and other auto-immune disease, like thyroid disfunction, amplifies cardiovascular risk. In **chapter seven**, we used data from a longstanding prospective cohort to investigate the effect of thyroid dysfunction on incident CVD compared to euthyroid RA patients. We found that patients with RA and subclinical hypothyroidism had an increased risk for new CVD.

In **chapter eight**, we demonstrated associations between RA disease activity and the biomarkers NT-proBNP and sRAGE in a cohort of very early arthritis patients that started anti-rheumatic treatment. During 6 months of treatment with anti-inflammatory medication, NT-proBNP decreased and sRAGE increased, independent of the type of medication used. Therefore, we conclude that suppressing disease activity, independent of the drug used, increases sRAGE levels and decreases NT-proBNP levels.

In **chapter nine** the effects of etanercept on lipid metabolism and other cardiovascular risk factors in patients with psoriatic arthritis are investigated in an observational cohort using mixed model analyses to assess CVD risk factors over 5 years during etanercept treatment. We found that during etanercept use, mainly changes in lipid levels were seen, consisting of an increase in total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), and low-density lipoprotein cholesterol. The apolipoprotein B to apolipoprotein A-I (apoB/apoA-I) ratio decreased significantly. However, we observed only modest changes; therefore, we hypothesize that the previously described beneficial effects of etanercept on CVD is more likely exerted through other inflammation-related mechanisms.

As coagulation and inflammation are closely linked, we investigated the changes in markers of coagulation in patients with AS starting the TNF-blocker golimumab, and the results are described in **chapter ten.** We found that after 4 weeks of treatment, markers of disease activity decreased, as well as all markers of coagulation activation. We found significant associations between CRP and ESR and PAP and D-Dimer levels at baseline, and after 4 weeks of treatment, that markers of coagulation decreased to a larger extent in patients with a greater decrease in CRP and ESR.

FUTURE PERSPECTIVES

This thesis adds new evidence relating to cardiovascular disease in inflammatory arthritis, but still, mechanisms underlying the increased cardiovascular risk are not yet clear, as is the influence of anti-rheumatic treatment. For example, we found an association between the magnitude of change in inflammatory markers (ESR and CRP) and change in NT-proBNP and sRAGE and hypothesized that suppression of inflammation benefits the myocardium and endothelium. It would be interesting to further unravel this mechanism and correlate it with 'hard' cardiovascular endpoints, to provide more evidence that prompt suppression of inflammation prevents cardiovascular disease. Furthermore, in our cohort of PsA patients starting etanercept, we found little change in the cardiovascular risk factors, suggesting that beneficial effects of etanercept on CVD are likely caused by suppression of inflammation, or perhaps a direct effect of the drug, but not mediated by improvement of cardiovascular risk factors. To study the effects of different treatment regimens on cardiovascular outcomes (large) randomized controlled trials are needed. In chapter ten, we performed a small study investigating markers of inflammation and coagulation. In contrast to arterial embolism, like CVD, less is known about the risk for venous thromboembolism. The activation of coagulation in active disease, and its normalization after the start of a TNFi, might have implications for future treatment with these drugs. But before any practical recommendations can be given, we first need to investigate whether or not TNFi therapy results in a lower risk for VTE, and therefore prospective clinical studies are needed.

Moreover, this thesis showed that there is still a lot to improve in the management of cardiovascular disease. From the I-CaRe project we learned that cardiovascular risk management in RA patients is still suboptimal. Several research topics need to be addressed to improve this. First, current cardiovascular risk screening tools are insufficient for patients with inflammatory arthritis, and future research using, for example, large databases is needed to develop more specific tools. However, the tools that are currently available need to be employed properly and therefore we need to optimize our strategy, including systematic screening and collaboration between rheumatologists, (vascular) internists, cardiologists and general practitioners.

CONCLUSION

Further research must be done to delineate specific mechanisms in the pathogenesis of ischaemic heart disease. Prospective clinical trials are needed to assess the roles of antirheumatic therapies, pharmacological control of traditional risk factors and lifestyle-modification strategies in the potential reduction of cardiovascular risk. In the meantime, cardiovascular risk management in patients with inflammatory arthritis remains of utmost importance. The existing models for the prediction of cardiovascular risk are not sufficiently accurate in these patients and the development of disease-specific approaches is necessary—although very challenging. Systematic screening for cardiovascular risk and coordination of care between rheumatologists, (vascular) internists, cardiologists and general practitioners is essential to achieve optimal management of cardiovascular risk and cardiovascular disease in our patients.

