Chapter 10

General discussion and summary

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Studies in inflammatory arthritis, a complex, multi-facetted ailment of the joints and bones, have consequently shown an increased propensity for CV morbidity and mortality.[1] This thesis aims to give insight into several aspects that are currently under investigation in the field of rheumatology and CV disease.

**Study populations**
The CArdiovascular Risk in patients with RhEumatoid arthritis (CARRÉ) study is a prospective population-based cohort study designed to ascertain CV disease in RA to investigate the role of traditional and novel CV risk factors as well as the effect of disease activity on the development of CV disease in RA. The prospective design makes this study particularly suitable for comparing CV risk in patients with RA to risk in other populations [2;3], assessing novel risk factors for CV disease [4], investigating changes in CV risk factors and inflammatory parameters while also studying changes in cardioprotective and anti-inflammatory treatment. In addition to the possibility of comparing risk factors or co-morbidity incidences in patients with RA to other diseases or healthy controls, the CARRÉ study also enables comparisons with cohorts in which patients who receive anti-inflammatory treatment (such as TNF inhibitors) are followed longitudinally. These comparisons can yield interesting results that corroborate results found in randomised clinical trials and convey a more realistic representation of the efficacy of these drugs.[5;6] Through comparison of these cohorts additional unexpected findings relating to safety and efficacy of specific medications has been found.[7] These cohorts also provide us with ample opportunity to study certain metabolic, inflammatory and vascular changes that occur due to treatment with these anti-inflammatory medications.[8]

**Epidemiological science: generalisability of findings from smaller studies**
Numerous epidemiological studies have previously shown an increased risk of CV disease in individuals with inflammatory arthritis [1], however the precise magnitude of this CV burden is still debated. Direct comparisons of cohort studies can be difficult due to differences in study design and study populations.[5] CV burden might be overestimated in these studies as CV disease rates are obtained from clinic-based cohorts. Often this captures inflammatory arthritis patients with a
more severe disease, which could falsely inflate the CV disease rate (i.e. selection bias).

Hence, observations obtained from community-based cohorts, including arthritis patients with a broader spectrum of disease severity, may give a more accurate CV disease estimate. To that end, we studied the CV disease prevalence rates of inflammatory arthritis, diabetes mellitus (a disease with known CV disease risk), hip- and/or knee osteoarthritis (non-inflammatory comparator) in a representative primary care population in the Netherlands and compared these to those in the general population. (chapter 1) We previously demonstrated that the increased CV burden in inflammatory arthritis is similar to that seen in diabetes mellitus.[3] These results were confirmed in chapter 1. In addition, the lack of excess CV disease in osteoarthritis further suggests that the systemic inflammatory load is critical to the CV disease burden in inflammatory arthritis.[10;11]

Clinical science: identification of novel risk factors and discovery of mechanisms

Studies from registers, such as in chapter 1, focus on the dynamics of large populations and its risk factors on disease incidence. Population- or hospital-based studies can be helpful to elucidate additional clinically relevant processes that influence the complex interplay between CV risk factors and inflammation that ultimately lead to CV disease.

One such mechanism is described in chapter 2, in which we provide evidence that even a small loss of renal function (i.e. 5 ml/min) in a large population of patients with RA is associated with a 30% increased risk of CV disease.[4] Furthermore, chapter 3 describes that individuals at risk of developing RA (individuals with arthralgia and positive antibodies for anti-cyclic citrullinated peptide antibodies) indeed developing arthritis had an unfavourable lipid profile as compared to those not developing arthritis. Therefore, an unfavourable lower lipid profile, present prior to arthritis, might indicate a subclinical inflammatory process preceding development of arthritis and on the long term CV disease.[12]
Imaging of CV risk: correct ascertainment of vascular involvement in inflammation

