INTRODUCTION

Cardiovascular risk reduction in rheumatic diseases: How can it be achieved?

Parts of this introduction have been published:
Cardiovascular risk in rheumatic diseases
Cardiovascular disease (CVD) is more prevalent in patients with chronic inflammatory diseases (CID), like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) than in the general population(1-5). Even a less systemic inflammatory rheumatic disease as osteoarthritis is associated with an increased cardiovascular (CV) risk (6). To date, the exact pathophysiologic mechanism by which this relation between cardiovascular disease and all these rheumatic diseases can be explained is not completely clear.
What causes the excess cardiovascular risk in rheumatoid arthritis?

Rheumatoid arthritis is a chronic systemic autoimmune disease, characterized by a symmetrical inflammation of the joints in the hand and feet, affecting up to 1 per cent of the population, women more often than men (7). As mentioned above this CID is associated with an increased CV risk. To decrease the excess CV risk in RA it is essential to know what causes this problem. One of the reasons why this puzzle is not solved yet is because there are many pathophysiological mechanisms involved that influence each other. Three main factors can be identified: genetic background, inflammation and traditional CV risk factors.

The first factor that may link atherosclerosis to RA is a common genetic background. An increasing number of studies report gene polymorphisms that are associated with a higher CV risk in RA (8). The major histocompatibility complex, class II, DR beta 1 gene, also known as Human Leucocyte Antigen (HLA)-DRB1 gene is a typical example of a gene that seems associated with CV mortality in RA (9). Next to the question what causes the relationship between RA and atherosclerosis, is the question at what time the CV risk rises. Actually, there is accumulating (circumstantial) evidence that CV risk is already increased before the clinical onset of RA. Some studies show that endothelial dysfunction and the first signs of atherosclerosis are already present in patients with recent-onset RA. Also dyslipidemia is already present in rheumatoid factor positive persons who later develop RA (10). One population-based cohort study reported an increased risk of coronary heart disease and myocardial infarction two years prior to RA diagnosis using the ACR 1987 criteria (11). More recent studies reported increased CV risk and mortality early in the RA disease course (12-15). Altogether, it appears that CV risk already starts to increase as soon as the first signs of autoimmunity and inflammation appear which is often a few months to years prior to the actual RA diagnosis and increases further during disease progression as the inflammatory burden accumulates.
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The link between inflammation and cardiovascular disease

Inflammation is regarded as an important independent CV risk factor and is associated with endothelial dysfunction, which in turn leads to atherosclerosis (16, 17). Nowadays, RA and atherosclerosis are both regarded as inflammatory-driven diseases and this appears to be the most important reason why these two diseases coincide (18, 19). There is much evidence that endorses this hypothesis. For instance, the inflammatory and immunological processes that occur in atherosclerotic plaques are very similar to those in inflammatory synovitis and markers of inflammation, as C-reactive protein (CRP), predict CV disease not only in healthy men and women but also in RA patients (20-22). Furthermore, indicators of more severe disease and more systemic inflammation in RA, like decreased functional capability, presence of extra-articular manifestations, longer disease duration and seropositivity, are also associated with higher CV risk (23, 24). There are many ways by which RA-related inflammation may lead to atherosclerosis. Inflammation seems to play a key role in all stages of atherosclerosis: from endothelial dysfunction to plaque rupture and thrombosis (25). Inflammatory cytokines/chemokines increase vascular permeability, change vasoregulatory responses, increase leukocyte adhesion to endothelium and facilitate thrombus formation by inducing pro-coagulant activity, inhibiting anti-coagulant pathways and impairing fibrinolysis via stimulation of plasminogen activator inhibitor-1 (PAI-1) (26, 27). Inflammation also influences and accentuates some traditional CV risk factors, like dyslipidemia, obesity and insulin resistance (IR), as they behave differently in the RA population with regard to CV risk than in the general population (18, 28, 29). The link between synovitis and atherosclerosis is illustrated in figure 1.
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**Figure 1 An illustration of the pathways and cytokines by which synovitis can contribute to the formation of an atherosclerotic plaque and eventually cardiovascular events**