APPENDICES

NEDERLANDSE SAMENVATTING

Patiënten met reumatoïde artritis (RA), maar ook andere auto-immuunziekten, hebben ongeveer tweemaal zoveel kans op het krijgen van hart- en vaatziekten (HVZ) als mensen zonder RA. De laatste jaren wordt steeds meer bekend over de mechanismen die dit veroorzaken. Zo weten we dat deze verhoogde kans op HVZ deels komt door de traditionele risicofactoren, zoals roken, hypertensie en een verhoogd cholesterol. Echter, bij patiënten met een auto immuun aandoening zoals RA speelt ook de chronische ontsteking een rol. Daarnaast kan ook de behandeling van RA een effect hebben op het risico om HVZ te ontwikkelen. Nu we steeds meer weten over het voorkomen van HVZ bij deze patiëntengroepen, is het logisch om ook onze aandacht te richten op preventie van HVZ. Hierover valt nog veel te leren.

Het eerste deel van dit proefschrift gaat over cardiovasculair risicomanagement bij patiënten met auto-immuunziekten, voornamelijk RA. Hoofdstuk twee bestaat uit een 10-tal aanbevelingen vanuit de European League Against Rheumatism (EULAR) werkgroep. Deze 10 aanbevelingen zijn geformuleerd op basis van de laatste wetenschappelijke inzichten alsmede 'expert' opinion, met als doel richting te geven aan cardiovasculair risicomanagement in de dagelijkse reumatologie praktijk. Daarnaast zijn er drie overkoepelende principes geformuleerd: 1. Artsen moeten zich bewust zijn van het verhoogde risico op HVZ bij patiënten met inflammatoire gewrichtsaandoeningen; 2. De reumatoloog is als hoofdbehandelaar van deze patiëntengroep ervoor verantwoordelijk dat cardiovasculair risicomanagement wordt uitgevoerd, en betrekt hier de nodige collega's bij en 3. Het voorschijven van NSAIDs en corticosteroïden, die potentieel nadelige cardiovasculaire bijwerkingen hebben, gebeurd volgens de behandelrichtlijnen van EULAR en ASAS. In hoofdstukken drie en vier worden de resultaten van het I-CaRe onderzoek beschreven. In dit onderzoek, wat een samenwerking was tussen Reade in Amsterdam en het Antonius ziekenhuis in Sneek, werd het cardiovasculaire risicoprofiel van patiënten met RA in kaart gebracht, met als doel het management van deze patiënten te verbeteren. We vonden dat meer dan de helft van onze patiënten een verhoogd risico op HVZ had, en dat een verhoogde bloeddruk of verhoogd cholesterol vaak onvoldoende werd behandeld. Als er bij patiënten een (onvoldoende behandeld) verhoogd cardiovasculair risico werd gevonden, werd de huisarts hiervan op de hoogte gesteld met het verzoek om behandeling te optimaliseren. Na een jaar evalueerden we het cardiovasculair risicoprofiel opnieuw. Daarbij viel op dat medicamenteuze therapie in de vorm van cholesterolverlagers of antihypertensiva bij slechts een derde van de patiënten

