Determinants of cardiovascular risk in current rheumatic practice

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DETERMINANTS OF CARDIOVASCULAR RISK IN CURRENT RHEUMATIC PRACTICE

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Chapter 1

General introduction

The first report that described increased mortality in patients with rheumatoid arthritis (RA), a chronic systemic inflammatory disease predominantly located in the joints, was published in 1953. In 583 rheumatoid arthritis patients once hospitalized at the Massachusetts General Hospital and subsequently followed up for 6.5 years, the mortality rate was significantly increased in subjects below 50 years of age (men 20.6 per 1000 py (3.9/1000 py expected), women 10.7 per 1000 py (2.9/1000 py expected)). Cardiovascular (CV) disease was the major cause of death in the rheumatoid arthritis patients included in this study, and with increasing age the mortality rates of rheumatoid arthritis patients approached the expected mortality for the patients' age and sex. The author concluded that 'to acquire rheumatism is not the way to live a long life'.[1] Since then, many studies in different rheumatoid arthritis cohorts confirmed an approximately 5-15 years reduction in life expectancy in rheumatoid arthritis patients compared to the general population.[2] In the second half of the 20th century, the general population mortality rates decreased due to the improvements in socioeconomic conditions.[3] However, mortality in rheumatoid arthritis patients remained unchanged, resulting in a widening of the mortality gap.[4-6]

Approximately 40-50% of rheumatoid arthritis patients die from cardiovascular disease, which is the leading cause of death followed by respiratory disease, infections and malignancies.[1;4;7] Cardiovascular event and death rates in rheumatoid arthritis are 40-50% higher compared to the general population and the estimated risk of ischemic heart disease is slightly higher than that of stroke (all CV disease RR 1.48, 95% CI 1.36-1.62; myocardial infarction RR 1.68, 95% CI 1.40-2.03; cerebrovascular accident RR 1.41, 95% CI 1.14-1.74).[5;8;9] The extent of the rheumatoid arthritis associated increase in cardiovascular events is comparable to that in established high cardiovascular risk populations, such as patients with type 2 diabetes mellitus (type 2 DM) (comparison to non-diabetic subjects, RA HR 2.16, 95% CI 1.28-3.63; type 2 DM HR 2.04, 95% CI 1.12-3.67).[10] Only inception cohort studies with a short follow up failed to show a significant increase in cardiovascular complications. This can be explained by the observation that the excess mortality may only appear after 10 years of rheumatoid arthritis disease duration.[7-9]

The presentation of cardiovascular disease in rheumatoid arthritis is probably somewhat different from the signs, symptoms and course that is known in the general population. One study showed that rheumatoid arthritis patients present more frequently with silent ischemia and sudden death compared to their non-rheumatoid arthritis counterparts (silent ischemia HR 2.13, 95% CI 1.13-4.03; sudden death HR 1.94, 95% CI 1.06-3.55).[11] Also, rheumatoid arthritis patients were found to have an increased risk of death within the first 30 days after a myocardial infarction (RA 17.6% vs non-RA 10.8%; OR 1.6, 95% CI 1.2-2.2).[12] Inadequate recognition of symptoms, such as cardiac chest pain mistakenly assessed as musculoskeletal pain, by patients and/or their physicians may contribute to a more severe disease at presentation.

Recent literature suggests that, like in rheumatoid arthritis, other chronic rheumatic diseases may also be associated with increased cardiovascular comorbidity and death. Although smaller in size and less in number, studies in diseases such as gout, psoriasis and psoriatic arthritis, spondyloarthropathies and osteoarthritis deserve to be mentioned.

Gout is a common form of arthritis caused by deposition of monosodium urate crystals within joints, but also other tissues, due to chronic hyperuricaemia. Some recent multivariate analyses in large cohorts of gout patients, found independent associations between gout and/or hyperuricaemia, and cardiovascular events and death.[13-17] The estimated excess cardiovascular risk is 1.5 to 2 compared to the general population. However, in gout, historically known by its association with abundance and the unhealthy lifestyle of kings, the increased cardiovascular risk may disappear after correction for traditional cardiovascular risk factors, such as hypertension, renal disease and diabetes.[18;19]

Psoriatic arthritis is a chronic inflammatory rheumatic disease that is associated with the skin disease psoriasis. In psoriatic arthritis the evidence on excess cardiovascular disease is less strong than in rheumatoid arthritis. The patterns of cardiovascular risk factors, subclinical atherosclerosis and cardiovascular events are comparable to those in rheumatoid arthritis patients, but the absolute risk of cardiovascular events may be slightly lower in patients with psoriatic arthritis.[20-26] This was confirmed by a systematic meta-analysis of 33 studies on cardiovascular disease in psoriatic arthritis that showed a small but significantly increased risk of cardiovascular events, but no increased cardiovascular mortality compared to the general population (RR for myocardial infarction 1.25, 95% CI 1.03-1.52; RR for stroke 1.02, 95% CI 0.92-1.14; RR for mortality non-significant, data not shown).[27]

Ankylosing spondylitis is an inflammatory rheumatic disease of the axial skeleton with extra-articular manifestations in the cardiovascular system. Aortic valve disease and aortitis are known disease manifestations of ankylosing spondylitis. Scarce reports also show excess cardiovascular mortality that cannot be fully explained by these disease specific manifestations and, as in rheumatoid arthritis, is thought to be mediated by chronic systemic inflammation.[25;28] In a retrospective cohort of 8616 patients diagnosed with ankylosing spondylitis between 1996 and 2006, the estimated age- and sex- standardized excess cardiovascular disease was 1.37 (95% CI 1.31-1.44) for ischemic heart disease and 1.25 (95% CI 1.15-1.35) for cerebrovascular disease.[29]

Finally, osteoarthritis is a degenerative joint disease, either mono-, oligo- or polyarticular, that can be accompanied by low grade inflammation. It is highly prevalent in the elderly population, a common cause of reduced mobility, and is associated with increased comorbid traditional cardiovascular risk factors such as obesity, hypertension, dyslipidemia and diabetes.[30;31] Some studies showed increased cardiovascular disease and mortality in osteoarthritis.[32;33] A study

evaluating cardiovascular disease prevalence in inflammatory arthritis, diabetes and osteoarthritis in comparison to general population controls demonstrated that the association between osteoarthritis and cardiovascular disease may disappear after correction for age, gender, hypertension and hypercholesterolaemia (Unadjusted OR 1.9, 95% CI 1.6-2.2; adjusted OR 0.8, 95% CI 0.7-1.0).[34] Studies comparing cardiovascular disease in osteoarthritis and inflammatory arthritis showed lower frequencies of cardiovascular disease in osteoarthritis patients.[34;35]

The inflammatory hypothesis of atherosclerosis

Although the coincidence of traditional cardiovascular risk factors such as smoking, diabetes, hypertension, obesity and unfavourable lipid profiles may be increased in patients with rheumatoid arthritis and other rheumatic diseases, these cannot fully explain the excess cardiovascular events and death in patients with different forms of chronic inflammatory arthritis.[6;19;36-38] The inflammatory hypothesis of atherosclerosis, in which the presence of chronic systemic inflammation causes vascular wall activation and formation of instable atherosclerotic plaques, may explain the arthritis specific risk.

Atherosclerosis is a chronic disease of the arterial wall in which atheromatous plaques cause disruption of the inner lining of arteries.[39;40] As in chronic inflammatory polyarthritis, atherosclerosis is characterized by a systemic inflammatory state. Some of the same immune cells and soluble inflammatory mediators play a crucial role in both diseases.[41] The first step in atherogenesis is the activation of the endothelial cells that line the inner arterial surface by irritative stimuli, such as dyslipidaemia, hypertension or pro-inflammatory mediators. Then, expression of adhesion molecules allows activated leucocytes to adhere to and enter the vessel wall. At the same time, increased permeability of the endothelial lining and changes in the extracellular matrix below, facilitates the entry of cholesterol-containing low-density lipoprotein (LDL) particles into the arterial wall.[39] In the arterial wall, the LDL particles are oxidized and undergo endocytosis by monocyte-derived macrophages, leading to intracellular cholesterol accumulation and the formation of so called "foam cells" in the innermost layer of the artery, the tunica intima. Then, macrophages that are present in the developing atheroma are in their turn activated by oxidized LDL to produce high levels of chemo-attractant mediators and pro-inflammatory cytokines, thus causing sustained endothelial activation and amplification of the process of atheromatous plaque formation.[39;41] Atheromatous plaques vary in their composition and the proportion of their collageneous, cellular and lipid components. Those plaques with thin fibrous caps and a core with abundant macrophages that produce collagenolytic enzymes which degrade vessel wall collagen fibers, have the highest risk of rupture and subsequent arterial thrombosis. Arterial thrombosis is the major cause of atherosclerotic ischemic vascular events.[39]

The key inflammatory mediators involved in chronic rheumatic diseases are also important in atherosclerosis. Levels of circulating high sensitivity C-reactive protein and interleukin-6, which are increased in active inflammatory arthritis, are predictive of cardiovascular events both in the general population and in patients with chronic rheumatic diseases.[42-47] The cytokines tumour necrosis factor alpha (TNFα), interleukin-1 and interleukin-6 have been found to be increased in atheromatous plaques and have been associated with formation of instable plaques.[39] Also, patients with rheumatoid arthritis have increased native levels of circulating oxidized LDL-cholesterol, which promotes the formation of foam cells at loci of atherogenesis.[41]
The above mentioned observations suggest an underlying causal relationship that contributes to the observed association between different types of chronic inflammatory polyarthritis and the excess incidence of cardiovascular events.

Arthritis treatment and cardiovascular risk

Arthritis treatment may modulate cardiovascular risk. Some frequently prescribed medications are associated with an increased risk of cardiovascular events, while others may reduce the risk of cardiovascular complications. The impact of medical treatment on cardiovascular risk in arthritis may be drug specific, or may be the consequence of non-drug specific reduction of systemic inflammation. This section will provide a concise overview of the cardiovascular effects of treatment with the most commonly prescribed drugs in chronic inflammatory arthritis: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs), as well as the non-drug specific effect of reduction of systemic inflammation on cardiovascular risk in rheumatoid arthritis.

Non-steroidal anti-inflammatory drugs

NSAIDs are highly effective for the treatment of nociceptive pain in inflammatory arthritis. NSAIDs act through the inhibition of prostaglandin synthesis by blocking the cyclo-oxygenase (COX) enzyme. COX exists in two iso-enzymes, COX-1 and COX-2, the latter of which is involved in inflammation and inflammatory pain.[48] Because concurrent inhibition of COX-1 by traditional nonselective NSAIDs is the cause of important gastro-intestinal side effects, COX-2 selective NSAIDs or COXIBs were developed. Only shortly after the registration of the first COXIBs, it was observed that the use of these drugs was associated with increased cardiovascular events and mortality.[49;50] Within the following years it became clear that actually none of the NSAIDs are cardiovascular safe.[51;52] Risks vary by NSAID, dosage and dosage interval, in which naproxen and once daily low dose celecoxib (100 mg) appear to be least harmful. A recent meta-analysis of 31 randomized controlled trials demonstrated rate ratio's between 1.21 (naproxen, 95% CI 0.78-

1.93) and 2.26 (ibuprofen, 95% CI 1.11-4.89) for the composite outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.[51] The NSAID associated cardiovascular risk is at least twofold. Firstly, a COX-2 mediated class specific risk that adds to other patient specific traditional cardiovascular risk factors.[51-53] Thus, the absolute NSAID related cardiovascular risk in a young and otherwise healthy individual will be small, whereas it may become clinically significant in older patients with multiple traditional cardiovascular risk factors. Secondly, some NSAIDs have a potential for a COX-1 mediated interaction with low dose aspirin, a drug prescribed for secondary prophylaxis of cardiovascular events.[54-56] This interaction, which was observed in ibuprofen, indomethacin and naproxen, causes inhibition of the antithrombotic effects of aspirin, and thus causes exposition of the patient to his or her original risk for recurrence of cardiovascular events.

Glucocorticosteroids

The role of glucocorticosteroids in arthritis associated cardiovascular disease is controversial. Treatment with glucocorticosteroids is associated with increased blood pressure, insulin resistance, dyslipidaemia, increased body weight and increased abdominal fat distribution.[57] These unfavourable side effects are dose dependent and more severe with longer duration of treatment. A recent study found myocardial infarctions to occur more frequently in rheumatoid arthritis patients using oral corticosteroids (HR 1.68, 95% CI 1.14-2.47).[58] The current daily dosage and cumulative exposure were independently associated with excess cardiovascular events. However, treatment with glucocorticosteroids may also reduce vascular wall inflammation and thus inhibit progression of atherosclerotic plaque formation. This may explain another observation, in which cardiovascular events were not increased after long term treatment by daily use of <7.5 mg prednisolon, but increased by a factor 2.6 (95% CI 2.2-3.0) in patients using ≥7.5 mg daily.[59]

Synthetic and biologic disease modifying antirheumatic drugs

In rheumatoid arthritis, the prolonged use of DMARDs is associated with a reduced risk of cardiovascular events and improved overall patient survival.[60-65] The evidence is particularly strong for methotrexate (MTX). One meta-analysis found the use of methotrexate to be associated with a 21% risk reduction (10 studies, RR 0.79, 95% CI 0.73-0.87) for total cardiovascular disease and a 18% reduction of myocardial infarctions (5 studies, RR 0.82, 95% CI 0.0.71-0.96).[63] A study comparing cardiovascular disease risk in rheumatoid arthritis patients, according to different synthetic DMARDs and DMARD combinations used, found that methotrexate, alone or in combination with sulfasalazine (SSZ) or sulfasalazine and hydroxychloroquine (HCQ) was associated with a significant risk reduction after correction for traditional cardiovascular risk

factors and rheumatoid arthritis disease duration (MTX OR 0.11, 95% CI 0.02-0.56; MTX+SSZ OR 0.16, 95% CI 0.06-0.42; MTX+SSZ+HCQ OR 0.16, 95% CI 0.06-0.43), whereas the use of sulfasalazine monotherapy was associated with a smaller risk reduction (SSZ OR 0.37, 95% CI 0.14-0.99) and the use of hydroxychloroquine monotherapy was not associated with a significant effect on the occurrence of cardiovascular disease (HCQ OR 0.47, 95% CI 0.15-1.46).[64] The use of TNF inhibiting biologic DMARDs has also been associated with a reduction in cardiovascular event risk in rheumatoid arthritis (myocardial infarction RR 0.81, 95% CI 0.68-0.96, cerebrovascular accident RR 0.69, 95% CI 0.53-0.89).[62;66-68] Whether TNF antagonists perform better than synthetic DMARDs, in particular methotrexate, in improving cardiovascular outcomes in rheumatoid arthritis is uncertain, and may be dependent on the patients' general response after six months of treatment.[68]

Reduction of systemic inflammation

In recent years the treatment of inflammatory polyarthritis, in particular rheumatoid arthritis, has changed dramatically through the wide availability of potent synthetic and biologic DMARDs and the introduction of protocolled treatment strategies aiming at achieving remission within the shortest possible interval after diagnosis. If chronic systemic inflammation really is an important arthritis specific cardiovascular risk factor, one may thus expect a fall in arthritis associated cardiovascular events in current inception cohorts of low disease activity arthritis patients. This hypothesis is supported by several studies, finding significantly lower cardiovascular disease biomarkers such as HDL-cholesterol, total cholesterol/HDL ratio, NT-pro-BNP, carotid artery intima-media thickness and endothelial function measurements in patients in remission of clinical arthritis compared to patients with active disease.[69-71] However, studies evaluating cardiovascular morbidity and mortality in rheumatoid arthritis over the past 50 years report conflicting results, some showing stable standardized mortality ratios compared to the general population, others finding a decline in cardiovascular mortality in subsequent birth cohorts of rheumatoid arthritis patients.[5;72;73] To date, large prospective studies that have evaluated cardiovascular risk in recent onset, intensively treated, low disease activity rheumatoid arthritis patients are not available.

Cardiovascular risk management in arthritis

Recently, several guidelines and recommendations on the management of rheumatic diseases that include remarks on screening for and/or treatment of cardiovascular disease have been published for rheumatic diseases like ankylosing spondylitis and gout.[74-77] However, the hallmark of the wide recognition of the importance of cardiovascular complications in inflammatory polyarthritis was the publication of the European League Against Rheumatism (EULAR)

recommendations for cardiovascular risk management in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis in 2009.[78] Even though the level of evidence on the effectiveness of risk interventions was generally low, and even if studies were available these often only applied to rheumatoid arthritis patients, the authors strived to provide a framework for initiating cardiovascular risk management in daily rheumatologic practice. Following these recommendations and considering the accumulating evidence that rheumatoid arthritis patients constitute a high cardiovascular risk population, the Dutch Institute for Healthcare Improvement (CBO) and the Dutch College of General Practitioners (NHG) included rheumatoid arthritis, like diabetes mellitus, in the definition of high cardiovascular risk populations in their 2011 revision of the National Guideline for Cardiovascular Risk Management.[79] Healthcare professionals are encouraged in these recommendations and guidelines to adjust common cardiovascular risk estimation scores, ie the Systematic Coronary Risk Estimation (SCORE) or Framingham score, which were developed for general population cardiovascular risk management, to high risk rheumatoid arthritis patients by either applying a multiplication factor to the risk estimation score, or by the addition of 15 years to the patients' age.[78;79] Neither the EULAR nor the CBO adaptation of these cardiovascular risk scoring instruments have been validated in cohorts of patients with chronic inflammatory arthritis.

After the publication of these guidelines, several studies were done to evaluate the identification and management of cardiovascular risk factors in rheumatoid arthritis patients. The results show that despite the many publications on cardiovascular complications in rheumatoid arthritis, rheumatoid arthritis patients generally remain undertreated, even according to the general population guidelines for primary and secondary cardiovascular prophylaxis.[80-82]

The ACT-CVD cohort

In 2009 the Arthritis Centre Twente (ACT) established a per protocol cardiovascular screening as part of standard care for patients with rheumatic diseases. At their first consultation following the introduction of this cardiovascular screening protocol, all prevalent and incident patients of the ACT outpatient clinic receive patient information documents and additional personal information concerning the purpose and procedure of cardiovascular screening from their attending rheumatologist. Patients that consent to participate are welcomed by a trained assistant who fills out a questionnaire recording demographical data, medical history, and cigarette smoking habits. A short standardised physical examination is performed, recording weight, length and blood pressure, and fasting blood samples are taken for assessment of total cholesterol, HDL cholesterol, glucose, urate, and inflammatory parameters (i.e. erythrocyte sedimentation rate and C-reactive protein).

With the objective of evaluating the results of the screening project and to study current cardiovascular morbidity and mortality in the rheumatic patient population the ACT-CVD cohort was created. All patients that participated in screening were requested informed consent for inclusion in the database and follow up for the occurrence of major cardiovascular events and death.