**Tumor necrosis factor and cardiovascular disease**

The tumor necrosis factor (TNF)-family of cytokines plays an important role in regulating the immune response, inflammation and apoptosis. The first cytokine discovered is TNFα, which is produced by i.e. neutrophils, macrophages and adipocytes and can induce other powerful pro-inflammatory cytokines such as interleukine-6 (IL-6), which in turn regulates the expression of CRP (30). CRP increases the expression of endothelial intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, monocyte chemotactic protein-1 (MCP-1) and increases the secretion of endothelin-1 (ET1). Moreover CRP decreases endothelial nitric oxide synthase (eNOS) expression and elevates the expression of angiotensin receptor type 1 in the vessel wall (21, 31, 32).

TNFα can induce insulin resistance (IR) and this is probably a part of the explanation why IR, endothelial dysfunction and atherothrombosis are so closely related (33). Recent studies indicate that TNFα is likely involved in the pathogenesis of diabetic nephropathy and retinopathy. A recent study with animal models of type 1 diabetes (T1DM) and type 2 diabetes (T2DM) shows that TNFα plays an important role in micro vascular apoptosis (34).
When the diabetic rats were treated with pegsunerce pt, a TNFα inhibitor, a significant reduction of the number of endothelial cells that expressed activated caspase-3 by 76 to 80% occurred. TNFα inhibition decreases ICAM-1 levels and Nuclear Factor kappa B (NF-kB) activity in diabetic retina (35).

NF-kB consists of a family of transcription factors that regulate the inflammatory response of vascular cells by transcription of various cytokines, which causes an increased adhesion of monocytes, neutrophils and macrophages, resulting in cell damage (36). On the other hand NF-kB is also a regulator of genes that control cell proliferation and cell survival and protects against apoptosis, amongst others by activating the antioxidant enzyme superoxide dismutase (SOD) (37). NF-kB is activated by TNFα and interleukin-1 (IL-1) next to hyperglycemia, advanced glycation end products (AGEs), Angiotensin II (ANG-II), oxidized lipids and insulin. Once activated, NF-kB translocates from the cytoplasm to the nucleus to activate gene transcription. NF-kB-regulated genes are VCAM-1, E-selectin, ICAM-1, IL-1, IL-6, interleukin-8 (IL-8), tissue factor (TF), PAI-1 and NOS (38).

*Figure 2* mechanisms of insulin resistance and adipose tissue in relation to endothelial dysfunction and apoptosis
The role of traditional cardiovascular risk factors

The classical CV risk factors, including smoking, hypertension, dyslipidemia, obesity, physical inactivity, IR and diabetes mellitus (DM) do not seem to explain fully the excess CV risk in RA. They do contribute, albeit in a different way or to a lesser extent in RA in comparison with the general population. The following paragraphs summarize and interpret data from recent studies on individual traditional CV risk factors and their contribution to CV risk in RA specifically.

Smoking

Cigarette smoking is classified not only as a predisposing factor for CV events but also for RA, particularly rheumatoid factor positive RA (39, 40). For rheumatologists this alone should be a trigger to advise every newly diagnosed RA patient who smokes to quit, apart from the notion that smoking probably also has an adverse influence on RA disease severity, prognosis and effect of antirheumatic treatment (41).

Hypertension

Hypertension can induce endothelial dysfunction and is associated with IR. This relation can partly be explained by decreased capillary density and impaired capillary recruitment seen in insulin resistant states. Another explanation is the fact that NO availability is diminished and ET-1 availability is increased in both IR and hypertension (42). Whether hypertension is more common in RA than in the general population has not been elucidated yet, because reports are contradictory (29). However, one of the most recent studies found a significant increased prevalence of hypertension in RA patients versus controls (43). The reported prevalence of hypertension in RA varies substantially, depending on study population, sample size and definition of hypertension used in the different studies (44). This does not mean hypertension has no impact on CV risk in RA. Hypertension is a very common problem in the general as well as the RA population and is still underdiagnosed and undertreated, particularly in young RA patients (45). There is no real evidence that the current disease modifying drugs (DMARDs) have a beneficial effect on blood pressure. In contrast, there are DMARDs and other drugs used for the treatment of RA that may induce high blood pressure, like leflunomide, cyclosporine, glucocorticoids and the non-steroidal anti-inflammatory drugs (NSAIDs) (44). This means adequate blood pressure control and treatment could be of great influence to the CV risk in the RA population.
Dyslipidemia