was aangepast. Gelukkig had 42% van de onderzochte populatie wel veranderingen in hun leefstijl doorgevoerd, zoals afvallen, meer bewegen of gezonder eten. Naar aanleiding van deze resultaten concludeerden wij dat ondanks de bestaande richtlijnen voor cardiovasculair risicomanagement, de praktische uitvoering ervan nog vele haken en ogen kent. In hoofdstuk vijf gaan we dieper in op de cardiovasculaire risicoberekening door het 10-jaars risico op HVZ op verschillende tijdstippen in het ziektebeloop en met verschillende modellen te berekenen. Dit laat zien dat de 'score' die uit deze berekening komt verschillend is afhankelijk van wanneer en hoe de berekening wordt gemaakt. Hierdoor kan het advies om wel of niet te starten met bijvoorbeeld bloeddrukverlagers verschillen. Dit was met name sterk afhankelijk van het moment van berekening; voor of na starten van anti-reumatische medicatie. Het lijkt het meest logisch om het cardiovasculaire risico te berekenen in de periode dat patiënten zich in een toestand van lage of stabiele ziekteactiviteit bevinden. Dit moet natuurlijk verder worden onderzocht en bevestigd door studies met een langere follow-up. Zoals al eerder genoemd in bijvoorbeeld de EULAR aanbevelingen, hebben niet alleen patiënten met RA een verhoogd risico op HVZ, maar ook patiënten met andere auto-immuunziekten. In hoofdstuk zes kijken we daarom naar het voorkomen van HVZ bij patiënten die naast een vorm van artritis ook nog een andere auto-immuunziekte hebben. We vonden dat bijvoorbeeld diabetes, specifiek type 1, hypothyreoïdie en psoriasis meer voorkwamen bij patiënten met RA dan bij gezonde controles. Daarnaast bleken de patiënten die RA hadden en daarnaast nog een van deze aandoeningen, een nog verder verhoogd cardiovasculair risico te hebben vergeleken met de groep met alleen RA. Omdat RA dus vaak samen met andere auto-immuunziekten voorkomt, willen wij ervoor pleiten om bij deze groep extra aandacht te besteden aan cardiovasculair risicomanagement. In hoofdstuk zeven hebben we gekeken naar het effect van schildklierproblemen bij RA patiënten op de kans op HVZ omdat deze twee aandoeningen frequent samen voorkomen. Middels analyse van data van een groot langlopend cohort toonden we aan dat patiënten met RA met tegelijk ook subklinische hypothyreoïdie een (extra) verhoogde kans hadden op het optreden van nieuwe HVZ. Deze groep verdient dus ook zeker extra aandacht voor cardiovasculair risicomanagement.

In deel twee van dit proefschrift worden de resultaten beschreven van studies naar het effect van verschillende behandelregimes op uitkomstmaten gerelateerd aan hart en vaatziekten. In hoofdstuk acht keken we naar het verband tussen de ziekteactiviteit van patiënten met RA en de biomarkers NT-proBNP en sRAGE, zowel voor als na behandeling met anti-reumatische medicatie. We zagen daarbij

dat onderdrukking van inflammatie leidde tot een verbetering van deze biomarkers, waarbij het type medicatie in dit onderzoek niet uitmaakte. Het effect van behandeling van patiënten met artritis psoriatica met het anti-reumatische middel etanercept (een TNF blokker) op verschillende cardiovasculaire risicofactoren wordt beschreven in hoofdstuk negen. Daarbij vonden we dat het gebruik van etanercept tot vrij kleine veranderingen in cholesterolwaarden leidde. Het lijkt niet aannemelijk dat deze kleine veranderingen het gunstige effect van etanercept op HVZ verklaren; dit lijkt eerder het anti-inflammatoire effect of misschien een direct effect van het medicijn te zijn. In hoofdstuk tien hebben we gekeken naar de veranderingen die optreden in het stollingssysteem nadat patiënten met Bechterew werden behandeld met golimumab, (ook) een TNF blokker. Stolling en ontsteking zijn namelijk nauw verbonden. Na 4 weken behandeling met dit medicijn zagen we dat verschillende stollingswaarden, die verhoogd waren voor start van behandeling, normaliseerden. Of dit ook gevolgen heeft voor het optreden van trombose moet verder onderzocht worden.

TOEKOMSTPERSPECTIEF

Dit proefschrift levert nieuwe inzichten in de wisselwerking tussen inflammatie en risico op hart en vaatziekten. Er blijven echter nog vele mechanismen onbekend. Wij hebben bijvoorbeeld gevonden dat veranderingen in de inflammatiewaarden BSE en CRP leidden tot veranderingen in NT-proBNP en sRAGE. Het is daarom waarschijnlijk dat het onderdrukken van de inflammatie een positief effect heeft op de cellen van de hartspier. Het zou interessant zijn om dit verder uit te diepen, en vooral om ook te laten zien dat dit daadwerkelijk leidt tot minder HVZ. Daarnaast wat het opvallend dat er bij patiënten met artritis psoriatica die startten met etanercept nauwelijks veranderingen waren in de cardiovasculaire risicofactoren, terwijl we weten dat etanercept over het algemeen wel een gunstig effect heeft op het voorkomen van HVZ. Dit impliceert dat die positieve effecten eerder zijn toe te schijven aan de onderdrukking van de inflammatie, of wellicht bestaat er een direct effect van het medicijn zelf op HVZ. Om dit verder te onderzoeken zouden (grote) klinische trials uitkomst kunnen bieden.