The ACT-CVD database contains the baseline demographics, medical history and rheumatic disease characteristics of each patient, as well as the lifestyle related cardiovascular risk factors and cardiovascular biomarkers that were collected during the cardiovascular screening. Patients are classified according to their clinical diagnosis as registered by their attending rheumatologist. Rheumatoid arthritis disease activity is systematically measured by the Disease Activity Score in 28 joints (DAS-28), rheumatoid arthritis remission being defined as a DAS-28 $\leq$ 2.6.[83] After inclusion in the database, SCORE 10-year risk of fatal cardiovascular events estimates are calculated and patients are described previously, and patients are followed up for incident cardiovascular events and/or death. Follow up data concerning incident cardiovascular events and causes of death are extracted from the hospital electronic registration system and are validated by medical chart review. For the registration of out of hospital events and death, attending general practitioners receive periodic questionnaires and data is extracted from the Dutch National Registry of Death Certificates.

The anonymized patient data in the ACT-CVD database are available for research purposes, in accordance with the primary objectives of the ACT-CVD project, after revision and approval of the research protocol by the Arthritis Center Twente Institutional Research Board.

This thesis

Despite the extensive literature on cardiovascular disease in inflammatory arthritides, several questions remain to be answered.

First, what is the distribution of traditional cardiovascular risk factor profiles within a rheumatology practice. Where previous literature focussed primarily on rheumatoid arthritis, in **Chapter 2** we set out to compare cardiovascular risk factor profiles in different rheumatic diseases with the cardiovascular risk factor profile in the general population.

Second, what is the relationship between uric acid levels and excess cardiovascular risk factors and mortality in patients with gout, and in patients with non-gouty rheumatic disease. Previous studies that evaluated serum uric acid as a cardiovascular risk factor gave conflicting results: hyperuricaemia has often been found to be an independent cardiovascular risk factor, but in some studies the association was lost after correcting for traditional cardiovascular risk factors, and other studies only found an association between gouty arthritis and cardiovascular disease.

In **Chapter 3** we performed a study that evaluated the association of serum uric acid level with the prevalences of traditional cardiovascular risk parameters and with the prospective incidence of cardiovascular events in patients with gout and non-gouty rheumatic disease.

Third, what are the trends in cardiovascular morbidity and mortality in low disease activity rheumatoid arthritis patients that are intensively treated according to a tight control strategy aiming at remission. To address this question, two preliminary analyses of ACT-CVD cohort follow up data were performed, each evaluating the incidence of cardiovascular events in rheumatoid arthritis patients included in the ACT-CVD cohort. In the Arthritis Center Twente rheumatoid arthritis patients are treated according to a tight-control, DAS-28 steered treatment protocol aiming at remission (DAS-28 $\leq$ 2.6).[83-85] Therefore, the rheumatoid arthritis patients included in the ACT-CVD cohort are characterized by a low mean disease activity (mean DAS-28 2.6 $\pm$ 1.2) and high prevalence of rheumatoid arthritis remission (DAS-28 $\leq$2.6, 72%). In **Chapter 4** we evaluated the incidence of first cardiovascular events in these tightly controlled, low disease activity rheumatoid arthritis patients in comparison to patients with osteoarthritis, and in comparison to the self-reported incidence of cardiovascular disease in the Dutch general population. In **Chapter 5** we studied the fatality of first cardiovascular events in the ACT-CVD rheumatoid arthritis patients, and put these results into the context of previous studies with data on cardiovascular event fatality in rheumatoid arthritis.

Fourth, what is the contribution of NSAID use to excess cardiovascular events in rheumatoid arthritis patients. To answer this question, in **Chapter 6** we performed a confirmative study to evaluate the potential clinically relevant interaction between different NSAIDs and acetylsalicylic acid. With this study, we could suggest which NSAIDs can be co-prescribed with acetylsalicylic acid, without inhibition of its cardioprotective action. To evaluate the inherent class specific NSAID associated cardiovascular risk, in **Chapter 7** we prospectively studied the occurrence of cardiovascular events in the ACT-CVD cohort according to the chronic use of different NSAIDs by rheumatoid arthritis patients. **Chapter 8** is a narrative review that summarizes the literature on the different mechanisms underlying the cardioprotective effect of low dose aspirin, the possible renovascular and cardiovascular complications of NSAIDs, and the potential for pharmacodynamic interaction between both drugs.

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Chapter 2

Increased cardiovascular risk factors in different rheumatic diseases compared to the general population

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Abstract

Objectives: To study the prevalence of cardiovascular risk factors among patients attending a rheumatology outpatient clinic in comparison with the general population.

Methods: Cross-sectional comparison between a rheumatic outpatient cohort of consecutive patients (n=1233) between 36 and 75 years of age attending the Arthritis Center Twente (ACT) in 2009: rheumatoid arthritis (RA; n=546), gout (n=129), osteoarthritis (OA; n=168), connective tissue disease (CTD; n=85), polymyalgia rheumatica (PMR; n=91), and chronic localized or generalized pain syndromes (CPS; n=214) and a random sample of a long-lasting population based health study in the Netherlands (n=4523). Main outcome measures: hypertension (systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication), abnormal cholesterol profile (TC≥6.5 mmol/L, and/or HDL<0.9 mmol/L and/or use of lipid lowering medication), overweight (BMI ≥25 kg/m^2), obesity (BMI ≥30 kg/m^2) and cigarette smoking habits (self reported current smoking).

Results: Compared to the general population, patients with rheumatic diseases have a significantly higher prevalence of hypertension (P_{ACT}=68%, $P_{general}$=57%), overweight (P_{ACT}=72%, $P_{general}$=62%), obesity (P_{ACT}=30%, $P_{general}$=17%) and cigarette smoking (P_{ACT}=26%, $P_{general}$=21%). The worst risk profile was found in gout patients, with higher prevalence of all cardiovascular risk factors studied.

Conclusion: lifestyle associated potentially modifiable cardiovascular risk factors are overrepresented along the whole spectrum of chronic rheumatic diseases, and not only in RA as suggested by preceding studies.

Introduction

Chronic rheumatic and cardiovascular diseases share common pathophysiological factors; immobility, obesity, inflammation and smoking. Diseases such as rheumatoid arthritis (RA), gout, polymyalgia rheumatic (PMR), and connective tissue diseases (CTD) are characterised by chronic or intermittent inflammation, and are treated with anti-inflammatory drugs. The relationship between different chronic rheumatic and cardiovascular diseases has not been studied. Most research has been done on increased cardiovascular morbidity and mortality in RA patients [1-4]. The high prevalence of cardiovascular disease in RA might be explained by clustering of lifestyle associated cardiovascular risk factors, chronic inflammation, and/or the use of medication such as non steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs). Other rheumatic diseases have also been associated with raised cardiovascular risk. Gout may be part of the metabolic syndrome, i.e. abdominal adiposity, glucose intolerance, hypertension and dyslipidemia, a complex of abnormalities accompanying unhealthy Western lifestyles associated with increased cardiovascular morbidity and excess mortality [5-7]. Some small studies in PMR have found increased prevalence of arteriovascular disease [8-10]. Vascular dysfunction and accelerated atherosclerosis are established features of systemic lupus erythematodes, especially when accompanied by antiphospholipid antibodies, and have also been observed in other CTD such as systemic sclerosis [11-13]. The impact of traditional cardiovascular risk factors on CTD-associated cardiovascular complications remains uncertain.

Less is known about rheumatologic disorders without systemic inflammation, such as osteoarthritis (OA) and chronic widespread pain syndromes (CPS). Recent data have suggested these may also be associated with cardiovascular disease, possibly due to high prevalence of lifestyle associated risk factors [14;15].

The aim of this study was to compare prevalences of traditional cardiovascular risk factors in different rheumatic diseases with the general population.

Methods

Data sources

Data for this study were obtained from two databases on lifestyle associated cardiovascular risk factors in individuals from the same geographic region in the eastern part of the Netherlands. Data recorded include demographics, medical diagnoses, cigarette smoking habits, laboratory test results, recordings of height, weight and blood pressure and current drug prescriptions. The databases are briefly described below.

Arthritis Center Twente CardioVascular Disease (ACT-CVD) project

In 2009 the Arthritis Center Twente (ACT) established a per protocol cardiovascular screening as part of our standard of care. After one year of screening the database contained the completed data of 1500 patients who were representative of the entire outpatient population. Patients were categorized into six groups by their primary diagnosis: 1. rheumatoid arthritis (RA), 2. gout, 3. osteoarthritis (OA), 4. connective tissue diseases (CTD; systemic lupus erythematodes (SLE), systemic sclerosis (SSc), Sjogren's syndrome (SS), systemic vasculitis (SV)), 5. polymyalgia rheumatica and/or arteriitis temporalis (PMR), 6. and chronic generalized pain syndromes (CPS; fibromyalgia (FM), noninflammatory tendinopathies (NT), hypermobility and noninflammatory arthralgia (NA)). Data collection on cardiovascular risk factors took place by standardized physical examination and fasting blood sample at one regular visit to the outpatient clinic. RA disease activity was measured by Disease Activity Score in 28 joints (DAS-28). The protocol for data collection and storage was approved by the institutional review board.

Doetinchem Cohort Study (fourth measurement round; 2003-2007)

Data from the general population were derived from the fourth measurement round of the Doetinchem Cohort, which was conducted as part of a long-lasting, population based health study (DCS). All participants gave written informed consent, and the study was approved according to the guidelines of the Helsinki Declaration by the Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research. Data collection took place by standardized physical examination by trained personnel during a visit to the municipal health service, a non-fasting blood sample, and self-reported questionnaires for demographic and life style characteristics, as described previously.[16]

Study population

For each database, individuals were eligible for inclusion when aged 36-74 years at the time of examination. From the ACT-CVD cohort 1233 patients met this criterion, and 4523 individuals from the DCS.

Cardiovascular risk factor measurements in both study protocols

Cardiovascular risk factors assessed during physical examination were body mass index and blood pressure. In both study protocols height and weight were measured barefoot wearing light clothes only. At the ACT outpatient clinic body weight was measured by mechanical scales to the nearest 1 kg, body weight measurement in the DCS was by balance beam scale to the nearest 0·5 kg. To adjust for light indoor clothing, 1 kg was subtracted from the measured weight.

Height measurement procedures were the same in both study protocols, using a wall-mounted stadiometer to the nearest 0·5 cm. BMI was calculated as the ratio of weight (kg) and squared height (m). Overweight was defined as a BMI≥25 kg/m^2, obesity as a BMI≥30 kg/m^2.
Readings of systolic and diastolic blood pressure were obtained in rest on the right arm with the patient in sitting position using a calibrated blood pressure instrument. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication. Measurements of cholesterol values were performed in two laboratories, both using standardised CHOD-PAP and HDL-C 3rd generation assays for assessment of total and HDL cholesterol, respectively. Hypercholesterolaemia was defined as TC≥6.5 mmol/L and/or use of lipid lowering medication, low HDL as HDL-cholesterol values <1,0 mmol/L.

Statistical analysis

Prevalences of cardiovascular risk factors in patients with rheumatic diseases and controls were presented by descriptive statistics (mean or percentage prevalence) adjusted for differences by sex and age. Differences between patients with rheumatic diseases and controls were tested with ANOVA (for continuous cardiovascular risk factors) or logistic regression analyses (for dichotomous cardiovascular risk factors). Differences in dichotomous risk factors between patients and controls were also presented by odds ratios (ORs) with 95% confidence intervals (CI). Data analysis was performed using SAS version 9.1 (SAS Institute).

Results

The overall rheumatology outpatient population

Both populations showed comparable distributions of age, women being slightly overrepresented in the ACT-CVD cohort (ACT-CVD 62% vs. DCS 53%, table 1). Most patients were diagnosed with RA (546), followed by CPS (214; 34 FM, 49 NT, 131 NA), OA (168), gout (129), PMR (91), and CTD (85; 28 SLE, 18 SSc, 14 SS, 25 SV). When comparing the complete ACT-CVD cohort to the DCS cohort, most risk factors were increased, with significantly higher prevalences of overweight, current smoking, and hypertension (Table 2). Hypertension was quite uniformly increased among all specific rheumatic diseases, as were measures of weight, i.e. overweight and obesity, with the exception of the group of CTD. In specific diseases the prevalences of other risk factors differed substantially as compared to the DCS cohort (tables 2 and 3, figure 1), and discussed in the following subsections.

Table 1. Age and sex distributions of study populations

	Doetinchem Cohort Study	Rheumatic diseases	By specific diseases					
		All	RA	Gout	OA	CTD	PMR	CPS
	4523	1233	546	129	168	85	91	214
Age group (%)								
30-40 yr	6.2	6.1	5.7	4.7	1.8	10.6	0	12.2
40-50 yr	25.9	21.4	22.2	13.2	16.7	28.2	1.1	34.1
50-60 yr	35.2	31.1	30.6	27.9	38.1	29.4	18.7	35.1
60-70 yr	24.0	29.3	28.8	41.1	32.7	25.9	45.1	15.4
70-80 yr	8.7	12.1	12.8	13.2	10.7	5.9	35.2	3.3
Sex (%)								
men	47.4	38.1	37.6	89.9	22.0	25.9	37.4	26.2
women	52.6	61.9	62.5	10.1	78.0	74.1	62.6	73.8

Figure 1. Prevalence of cardiovacular risk factors in RA, gout, OA, CTD, PMR and CPS; Ors in comparison with the general population.

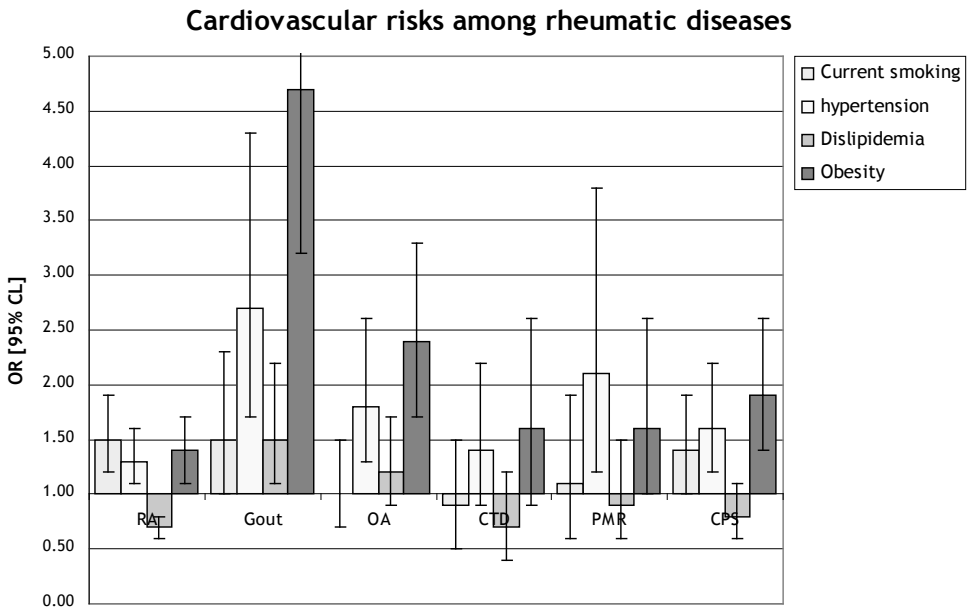

Table 2. Cardovascular risk factors among patients with rheumatic diseases and controls

	Doetinchem	Rheumatic diseases	By specific diseases					
	Cohort Study	All	RA	Gout	OA	CTD	PMR	CPS
n	4523	1233	546	129	168	85	91	214
Current smoking (%)	20.5	25.9*	28.1*	26.4	20.6	19.0	22.6	27.0
Ever smoking (%)	62.7	64.6	67.3	74.4*	61.1	61.7	54.7	64.4
Systolic blood pressure (mmHg, mean)	135.7	143.4*	141.6*	149.2*	146.7*	137.6	148.8*	142.1*
Diastolic blood pressure (mmHg, mean)	85.0	84.1*	84.2	86.9*	84.2	82.0*	81.3*	84.1
BP> 140/90 mm Hg (%)	41.8	57.9*	55.0*	71.3*	60.8*	50.6	63.0*	59.3*
Use of antihypertensive medication (%)	16.6	28.3*	25.2*	43.4*	32.4*	28.7*	30.1*	24.5*
Hypertension (BP > 140/90 mmHg or med) (%)	56.0	65.7*	62.2*	83.0*	68.1*	62.8	68.8*	66.6
Total cholesterol (mmol/l, mean)	5.58	5.29*	5.28*	5.21*	5.53	5.11*	5.35*	5.24*
HDL cholesterol (mmol/l, mean)	1.43	1.45	1.45	1.14*	1.47	1.53*	1.70*	1.46
TC/HDL ratio (mean)	4.2	4.0*	3.9*	4.9*	4.0*	3.6*	3.3*	3.8*
High total cholesterol (>6.5 mmol/l, %)	16.3	10.4*	8.7*	13.2	15.9	7.4*	11.5	9.1*
Low HDL cholesterol (<0.9 mmol/l, %)	8.2	8.7	8.8	18.6*	8.1	8.9	3.2	6.9*
Use of lipid lowering medication (%)	10.1	12.1*	8.6	22.5*	13.1	11.7	17.3*	14.1
Abnormal cholesterol profile (incl. med) (%)	31.5	28.5	20.0*	46.5*	35.5	25.1	31.4	26.9*
BMI (kg/m^2, mean)	26.6	28.0*	27.3*	30.7*	29.1*	27.1	28.0*	27.7*
Overweight (BMI ≥25 kg/m^2) (%)	61.9	72.2*	68.3*	93.8*	80.5*	64.4	65.8	74.1*
Obesity (BMI ≥30 kg/m^2) (%)	17.3	28.2*	22.6*	48.1*	34.0*	24.4	26.6*	28.0*

Figures adjusted for differences in sex and age. *P<0.05. BP: blood pressure.

Rheumatoid arthritis

RA patients (341 women and 205 men, mean disease duration 81 months, 69% in remission according to DAS-28 score ≤2.6) had significantly higher prevalences of overweight, obesity and hypertension compared to the DCS cohort. RA patients were characterised by an increased prevalence of current smoking.

Gout

In gout patients (116 men and 13 women, 76% treated with uric acid lowering medication) all risk factors measured were significantly more prevalent compared to the DCS cohort. In comparison to the DCS cohort these patients showed the highest prevalence of overweight and obesity. Gout was the only disease with unfavourable TC/HDL ratios compared to the DCS cohort, while gout patients were also significantly more frequently treated with lipid lowering drugs.

Osteoarthritis

OA patients (131 women and 37 men) had a significantly higher prevalence of hypertension compared to the DCS cohort. Furthermore, OA patients were characterised by high prevalences of overweight and obesity.

Connective tissue disease

Patients with CTD (63 women and 22 men) did not differ significantly from the DCS cohort in lifestyle associated cardiovascular risk factors, except for a lower, more favourable mean TC/HDL ratio.

Polymyalgia rheumatica

PMR patients (57 women and 34 men) had significantly increased frequencies of obesity and hypertension compared to the DCS cohort.

Chronic general and localized pain syndromes

CPS patients (158 women and 56 men) had significantly increased prevalences of current smoking, overweight, obesity, and hypertension compared to the DCS cohort. Statins were significantly more frequently prescribed in CPS patients compared to the DCS cohort, and total cholesterol values were significantly more favourable.