Dyslipidemia is characterized by low HDL-cholesterol levels and an excess of small-dense LDL and is associated with obesity, IR, diabetes and CVD in general (46, 47). LDL particles can transport cholesterol into the arterial wall, which leads to atherosclerosis, while HDL particles are able to remove cholesterol from the arterial wall. The data on total cholesterol, LDL and triglyceride levels in patients with RA are not conclusive (48). However, many studies demonstrate a very similar lipid pattern as seen in several other inflammatory conditions, consisting of decreased levels of total cholesterol, LDL cholesterol, and HDL cholesterol, indicating a profound influence of inflammation on lipid profile in RA. (49, 50). Most studies that have investigated cholesterol levels in RA have found lower HDL levels resulting in an unfavourable lipid profile (Total cholesterol/HDL-cholesterol ratio) compared to healthy controls, even 10 years before the onset of RA (10, 51-56). Another explanation for an unfavourable lipid profile is the modification of lipids by inflammation, which not only lowers lipid levels, but also alters lipid structure and function, changing the usual beneficial effects of HDL cholesterol into more detrimental effects (57). Altogether, when LDL and HDL composition are also taken into account, the lipid profile in active RA tends to be highly proatherogenic (58).

Obesity

Obesity, specifically central or abdominal obesity, characterized by a high waist circumference, is a risk factor for CV disease in the general population (59). The adipose tissue has become known to be a highly active endocrine organ, releasing hormones, cytokines and enzymes with the tendency to impair insulin sensitivity (IS) (60, 61). It is an important modulator of endothelial function via secretion of a variety of hormones, including adiponectin, resistin, leptin, PAI-1, angiotensin, estradiol and the cytokines TNFα and IL-6 (62).

Surprisingly, most studies reported a higher CV mortality in RA patients with a low body mass index (BMI) (<20 kg/m2) compared to patients with a higher BMI (≥ 30 kg/m2), although prevalence of adiposity did not differ in RA compared to the general population (28, 43, 63-66). This discrepancy can be explained by a phenomenon called rheumatoid cachexia, a condition characterized by decreased lean muscle mass and increased adiposity, which leads to an abnormal body composition in RA (65-67). One study clearly demonstrated that RA patients had a higher fat percentage and especially visceral fat compared to non-RA controls (68). The accumulation of visceral fat is a risk factor for the development of T2DM and CVD. Loss of lean muscle mass in RA seems associated with TNFα (66, 69), increasing the risk even more. In conclusion, the chronic inflammatory
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state in RA creates an abnormal body composition characterized by muscle wasting and increasing visceral fat without significantly altering BMI, which is, therefore, less reliable when it comes to predicting CV risk.

**Physical activity**

RA patients tend to be less physically active due to disease symptoms, like joint pain and stiffness and fear of aggravating their disease (70-73). Exercise can prevent CV disease and it has a positive impact on all the individual CV risk factors, like adiposity, dyslipidemia, insulin resistance and DM, hypertension and possibly even inflammation (74-78). Physical inactivity has been associated with CV risk in RA (79). This could mean that stimulating RA patients to be more physically active could have even more effect on CV risk in RA patients than in healthy persons.

**Insulin resistance**

Insulin resistance is defined as the decreased ability of insulin to promote glucose uptake in skeletal muscle and adipose tissue and the decreased hepatic output of glucose. This may be present years before the development of abnormal plasma glucose levels becomes evident (80, 81).

Insulin resistance is associated with an increased free fatty acids (FFA) release from adipose tissue, which results in dyslipidemia, including very low density lipoproteins (VLDL)-hypertriglyceridemia, high plasma FFA and low high density lipoproteins (HDL)-cholesterol concentrations (82). High FFA levels and hypertriglyceridemia are associated with endothelial dysfunction. FFA-mediated endothelial dysfunction is probably caused by reduced availability of L-arginine and/or Nitric Oxide (NO) and oxidative stress. It has been proven that increased saturated and polyunsaturated FFA concentrations, except for oleic acid, directly induce cell cycle arrest and apoptosis in vascular endothelial cells (83).