Hoewel er al veel bekend is over het risico op arteriële trombo-embolieën, waaronder het myocardinfarct, weten we minder over het optreden van veneuze trombo-embolie. In hoofdstuk tien worden de effecten van een kleine studie beschreven waarin we zagen dat biomarkers van de stolling geactiveerd zijn bij actieve ziekte,

en lijken te normaliseren na start van therapie. Het is daarom interessant om te kijken hoe dit zich vertaald naar de klinische praktijk.

Uit dit proefschrift valt verder op te maken dat er in het veld van cardiovasculair risicomanagement bij patiënten met bijvoorbeeld RA nog veel te verbeteren is. De resultaten van het I-CaRe project lieten zien dat cardiovasculair risicomanagement vaak nog suboptimaal is. Om dit te verbeteren zijn er meerdere stappen nodig. Allereerst zijn de huidige modellen om het 10-jaars risico op HVZ te voorspellen niet voldoende gespecificeerd voor patiënten met een auto immuun aandoening. Door bijvoorbeeld het gebruik van grote datasets zouden meer specifieke modellen ontwikkeld kunnen worden. Ondertussen kunnen we beter gebruik maken van de modellen die er al wel zijn. Hiervoor is samenwerking tussen onder meer reumatologen, huisartsen en (vasculair) internisten onontbeerlijk.

CONCLUSIE

Er is steeds meer bekend over de verschillende mechanismen die zorgen voor het verhoogde risico op hart en vaatziekten bij patiënten met auto-immuun aandoeningen, maar (inflammatie) specifieke mechanismen dienen in de toekomst nog verder onderzocht te worden. Wellicht kunnen de inzichten die zo verkregen worden helpen bij het opzetten van prospectieve klinische trials waarin de rol van verschillende anti-reumatische medicijnen bij het voorkomen van HVZ kan worden onderzocht. Daarnaast is meer onderzoek nodig naar het effect van verbetering van leefstijl en de behandeling van de traditionele risicofactoren, zoals hypertensie en hypercholesterolemie, in deze specifieke groep patiënten.

Ondertussen moeten we ons blijven richten op verbetering van het cardiovasculair risicomanagement van patiënten met auto-immuun aandoeningen. Ofschoon nog geen optimale strategieën bestaan, is duidelijk dat samenwerking van verschillende specialismen zoals reumatologen, internisten en cardiologen met huisartsen hierbij essentieel is .

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BIOGRAFIE

Maaike Heslinga werd geboren op 26 oktober 1989 in Purmerend. Zij behaalde haar vwo-diploma in 2008 aan het Damstede college in Amsterdam. Zij startte aansluitend met de opleiding geneeskunde aan de Vrije Universiteit en haalde in 2011 cum laude haar Bachelor of Science. Daarna startte zij met haar co-schappen in verschillende ziekenhuizen, waarvan zij in 2012 het co-schap Chirurge aan de Universiteit van Pretoria in Pretoria, Zuid-Afrika voltooide. In 2014 deed zij voor haar wetenschappelijk stage in het kader van de geneeskundestudie onderzoek naar het optreden van orgaanschade en kwaliteit van leven bij patineten met systemische lupus erythematosus, onder begeleiding van prof. dr. Voskuyl en dr. Bultink. Na het afronden van de studie geneeskunde start zij met een promotietraject als arts-onderzoeker bij Reade (inmiddels het Amsterdam Rheumatology and immunology center) onder leiding van prof. dr. Nurmohamed en prof. dr. Smulders. Haar onderzoek was gericht op het cardiovasculaire risico voor patiënten met verschillende reumatische aandoeningen. Resultaten van dit onderzoek werden gepresenteerd op verschillende congressen, en hebben geleid tot het proefschift voor u. Op 1 oktober 2018 is zij gestart met haar opleiding tot reumatoloog, en is in dat kader bezig met de vooropleiding interne geneeskunde in het Amsterdam UMC, locatie VUmc.

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