Table 3. Cardovascular risk factors among patients with rheumatic diseases, OR (95% CI) versus controls

	Rheumatic diseases	By specific diseases					
	All	RA	Gout	OA	CTD	PMR	CPS
n	1233	546	129	168	85	91	214
	OR (95%CL)						
Current smoking (%)	1.3 (1.2 1.6)*	1.5 (1.2 1.9)*	1.5 (1.0 2.3)*	1.0 (0.7-1.5)	0.9 (0.5-1.5)	1.1 (0.6-1.9)	1.4 (1.0 1.9)*
Ever smoking (%)	1.1 (0.9 1.2)	1.2 (1.0 1.5)	1.3 (0.8 1.9)	1.0 (0.7 1.3)	0.9 (0.6 1.5)	0.7 (0.4 1.0)	1.1 (0.8 1.4)
BP>140/90 mmHg (%)	2.0 (1.7 2.6)*	1.8 (1.5 2.1)*	2.5 (1.7 3.7)*	2.3 (1.7 3.2)*	1.5 (0.9 2.3)	2.5 (1.6 4.0)*	2.1 (1.6 2.9)*
Use of antihypertensive medication (%)	2.0 (1.7 2.3)*	1.7 (1.4 2.1)*	3.6 (2.4 3.4)*	2.4 (1.7 3.4)*	2.2 (1.3 3.6)*	1.8 (1.2 2.8)*	1.8 (1.3 2.5)*
Hypertension (BP>140/90 mmHg, incl. med) (%)	1.6 (1.4 1.8)*	1.3 (1.1 1.6)*	2.7 (1.7 4.3)*	1.8 (1.3 2.6)*	1.4 (0.9 2.2)	2.1 (1.2 3.8)*	1.6 (1.2 2.2)*
High total cholesterol (>6.5 mmol/l, %)	0.6 (0.5 08)*	0.5 (0.4 0.7)*	0.8 (0.4 1.3)	1.0 (0.7 1.5)	0.5 (0.2 1.0)*	0.7 (0.4 1.2)	0.5 (0.3 0.8)*
Low HDL cholesterol (<0.9 mmol/l, %)	1.1 (0.9 1.4)	1.1 (0.8 1.6)	1.8 (1.1 2.8)*	1.0 (0.5 2.1)	1.2 (0.5 3.0)	0.3 (0.1 1.3)	0.7 (0.4 1.5)
Use of lipid lowering medication (%)	1.2 (1.0 1.50)*	0.8 (0.6 1.1)	1.9 (1.2 2.9)*	1.4 (0.9 2.2)	1.2 (0.6 2.5)	1.5 (0.9 2.6)	1.6 (1.0 2.6)*
Abnormal cholesterol profile (incl. med, %)	0.9 (0.8 1.0)*	0.7 (0.6 0.8)*	1.5 (1.1 2.2)*	1.2 (0.9 1.7)	0.7 (0.4 1.2)	0.9 (0.6 1.5)	0.8 (0.6 1.1)
Overweight (%)	1.6 (1.4 1.9)*	1.3 (1.1 1.6)*	6.6 (3.2-13.7)*	2.5 (1.7-3.6)*	1.1 (0.7-1.8)	1.2 (0.7-1.9)	1.7 (1.3 2.3)*
Obesity (%)	1.9 (1.6 2.2)*	1.4 (1.1 1.7)*	4.7 (3.2-6.7)*	2.4 (1.7-3.3)*	1.6 (0.9-2.6)	1.6 (1.0-2.6)*	1.9 (1.4 2.6)*

Figures adjusted for differences in sex and age. *P<0.05. BP: blood pressure.

Discussion

This study shows that cardiovascular risk factors are overrepresented in all the rheumatic diseases studied. There may be different patterns of risk factors in specific rheumatic diseases. Overweight and hypertension were consistently present in all rheumatic diseases studied. RA patients are further characterized by a high prevalence of smoking, while gout patients show an increase of all risk factors measured.

RA being associated with current smoking is in line with the concept of cigarette smoking in the pathogenesis of RA [17-19]. Cigarette smoking is a major health problem in RA, as it not only affects the disease itself, but also the development of RA's most prevalent fatal comorbidities; chronic obstructive pulmonary disease and cardiovascular events [3;20]. Cholesterol profiles in RA compared favourably to the general population. This seems remarkable since previous studies in predominantly untreated patients showed increased dyslipidemia in RA.[21] However, cholesterol values have been shown to decrease with lower disease activity and levels of inflammation. Our study included treated patients with average low disease activity.[22] When looking at the number of risk factors, gout patients showed the worst traditional cardiovascular risk profile compared to the general population. Gout was characterised by increased prevalences of all the evaluated risk factors compared to the general population, and it was the only group with significantly increased prevalence of abnormal cholesterol profiles. Previous studies evaluating cardiovascular risk in hyperuricemia and gout show conflicting results. Some show hyperuricemia to be an independent risk factor for cardiovascular events and death, others find no such associations or only with gouty arthritis.[7;23-25] Gout and hyperuricemia have also been associated with the metabolic syndrome, a complex of the individual cardiovascular risk factors overweight, hypertension, dyslipidemia and diabetes.[5-7] These results are in line with previous studies on associations between the complex of metabolic cardiovascular risk factors called the metabolic syndrome and gout. [7;21;22] Other studies have shown associations between gout or serum uric acid levels and cardiovascular morbidity and mortality. [23-25] In the CTD group none of the traditional cardiovascular risk factors was significantly increased compared to the general population. This seems remarkable because several diseases in this category have previously been associated with increased cardiovascular morbidity and mortality. [11;13] One explanation could be that cardiovascular disease in CTD is primarily the result of the disease itself, due to involvement of the vascular system, resulting in vascular dysfunction predisposing to cardiovascular events.[11] This is the first study evaluating cardiovascular risk factors among a broad spectrum of rheumatic diseases and comparing these with the general population. While interpreting these results some limitations should be taken into account. The data on patients and the general population were extracted from two independent studies; the

ACT-CVD cohort and DCS. Data collection in these studies took place within six years, and both were conducted in the same geographic region in the Eastern part of the Netherlands. For this study risk factors with equivalent measurement procedures were included. Because of limited registration of data on the use of medication in the DCS only associations with the use of anti-hypertensives and lipid lowering drugs could be evaluated.

Blood pressure measurement instruments differed, which might have affected the comparison of blood pressure values between rheumatic diseases and the general population. Since original data were available the same definitions of hypertension and dyslipidemia could be applied in both cohorts. Laboratory measurements were performed in single laboratories at different institutions for each study. Both laboratories were reference laboratories using the same standardised testing methods and participating in national calibration procedures. Therefore, comparison of cholesterol measurements was regarded justified.

Lastly, the DCS is a long-lasting population based health study, and data for this study were taken from the fourth measurement round. The "worried well", i.e. concerned individuals from a low risk population that frequently seek contact with health care institutions, are usually overrrepresented in these studies, resulting in a relatively healthier sample. However, no selection for the population based sample was made and it also includes individuals with rheumatic diseases. Altogether we expect that this might have caused a minor overestimation of the differences with rheumatic diseases.

Conclusions

In rheumatic diseases the prevalence of cardiovascular risk factors is high. Overweight and obesity are almost uniformly present. Gout has the most unfavourable risk profile, including the whole spectrum of traditional cardiovascular risk factors. Cigarette smoking is a highly prevalent health hazard in RA.

What is already known on this subject

Cardiovascular disease is the major cause of death among RA patients.

Cardiovascular disease in RA is supposed to be caused by chronic systemic inflammation, lifestyle associated cardiovascular risk factors and medication use.

Rheumatic and cardiovascular diseases share common pathophysiological processes.

What this study adds

The prevalence of lifestyle associated cardiovascular risk factors is high in different rheumatic diseases.

Specific rheumatic diseases may have different cardiovascular risk patterns.

Gout is a flaming red flag for lifestyle associated cardiovascular risk.

Smoking is highly prevalent in RA, and importantly boosts RA associated cardiovascular risk.

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Chapter 3

Hyperuricaemia: a marker of increased cardiovascular risk in rheumatic patients: analysis of the ACT-CVD cohort

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Abstract

Background: Gout and hyperuricaemia may be associated with increased cardiovascular risk, but analyses in different populations show conflicting results. Studies that evaluate the associations between gout, serum uric acid, inflammation and CV risk in rheumatic disease are scarce. This study investigates the impact of serum uric acid, inflammation and traditional CV risk parameters on CV event risk in patients with gouty arthritis and patients with non-gouty rheumatic disease.

Methods: cross-sectional and prospective multivariate analysis of the relation between tertiles of serum uric acid and individual traditional CV risk factors in a cohort of gouty arthritis (GA, n=172), rheumatoid arthritis (RA, n=480) and osteoarthritis (OA, n=206) patients. Main outcome measures: systolic blood pressure, TC/HDL ratio, GlyHb, BMI and first CV events.

Results: individual CV risk factors were significantly less favourable in GA (systolic blood pressure, TC/HDL ratio, BMI, $p<0.05$). In RA and OA individual cardiometabolic parameters correlated with serum uric acid values (RA: systolic blood pressure, TC/HDL ratio, BMI; OA: systolic blood pressure, TC/HDL ratio, GlyHb, BMI; $p<0.05$). These correlations were not present in GA. In non-GA individuals the highest tertile of serum uric acid (>0.34 mmol/L) and NT proBNP level were independent predictors of first CV events, against age and GlyHb level in GA ($p<0.05$). The hazard of first CV events was equally significantly increased in GA patients (HR 3.169, 95% CI 1.287-7.806) and non-GA individuals with a serum uric acid $\geq$ 0.34 mmol/L (HR 3.721, 95% CI 1.603-8.634) compared to non-GA individuals with a serum uric acid < 0.27.

Conclusions: GA and, in non-GA rheumatic patients, upper range serum uric acid are associated with an approximately 3-fold hazard of first CV events. CV risk in GA is independent of serum uric acid values and remains important in patients treated with uric acid lowering therapy. The presence of GA or a baseline serum uric acid in the upper range are possibly stronger predictors of first CV events than some traditional CV risk factors or parameters of inflammation.

Background

Gouty arthritis (GA) was historically regarded "the king of diseases and the disease of kings". In modern times GA has become the most prevalent form of inflammatory arthritis and now it is primarily considered a complication of unhealthy Western lifestyles. Approximately 5 in every 1000 individuals In European and North American populations suffer from gouty attacks. These individuals also have increased risk for other lifestyle diseases, most notably cardiovascular (CV) events.[1]

Gouty inflammation is caused by crystallisation and deposition of uric acid in joints and surrounding tissues. Thus, authors evaluating CV disease in gout have focussed both on hyperuricaemia in a variety of patient populations, and on gouty arthritis (GA) as a clinical entity. These studies show conflicting results. Often hyperuricaemia is found to be an independent risk factor for CV events and death, but in other studies these associations are lost after correcting for traditional CV risk factors. Some studies only find an association with the disease GA.[2-15] There are different pathophysiologic hypotheses that may explain the observed associations: shared risk factors, direct metabolic actions of uric acid on the vascular wall and/or on renin-angiotensin-aldosterone and insulin resistance pathways, or vascular involvement in systemic inflammatory activation. Even though all of these hypotheses are supported by experimental and/or epidemiologic data, none have been definitely confirmed.[16;17] Causality in gout associated cardiovascular risk thus remains unelucidated and pathways are probably complex.

Studies that evaluate the associations between serum uric acid, inflammation and CV risk in rheumatic disease are scarce[18;19]. We therefore investigated the associations between serum uric acid and CV risk parameters and events in patients with different rheumatic diseases. To explore the value of serum uric acid level as a marker of future CV event risk in rheumatic patients a prospective multivariate analysis in GA and non-GA individuals was performed.

Methods

Data for this study were obtained from the Arthritis Center Twente CardioVascular Disease (ACT-CVD) database. In 2009 the Arthritis Center Twente in Enschede, the Netherlands, established a per protocol cardiovascular screening as standard care, which details have been described previously.[20] Both existing and new patients are screened for traditional CV risk factors and followed for the occurrence of CV events. Briefly, the ACT-CVD database is a collection of the routine clinical care parameters obtained at the initial screening (demographics, traditional

CV risk factors, inflammatory parameters, rheumatic disease characteristics and medication), as wel as CV event follow up data for each patient. Patients are classified according to their clinical diagnosis as registered by their attending rheumatologist. After screening, each patient is followed for the occurrence of CV events or death. CV events are defined as (1) myocardial infarction; (2) coronary intervention, i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); (3) angina pectoris, confirmed by a cardiologist as cardiac chest pain; (4) acute heart failure; (5) cerebral vascular accident (CVA); (6) death due to cardiac causes; (7) sudden death. Follow up data are extracted from the hospital electronic registration system and subsequently validated by medical chart review. Out of hospital events and death are documented by periodic questionnaires sent to attending general practitioners and by review of the Dutch national registry of death certificates. For this study the data of all patients with rheumatoid arthritis (RA), osteoarthritis (OA) or gouty arthritis (GA) that were screened before December 2011 were selected, and patient follow up ended at December 2012.

In the analysis we used the following definitions: hyperuricaemia: serum uric acid above 0.36 mmol/l in women or 0.40 mmol/l in men; uric acid lowering therapy (ULT): two or more consecutive prescriptions of allopurinol and/or benzbromarone covering at least a 3 months interval; antihypertensive therapy: the use of beta-blocking agents, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors and/or diuretics registered for use as an antihypertensive agent; smoking: the current use of inhaled tobacco; diabetes: the use of glucose lowering medication and/or a fasting plasma glucose above 6.9 mmol/l. Glomerular filtration rate (GFR) as a parameter of renal function was estimated using the 'modification of diet in renal disease' (MDRD) formula. [21] Body mass index (BMI) was calculated as the ratio between weight and the square of length.

To evaluate patterns in associations between uric acid and CV risk parameters among rheumatic patients and to define homogeneous groups for the prospective analysis a first cross sectional analysis was performed of the relation between tertiles of serum uric acid and the baseline traditional CV risk parameters systolic blood pressure, total cholesterol/high density lipoprotein (TC/HDL) ratio, glycated haemoglobin (GlyHb) and BMI in patients with individual rheumatic diagnoses. In the prospective COX-regression analysis the predictive value of uric acid tertiles for the occurrence of first CV events in the ACT-CVD population was evaluated considering all abovementioned traditional CV risk parameters and the variables age, sex, high sensitivity CRP (hsCRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), estimated GFR, use of antihypertensive therapy or statins, and in GA patients use of allopurinol or ULT in general. For the prospective analysis duration of follow up was calculated as the interval between inclusion into the cohort and the occurence of a first CV event or death, or censored at December 1st 2012, whichever came first.

The protocol for data collection, storage, and use in the present study was approved by the Arthritis Center Twente Institutional Review Board. Because the study uses data collected as part of daily clinical care the ethics committee determined, in accordance to Dutch law, that no approval was requiered. Nontheless, patients were fully informed and only the data of patients that gave informed consent were entered into the ACT-CVD database.

Statistical analysis

Prevalence of CV risk factors in patient groups and 10-year CV risk estimates were presented by descriptive statistics (mean or percentage prevalence). Differences between groups and associations between CV risk variables and tertiles of serum uric acid were tested with ANOVA (for continuous CV risk factors) or Chi squared statistics (for nominal CV risk factors), adjusted for differences by age and sex. For the survival analysis those groups that showed similar baseline patterns of CV risk parameters in tertiles of serum uric acid and equal occurrence of first CV events were combined. Kaplan Meier curves were made for CV event free survival over time, and backwards stepwise COX regression analysis was performed to determine the value of tertiles of uric acid as an independent predictor for CV event risk over time. Data analysis was performed using PASW Statistics version 18.0.

Results

After the first year of screening the completed data of 973 individuals with GA (n=204), RA (n=533), or OA (222) were available for analysis. Of these individuals 133 (32 GA, 38 RA, 14 OA) were excluded because of previous CV events. Previous CV events were significantly more frequent in GA patients ($p<0.05$).

Baseline CV risk

The baseline characteristics of the study population are presented in table 1. Distributions of age and sex were as expected. Individuals were predominantly late middle aged, with overrepresentation of women in RA and OA, and men in GA. The hsCRP level, a measure of systemic inflammation, was significantly lower in OA.

Table 1. Baseline characteristics

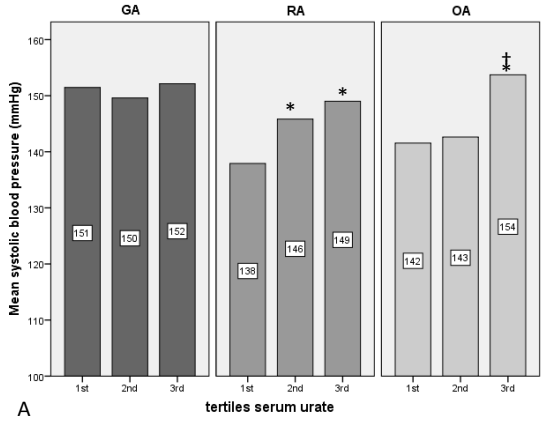
	GA (172)	RA (480)	OA (206)
hsCRP, mean, g/L (SD)	6.3 (11.2)	7.0 (10.0)	3.8 (4.9)*
Serum uric acid, mean, mmol/l (SD)	0.36 (0.14)	0.31 (0.075)**	0.31 (0.0832)**
Hyperuricemia, n (%)	54 (32) †	62 (14)†	34 (17)†
Uric acid lowering therapy, n (%)	126 (73)	0	0
Allopurinol, n (%)	111 (65)	0	0
Sex, n (%) male	154 (89)	133 (28)**	43 (21)**
Age, mean, years (SD)	59.6 (10.8)	59.0 (13.0)	59.2 (11.0)
Systolic blood pressure, mean, mmHg (SD)	151.0 (21.3)	144.0 (22.9)**	145.5 (20.2)**
Antihypertensive therapy, n (%)	67 (39.0)	118 (24.6)	71 (34.5)
Smoking, n (%)	43 (25)	114 (24)	38 (18)
TC/HDL ratio, mean (SD)	4.82 (1.4) †	3.65 (1.1)†	4.0 (1.2)†
Statin therapy, n (%)	22 (12.8)	32 (6.7)‡	26 (12.6)
Diabetes, n (%)	11 (6.4)	28 (5.8)	16 (7.8)
GlyHb, mean, %Hb (SD)	6.1 (1.4)	5.5 (1.8)	6.0 (4.2)
BMI, mean, kg/m^2 (SD)	30.4 (4.7)†	27.0 (4.3)†	28.8 (5.3)†
MDRD, mean, ml/min (SD)	80.8 (21.8)	89.9 (19.5)**	87.7 (18.7)**
NT proBNP, mean, nmol/L (SD)	37.6 (170.6)	15.9 (25.8)**	15.1 (32.8)**

GA: gouty arthritis; OA: osteoarthritis; RA: rheumatoid arthritis; hsCRP: high sensitivity C-reactive protein; SD: standard deviation; CV: cardiovascular; TC: Total cholesterol; HDL: high density lipoprotein; GlyHb: glycated haemoglobin; BMI: body mass index; MDRD: modification of diet in renal disease; NT-proBNP: N-terminal pro-brain natriuretic peptide. *p<0.05 OA vs. RA and GA, **p<0.05 RA and OA vs. GA, †p<0.05 RA vs. OA vs GA, ‡p<0.05 RA vs. OA and GA.