Insulin is a vasoactive hormone and enhances muscle blood flow and vasodilation via stimulation of NO production (84). The increased blood flow caused by insulin differs between different types of vessels. Insulin can also redirect blood flow in skeletal muscles so that more glucose can be up taken by muscle cells. This process is called capillary recruitment (85). In T2DM, hypertension and obesity, insulin’s vasodilator actions are impaired, probably for a large part because of low NO action. Normally stimulation of NO production by insulin is mediated by signaling pathways involving activation of phosphoinositide-3 (PI-3) kinase leading to phosphorylation of eNOS. It is suggested that endothelial dysfunction and impaired capillary recruitment can cause IR because the
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Microvascular endothelium cannot react properly to insulin and glucose disposal is decreased (86). This is called endothelial IR. How metabolic and endothelial IR originate and their exact relationship are not fully understood. Both TNFα and non-esterified acids (NEFAs) can cause metabolic and endothelial IR. Inflammatory cytokines like TNFα, can act as mediators of IR by impairing the tyrosine kinase activity of both the insulin receptor and insulin receptor substrate (IRS-1), thus inhibiting insulin signaling. It is suggested that a bidirectional relationship exists between hyperinsulinemia and low-grade chronic inflammation, by which hyperinsulinemia can lead to vascular inflammation and vascular inflammation causes IR and finally compensatory hyperinsulinemia. At normal physiological concentrations insulin exerts prevailing anti-inflammatory effects, while hyperinsulinemia increases levels of oxidative stress and inflammation. A recent study with human umbilical vein endothelial cells (HUVECs) shows that insulin, at pathophysiological concentrations and alone or in combination with low concentrations of TNFα, has the ability to promote VCAM-1 expression, through increasing the steady state levels of messenger ribonucleic acid (mRNA) via the activation of transcription factors, such as NF-kB, which has been linked to VCAM-1 transactivation before (87). This way hyperinsulinemia leads to increased monocytoid cell adhesion to HUVECs.

A very important effect of IR is the fact that the normal route for insulin to activate the PI-3 kinase and Akt-dependent signaling pathways are impaired, whereas hyperinsulinemia over activates mitogen activated protein kinases (MAPK)- pathways, thereby creating an imbalance between PI-3 kinase and MAPK-dependent functions of insulin. This probably leads to decreased NO production and increased ET-1 secretion, characteristic of endothelial dysfunction. Through activation of the MAPK signaling pathways, hyperinsulinemia promotes secretion of ET-1, activates cation pumps and increases expression of VCAM-1 and E-selectin (88). ET-1, a vasoconstrictor, can increase serine phosphorylation of IRS-1, causing a decreased activity of PI-3 kinase in vascular smooth muscle cells (89). Moreover ET-1 may also impair insulin-stimulated translocation of glucose transporter-4 (GLUT-4) in adipocytes(90).

There is a lot of data that points to an association between RA and IR, which is very likely caused by inflammation, as many studies showed a correlation between IR and disease activity or markers of inflammation like CRP and ESR (91-96).

Several studies have investigated the prevalence of T2DM in RA patients, expecting to find a positive association. However, except for two, that found a modest significantly higher occurrence of T2DM in RA patients (97, 98), all other studies found no significantly increased prevalence (99-102). This seems quite remarkable given the fact that IR often precedes T2DM and indicates that further research is needed to clarify this issue.
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However, both IR and DM appear to be independent CV risk factors in patients with RA, as also seen in the general population (91, 95, 103-105).

Non-enzymatic glycation products (advanced glycation end-products; AGE)

Non-enzymatic glycation products are a complex and heterogeneous group of compounds which accumulate in plasma and tissues in diabetes and renal failure (106, 107). Research in non-diabetic animals showed that typical micro vascular complications developed following injections of AGE-modified proteins (108).