There are many non-invasive ultrasonography based imaging modalities for examining the increased risk of CV disease in inflammatory arthritis.[13;14] However, these modalities are mostly validated in the general population and sometimes do not reflect the actual atherosclerotic process.[15] Therefore, traditional surrogate markers of CV risk, such as intima-media thickness, as well as novel non-invasive imaging techniques are discussed in section II. Chapter 4 presents a meta-analysis of 22 observational studies that examined intima-media thickness (cIMT), a well-known surrogate marker for CV risk, in patients with RA as compared to controls. The results show a higher cIMT in RA patients as compared to controls, which support the current evidence base for an increased cardiovascular burden in RA.[16] However, when carefully extrapolating the results beyond cIMT, the results underestimate the actual CV risk reported in prospective observational studies. This might indicate that in RA less atherosclerosis is needed to cause CV events or that another pathogenetic mechanism is present. One such alternative mechanism is called outward arterial remodelling. This is a maladaptive process of the arterial walls in response to changes in hemodynamic or metabolic factors.[17] This process is characterized by an increased lumen and diameter of the artery, thereby elevating the arterial wall stress and tension.[18;19] This process has been shown to be associated with degradation of subendothelial matrix by metalloproteinases, and may increase the risk of plaque rupture.[20-22] In chapter 5, we showed that RA is associated with maladaptive outward carotid arterial remodelling demonstrated by a higher mean circumferential wall stress and tension. Hence, we postulate that outward arterial remodelling contributes to a higher chance of plaque instability and rupture in RA patients.[23]

Next to structural changes, such as intimal media thickening and outward arterial remodelling, the arterial wall might also exhibit changes in inflammatory activity, which can also be visualized. Chapter 6 describes such a novel imaging modality, namely 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET). This modality uses a radioactively labelled glucose analogue that is taken up by highly active cells, such as inflammatory cells. As the radioactive isotope decays, it emits a signal that can be picked up by a PET-scanning machine.[24] Although the
essence of this technique seems quite elegant at estimating inflammation of the vascular wall and is being used more often to assess vascular wall involvement in chronic inflammatory diseases [25;26], there is still large variability in the quantification of vascular inflammation. Chapter 6 examines several factors that cause variability in measurements that may be paramount to the development of standardization of quantification of vascular wall inflammation in RA.

Effect of interventions on CV risk: balancing CV risk management and anti-inflammatory treatment for the benefit of the patient

Prior findings that inflammation plays a pivotal role in the development of CV disease in inflammatory arthritis [15;27-29] can also be replicated by performing studies in which inflammation is reduced by means of treatment. As such, TNF inhibitors (one of the most potent anti-inflammatory drugs in the rheumatologic armamentarium) are thought to play a ubiquitous role in amelioration of CV disease and its risk factors.[30] However, as chapter 7 shows in a meta-analysis of observational prospective studies, TNF inhibitors exhibit only a modest effect on total cholesterol and high-density lipoprotein (HDL) cholesterol levels in RA patients with no significant overall effect on the total-to-HDL-cholesterol ratio (atherogenic index).[31] Conversely, chapter 8 describes a study in which preclinical markers of atherosclerosis (cIMT) do not deteriorate in patients with AS who continue treatment with TNF inhibitors as compared to a deterioration in patients with AS who discontinue treatment with TNF inhibitors. We corroborate this finding in chapter 9, in which we compared the CV disease incidence in a large cohort of patients with RA, treated with TNF inhibitors, and RA patients from the CARRÉ study, who did not use TNF inhibitors. We found a statistically significant decreased incident rate (ratio) for patients who were treated with TNF inhibitors that remained after additional adjustment for traditional CV risk factors. This association seemed to be mediated by a concomitant reduction in DAS-28, a disease activity score in RA.
Cardiovascular risk management or strong inflammatory modulation in preventing cardiovascular disease

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.[32] 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. There is indirect evidence that this multiplication factor improves CV risk estimation in RA [33], but validation is urgently warranted. With regard to the three above-mentioned criteria it is important to realize that although cumulative disease and therefore disease duration probably enhances CV risk, this does not mean CV risk is evident after 10 years disease duration.[34] Whether anti-CCP or rheumatoid factor positivity are independent 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 three criteria. 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. For both DM and RA patients, 15 years are added to the actual age of all patients to express the excess CV risk burden. When it comes to CV risk treatment in RA the first step is life style adaptation. The two key messages for the rheumatologist to convey to patients are smoking cessation and becoming physically active.[35] 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 risk factors (e.g. age, sex, family history of premature cardiovascular heart disease etc.) and the aid of calculators such as Framingham and SCORE, the 10-year CV risk 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 interventional trials with statins or antihypertensives for 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.[36-38] In contrast, one recently published population based longitudinal study found that the efficacy of statins varied in chronic diseases, including RA, and tended to be less effective than in the rest of the population.[39] There are, however, numerous other studies that show beneficial effects of statins and angiotensin-converting enzyme (ACE) inhibitors on CV risk in RA.[40-45] 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.[46-49]

Randomized controlled intervention trials are necessary to assess the true effect of statins, ACE-inhibitors and other life style intervention strategies on CV risk in RA.