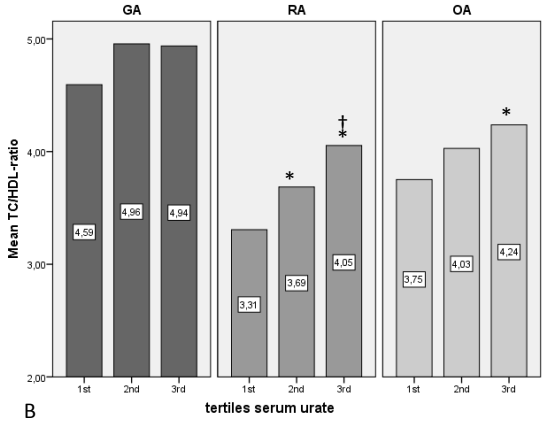
At baseline the distributions of the traditional CV risk parameters male sex, systolic blood pressure, TC/HDL ratio, and BMI were significantly less favourable in GA patients (p<0.05). In RA and OA the individual CV risk parameters systolic blood pressure, TC/HDL ratio and BMI, and in OA also GlyHb, all correlated with serum uric acid levels. (figure 1) In GA no associations between serum uric acid and individual CV risk parameters were observed.

The majority of gout patients (73%) used ULT (88% allopurinol, 12 % benzbromarone). Mean serum uric acid was significantly lower in patients using ULT (0.32 mmol/l ULT vs. 0.48 mmol/l non-ULT, p<0.05). Patients treated with allopurinol had significantly lower hsCRP (14.1 ± 22.6 vs. 4.40 ± 4.41 g/L) and NTproBNP (76.7 ± 313.7 vs. 24.0 ± 70.2 pmol/L) levels than non-allopurinol treated patients. Otherwise, these patients did not differ in baseline measurements of traditional CV risk factors, nor in frequency of treatment with statin or antihypertensive therapy.

Figure 1. Associations between baseline cardiovascular risk parameters (A-C) and tertiles serum uric acid in GA, RA and OA



A



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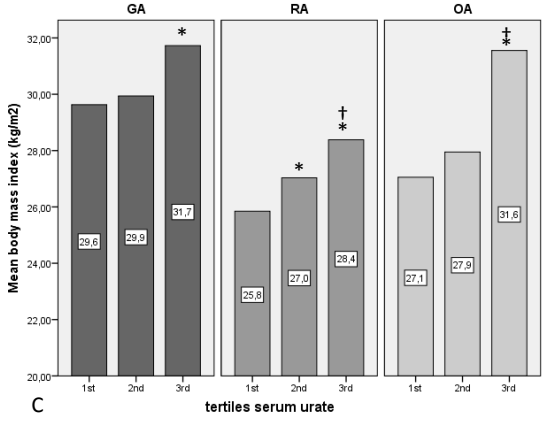


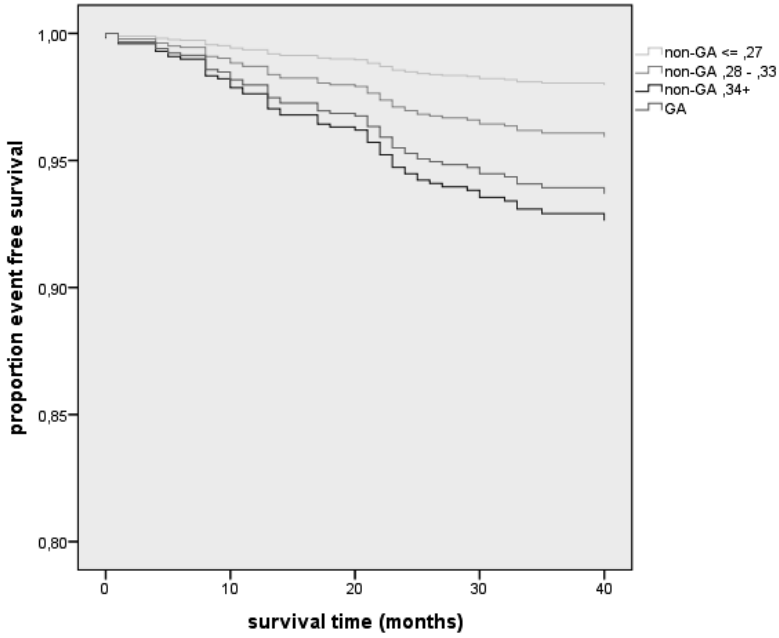
C

Tertiles serum uric acid (1st, 2nd, 3rd): GA: <0.29 mmol/L, 0.29-0.38 mmol/L, and ≥0.39 mmol/L; RA: <0.27 mmol/L, 0.27-0.34 mmol/L, and ≥0.34 mmol/L; OA <0.27 mmol/L, 0.27-0.34 mmol/L, and ≥0.34 mmol/L. GA: gouty arthritis; RA: rheumatoid arthritis; OA: osteoarthritis; TC: total cholesterol; HDL: high density lipoprotein; BMI: body mass index. (*p<0.05 vs. 1st tertile; †p<0.05 vs. 2nd tertile)

Prospective analysis of CV events

After a median follow up of 36 months (25th- 75th percentile 30-41) 64 CV events had occured, 29 (6.0%) RA, 17 (8.3%) OA, and 18 (10.5%) GA. Because baseline patterns of traditional CV risk factors in tertiles of uric acid were similar and the occurrence of CV events did not differ significantly between RA and OA patients, the data of RA and OA groups were combined as 'non-GA' for further survival analysis. Table 2 shows the univariate associations between baseline variables and occurence of CV events in non-GA and GA groups. For both groups, all variables with a p≤0.150 were included in the backwards stepwise COX regression analyses. The use of uric acid lowering, antihypertensive and/or statin therapy were considered as possible confounders. In the non-GA group the highest tertile of serum uric acid (≥ 0.34 mmol/L; HR 3.896, 95% CI 1.677-9.051) and NT proBNP (HR 1.012, 95% CI 1.008-1.016) level remained as independent predictors of CV events, against age (HR 1.073, 95%CI 1.022-1.127) and GlyHb level (HR 3.273, 95% CI 1.971-5.434) in the GA group (p<0.05). Compared to non-GA individuals with a serum uric acid < 0.27, non-GA individuals with a serum uric acid ≥ 0.34 mmol/L (HR 3.721, 95% CI 1.603-8.634) and GA patients (HR 3.169, 95% CI 1.287-7.806) showed equally increased hazard ratio's for first CV events. (figure 2)

Figure 2. Comparison of cardiovascular event-free survival in GA and non-GA patients



Tertiles serum uric acid in non-GA patients:<0.27 mmol/L, 0.27-0.34 mmol/L, and ≥0.34 mmol/L). GA: gouty arthritis.

Table 2. Univariate associations between CV risk variables and prospective CV events in GA and non-GA patients

	GA (172)			**Non-GA(686)**		
	Event-free (154)	Event (18)	*p (event vs none)*	Event-free (640)	Event (46)	*p (event vs none)*
hsCRP, mean, g/l	5.76	9.44	0.238	5.90	7.21	0.390
Tertiles serum uric acid (% 1st /2nd /3rd)	37.3/32.0/30.7	33.3/16.7/50.0	0.208	40.6/28.3/31.2	15.9/25.0/59.1	0.000*
Uric acid lowering therapy, %	74.0	66.7	0.504	0	0	n.a.
Allopurinol, %	64.3	66.7	0.842	0	0	n.a.
Sex, % male	91.6	72.2	0.011*	24.8	37.0	0.069*
Age, mean, years	58.5	68.8	0.000*	58.6	64.9	0.001*
Systolic blood pressure, mean, mmHg	152.0	143.0	0.092*	143.9	152.1	0.015*
Antihypertensive therapy, %	34.4	77.8	0.000*	26.3	45.7	0.004*
Smoking, %	26.0	11.1	0.147*	22.0	23.9	0.767*
TC/HDL ratio, mean	4.83	4.71	0.623	3.74	3.95	0.265
Statin therapy, %	11.7	22.2	0.205	8.0	15.2	0.088*
Diabetes, %	5.8	11.1	0.387	6.4	6.5	0.975
GlyHb, mean, %Hb	5.83	6.58	0.004*	5.83	5.91	0.408
BMI, mean, kg/m^2	30.1	32.9	0.017*	27.4	28.8	0.058*
MDRD, mean, ml/min	83.5	58.1	0.002*	89.7	83.2	0.091*
NT proBNP, mean, nmol/L	14.5	230.9	0.083*	14.1	45.4	0.005*

GA: gouty arthritis; hsCRP: high sensitivity C-reactive protein; TC: Total cholesterol; HDL: high density lipoprotein; GlyHb: glycated haemoglobin; BMI: body mass index; MDRD: modification of diet in renal disease; NT proBNP: N-terminal pro-brain natriuretic peptide. *variable included in the respective COX regression analyses.

Discussion

Our data show that both GA and, in non-GA individuals, a serum uric acid ≥ 0.34 mmol/L are associated with a more unfavourable traditional CV risk profile and an approximately 3.5-fold hazard of first CV events.

Individual traditional CV risk factors, such as systolic blood pressure, serum lipoproteins, and body mass index, and occurrence of first CV events were increased at the same level in subsequent tertiles of serum uric acid in both RA and OA. These associations thus seem relatively independent from chronic inflammation. Compared to the other rheumatic populations mean serum uric acid values were highest in GA, as were values of traditional CV risk factors. First CV events were also more frequent in GA individuals than in non-GA patients. In contrast with the non-GA group individual CV risk factors and prospective CV events were unrelated to tertiles of serum uric acid in GA patients. This may be due to confounding by the use of uric acid lowering therapy or more specifically the xantine oxidase inhibitor allopurinol, or to a ceiling effect in the generally high risk GA patients. CV risk factor values were not lower in GA patients treated with ULT or specifically allopurinol, and CV events were as frequent. The only suggestion in our data that treatment with allopurinol may be beneficial was the significantly lower mean level of NT-proBNP, a marker of cardiac dysfunction, in this group.

Comparison to the literature

Previously, several large studies found increased CV disease and mortality in patients with gout, approximately two-fold compared to the general population.[22-24] To determine if hyperuricemia per se confers the same risk of increased CV disease different populations have been studied; the general population, young and elderly, diabetics and patients with chronic kidney disease.[2;7-15;29] Many studies did find hyperuricaemia to be an independent risk factor, but in others the association disappeared after correction for the traditional CV risk factors obesity, hypertension, dislipidemia and/or insulin resistance. Some studies found a U- or J-shaped association between serum uric acid level and mortality, suggesting an optimal level between 0.30 and 0.41 mmol/L. [28-30] Only one study specifically addressed the role of systemic inflammation in GA related CV disease, and found no association with CV events.[26]

The question remains if serum uric is only a potentially useful marker to improve the selection of high CV risk individuals for CV risk management, or if it is causally related to the progression of CV disease. Different hypotheses have been suggested: 1) the presence of shared risk factors in CV disease and GA, 2) vascular wall activation and accelerated atherosclerosis by chronic systemic inflammation, or 3) a direct interaction of uric acid with diverse metabolic pathways involved in

CV disease.[16;17] Several experimental studies have provided insight into possible actions of uric acid in diverse metabolic pathways, i.e. glucose and lipoprotein handling, nitric oxide metabolism, the renin-angiotensin-aldosterone system (RAAS), and inflammatory signalling and activation.[31-33] These observations suggest that uric acid itself can at least modulate CV risk factors such as blood pressure, cholesterol, diabetes and chronic inflammation.[34] Uric acid clearance may be decreased in states of hypertension and RAAS activation, with consequent increasing hyperuricaemia and amplification of metabolic derangements. However, other studies suggest that the metabolic effects attributed to uric acid are actually mediated by xantine oxidase, which is also the key enzyme in uric acid production in man. Increased serum uric acid may thus only be be an epiphenomenon of other pathologic metabolic pathways that cause increased CV risk, and treatment with the xantine oxidase inhibitor allopurinol may be directy beneficial by improving vascular function in stead of by improving the CV risk profile through the reduction of serum uric acid levels.[35]

Strengths and limitations

Our study adds to the knowledge on hyperuricaemia and CV risk bij comparing the association between serum uric acid and CV-risk in a mixed rheumatic population including GA. Thus we saw that in this population either the presence of GA or a baseline serum uric acid in the upper range are stronger predictors of first CV events than some traditional risk factors or parameters of inflammation. Epidemiologic studies that evaluate associations of serum uric acid with traditional CV risk factors and prospective CV events in a rheumatic population are scarce. In this study the study groups were well defined and measurements of risk factors were performed within the same protocol.

However, this study has some important limitations. First, the observational study design precludes any suggestions on causal relationships. The absence of an association between serum uric acid and CV risk in GA was difficult to interpret due to the pretreated population. Because we only had data on baseline variables we could not evaluate of the effect of medical interventions and changes in serum uric acid on CV outcome. A possible risk reduction by allopurinol may not have followed from our data due to insufficient numbers of patients, too short period of exposure or too short follow up. Following the data one can only conclude that also in a ULT treated GA population with satisfactory mean uric acid levels CV risk is high.

The prospective analysis, evaluating the associations of a limited set of traditional CV risk factors and serum uric acid tertiles in a mixed population of articular diseases, is a simplification that may ignore any disease specific CV risk factors. However, diagnosis and hsCRP were considered as variables in the COX regression analysis in stead, and proved non-significant. The influence

of some other potential confounders such as use of NSAIDs and relative physical inactivity was not covered by separate variables, but regarded to be limited by including only patients with rheumatic diseases.

Some important questions remain for further research. First, the predictive value of pre-ULT treatment uric acid level for the occurrence of CV events in GA patients. Second, the positioning of uric acid and xantine oxidase in pathofysiologic pathways that cause CV events in GA and hyperuricaemia. And finally, what is the optimal risk intervention strategy in high CV risk patients characterised by an upper range uric acid level.

Conclusions

Both gouty arthritis and, in non-gouty arthritis, upper range serum uric acid are associated with an approximately 3-fold hazard of first CV events. CV risk in gouty arthritis is independent of serum uric acid values and remains important in patients treated to satisfactory uric acid values by uric acid lowering therapy. The presence of a diagnosis of gouty arthritis or a baseline serum uric acid in the upper range are possibly stronger predictors of first CV events than some traditional CV risk factors or parameters of inflammation.

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Chapter 4

Cardiovascular risk in intensively treated rheumatoid arthritis: comparison to an osteoarthritis population

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Abstract

Background: Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity compared to the general population and to individuals with degenerative joint diseases such as osteoarthritis (OA). This is thought to be facilitated by chronic inflammatory activity. There are no prior studies on CV risk in intensively treated RA.

Objective: To study first CV events in tightly controlled low disease activity RA primarily compared to patients with osteoarthritis (OA) and secondarily to general population self-reported incidence of CV disease. To estimate the contribution of treatment on CV event risk in RA.

Design: Prospective analysis of CV event free survival in the ACT-CVD cohort.

Setting: The Arthritis Center Twente (ACT) rheumatology outpatient clinic in The Netherlands.

Patients: RA (480) and OA (206) patients without prior CV disease.

Measurements: CV risk screening protocol as part of ACT routine clinical practice. Variables included baseline demographics, comorbidities, traditional CV risk parameters and 10-year risk of CV death estimates, and rheumatic disease characteristics and medications.

Results: After 3 years follow up, RA and OA patients showed equal frequencies of first CV events (RA 21.0/1000 py, 95% CI 13.0-32.1 vs OA 29.7/1000 py, 95% CI 19.4-41.7). There was no trend towards increased CV events in RA. RA and self-reported general population CV event incidence did not differ. Use of methotrexate was significantly associated with increased CV event free survival in RA (HR 3.89, 95% CI 1.77-8.55).

Limitations: Self -reports may have over-estimated general population CV disease incidence. Due to short follow up only strong predictors of CV events could become statistically significant.

Conclusions: state-of-the-art tightly controlled RA patients and OA patients have equal CV-event incidence after 3 years follow up of the ACT-CVD cohort. Use of methotrexate was associated with increased CV event-free survival in RA.

Introduction

Cardiovascular (CV) disease is a major complication in patients with rheumatoid arthritis (RA), a common chronic auto-immune disease, characterized by systemic inflammation and destructive polyarthritis. Previous studies have estimated RA associated CV event rates by comparing RA to different populations. They have shown that CV events in RA were increased by 30-50% compared to the general population and to individuals with degenerative joint disease like osteoarthritis (OA).[1-5] Other studies have shown the frequency of CV events in RA to equal that of established high CV risk populations, like patients with type 2 diabetes.[4;6] The etiology of the increased CV risk in RA has not been entirely explained. Two major contributing factors are generally accepted. Firstly, the extent of chronic rheumatoid inflammation has been shown to be importantly associated with the development of CV disease.[7-9] Secondly, traditional CV risk factors such as cigarette smoking, obesity and inactivity are more common in RA patients than in the general population.[10;11]

Most studies on CV risk in RA have been performed in cohorts that were initiated before the general practice of intensive disease modifying anti-rheumatic drug (DMARD) therapy and 'tight control' treatment strategies.[1;2] Due to these intensified treatment strategies, a sustained state of low disease activity or even disease remission can now be accomplished in most RA patients within the first months after presentation.[12-15] Since the introduction of intensive combination DMARD therapy, the extent and progress of articular damage has fallen dramatically.[16-18] The excellent treatment results seen in clinical trials are now being achieved in daily clinical practice also.[14;19]

Because of the surmised association between chronic inflammation in persistent RA disease activity and the development of CV morbidity, it is possible that these intensive treatment strategies will also reduce the incidence of CV events. We therefore compared the occurrence of first CV events in a cohort of state-of-the-art intensively treated RA patients to individuals with OA from the same background population. Moreover, we mirrored our findings with the self-reported incidence of ischemic heart disease and stroke in the Dutch general population. Secondary outcomes were the contribution of disease duration, DMARD treatments and measures of disease activity on CV event risk in RA.

Methods

The ACT-CVD cohort

The Arthritis Center Twente Cardiovascular Disease (ACT-CVD) cohort was established in 2009. The methods of patient inclusion and baseline data collection in this cohort have been previously described.[10] Briefly, the database contains baseline demographics, CV risk factors and rheumatic disease characteristics of both incident and prevalent outpatients, attending the Arthritis Center Twente (ACT) in Enschede, The Netherlands. In the ACT-CVD database, patients are classified according to their clinical diagnosis as registered by experienced attending rheumatologists. RA patients are treated according to a 'disease activity score in 28 joints' (DAS-28) steered tight control strategy with fixed treatment protocol, targeting remission (DAS-28 $\leq$ 2.6), results of which have also been previously published.[19] After inclusion in ACT-CVD, patients are followed up for a first CV event or death. Follow-up data are extracted from the hospital electronic registration system and are validated by medical chart review. Out of hospital events and death are documented by periodic questionnaires to attending general practitioners and by review of the Dutch national registry of death certificates.

For this study, the data of all RA and OA patients without prior CV disease who completed the initial CV risk factor screening before December 2011 were used. The protocol for data collection and storage was approved by the Arthritis Center Twente Institutional Review Board. Patients were fully informed and only the data of patients that gave informed consent were entered into the ACT-CVD database.