The advanced glycation end-products (AGE) concept proposes that chemical modification and cross linking of tissue proteins, lipids and DNA affect their structure, function and turnover, contributing to a gradual decline in tissue function and to the pathogenesis of diabetic complications (109). Non-enzymatic glycation of proteins is a condensation reaction between the carbonyl group of free glucose and the N-terminus of reactive-protein amino groups, like lysine or arginine, yielding Schiff-base intermediates that undergo Amadori rearrangement to form stable proteinglucose adducts, for example glycated hemoglobin A1c (HbA1c) and fructosamine (fructoselysine). AGEs can interfere with the endothelial function in several ways. They can act as oxidants and cause generation of reactive oxygen species (ROS). AGEs can decrease arterial elasticy and AGE modified type I and IV collagen can prevent normal matrix formation and cross-linking. Interactions with mononuclear cells and macromolecules like LDL to the endothelial wall are stimulated by AGE-modified matrix, through increased expression of endothelial adhesion molecules. AGEs can also impair the binding of heparan sulfate to the extra cellular matrix, which results in a loss of anionic sites and thus in an increase in endothelial permeability. Early diabetic micro angiopathy is characterized by vasodilation, increased blood flow and increased capillary permeability. AGE-modified proteins may lead to all these changes.

When AGEs get into the blood circulation they are highly reactive but are often detoxified by various enzymes. When they are not eliminated by the kidneys, recirculating AGE peptides can generate new AGEs reacting with plasma or tissue components. At this stage glycation accelerates the progress of deterioration (106, 110). Age-modified plasma proteins can bind to AGE receptors (RAGE = AGE-receptor, macrophage scavenger receptor A) on different cell-types like endothelial cells, where it can adversely affect the expression of thrombomodulin, tissue factor and VCAM-1 genes (111). RAGE-binding mediates signal transduction via a receptor-mediated induction of ROS and activation of transcription factors NF-kB and p21-ras, leading to apoptosis. The soluble form of RAGE (sRAGE) can bind the same pro-inflammatory ligands as membrane bound RAGE and
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thereby prevent the activation of a range of signaling pathways that can generate ROS. In atherosclerosis, but also in RA, sRAGE levels have been found to be decreased (112). However, not much research has been performed to investigate the role and meaning of AGE, RAGE and sRAGE in the link between atherosclerosis and RA.
Cardiovascular risk scores, are they useful in RA?
Large longitudinal cohort studies performed in the twentieth century have discovered which factors most adequately predict the risk for cardiovascular disease in the general population resulting in several CV risk estimation models, such as the Framingham Risk Score (FRS), the Reynolds Risk Score (RRS) and the systematic Coronary Risk Evaluation (SCORE) (113-115). Although these CV risk assessment tools are based on the whole population, including people with chronic diseases, they often cannot be used for accurately predicting CV risk in these specific populations. A very good example of such a group, are DM patients. They have a higher CV risk and therefore special risk scores, like the UKPDS-score, have been developed (116). In the Netherlands, another way of calculating the excess CV risk of DM is used. Instead of a separate risk model for DM, the SCORE risk model is adjusted (table 1), by adding fifteen years to the actual age of DM patients, because the excess CV risk in DM seems to match that of fifteen year older healthy persons, the so called ‘vascular age’ (117).

The same holds true for RA patients, their vascular age also seems to be similar to that of healthy persons of 10-15 years older and there are actually studies that have shown a CV risk that resembles the CV risk of DM patients (118-121). The European League Against Rheumatism (EULAR) has set up guidelines with recommendations regarding CV risk management in RA and advised to add a multiplier of 1.5 to conventional risk assessment tools for estimating CV risk in RA patients, based on the evidence present at that time (122).

However, to date there is no evidence that this multiplier or any other CV risk estimation model or adjustment method accurately predicts CV risk in RA. Future research should therefore focus on developing accurate CV risk prediction models for the RA population.
Table 1. 10 year risk on death or disease by CVD for persons without a history of CVD

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Introduction
Cardiovascular disease prevention in rheumatoid arthritis: what (not) to do?