**Inflammation modulation**

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 not only of the joints but also the arteries. Although we do not know when the CV risk exactly starts to arise, it is likely that this will start at the same time as 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, as summarized in figure 1.[50] Indirectly, effective treatment (or effective inflammation modulation) can result in improved physical activity, subsequently leading to a decreased risk of obesity, diabetes and
hypertension, and in the end CV disease. The thrust of recent research has clearly identified disease modifying anti-rheumatic drugs (DMARDs) as potentially attenuating the excess CV burden either directly by dampening inflammation or indirectly through modulation of CV risk factors, i.e. specific lipid moieties (e.g. HDL levels and composition), blood pressure, and insulin resistance. Whether these effects are directly influenced by the intrinsic properties of DMARDs or due to improvement in disease activity, remains to be elucidated. Future intervention studies examining risk factor pathways, novel surrogate markers of CV disease, but ideally and most importantly, CV disease end-points upon inflammatory suppression would help to confirm this notion.

Directions for future research
The studies of this thesis can be condensed into several implications to the research setting. There is clear evidence for an increased risk of CV disease in inflammatory arthritis and this risk seems to be caused (at least in part) by chronic inflammation, which can be positively modulated by the use of anti-inflammatory treatment. However, questions remain with respect to correct ascertainment and treatment of CV risk in inflammatory arthritis. Future work designed to address these questions is outlined below:

- In collaboration with other institutes, steps have been taken to develop a new CV risk score for rheumatoid arthritis and other forms of inflammatory arthritis. Ideally, this will lead to specific and efficient use of anti-inflammatory and/or cardioprotective interventions to lower the established CV risk in inflammatory arthritis.
- Research into soluble biomarkers, genetic polymorphisms and gene-expression signatures may shed light on the exact pathogenesis of CV disease in patients with inflammatory arthritis, as well as predict CV risk.
- Most importantly, the strong interrelation between the chronic inflammatory state and the development of CV disease enables us to translate findings from the field of cardiovascular medicine to the field of rheumatology and vice versa. For example, individuals with preclinical RA might benefit from low-grade anti-inflammatory lipid-lowering agents, such as statins, with the specific purpose to prevent the development of CV disease.
• Findings from the field of rheumatology with regard to anti-inflammatory treatment (such as methotrexate) and reduction of CV disease (risk) in inflammatory arthritis might be translated into possible anti-inflammatory interventions in patients with a high risk of CV disease, but without any chronic inflammatory disease.

• An interesting method to translate findings from the laboratory to the clinic, is to examine the inflammatory process in crucial tissue implicated in CV disease (coronary arteries and myocardial tissue), thus investigating the driving factors behind the increased CV risk and mortality of CV disease in patients with inflammatory diseases. Insights gained from such a study could enable us to design a clinical trial investigating the effects of specific anti-inflammatory drugs on reducing the CV risk or ameliorating the damage of CV disease.

CONCLUSION
In this thesis, we have demonstrated that CV disease is a disconcerting problem in inflammatory arthritis due to a combination of CV risk factors and inflammation. Also, we provide a novel non-invasive imaging tool for effective CV risk ascertainment, as well as a novel method of CV risk protection through anti-inflammatory treatment. A more sensitive predictive model and therapeutic rationale for patients with inflammatory arthritis is needed.
REFERENCES


11. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C et al. The risk of myocardial infarction in rheumatoid arthritis and


23. van Sijl AM, Van Den HK, Peters MJ, van Halm VP, Niijpels G, Stehouwer CD et al. Different type of carotid arterial wall remodeling in rheumatoid