Primary and secondary outcome measures

The primary research question was to compare CV event-free survival in RA an OA patients, adjusted for differences in baseline CV risk parameters. All eligible subjects in the ACT-CVD cohort were followed up for the occurrence of first CV events. The following were defined as a CV event: (1) myocardial infarction; (2) coronary intervention, i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); (3) angina pectoris, confirmed by a cardiologist as cardiac chest pain; (4) acute heart failure; (5) stroke; (6) death due to cardiac causes; (7) sudden death. Duration of follow up was calculated as the interval between inclusion and first CV event or death, or censored at December 1st 2012, whichever came first.

As a secondary analysis we compared the incidence of first CV events in RA patients to the self-reported incidence of ischemic heart disease and (CVA) in the Dutch general population in 2012 (source 2012 Health Interview Survey by Statistics Netherlands, September 19th 2013), standardised for differences by sex and age.[20] Statistics Netherlands is responsible for collecting

and processing data in order to publish statistics to be used in practice, by policymakers and for scientific research in The Netherlands. The annual Health Survey is performed on a representative sample of the general adult population in The Netherlands. The data collection uses validated questionnaires which include 3 categories of self-reported CV disease: 'stroke', 'heart disease' and 'myocardial infarction'. The internal consistency and completeness of the Health Survey data are regularly checked every year. Because ICD-code registrations show that 34-50% of hospitalisations for cardiac disease in the Netherlands are of ischemic origin, we corrected the category 'heart disease' with a factor 0.35 in our analyses.[21] In another secondary analysis we determined the contribution of time from RA diagnosis, measures of disease activity and continuous DMARD treatments on RA CV event-free survival. Continuous use of DMARDs was defined as a minimum of 2 prescriptions with a 3 month interval prior to baseline screening.

Statistical analysis

Baseline characteristics and incidence of CV events were presented by appropriate descriptive statistics, and differences between groups were analysed by chi-squared and Student's t-test or ANOVA for categorical and continuous variables, respectively. Kaplan-Meier survival analysis and COX regression were performed to determine CV event risk and contributing risk factors over time, and controlled for baseline SCORE 10-year CV risk estimates.[22] Incidence of first CV events in RA patients and general population self-reported incidence of ischemic heart disease and CVA were compared by Fisher exact test. Statistical analyses were performed using IBM-SPSS statistics software version 20.0.

Results

Between February 2009 and December 2011 the ACT-CVD cohort included 1668 subjects; 508 with a diagnosis of RA and 222 with OA. From these, 28 RA and 16 OA patients were excluded because of documented prior CV disease.

Baseline characteristics

The present study included 480 RA and 206 OA patients. The baseline characteristics of the study population are listed in table 1. As expected for these diagnoses, the majority of patients were female and late middle aged. Median time from RA diagnosis was 4 years with a range of 0 to 53 years, significantly longer than in OA. OA patients were mostly included at first presentation (median disease duration 0 years, range 0-24). The majority of RA patients received DMARD

treatment. Methotrexate was most frequently prescribed, alone or in combination with other DMARDs (298 out of 480 RA patients, 62.1%). Mean RA disease activity was low, DAS-28 2.5, 72% of patients being in clinical remission.

Comparison of baseline CV risk profiles between RA and OA patients showed a slightly lower TC/HDL ratio in RA, but otherwise similar CV risk parameters. Overall there was no difference in SCORE 10-year CV risk estimate values (table 1). As expected, systemic inflammatory parameters and auto-immune markers were both significantly higher in RA.

Table 1. Baseline characteristics of RA and OA patients

	RA (n=480)	**OA (n=206)**	**p**
Demographics			
Sex (n, % female)	347 (72.3)	163 (79.1)	0.075
Age (mean, SD)	59.0 (13.0)	59.2 (11.0)	0.779
Traditional CV risk factors			
Smoking, current (n, %)	114 (23.8)	38 (18.4)	0.152
Systolic blood pressure (mmHg, mean, SD)	144.0 (22.9)	145.5 (20.2)	0.399
Atherogenic index (mean, SD)	3.7 (1.1)	4.0 (1.2)	0.001*
GlyHb (%, mean, SD)	5.8 (0.67)	5.9 (0.59)	0.592
SCORE 10-year CV risk (%, SD)	5.7 (4.9)	5.5 (4.4)	0.639
Inflammatory markers			
ESR (mm/hr, mean, SD)	16.5 (14.9)	12.7 (18.4)	0.005*
hsCRP (mg/L, mean, SD)	7.0 (10.0)	3.8 (4.9)	0.000*
Auto-immune markers			
Seropositive (n, %)	286 (63.3)	12 (6.1)	0.000*
Anti CCP (kU/L, mean, SD)	121.1 (145.3)	3.2 (21.2)	0.000*
IgM RF (U/L, mean, SD)	93.8 (223.3)	4.5 (31.8)	0.000*
RA disease activity			
DAS28 (mean, SD)	2.5 (1.2)	n.a.	n.a.
Remission (%)	338 (72.1)	n.a.	n.a.
Current medication			
NSAID (n, %)	177 (36.9)	47 (22.8)	0.000*
DMARD (n,%)	350 (72.9)	0 (0)	0.000*
DMARD combination (n,%)	135 (28.1)	0 (0)	0.000*
MTX (n, %)	298 (62.1)	0 (0)	0.000*
TNF inhibitor (n, %)	105 (21.9)	0 (0)	0.000*

RA: rheumatoid arthritis; OA: osteoarthritis; ACT-CVD: Arthritis Center Twente CardioVascular Disease cohort; CV: cardiovascular; SD: standard deviation; atherogenic index: HDL/LDL cholesterol ratio; GlyHb: glycated hemoglobin; SCORE: Systematic Coronary Risk Evaluation; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity C-reactive protein; anti CCP: anti cyclic citrullinated protein; IgM RF: IgM rheumatoid factor; DAS28: disease activity score in 28 joints; NSAID: non steroidal anti inflammatory drug; DMARD: disease modifying antirheumatic drug; MTX: methotrexate; TNF inhibitor: tumor necrosis factor α inhibitor

Occurrence of first CV events in RA and OA patients

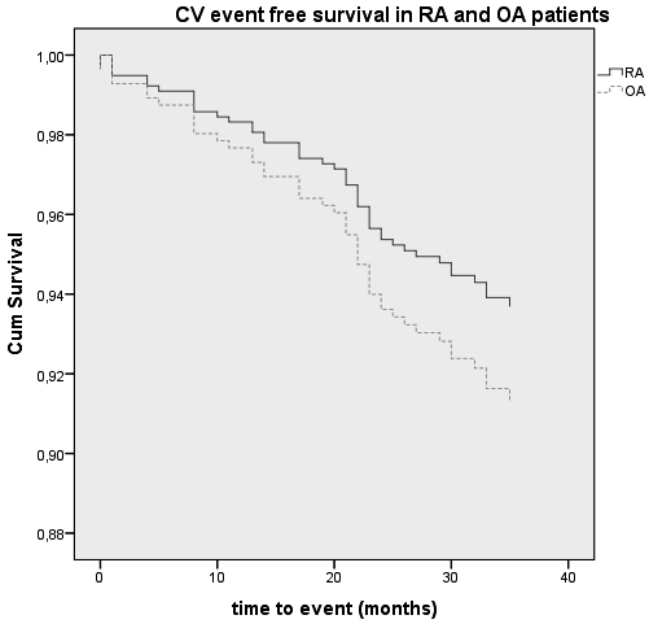
After 3 years of follow-up there were 29 first CV events in the RA group and 17 in the OA group. All first CV event diagnoses are listed in table 2. There was no difference in the frequency of first CV events between the groups: 21.0/1000 patient years (95% CI 13.0-32.1) in RA and 29.7/1000 patient years (95% CI 19.4-41.7) in OA (p=0.25). There were also no differences in the frequencies of specific CV diagnoses (p=0.835). The CV-event free survival functions for RA and OA patients are shown in figure 1. The curves overlap and there is no trend towards decreased event-free survival in RA.

Table 2. Distributions of cardiovascular events in RA and OA patients

Event type	RA (n,%)	OA (n,%)
Myocardial infarction	2 (6.9)	0 (0.0)
Acute coronary syndrome	10 (34.5)	7 (41.2)
Acute heart failure	4 (13.8)	3 (17.6)
Coronary intervention	5 (17.2)	2 (11.8)
Cerebrovascular accident	5 (17.2)	4 (23.5)
Cardiac death	2 (6.9)	1 (5.9)
All	29 (100)	17 (100)

RA: rheumatoid arthritis; OA: osteoarthritis

Figure 1. Cardiovascular event free survival in RA and OA patients in the ACT-CVD cohort



CV: cardiovascular; RA: rheumatoid arthritis; OA: osteoarthritis

Comparison of incident first CV events in RA and the general population

The estimated 2012 incidence of self-reported ischemic heart disease and CVA in the Netherlands according to age category is shown in table 4. The incidence of CV events in the ACT-CVD population was comparable with the standardised for sex and age self-reported incidence rates of CV disease in the general population (RA 21.0/1000 patient years, 95% CI 13.0-32.1; GP 21.7/1000 patient years, 95% CI 13.6-33.0; p>0.999).

Table 3. Estimated self reported incidence of ischemic heart disease and stroke in The Netherlands in 2012, standardised for differences in age and sex with the ACT-CVD RA population.

Age category (years)	ACT-CVD RA cohort age distribution (%)	GP self-reported CV disease incidence (%)
<30	1.5	0.14
30-39	5.2	0.24
40-49	17.1	0.85
50-54	10.4	1.2
55-64	31.5	1.8
65-74	22.1	3.0
≥75	12.3	5.9
All	100	2.4
Standardised for differences in age and sex		2.2

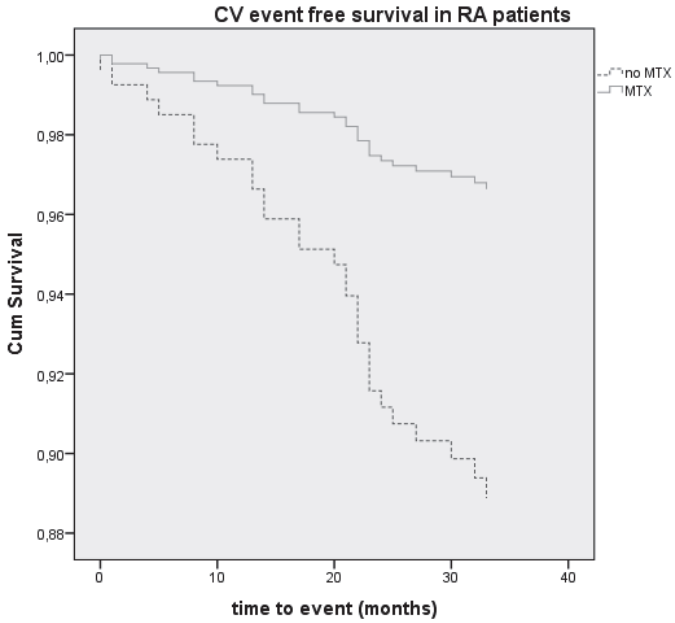
RA: rheumatoid arthritis; GP: general population; CV: cardiovascular; py: patient years

Table 4. Cardiovascular events in RA patients according to treatment with methotrexate.

Methotrexate (n, %)	All RA (480)	Events (29)
MTX treated	298 (62.1)	12 (41.4)
Non-MTX treated	182 (37.9)	17 (58.6)
Other primary DMARD	58 (12.1)	7 (24.1)
Gastrointestinal intolerance	39 (8.1)	1 (3.4))
New RA diagnosis	16 (3.3)	2 (6.9)
RA Remission	14 (2.9)	2 (6.9)
Elevated liver enzymes	12 (2.5)	1 (3.4)
MTX ineffectiveness	10 (2.1)	0 (0.0)
Pneumonitis	8 (1.7)	3 (10.3)
Unknown	8 (1.7)	0 (0.0)
Haematologic abnormality	5 (1.0)	1 (3.4)
Pregnancy wish	4 (0.8)	0 (0.0)
Malignancy	3 (0.6)	0 (0.0)

DMARD: disease modifying antirheumatic drug; RA: rheumatoid arthritis; MTX: methotrexate

Figure 2. Cardiovascular event free survival in RA patients in the ACT-CVD cohort acording to the prescription



CV: cardiovascular; RA: rheumatoid arthritis; OA: osteoarthritis; MTX: methotrexate) Analyses were corrected for differences in baseline 10-year CV risk estimates

Treatment factors contributing to CV event-free survival in RA

Stepwards backwards COX regression analysis considering time from RA diagnosis, hsCRP, RA disease activity, and continuous use of either methotrexate, DMARD combination therapy and/or biologic DMARDs, and controlling for baseline SCORE 10-year CV risk estimates, showed only a significant association between CV event-free survival in RA and the continuous use of methotrexate at baseline (HR 3.89, 95% CI 1.77-8.55, figure 2). Eighty seven percent of methotrexate prescriptions were between 15mg and the maximum dosage of 30 mg weekly, no association was found with methotrexate dosage. Table 4 shows that 17 out of the 29 first CV events in the RA group were associated with the absence of methotrexate use at baseline. From these events, 2 occurred in patients with newly diagnosed RA. Exclusion of the group of newly diagnosed patients did not alter the association between methotrexate and CV event-free survival. A total of 65 RA patients had never received methotrexate and these patients experienced 7 out of 29 first CV events in the RA group (table 4). Patients that had never received methotrexate were characterised by older age (OR 1.055, 95% CI 10.28-10.83 for each year), negative IgM rheumatoid factor and non-erosive articular disease.

Discussion

Summary of findings

This is the first study evaluating the incidence of first CV events in a recent, intensively treated low disease activity RA cohort. Compared to OA patients from the same background population, we found comparable incidences of first CV events. Within the first three years of follow up there was no trend towards increased CV event rates in RA either. This is an important finding because previous studies in older cohorts showed 30-40% more CV disease in RA patients when compared to OA populations.[3;4] Moreover, the results of our secondary analysis suggest that the incidence of first CV events in the RA cohort was comparable to the incidence of estimated self-reported ischemic heart disease and stroke in the general population. In the RA cohort, use of methotrexate was associated with increased CV event-free survival, whereas other tested RA treatment variables were not significantly associated with CV event risk.

Comparison with previous studies

Endothelial damage caused by chronic rheumatic inflammation is thought to be a key factor in the pathogenesis of RA associated CV disease.[7-9] After the introduction of tight control treatment protocols and biologic DMARD therapy from the 2000s onward, the average levels of systemic inflammation have importantly decreased in the majority of RA patients.[12-15;23] Between 1989 and 2008 the proportion of RA patients using methotrexate has increased from 5% to 62%.[23] Likewise in our cohort of intensively treated patients, the proportion on methotrexate was 62,1%. Also, methotrexate dosages are now on average 2-3 fold higher.[23;24] These treatment changes have resulted in an important reduction of articular damage, even in those patients with persistent joint swelling despite combination DMARD therapy.[16-18] Studies evaluating the effect of RA treatment on vascular function and on the occurrence of RA associated CV events suggest that methotrexate and possibly also TNF inhibiting biologic DMARDs may be beneficial in reducing CV risk.[25-32]

The ACT-CVD cohort was established in 2009 to study CV risk in tightly controlled RA. This first analysis with 3 years of follow up suggests a favourable development in RA associated CV risk, as compared to OA patients. Alternative explanations for our results could be that the comparator OA population was atypical in its CV risk characteristics, or that the CV risk of OA patients in general has developed unfavourably over time. Previous studies in OA cohorts have shown a stable high frequency of traditional CV risk factors, such as obesity, inactivity and diabetes.[33-35] In a previous cross-sectional comparison of the baseline CV risk profiles of different rheumatic diseases in the ACT-CVD cohort to the general population we found equivalent, but moderately

increased traditional CV risk parameters in the RA and OA patient subgroups.[10] Also, a specifically OA associated increase in CV events over the last decades is unlikely, because this would entail a trend contrary to the decrease in CV events in the general population and OA specific CV risk factors are not known.[36]

Therefore, in a secondary analysis we compared the incidence of first CV events in the ACT-CVD RA cohort to Dutch national Health Survey statistics. We found that the incidence of first CV events in the ACT-CVD RA cohort was comparable to the incidence of self-reported ischemic heart disease and stroke in the general population. These findings are in line with our primary analysis, and reinforce the suggestion of favourable CV outcomes in current intensively treated low disease activity RA compared to previous studies.[2;5] Only one previous study that was published in 2003 investigated the risk of first CV events in RA an OA patients and in non-arthritic patients from a general practice database. In this study, age adjusted CV event incidence rates in RA were increased compared to OA and the general population, both in women and men: women RA 12.6/1000 patient years vs OA 9.8/1000 patient years and no arthritis 8.4/1000 patient years; men RA 17.6/1000 patient years vs OA 13.9/1000 patient years and no arthritis 12.1/1000 patient years.[3] Because of differences in CV event definition, which included only cerebrovascular events, myocardial infarction and CV and sudden death, these incidence rates cannot be directly compared with the CV event incidence rates in our study.

In a secondary analysis we also evaluated possible associations between time from RA diagnosis and RA treatment variables, and the occurrence of first CV events. Our finding of longer first CV event-free survival in patients using methotrexate is in line with previous studies on the relationship between DMARD treatment and CV risk.[25;26;29;31] The strength of the association is striking, considering the low mean rheumatic inflammatory activity in the ACT-CVD RA cohort, the relatively short follow up and the low number of CV events. The latter two considerations probably also precluded us from finding any associations with measures of inflammation, RA disease activity and biologic DMARD treatment. Seven out of 29 RA associated CV events occurred in patients that had never received methotrexate. Non-prescription of methotrexate was associated with increasing age, negative IgM rheumatoid factor and absence of articular erosions, factors generally associated with a milder disease course.[37] However, studies in elderly onset RA have demonstrated that methotrexate can be safely utilized in elderly patients, and improves disease outcome in elderly onset RA.[38;39] Possible prevention of RA associated CV disease may be another argument to encourage physicians to consider methotrexate as a first treatment option for all patients.

Strengths and limitations

This study has strengths and limitations that should be considered. The major strengths of this study are the longitudinal design in a current daily clinical practice setting and the per protocol tightly controlled low disease activity RA population. Also, the ACT-CVD screening protocol included measurements on both traditional CV risk parameters and RA-specific variables, which data allowed us to adequately adjust for baseline CV risk factors by introducing them as variables in the multivariate analyses.

Limitations of the study are in the comparison to the general population, in which the definitions of CV disease in both populations differed. This secondary analysis compared the incidence of physician diagnosed CV events in the ACT-CVD cohort with self-reported incidence of CV disease in the general population. Publications on the validity of self-reported CV disease have shown that this method will most likely overestimate CV disease prevalence. Agreement between self-reports and medical records has been found moderate to high for angina and myocardial infarction, with positive predictive values of 70-80%.[40-43] For stroke the reported level of agreement is lower.[41;42] However, the statistics provided by the Dutch annual Health Survey are regarded to be of high quality. Also, even though we used a conservative 35% correction within the Health Survey category 'heart disease', the confidence intervals for CV disease incidence in the ACT-CVD RA and general population widely overlap. In the context of our primary analysis this result is important, because it provides an anchor for the interpretation of the clinical significance of the equivalence in CV event incidence in RA and OA patients.

As in any retrospective study events may have been missed. In the Dutch healthcare system the general practitioner has a coordinating role, keeping records of all medical events of his/her patients. Moreover, in the study region there is only one hospital that provides all secondary care services. Therefore we are quite confident that all CV events were captured by our methodology of follow up.