Tight disease control
As stated above, CV risk in RA cannot be explained by traditional CV risk factors alone and is for a large part increased because of chronic systemic inflammation. Therefore, tight and sustained control of RA disease activity is necessary to effectively prevent CV disease development in RA. This starts by early recognition and diagnosis of RA followed by immediate aggressive treatment to diminish the grade of inflammation as quickly as possible to prevent damage in not only the joints but also the arteries. Although we don’t know when the excess CV risk exactly starts to arise, it is likely at the same time signs of inflammation occur and it could even be sooner than that. The treatment goal should be remission, since even low grade inflammation and especially cumulative (low grade) inflammation can eventually cause atherosclerosis and CV events (123). Indirectly, effective treatment can result in improved physical activity, subsequently leading to a decreased risk of obesity, diabetes, and hypertension and in the end CV disease. Effective treatment of RA can therefore substantially reduce CV risk in RA, however some medications, like corticosteroids and NSAIDs, often used in RA are known to enhance CV risk.

Anti-tumor necrosis factor therapy
Tumor necrosis factor (TNF) blockers are very effective drugs for RA and multiple other inflammatory diseases. Moreover, TNF-blockers also seem to reduce CV risk in RA (124). This could be explained by the fact that TNF-blockers have a positive influence on several CV risk factors, like IR, HDL-composition and endothelial function (125).

Cardiovascular risk management
Although traditional CV risk factors may not explain the excess CV risk in RA, they do play an important role and should not be neglected when it comes to CV risk prevention. Since there are no CV risk assessment models for RA specifically, the national guidelines for CV risk management can best be used to determine CV risk and treatment, as advised by the EULAR guidelines for CV risk management in RA (122). To adjust for the excess CV risk in RA, a multiplication factor of 1.5 is recommended in the presence of two of the following criteria: disease duration of more than 10 years, rheumatoid factor and/or anti-CCP positivity or the presence of extra-articular manifestations. However, this multiplication factor needs validation, as there is only indirect evidence that this multiplication factor
improves CV risk estimation in RA. The same applies for the 3 above-mentioned criteria that are taken up in the first EULAR recommendations to filter the RA patients that presumably have the highest CV risk. Although cumulative disease and therefore disease duration probably enhances CV risk, this does not mean CV risk treatment should only be started after 10 years disease duration (126). Whether anti-CCP or rheumatoid factor positivity are real risk factors for CV disease or simply associated with CV disease because they are also associated with disease severity, remains to be investigated. This means CV risk could be underestimated in RA patients who do not qualify to two of the 3 criteria. New EULAR recommendations are in preparation, in which these criteria are rejected. In the Dutch multidisciplinary guidelines for cardiovascular risk management RA has been recognized as an independent CV risk factor, equal to DM, and CV risk estimations are calculated using the SCORE formula, adjusted for data from Dutch studies (127). For both DM and RA patients, 15 years are added to the actual age of all patients to express the excess CV risk burden. However, this is also based on expert opinion and indirect evidence and hence needs to be validated.

When it comes to CV risk treatment in RA the first step is life style adaptation. The two key messages for the rheumatologist to patients are to stop smoking and to get physically active (128). The second step involves the determination of the CV risk profile, including at least assessment of blood pressure and lipid profile. On the basis of these and other easily accessible data (e.g. age, sex, family history of premature cardiovascular heart disease etc.) and the aid of calculators such as Framingham and SCORE, the 10-years CV risk of a particular RA person can be calculated. Primary prevention involving treatment with statins and/or antihypertensives is only necessary if this 10 years CV risk is above a certain value. For instance, in the Netherlands this would be a 10 year risk of CV morbidity or mortality of 20 per cent or more, based upon a Dutch version of the SCORE. Unfortunately, thus far no intervention trials with statins or antihypertensives and CV disease prevention in RA have been published. Based on data from epidemiological studies and post-hoc subgroup analyses of large, secondary cardiovascular prevention trials, 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 (129-131). However, one recently published population based longitudinal study found that the effectiveness of statins varied in chronic diseases, including RA, and tended to be less effective than in the rest of the population (132). There are, however, numerous other studies that show beneficial effects of statins and angiotensin-converting enzyme (ACE) inhibitors on CV risk in RA (132-137). Actually, in RA the effects of cardio-protective agents might be more pronounced as the pleiotropic effects of statins, ACE inhibitors and angiotensin blockers include anti-
inflammatory properties (138-141). Randomized controlled intervention trials are necessary to assess the actual effect of statins, ACE-inhibitors and other life style intervention strategies on CV risk in RA.
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What causes the excess cardiovascular risk in ankylosing spondylitis and osteoarthritis?