The last limitation of our study that should be considered is the relatively short duration of follow up. RA associated atherosclerosis is a chronically progressive disease and endothelial damage is thought to accumulate with longstanding, even low grade rheumatic inflammation. We think our results are reliable, because previous non-inception cohorts with similar duration of follow up did show increased CV disease incidence in RA, and the differences observed in our study are far from significant.[6;28] However, after longer follow up of our cohort our results will gain in reliability, and we will be able to discern more subtle associations with possible RA specific CV risk parameters.

Conclusions

Nowadays, RA patients are treated intensively, to quickly obtain disease remission and to maintain a state of minimal inflammation as long as possible. This study suggests that modern treatment strategies may reduce the increased CV risk in RA.

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Chapter 5

Cardiovascular case fatality in rheumatoid arthritis is decreasing; first prospective analysis of a current low disease activity rheumatoid arthritis cohort and review of the literature

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Abstract

Introduction: Previous studies found increased case fatality after myocardial infarction and more frequent sudden death in RA patients compared to non-RA subjects. The RA associated CV risk might be explained by the combined effects of chronic systemic inflammation and increased lifestyle associated cardiovascular risk factors, and modified by the use of medication such as non steroidal anti-inflammatory drugs, corticosteroids and disease modifying anti-rheumatic drugs. Trends in case fatality rate in RA after the introduction of potent anti-inflammatory biologic therapies and treat-to-target treatment strategies aiming at remission are not known. This study was performed to examine the cardiovascular fatality rate in current low disease activity RA, and to evaluate trends in RA associated CV case fatality over time.

Methods: Prospective study to determine the incidence of fatal and nonfatal CV events in 480 RA patients included in the ACT-CVD cohort between February 2009 and December 2011. Patients with prior CV disease were excluded. Cox regression analysis was performed to determine CV event risk and contributing risk factors over time. The results of the cohort analysis were put into the context of a review of the literature to evaluate trends in RA associated CV fatality rate over time.

Results: The study included 480 RA patients, 72.3% female with median disease duration of 4.2 years, 72.1% being in clinical remission (Disease Activity Score in 28 joints). During a mean follow up of 2.9 years 29 patients (6%) experienced a first CV event, 2 fatal and 27 non-fatal, corresponding to a 6.9 % case fatality rate. Comparison with previous studies in cohorts with successive enrolment periods shows a trend towards a decrease in CV case fatality in RA from 52.9% in 1998 to 6.9% in our study.

Conclusion: CV case fatality in current low disease activity RA is importantly lower than in previous studies, and a trend towards decreasing CV fatality in RA is suggested.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease involving multiple organ systems. RA is associated with a decreased life expectancy, and premature death is mainly due to accelerated atherosclerotic cardiovascular (CV) disease.[1-4] Recent meta-analyses confirmed that compared to the general population the overall increase of both CV disease and death in RA is approximately 50%.[5-7] CV disease in RA is more severe and associated with a worse prognosis, which was shown by studies in RA cohorts with enrollment in the 1990s that found significantly increased 30-day mortality after myocardial infarction and more frequent sudden death compared to non-RA patients. [8;9]

In the general population of high income countries the patients' prognosis after a CV event improved significantly during the second half of the 20th century. Thirty to fifty percent of the fall in general population CV mortality in this period can be attributed to improved survival.[10] Analyses of time trends in RA associated CV events show conflicting results and also recent studies show increased CV events in RA patients.[6;11;12]

It is generally thought that RA associated CV risk is the consequence of the combined effects of chronic systemic inflammation and increased traditional CV risk factors, and modified by the use non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease modifying anti-rheumatic drugs (DMARDs).[9;13;14-18] After the introduction of potent anti-inflammatory biologic therapies and tight control treatment strategies into daily clinical care the degree of systemic inflammation and severity of physical disability have importantly improved. Therefore we performed this study to examine if the high risk of death in RA associated CV disease persists in tightly controlled RA. We evaluated the incidence of fatal and non-fatal CV events in a cohort of established, currently low disease activity RA patients between February 2009 and December 2012 and calculated CV case fatality rates. Subsequently we put these results into the perspective of previous reports on mortality in RA associated CV disease to explore trends in RA associated CV case fatality over time.

Methods

Patients

The Arthritis Center Twente Cardiovascular Disease (ACT-CVD) project was established in 2009. The method of patient inclusion and baseline data collection in this cohort has been described previously.[19] Briefly, in 2009 the Arthritis Center Twente (ACT) in Enschede, the Netherlands,

introduced a CV screening protocol as part of routine daily clinical practice. The ACT-CVD database contains the anonimised baseline demographics, CV risk factors and rheumatic disease characteristics of all, both prevalent and incident, participating patients. Individuals are classified according to their clinical diagnosis as registered by experienced attending rheumatologists. Disease duration was calculated as time from RA diagnosis until the CV screening visit. At the ACT RA disease activity is systematically measured by Disease Activity Score in 28 joints (DAS-28), RA remission being defined as a DAS-28 $\leq$ 2.6.[20] After inclusion in the database, patients are followed up to a first CV event, death or censoring. Follow up data on incident cardiovascular events and causes of death are extracted from the hospital electronic registration system and are validated by medical chart review. For out of hospital events and death, attending general practitioners receive periodic questionnaires and data is extracted from the Dutch national registry of death certificates. For this study the data of all RA patients without prior CV disease in the ACT-CVD database that completed the CV screening protocol before December 2011 were used (all RA 508; included 480).

The protocol for data collection and storage in the ACT-CVD project was approved by the Arhtritis Center Twente Institutional Review Board. Because the study contains data from daily clinical practice the ethics committees determined, in accordance to Dutch law, that no approval was requiered. Nontheless, patients were fully informed and only the data of patients that gave informed consent were entered into the ACT-CVD database.

Follow up and definition of CV events

All participants were followed up for the occurrence of fatal and non-fatal CV events. The definition 'CV event' included (1) myocardial infarction; (2) coronary intervention, i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); (3) angina pectoris, confirmed by a cardiologist as cardiac chest pain; (4) acute heart failure; (5) cerebral vascular accident (CVA); (6) death due to cardiac causes; (7) sudden death. Sudden death was considered a CV event because it is generally from CV origin.[21] Duration of follow up was calculated as the interval between inclusion and first CV event or death, or censored at December 1st 2012, whichever came first.

Literature review

The Medline database was searched from its inception to April 2013 for research articles and reviews published in English studying CV disease in RA. The search terms RA, cardiovascular, CVD, CVA, risk, co morbidity, mortality, and death were used alone or in combination. Reference lists of key publications were hand searched for additional references. We selected peer reviewed articles

(cohort studies and meta-analyses) that met the following criteria: (1) predefined RA criteria; (2) inclusion of both male and female gender; (3) pre-specified CV disease criteria; (4) information on prior CV disease; (5) information on RA disease duration before inclusion; (6) information on events per patient year follow up. If data from a single study were reported in more than one article only the results from the most relevant publication were included in the literature review. Because a recent meta-analysis showed that inception cohorts were the only studies that did not find an increase of incident CV disease in RA, we considered inception and non-inception cohorts seperately.[6]

Statistical analysis

Baseline characteristics of the RA cohort and incidence of CV events were presented by appropriate descriptive statistics. Kaplan-Meier survival analysis and COX regression were performed to determine CV event risk and contributing risk factors over time. Statistical analyses were performed using IBM-SPSS statistics software version 20.0.

Results

The ACT-CVD cohort included 1668 subjects, 508 with a diagnosis of RA. From these, 28 were excluded because of prior documented CV disease.

Baseline characteristics of RA patients

The present study included 480 RA patients. The patients' mean age was 59.0 years and 72.3% were women. Median RA disease duration was 4 years, 63% was IgM rheumatoid factor and/or anti-CCP positive and 42% had erosive joint disease. At inclusion in the ACT-CVD cohort, 390 (81%) patients were using anti-inflammatory immunosuppressive therapy; synthetic disease modifying anti-rheumatic drugs (DMARDs, 72%), biologicals (in majority tumour necrosis factor α inhibitor, 23%) or corticosteroids (14%), either alone or in combination. Mean disease activity was low, DAS-28 2.5, 72% of patients being in clinical remission. (table 1).

Table 1. Distributions of potential risk factors for occurrence of cardiovascular events in RA patients at baseline

	N=480
Demographics	
Sex (n, % female)	347 (72.3)
Age (mean, SD)	59.0 (13.0)
Traditional CV risk factors	
Smoking, current (n, %)	114 (23.8)
Systolic blood pressure (mmHg, mean, SD)	144.0 (22.9)
Total cholesterol (mmol/L, SD)	5.3 (0.99)
LDL cholesterol (mmol/L, SD)	3.1 (0.83)
Triglycerides (mmol/L, SD)	1.3 (0.65)
Atherogenic index (mean, SD)	3.7 (1.1)
GlyHb (%, mean, SD)	5.8 (0.67)
SCORE 10-year estimated CV risk (%, SD))	5.7 (4.9)
Inflammatory markers	
ESR (mm/hr, mean, SD)	16.5 (14.9)
hsCRP (mg/L, mean, SD)	7.0 (10.0)
RA disease characteristics	
RA disease duration (years; median, 25^{th}-75^{th} percentile)	4.2 (1.5-11.3)
Seropositive (anti-CCP and/or IgMRF; n, %)	286 (63.3)
Erosions (n, %)	198 (42.2)
DAS 28 (mean, SD)	2.5 (1.2)
Remission (n, %)	223 (72.1)
Medication	
DMARD (n, %)	350 (72.9)
MTX (n, %)	291 (60.6)
TNF inhibitor (n, %)	105 (21.9)
NSAID (n, %)	177 (36.9)
Corticosteroids (n, %)	68 (14.2)

RA: rheumatoid arthritis; CV: cardiovascular; SD: standard deviation; LDL: low density lipoprotein; GlyHb: glycated hemoglobin; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity C-reactive protein; anti CCP: anti cyclic citrullinated protein; IgM RF: IgM rheumatoid factor; DAS28: disease activity score in 28 joints; DMARD: disease modifying antirheumatic drug; MTX: methotrexate; TNF inhibitor: tumour necrosis factor α inhibitor; NSAID: non steroidal anti inflammatory drug

Incident CV events

During the follow up period, 29 patients (6 %) experienced a first CV event. The mean follow up period was 2.9 years (SD 0.65) and total follow up of 1380 patient-years, resulting in a CV event rate of 21/1000 patient-years (95% CI 14.3-29.8). The different CV diagnoses are listed in table 2. There were 2 fatal CV events and 27 non-fatal. From the ten cases first presenting with cardiac chest pain, three underwent a coronary intervention procedure and three experienced

a second CV event during the total follow up period. None of the patients that experienced a non-fatal CV event died within the following 30 days, resulting in a 6.9% CV case fatality rate (table 3). COX regression analysis evaluating the relation between traditional CV risk factors, inflammatory parameters, RA disease duration, presence of IgM rheumatoid factor and/or anti-CCP antibodies and use of anti-inflammatory immunosuppressive therapy and the occurrence of CV events showed only statistically significant independent risks of increasing systolic blood pressure (HR 1.016, 95%CI 1.002-1.030) and use of antihypertensive medications (HR 2.829, 95%CI 1.358-5.891). The use of methotrexate was protective against incident first CV events (HR 3.436, 95%CI 1.553-7.576).

Table 2. Distributions of cardiovascular events in RA patients according to disease duration and IgM rheumatoid factor and/or anti-CCP positivity

Event type (n,%)	RA (n=480)	Incident RA (n=60)	Prevalent RA (n=240)	Seronegative RA (n=166)	Seropositive RA (n=286)
Myocardial infarction	2 (6.9)	1 (33.3)	1 (3.8)	1 (10.0)	1 (5.9)
Acute coronary syndrome	10 (34.5)	2 (66.6)	9 (34.6)	4 (40.0)	7 (41.2)
Acute heart failure	4 (13.8)	0 (0.0)	4 (15.4)	1 (10.0)	2 (11.8)
Coronary intervention	5 (17.2)	0 (0.0)	5 (17.2)	2 (20.0)	2 (11.8)
Cerebrovascular accident	5 (17.2)	0 (0.0)	5 (17.2)	1 (10.0)	4 (23.5)
Cardiac death	2 (6.9)	0 (0.0)	2 (7.7)	1 (10.0)	1 (5.9)
All	29 (100)	3 (100)	26 (100)	10 (100)	17 (100)
All, events/1000 py	21	18	21	20	21

RA: rheumatoid arthritis; <6 months: incident RA, ≥6 months: prevalent RA. py: patient years

Literature review

We identified 24 studies and 2 meta-analyses evaluating CV disease in RA, of which 15 studies reported patient-years of follow up. Only nine studies evaluated composite endpoints for CV disease and thus facilitated a comparison with our own data. From these nine studies, four reported on data from the same cohort. Only the article providing data most relevant to our research was selected. One study reported CV outcome after only one year of follow up, which we considered to be too short to evaluate CV mortality, and was excluded. Table 3 provides a summary of the characteristics and results of the five selected studies, as well as our own data.[9;22-25] There was considerable heterogeneity in study characteristics such as cohort type, sample size, RA disease duration and length of follow up.

Table 3. Characteristics of the 6 studies included in the literature review

Reference	Country	Enrolment period	Mean follow up (years)	Sample type	Inception cohort	RA definition	% female	Mean age at entry	Previous CVD excluded
Assous, 2007[22]	France	1998-1999	5.4	Clinic based	No	ACR 1987	83.8	55	Yes
Solomon, 2006[23]	USA	1999-2003	2.8	Population based	No	ICD code	71.1	NAV	No
Peters, 2009[24]	Netherlands	2001-2002	2.7	Clinic based	No	ACR 1987	65	63	Yes
Meek, 2013**	Netherlands	2009-2011	2.9	Clinic based	No	Clinical diagnosis	72.3	59	Yes
Maradit-Kremers, 2005[9]	USA	1955-1995	14.7	Population based	Yes	ACR 1987	73	58	Yes
Holmqvist, 2010[25]	Sweden	1995-2006	4.1	Population based	Yes	ACR 1987	71.0	56.9	Yes

Studies are placed in order of cohort type (non-inception vs inception) and enrolment period. RA: rheumatoid arthritis; CVD: cardiovascular disease; MI: myocardial infarction; CVA: cerebrovascular incident; CV: cardiovascular; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty; AP: angina pectoris; NAV: not available. * non-published data received from the authors. ** data from the ACT-CVD cohort presented in htis article

We distinguished two inception and four non-inception cohorts. The studies showed no trend in CV event rate over time. However, there was a trend towards decline in percentage fatal CV events within the composite CV disease outcome in both inception and non-inception cohorts with successive periods of enrolment.

	CVD included	Outcome ascertainment	N	Person-years at risk	CV events (n)	CV events/ 1000 person-years	Fatal CV events (%)
	MI, CVA, CV death	Medical record	239	NAV	17	13	52.9
	MI, CVA, CV death	ICD code	25,385	70,612	1,042	14.8	41.2
	Coronary disease, CVA, CV and sudden death	Medical record	272	729	19	26.1	12.9*
	Coronary disease, CVA, CV and sudden death	Medical record	480	1380	29	21	6.9
	MI, CABG, PTCA, AP, CV and sudden death	Medical record	603	8,672	109	13.0	23.8
	MI, AP, CABG, PTCA, CV death	Hospital discharge register	7,469	33,436	341	10.2	11.1

Discussion

Summary of findings

This is the first study to search for trends in case fatality in RA. The prospective analysis of the ACT-CVD cohort shows that first CV events were common, even though arthritis was tight controlled and overt inflammatory activity was low. However, the observed percentage CV deaths within the composite of CV events was importantly lower than observed in studies performed in older cohorts with successive periods of enrolment, suggesting a trend towards decreased case fatality.

Comparison with previous studies

Our finding of a composite CV event rate of 21/1000 patient-years does not differ importantly from earlier clinic based non-inception cohorts evaluating CV disease incidence in RA. From the 1970s onwards many studies have found increased CV disease in RA, which showed some variation in their exact estimates for incident RA associated CV morbidity and mortality depending on factors such as sample size, cohort type, disease duration and length of follow up.[5;26;27] In general, large community based and inception cohort studies found lower CV event risks than smaller clinic based studies or studies including patients with established RA. Two recent meta-

analyses confirmed an approximately 50% overall increase of both CV disease and death in RA compared to the general population. RA associated CV disease incidence was stable in the observation periods of the included studies which ranged from 1955 to 2006.[5-7] Increased CV disease in RA is thought to be caused by a combination of increased traditional CV risk factors and disease specific risks, probably most importantly chronic systemic inflammation.[28;29] Different large cohort studies in the late 20th and early 21st century showed that inflammatory disease activity and disability in RA could be importantly improved by tight control treatment strategies using traditional synthetic and/or novel biologic DMARDs.[38-40] These treatment strategies are currently implemented into daily clinical care. However, an important decline in RA associated CV disease has not yet been obeserved.[30-32]

In the general population CV disease is declining, largely due to improved prevention by general health and life style interventions. General population CV mortality is declining even faster because of better treatment of atherosclerotic vascular disease and improved event survival.[10;33] As mentioned previously, studies on CV disease in RA patients found increased CV event incidence, but some studies also observed that RA patients had a worse prognosis with more frequent fatality of CV events. In our cohort the proportion fatal among the composite of CV events was low. Comparison of our results with previous studies in non-inception cohorts with successive periods of enrolment suggests a trend of decreasing CV case fatality in RA from 1998 until now (52.9% vs. 6.9% fatal CV events, table 3). This finding is supported by the results of two studies in inception cohorts, showing stable composite CV event rates in successive enrolment periods but a lower proportion fatal CV events between 1995-2006 compared to 1955-1995 (11.1% vs. 23.8% fatal CV events, table 3).

A relative decrease in fatal CV events in RA over the last decades could be explained in different ways. On the one hand, reduction of the RA specific risk factors can result in a more benign course of RA associated CV disease and a CV event prognosis more similar to the general population. As mentioned previously, systemic inflammatory activity is thought to be the most important RA specific risk factor.[28;29] The majority of the patients in our cohort were treated following a tight control strategy targeted at remission induction that has been shown to establish stable low disease activity.[34] Also corticosteroid usage, associated with increased CV disease in RA, was very low in our cohort.[15] On the other hand, one might speculate that because of increased awareness, RA associated CV disease is now recognised at an earlier stage. In 2009 the EULAR published the first recommendations for CV risk management in RA. However, recent research has shown that implementation of these recommendations into clinical practice has not yet been widely established.[35-37] Our cohort was initiated before the publication of the EULAR recommendations, and in the ACT CV risk factor screening was not followed by a per protocol intensified CV risk management.

Strengths and limitations

This study has several limitations. The relatively short duration of follow up of our cohort does not allow evaluation of trends in CV event rate over time within the same population, and it may also cause an underestimation of fatal CV events. In a non-inception cohort such as the ACT-CVD cohort this will probably be of lesser importance, as CV disease in RA is thought to develop and accumulate with longer disease duration. Also, the literature review included two other non-inception studies with similar follow up duration in different periods of enrolment, which allows comparison of results. As mentioned previously, studies on RA vary importantly in study population characteristics, and this was also true in our comparison to the literature. The incidence of CV disease may vary with ethnicity and social status, which variables were not registered in our database. The ACT is situated in a rural region of the Netherlands, where the vast majority of the population is of Caucasian origin, and access to healthcare is guaranteed by the national healthcare insurance system. Only one of the studies included in the literature review mentioned ethnicity of the study population, which was over 90% white race, and no study described social status characteristics. The proportion seropositive RA, a possible indicator of more severe phenotype, varied between studies and was lowest in our cohort. However, the percentage seropositivity in our cohort does not differ importantly from the percentages seropositivity recently reported in the literature on tight control treatment in RA, and we think our cohort is representative of the current daily practice RA population.[30;32] Because we identified only a limited number of studies that reported composite and fatal CV outcome parameters which allowed comparison with our own data, selection bias should be considered when interpreting the literature review, but we were able to include data from cohorts that contributed importantly to the present knowledge on RA associated CV disease. Finally, our study was explorative, and cannot provide definite conlusions because we do not have control CV event data. The possible trend of decreasing CV case fatality in RA should be confirmed by further research comparing CV event and case fatality rates in RA patients to those in the general population in the same region and time period.

Conclusion

In this study in a current cohort of low disease activity RA the observed percentage CV deaths within the composite of CV events was importantly lower than in previous studies with successive periods of enrolment. A trend towards decreasing CV fatality in RA is suggested and should be re-evaluated in cohort studies with control populations and longer follow up.

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Chapter 6

The cardiovascular hazard of NSAIDs in daily practice: prospective analysis of the ACT-CVD cohort

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Abstract

Purpose: to study the cardiovascular (CV) hazard of NSAID treatment in unselected patients, including elderly patients and patients with comorbidities and comedication.

Methods: prospective analysis of the 3-year data of the Arthritis Center Twente CardioVascular Disease (ACT-CVD) cohort evaluating the association between continuous use of frequently prescribed non-steroidal anti-inflammatory drugs (NSAIDs; naproxen, diclofenac, ibuprofen, meloxicam or COXIB (etoricoxib or celecoxib)) and the occurrence of first CV events in rheumatoid arthritis (RA) and osteoarthritis (OA) patients. The ACT-CVD cohort includes unselected patients with both new and longstanding rheumatologic diagnoses, and thus represents a daily clinical rheumatology population. The statistical analysis was adjusted for baseline estimated 10-year CV risk score and intermittent NSAID usage.

Results: Of 686 patients 46, 37/552 non-NSAID and 9/134 NSAID users, had experienced a first CV event after a median follow up of 36 months. COX regression analysis showed a significant association between baseline continuous use of ibuprofen (HR 3.59, 95%CI 1.08-11.93) or COXIB (HR 4.86, 95%CI 1.47-16.11) and the occurrence of major CV events.

Conclusion: in an unselected population of RA and OA patients both the tNSAID ibuprofen and COXIBs are associated with a significant increase in CV event risk after only 3 years follow up.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs to patients with rheumatic diseases. Although very effective in the treatment of nociceptive pain, the chronic use of NSAIDs also carries important risks of severe cardiovascular (CV) and gastrointestinal side effects.[1-4] NSAIDs act through the inhibition of prostaglandin synthesis by the cyclo-oxygenase (COX) enzyme, which exists in 2 iso-enzymes, COX-1 and COX-2. The analgesic effects of NSAIDs are primarily due to inhibition of COX-2, whereas the gastro-intestinal side effects are mostly mediated by inhibition of COX-1.[5] With the intention to reduce NSAID associated gastrointestinal toxicity, COX-2 selective NSAIDs (COXIBs) were developed. However, post registration placebo controlled trials showed that the use of COXIBs was associated with increased risk of thrombotic CV events.[6;7]

Recently, large meta-analyses of randomised controlled trials evaluating CV safety of both traditional non-selective NSAIDs (tNSAIDs) and COXIBs found that the increased risk of thrombotic CV events is not class specific.[1;2] Indirect comparisons with placebo showed that the vascular risk of the tNSAIDs diclofenac and possibly ibuprofen were comparable to that of COXIBs, whereas high dose naproxen was least harmful.

Where randomised trials provide reliable and detailed estimates of the size and severity of the CV risk of NSAID regimens in carefully selected patient groups, observational studies can provide useful information on the CV hazard of NSAID treatment in unselected patients, including elderly patients and patients with comorbidities and comedication. Therefore, we performed a preliminary analysis of the Arthritis Center Twente CardioVascular Disease (ACT-CVD) cohort to explore the association between the use of frequently prescribed NSAIDs and the occurrence of first CV events in daily clinical rheumatologic practice.

Methods

The Arthritis Center Twente CardioVascular Disease (ACT-CVD) cohort was established in 2009. The method of patient inclusion and baseline data collection of this cohort has been described previously.[8] Briefly, the database contains baseline demographics, CV risk factors, rheumatic disease characteristics and medication, collected in routine clinical care of both prevalent and incident patients attending the Arthritis Center Twente in Enschede, the Netherlands. Patients are classified according to their clinical diagnosis as registered by their attending rheumatologist. After inclusion in the database, patients are followed up for CV events or death. Follow up data

are extracted from the hospital electronic registration system and are validated by medical chart review. Out of hospital events and death are documented by periodic questionnaires to attending general practitioners and review of the Dutch national registry of death certificates.

Patient selection, follow up and definitions of CV disease

Previous reports on the ACT-CVD database showed that the RA and OA patient subgroups showed comparable baseline CV risk profiles and CV event incidence rates after three years of follow up (Meek IL, et al. EULAR2013; OP2004).[8] Therefore, in the present study we used the combined RA and OA patient data to perform a prospective analysis of the association between the continuous use of the four most frequently prescribed individual tNSAIDs: naproxen, diclofenac, ibuprofen and meloxicam, and COXIBs (etoricoxib and celecoxib), and the occurrence of a first CV event. Continuous use was defined as a minimum of two consecutive prescriptions at regular dosages in a minimum once daily frequency. Only patients without prior CV disease with completed data, entered into the ACT-CVD database before December 2011 were included. CV disease was defined as (1) myocardial infarction; (2) coronary intervention, i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); (3) angina pectoris, confirmed by a cardiologist as cardiac chest pain; (4) acute heart failure; (5) cerebrovascular accident (CVA); (6) death due to cardiac causes; (7) sudden death. Duration of follow up was calculated as the interval between inclusion into the cohort and the occurrence of a first CV event or death, or censored at December 1st 2012, whichever came first. The protocol for data collection, storage and analysis was approved by the Arthritis Center Twente Institutional Review Board.

Statistical analysis

Baseline patient characteristics are presented by appropriate descriptive statistics. COX regression analysis adjusting for baseline CV risk and intermittent NSAID and/or acetylsalicylic acid usage was performed to determine CV event risk over time according to continuous use of individual tNSAIDs and COXIBs at baseline. To explore the influence of confounding by indication, i.e. a preference in the prescription of individual NSAIDs and/or NSAIDs in general according to baseline patient CV risk characteristics, differences in demographics, inflammatory parameters and baseline SCORE 10-year CV risk estimates according to the prescription of individual tNSAIDs and COXIBs were compared by chi squared and ANOVA testing for categorical and continuous variables respectively. Statistical analyses were performed using IBM-SPSS statistics software version 20.0.

Results

At December 1st 2012 The ACT-CVD cohort included 1668 subjects; 725 with a diagnosis of RA or OA. From these, 39 were excluded because of prior documented CV disease.

Baseline characteristics of the study population

The present study included 686 subjects; 480 RA and 206 OA patients. Table 1 shows the baseline characteristics of the total study population. The patients' mean age was 59.0 years (SD 1.4), 74.3% were women and median disease duration was 2.0 years (25^{th}-75^{th} percentile 0.0-7.0). Mean inflammatory activity was low, reflected by low median hsCRP levels (3.1 mg/L, 25^{th}-75^{th} percentile 1.4-6.3), and 72% remission of polyarthritis in the RA patients. At inclusion in the ACT-CVD cohort, 134 (19.5%) patients received continuous NSAID prescriptions; naproxen (41), diclofenac (34), ibuprofen (17), meloxicam (24), another tNSAID (7) or a COXIB (celecoxib or etoricoxib, 11). Baseline mean 10-year CV risk estimates, patient demographic and disease characteristics did not differ importantly between NSAID and non-NSAID users, or between users of the individual NSAIDs studied. (table 2) The only statistically significant difference was a longer mean disease duration in users of meloxicam compared to non-NSAID users (11.5 vs. 4.8 years, respectively, p=0.003) and patients on diclofenac (11.5 vs. 4.4 years; p=0.025)(data not shown).

NSAID use and occurrence of first cardiovascular events

After a total follow up of 1965 patient years, median 36 months (25^{th}-75^{th} percentile 31-41 months), there were 46 major CV events among 686 patients (37/552 non-NSAID, 0/41 naproxen, 2/34 diclofenac, 3/17 ibuprofen, 1/24 meloxicam, 3/11 COXIB). Univariate analysis of the occurrence of CV events according to patients' baseline characteristics showed significant associations with the variables age, SCORE 10-year CV risk estimate, continuous use of NSAIDs and use of acetylsalicylic acid. (table 1) COX regression analysis adjusting for baseline SCORE 10-year CV risk estimate, intermittent use of NSAIDs and acetylsalicylic acid usage showed a significant association between baseline continuous use of ibuprofen (HR 3.59, 95%CI 1.08-11.93) or COXIB (HR 4.86, 95%CI 1.47-16.11) and the occurrence of major CV events. (figure 1)

Table 1. Baseline characteristics of 686 RA and OA patients and univariate analysis of associations between baseline variables and prospective CV events

	Total	Event	No event	p event vs. no event
N	686	46	640	
Demographics				
Sex (n, % female)	510 (74.3)	29 (63.0)	481 (75.2)	0.069
Age (mean, SD)	59.1 (12.5)	64.9 (10.7)	58.6 (12.5)	0.001
Estimated 10-year cardiovascular risk				
SCORE 10-year estimated CV risk (%, mean, SD)	5.6 (4.7)	7.69 (4.57)	5.52(4.72)	0.003
Inflammatory markers				
hsCRP (mg/L, mean, SD)	7.0 (10.0)	7.21 (9.44)	5.90 (8.85)	0.390
Rheumatic disease characteristics				
Diagnosis (n, % RA)	480 (70.0)	29 (63.0)	451 (70.5)	0.289
Disease duration (months, mean, SD)	68.3 (103.5)	63.2 (97.0)	68.8 (104.0)	0.726
Seropositive (anti-CCP and/or IgMRF; n, %)	298 (45.8)	18 (40.9)	280 (46.2)	0.496
Medication				
NSAID continuous use (n, %)	134 (19.5)	9 (19.6)	118 (18.4)	0.016
- Naproxen	41 (6.0)	0 (0.0)	41 (6.4)	n.s.
- Diclofenac	31 (4.5)	2 (4.3)	32 (5.0)	n.s.
- Ibuprofen	17 (2.5)	3 (6.5)	14 (2.2)	s.
- Meloxicam	24 (3.5)	1 (2.2)	23 (3.6)	n.s.
- COXIB	11 (1.6)	3 (6.5)	8 (1.2)	s.
NSAID on demand (n, %)	94 (13.7)	8 (17.4)	86 (13.4)	0.451
DMARD (n, %)	354 (51.6)	18 (39.1)	336 (52.5)	0.080
Acetylsalicylic acid (n, %)	38 (5.5)	11 (23.9)	27 (4.2)	0.000

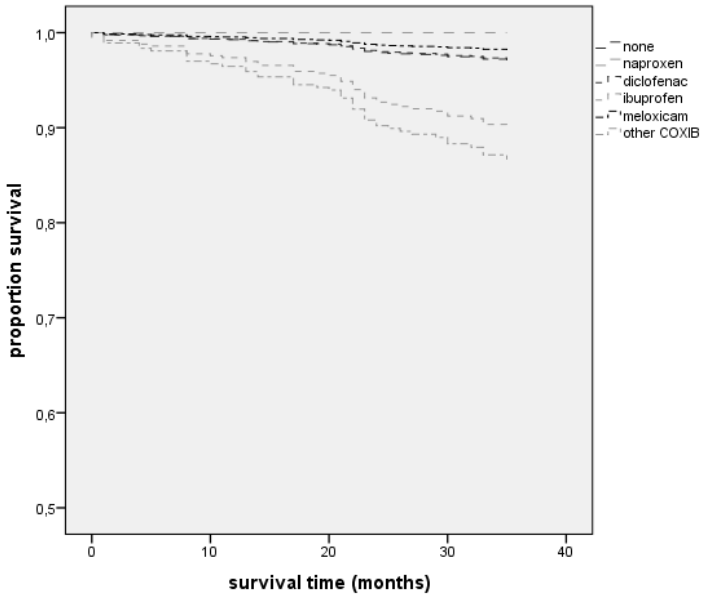
(SD: standard deviation; SCORE: systematic coronary risk evaluation; CV: cardiovascular; RA: rheumatoid arthritis; anti-CCP: anti cyclic citrulinated peptide; IgMRF: IgM rheumatoid factor; hsCRP: high sensitivity C-reactive protein; NSAID: non-steroidal anti-inflammatory drug; COXIB: cyclo-oxygenase 2 selective NSAID; DMARD: disease modifying anti-rheumatic drug)

Table 2. Occurrence of events and baseline values of variables considered as covariates in the survival analysis for different NSAIDs

	No NSAID	Naproxen	Diclofenac	Ibuprofen	Meloxicam	COXIB	p
N	552	41	34	17	24	11	
Events (n, %N)	37 (6.7)	0 (0.0)	2 (5.9)	3 (17.6)	1 (4.2)	3 (27.3)	0.016
Variables considered as covariates in surival analysis							
SCORE 10-year CV risk estimate (mean, SD)	5.78 (4.85)	4.43 (4.77)	5.88 (4.16)	4.59 (4.24)	6.08 (4.10)	5.00 (2.45)	0.494
NSAID on demand (n, %)	93 (16.8)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.000
Acetylsalicylic acid (n, %)	33 (6.0)	0 (0.0)	2 (5.9)	1 (5.9)	1 (4.2)	1 (9.1)	0.714

NSAID: non-steroidal anti-inflammatory drug; COXIB: cyclo-oxygenase 2 selective NSAID; SCORE: systematic coronary risk evaluation

Figure 1. CV event free survival according to the use of individual NSAIDs among 686 RA and OA patients



CV: cardiovascular; NSAID: non-steroidal anti-inflammatory drug; RA: rheumatoid arthritis; OA: osteoarthritis; COXIB: COX-2 selective NSAID

Discussion

This study confirms that in an unselected population of patients with RA or OA, tNSAIDs and COXIBs may be associated with comparable risks of thrombotic CV events. Even though the actual numbers of CV events were small, we still found a significant increase in the primary combined CV event endpoint for ibuprofen and COXIBs, after only three years follow up. This observation comes as an addition to the widely recognised gastro-intestinal hazards of tNSAIDs, and is of great importance because ibuprofen and other tNSAIDs are freely available as over the counter medication in many countries.

The strength of this study is that it provides information on NSAID associated CV risk in the unselected patient population that is seen in daily rheumatologic practice. The ACT-CVD cohort was designed to study CV disease in arthritis and provides detailed information on baseline rheumatic disease characteristics, CV risk parameters and potential confounders. To reduce confounding by indication and confounding by concomitant use of acetylsalicylic acid, only patients without prior CV disease were included and acetylsalicylic acid usage was included as a covariate in the survival analysis. Remarkably, acetylsalicylic acid usage was associated with

increased risk of CV events (HR 5.29, 95% CI 2.64-10.53). This is probably due to confounding by indication through prescription of acetylsalicylic acid as a primary CV prophylaxis in high CV risk patients, and not to a clinically significant NSAID-acetylsalicylic acid pharmacodynamic interaction since these medications were only incidentally combined. (table 2)[9;10] Finally, we compared baseline SCORE 10-year CV risk estimates, which were comparable across patients using the individual NSAIDs studied.

Weaknesses of this study lie in the relatively small numbers of patients and short period of follow up. Thus, we could only discern robust associations and provide hazard ratios with broad confidence intervals. Although we could not confirm the recently found association between the use of diclofenac and increased CV events, our study provides no evidence that the longterm use of diclofenac, or other tNSAIDs, is safe. The low incidence of CV events in patients using naproxen, which was also the most frequently prescribed NSAID in our study, however is in line with previous studies showing a relatively favourable CV risk profile of this drug when used without acetylsalicylic acid as a comedication. [1;2;10]

Conclusions

We conclude that in an unselected population of RA and OA patients multiple NSAIDs, both the tNSAID ibuprofen and COXIBs, are associated with a significant increase in CV event risk after only three years follow up. Naproxen is a possible favourable exception showing a neutral CV risk. Targeted CV risk management in RA and OA should include systematic evaluation of alternatives for NSAID prescriptions in the treatment of joint disease.

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Chapter 7

Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: A placebo-controlled, ex-vivo, serial crossover study

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Abstract

Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are often prescribed concurrently in patients with nociceptive pain and cardiovascular comorbidity. NSAIDs and ASA inhibit the same COX-enzymes, and thus may interact. ASA's cardioprotective antiplatelet effect is entirely COX-1 dependent. NSAIDs can be either non- COX-1 and COX-2 -selective or COX-2 selective. The aim of this study was to examine the interaction between ASA and different selective and non-selective NSAIDs on thrombocyte function.

Methods: Single blind, prospective, placebo controlled, ex-vivo, serial crossover trial of three-day cycles separated by washout periods of at least 12 days in 30 healthy volunteers, evaluating interaction on ASA's antithrombocyte effect by naproxen, ibuprofen, meloxicam, or etoricoxib taken two hours before ASA. Ex vivo thrombocyte function, closure time (CT) in seconds, was measured using the Platelet Function Analyzer 100 (PFA-100). CT-prolongation during a cycle reflects thrombocyte inhibitory effect. ASA nonresponse was defined as CT-prolongation <40% in the placebo cycle. ASA nonresponders were excluded. Wilcoxon signed-rank was used to evaluate NSAID effect on ASA induced CT prolongation.

Results: Ibuprofen and naproxen inhibit ASA's antithrombocyte effect below the nonresponse threshold. Etoricoxib and meloxicam do not cause relevant change in ASA thrombocyte inhibition. Naproxen has an inherent weak thrombocyte inhibitory action below the ASA response threshold.

Conclusions: COX-1 affinity determines the interaction between NSAIDs and ASA on thrombocyte adhesion and aggregation. Ibuprofen and naproxen, but not etoricoxib or meloxicam, taken two hours before ASA significantly inhibit ASA's antithrombocyte effect.