**Ankylosing spondylitis**
Ankylosing spondylitis is a CID of the axial skeleton with often involvement of peripheral joints and tendons, affecting approximately 1 per cent of the population, men more often than women. Overall mortality is increased in AS and this is primarily caused by CVD (142, 143). As in RA, the cause of this enhanced CV risk is probably multifactorial, whereby systemic inflammation also plays a significant role (144). Whether traditional CV risk factors are more prevalent in AS remains unclear, as study outcomes on this subject are heterogeneous (2, 97, 145). Apart from the question if CV risk factors are more prevalent in AS, it is well known that comorbidity is often undertreated in CID patients (146). However, because too less evidence is gathered concerning the exact relationship between AS, CV risk factors and CVD, AS is not yet acknowledged as a serious risk factor in CVRM guidelines (122, 127).

**Osteoarthritis**
Osteoarthritis is a very common and disabling joint disorder among middle-aged and older persons, often affecting the knee, hip and hands (147). Although OA is traditionally considered as a degenerative disease without systemic inflammation, recently OA has been associated with obesity and the metabolic syndrome and metabolic-triggered inflammation (148). Also in OA an excess CV risk is present and again this probably has a multifactorial origin, whereby inflammation, obesity, age, physical inactivity and even hormones could play a significant role (149). Unfortunately, therapeutic options in OA are limited and especially in patients with CVD as comorbidity, since joint-replacing operations are often riskier in this population and non-steroidal anti-inflammatory drugs (NAIDs) often contraindicated due to hypertension or kidney failure, leaving physical therapy as central treatment. Therefore the influence and prevention of CVD and CV risk factors on OA and OA treatment should be studied in more detail.
Cardiovascular risk reduction in rheumatic diseases: How can it be achieved?

Aims and outline of this thesis
The aims of this thesis were to further investigate the link between inflammation and cardiovascular risk in three very common rheumatic diseases, i.e. rheumatoid arthritis, ankylosing spondylitis and osteoarthritis and to determine if this excess cardiovascular risk can be reduced with cardiovascular risk management and/or anti-TNF treatment, a strong anti-inflammatory therapy.
This thesis is divided into three sections.

The first section contains three studies in which the link between cardiovascular disease and rheumatoid arthritis is investigated. Chapter 1.1 contains the first results of the I-CaRe study in which the cardiovascular risk profile of patients with rheumatoid arthritis have been assessed in a cardiovascular screening according to the Dutch cardiovascular risk management guidelines to eventually optimize cardiovascular risk management and thereby reduce the cardiovascular risk. The study in Chapter 1.2 investigated the association between renal dysfunction and cardiovascular events in rheumatoid arthritis. Chapter 1.3 is a post-mortem case-control study in which inflammatory cell density and depositions of the advanced glycation end-product (AGE) N-epsilon carboxy-methyl lysine (CML) was assessed in myocardial and coronary artery tissue of patients with rheumatoid arthritis and controls, who all died of a myocardial infarction.

The second section includes three chapters, that all look into treatment options to reduce the cardiovascular risk in rheumatoid arthritis. Chapter 2.1 describes high-density lipoprotein (HDL) profiling changes in patients with rheumatoid arthritis treated with anti-TNF. In Chapter 2.2 the effect of anti-TNF treatment on insulin resistance and body composition in patients with rheumatoid arthritis is investigated. Chapter 2.3 is a response letter to the editor, proposing a hypothesis that a treatment to enhance the atheroprotective properties of HDL could reduce cardiovascular risk, especially in inflammatory diseases, including rheumatoid arthritis, in which HDL is reduced and the HDL protein composition is altered.

In the third section the link between cardiovascular disease and two other common rheumatic diseases is investigated. Chapter 3.1 presents a detailed evaluation about cardiovascular risk management in patients with active ankylosing spondylitis and Chapter 3.2 presents the results from the Amsterdam osteoarthritis cohort study that assessed the association of cardiovascular diseases with muscle strength, proprioceptive accuracy and activity limitations in patients with knee and/or hip osteoarthritis.
Introduction

References
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