Clinical Trial Registration: Protocol ID APOMST003, EudraCT nr 2008-008954-22

Introduction

Polypharmacy is common in middle aged and elderly patients.[1;2] Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are among the most frequently prescribed drugs in patients with rheumatic diseases, providing targeted therapy for nociceptive pain and protection against thrombotic cardiovascular comorbidity respectively.[3] Nociceptive pain and thrombocyte aggregation are both mediated by cyclo-oxygenase (COX) enzymes, which exist in two isoforms, COX-1 and COX-2. Thrombocyte aggregation is COX-1 dependent, COX-2 is upregulated in case of tissue damage and is involved in the inflammatory response and pain.[4;5] COX-inhibitory drugs can be nonselective, inhibiting both COX isoforms, or selective, preferentially inhibiting the COX-2 isoform.[6;7] ASA and nonselective NSAIDs both block the catalytic site of the COX-1 enzyme, and thus have a potential for pharmacodynamic interaction on thrombocyte aggregation. In 2001 Catella-Lawson et al. were the first to publish in vivo proof of this interaction.[8] Ibuprofen was found to give clinically significant inhibition of the ASA thrombocyte inhibitory effect, but not diclofenac or rofecoxib. Other studies, both in vivo and in vitro, followed, adding naproxen and indomethacin to the list of potential ASA blocking agents, but clearing celecoxib and sulindac.[9;10] Findings on naproxen were confusing however, demonstrating an ASA-like, but less potent, inherent thrombocyte inhibitory effect.[11;12]

These experimental results are supported by multiple observational studies, finding more myocardial infarctions in patients using both ASA and NSAIDs compared to patients using the same NSAIDs as a single prescription. However, also negative studies have been published, leaving the literature on this subject inconclusive.[13-17] When studied as single prescriptions, naproxen appears to cause least cardiovascular complications of all NSAIDs.[18]

Even though our knowledge on the potential pharmacodynamic interaction between NSAIDs and ASA is incomplete, pharmacists' and medical authorities' common fear of such an interaction has great consequences for daily clinical practice. Patients and their physicians are regularly warned not to combine ASA and ibuprofen, while naproxen is recommended as the drug of choice in all patients at high cardiovascular risk.[19;20]

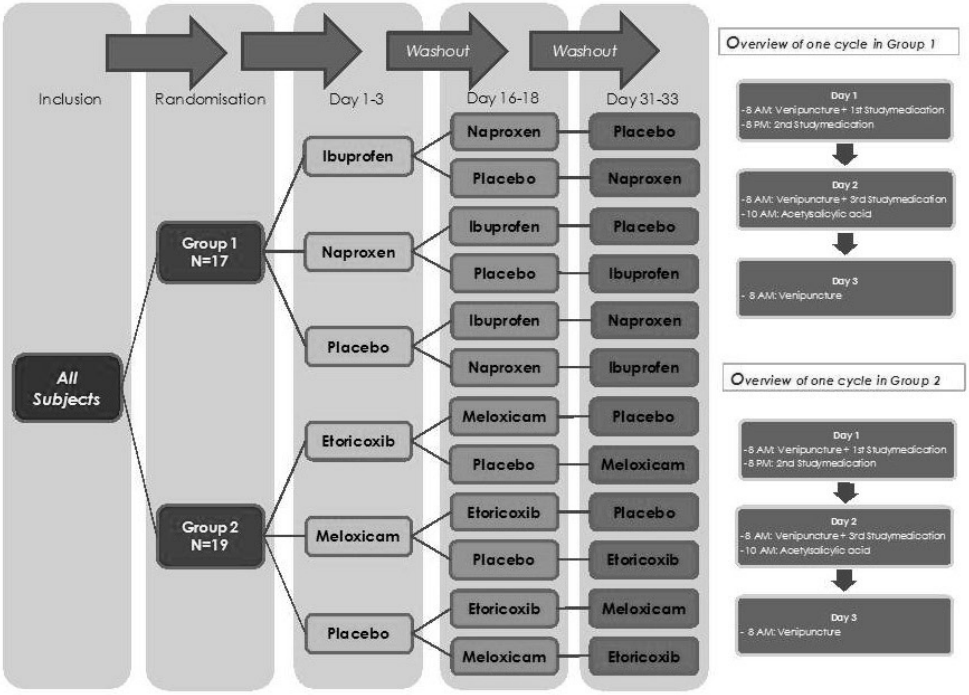
This study was designed to further examine the pharmacodynamic interaction between ASA, naproxen and other different selective and non-selective NSAIDs on thrombocyte function.

Methods

Subjects

The study subjects were thirty volunteers. Volunteers were eligible if healthy, defined as having an unremarkable medical history and laboratory examinations. At baseline haemoglobin, haematocrit, thrombocyte count, creatinine, alanine aminotransferase and von Willebrand activity were measured. Exclusion criteria were any contra-indication for ASA and/or NSAID-use, pregnancy or current pregnancy wish, and use of medication affecting haemostasis and/or having documented interaction with ASA or NSAIDs for at least two weeks before enrolment. Only eligible subjects with an ASA thrombocyte inhibitory response by PFA-100 measurement two hours after after a single trial dose of ASA were included in the study. The study protocol was approved by the Medical Ethical Review Committee (METC) of the Medisch Spectrum Twente hospital in Enschede. All subjects provided written informed consent.

Figure 1. Flowchart of study protocols



A: overview of study cycles. B: outline of study procedures within cycles in groups 1 and 2.

Study design

The study was a single blind, placebo controlled, serial crossover trial consisting of three-day study-cycles separated by a washout period of at least 12 days, evaluating interactions between ASA and four individual NSAIDs: the non-selective NSAIDs naproxen and ibuprofen, and the COX-2 selective NSAIDs meloxicam, and etoricoxib.[21] (figure 1) Standard preparations of all NSAIDs were used in regular dosing schedules conform their label; i.e. two daily doses of naproxen (500 mg non-coated tablets, Pharmachemie BV) and ibuprofen (600 mg coated tablets, Pharmachemie BV) (group 1) and single daily doses of meloxicam (15 mg non-coated tablets, Centrafarm BV) and etoricoxib (90 mg coated tablets, MSD BV) (group 2). Each cross-over schedule contained one placebo (Albochin FNA placebo, Pharmachemie BV) cycle. ASA was administered in an oral loading dose reflecting prolonged daily use of 80 mg (320 mg, four tablets Acetylsalicylzuur Cardio Disp 80 mg (Pharmachemie BV)).[22]

Volunteers were randomly allocated into one of two groups defining three successive study-cycles.(Figure 1) On the first day of each study-cycle blood was drawn for baseline thrombocyte function testing (Thrombocyte Function Analyzer 100; Dade Behring, Germany). A second thrombocyte function measurement was performed on the second day, after which subjects received the third (group 1) or second (group 2) dose of NSAID, followed two hours later by ASA. Thrombocyte function was measured again on the third day, 22 or 30 hours after ASA in groups 1 and 2 respectively.

Blood was obtained by venipuncture without veno-occlusion, and collected in 5 ml vacutainer tubes. For each measurement of thrombocyte aggregation a 4.5 ml blood sample was drawn in 3.2% buffered sodium citrate. Ex vivo thrombocyte function, expressed as closure time (CT) in seconds, was measured using the Thrombocyte Function Analyzer 100 (PFA-100), and Dade® PFA-100 epinephrine cartridge within four hours after the puncture following the manufacturers' user guide instructions. Data were quantitatively presented as closure time (CT) in seconds. To evaluate thrombocyte inhibitory response in study cycles the difference in CT before and after administration of trial medications (CT-shift) was calculated. As in previous literature a relative CT-shift ≥ +40% was regarded as a clinically significant thrombocyte inhibitory effect.[23]

Statistical analysis

Power calculations indicated that a sample size of 15 subjects was needed in each group to detect an absolute difference of 20% in CT between placebo and individual NSAIDs with a power of 90% and a two-sided significance of 0.5.

The PFA-100® has an upper limit of dynamic range of 300 seconds. Values >300 seconds were recorded as 300 seconds. Consequently, as CT values were non-normally distributed, calculated

differences in CT were compared using the Wilcoxon signed-rank test. Both CT-shifts within cycles and differences in CT-shifts between different NSAIDs or placebo were compared. All analyses were performed using SPSS (version 17).

Results

Between June and October 2010 thirty-three volunteers were included in the study. Table 1 summarizes the baseline characteristics of the participants. Two subjects experienced an adverse event after two cycles and stopped the study; one because of an allergic reaction and one because of heartburn and stomach pain. All other subjects completed the study according to the protocol.

Table 1 Baseline characteristics of study subjects

	Socio-demographics n=33	
Gender (n; male/female)	13/20	
Age (year; median, range)	33	22-56
	Laboratory assessment	
	mean	*95% CI*
Hb (mmol/L; mean, 95% CI)	8.7	8.5-9.0
Ht (mean, 95% CI)	0.42	0.41-0.43
Platelet count (10*9/L; mean, 95% CI)	250	128-361
Creatinin (mmol/L; mean, 95% CI)	69	49-93
ALAT (IU/L; mean, 95% CI)	17	11-57
vWF-activity (mean, 95% CI)	97	82-120

BMI body mass index, Hb haemoglobin, Ht haematocrit, ALAT alanine aminotransferase, CI confidence interval, vWF von Willebrandfactor

CT-shifts between days 1 and 2 showed no changes in thrombocyte function in placebo, ibuprofen, and etoricoxib cycles. After use of naproxen and meloxicam significant CT-shifts of 29 seconds (25^{th}; 75^{th} percentile: 13; 44, p=0.008), resp. 8 seconds (25^{th}; 75^{th} percentile: 2; 15, p= 0.003) were observed. CT shifts between days 1 and 2 in intervention cycles were compared with CT-shifts in the placebo cycles of corresponding individuals. Only naproxen caused significantCT-shifts (24 seconds: 25^{th}; 75^{th} percentile: 17; 39, p=0.003) compared to placebo, indicating an inherent thrombocyte aggregation inhibitory effect. (table 2)

As expected, evaluation of CT-shifts between days 1 and 3 showed that the combined use of placebo and ASA caused significant positive CT-shifts of 90 seconds (25^{th}; 75^{th} percentile: 56; 138, p=0.001) resp. 98 seconds (25^{th}; 75^{th} percentile: 72; 206, p=0.001) in groups 1 and 2. Such

a positive CT-shift was also observed in cycles combining ASA and naproxen (13 seconds: 25th; 75th percentile: 5; 43, p=0.004), etoricoxib (77 seconds: 25th; 75th percentile: 31: 187, p=0.001), and meloxicam (151 seconds: 25th: 75th percentile: 90; 234, p=0.001). The combined use of ibuprofen followed by ASA did not cause a significant CT-shift compared to baseline values. (table 3, figure 2)

Table 2. NSAID effect on thrombocyte function: CT-shifts between day 1 (baseline) and day 2 (following different NSAIDs or placebo)

	CT day 1	**CT day 2**	**CT-shift day 2 vs day 1**
	Seconds, median (25th 75th percentile)	*Seconds, median (25th 75th percentile)*	*% ΔCT, median (25th 75th percentile)*
Total placebo	97 (90 109)	93 (85 117)	0 (-16 11)
Ibuprofen	108 (93 115)	142 (107 157)	2 (-3 35)
Naproxen	107 (90 117)	114 (87 119)	29 (13 44)*
Etoricoxib	99 (93 114)	100 (88 111)	2 (-11 8)
Meloxicam	86 (85 91)	95 (88 101)	8 (2 15)*

**P*<0.05

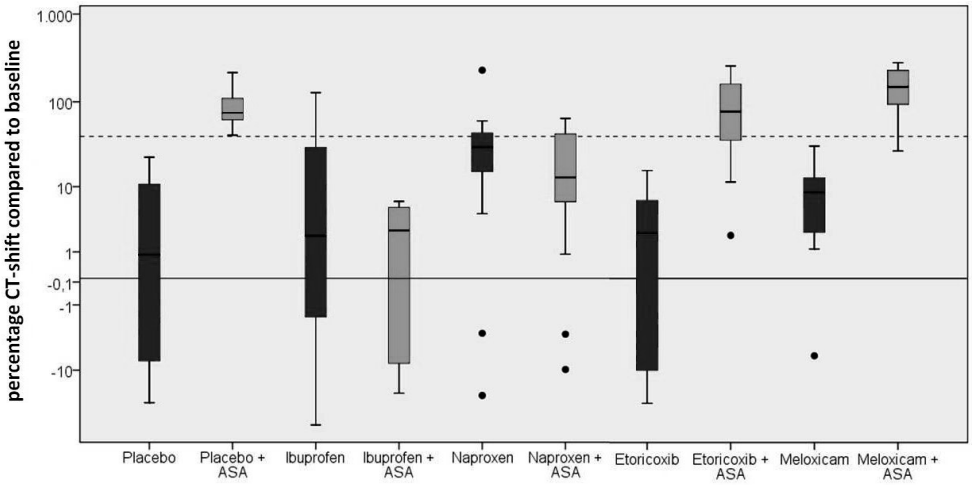
Table 3. ASA effect on thrombocyte function when administered two hours after different NSAIDs or placebo: CT-shifts between day 1 (baseline) and day 3 (following ASA)

	CT day 1	**CT day 3**	**CT-shift day 3 vs day 1**
	Seconds, median (25th 75th percentile)	*Seconds, median (25th 75th percentile)*	*% ΔCT, median 25th 75th percentile)*
Total placebo	97 (90 109)	201 (162 300)	94 (66 179)*
Ibuprofen	108 (93 115)	97 (87 117)	3 (-9 5)
Naproxen	107 (90 117)	125 (102 157)	13 (5 43)*
Etoricoxib	99 (93 114)	179 (123 300)	77 (31 187)*
Meloxicam	86 (85 91)	231 (163 300)	151 (90 234)*

**P*<0.05, day3 vs day1

Finally, CT shifts between first and third days were compared between intervention and placebo cycles. Cycles with ibuprofen or naproxen showed significantly smaller CT-shifts (-80 seconds (25th; 75th percentile: -149; -59, p=0.001), resp. -52 seconds (25th; 75th percentile: -130; -30, p=0.001) compared to placebo cycles, i.e. blocking of the ASA thrombocyte aggregation inhibitory effect. Cycles with etoricoxib or meloxicam showed no significant difference in CT-shifts compared to placebo. (figure 2)

Figure 2. CT-shifts from baseline two hours after different NSAIDs or placebo (day 1 vs. day 2), and two hours after these drugs in combination with ASA (day 1 vs. day 3)



CT-shifts are represented as percentage change in CT compared to baseline (log-scale). The dotted line represents the 40% ASA response threshold. Dark bars: percentage CT-shift day 1 vs. day 2. Light bars: percentage CT-shift day 1 vs day 3.

Discussion

This study shows that COX-1 affinity determines the pharmacodynamic interaction between NSAIDs and ASA on the main function of the thrombocyte: adhesion and aggregation. Ibuprofen, but also naproxen, a non-selective agent with an inherent weak thrombocyte inhibitory action and overall favourable cardiovascular risk profile, inhibits ASA's antithrombocyte effect. Etoricoxib and meloxicam, NSAIDs with low COX-1 affinity, cause no relevant change in ASA thrombocyte inhibition.

COX-inhibitory drugs and thrombocyte function

To interpret the results of this study one has to fully comprehend the working mechanism of COX-inhibitory drugs, i.e. ASA and NSAIDs, as they act on the thrombocyte. Because thrombocytes have no nucleus, COX-1 mediated thrombocyte adhesion and aggregation is entirely dependent on the thrombocyte's stock of constitutionally present COX-1. Importantly, NSAIDs and ASA fundamentally differ in the way they bind COX-1: NSAID's binding to COX-1 is reversible, while binding of aspirin to COX-1 is permanent. ASA therefore irreversibly inhibits thrombocyte aggregation during the thrombocyte's entire lifecycle and is thus, even at low dosage, a potent

antithrombotic agent.[24;25] Conversely, due to their competitive reversible binding of COX-1, most NSAIDs do not significantly influence thrombocyte aggregation. Due to the steric orientation of the COX-1 enzyme, ASA cannot bind COX-1 if the NSAID binding site of the enzyme is already occupied. ASA is virtually completely metabolised into inactive metabolites after a single pass through the liver, and thrombocyte exposure in the portal circulation is most likely responsible for the majority of ASA's antithrombocyte effect.[26] NSAIDs' concentrations in the portal circulation are highest in their absorption phase. Thus, administration of NSAIDs within few hours before ASA may interfere with the ASA's antithrombocyte effect.[24] The absorption kinetics, bioavailability, half-life and COX-1 affinity of a specific NSAID will determine the extent and duration of its actions on portal thrombocyte COX-1, and consequently presence and dynamics of any relevant ASA blocking effect. Depending on the pharmacokinetic properties of specific NSAIDs, the timing of administration of the NSAID and ASA and both drugs' dosing intervals may be of critical importance for their potential for interaction. This was confirmed by two studies on ibuprofen and naproxen, finding reduction of ASA antithrombocyte effect when single dosages of NSAID were administered two hours before ASA, but not if the same NSAID was used two hours after ASA.[11;12] However, a recent study evaluating the time-dependency of the interaction of ASA with ibuprofen using a pharmacokinetic/pharmacodynamic model predicted that prolonged use of three daily dosages of 150 mg ibuprofen on a background of continuous low dose aspirin (81 mg) administered two hours before the first daily dose of ibuprofen will cause significant reduction of ASA antithrombocyte effect.[27]

Comparison with previous studies

Previous pharmacodynamic research supports the hypothesis of a significant interaction between NSAIDs and ASA.[8-12] Different NSAIDs seem to differ in their interaction with ASA, and data on some individual drugs show non-conclusive results. Two ex-vivo studies using different methodologies found interactions between ASA and ibuprofen, and ASA and ibuprofen, indomethacin, and tiaprofenic acid respectively, whereas no interactions were found between ASA and diclofenac and rofecoxib, or ASA and sulindac and celecoxib. In vitro research showed an inhibitory effect of naproxen on ASA, an interaction that only just failed to reach significance when studied ex-vivo.[10;11] Also, naproxen showed an, albeit small, inherent thrombocyte inhibitory action, which complicates the interpretation of these results. A more recent study showed naproxen to interfere with thrombocyte COX-1 inhibition by ASA when taken before, but not when taken 2 hours after aspirin.[12] Our study confirms ASA inhibition by naproxen, with relevant preservation of thrombocyte aggregatory function when taken within a two hours interval.

Strengths and limitations

Various tests of diverse methodologies are available to measure thrombocyte aggregatory function, and are used as a derivative of ASA induced thrombocyte inhibition. A comparison of six current assays found poor correlation among the different tests.[19] The Thrombocyte Function Analyzer (PFA)-100 is designed to simulate the process of thrombocyte adhesion and aggregation following vascular injury in vitro and expresses this process in a numerical value called 'Closure Time' (CT). It is sensitive to many variables affecting the thrombocyte aggregatory response, and only one of these variables, i.e. COX-1 mediated Thromboxane A2 production, is inhibited by ASA. Therefore, the PFA-100 will not show complete thrombocyte function inhibition when investigating the ASA anti-thrombocyte effect, and other variables of thrombocyte aggregation may influence the test results.[23] Nonetheless, multiple studies have demonstrated a correlation between thrombocyte function measured by PFA-100 and clinical outcomes in ASA-treated patients.[24-26] The PFA-100 is the most generally used method to determine thrombocyte function, both in clinical practice and in pharmacodynamic studies.

The definition of ASA response in terms of PFA-100 testing results has been a matter of some debate. From a practical point of view the highest CT value found in healthy, non-ASA using subjects, 193 seconds, has been advised as the cut-off level to define thrombocyte ASA response in clinical practice. However, the optimal definition of non-responsiveness to an antithrombotic drug would be the failure of this drug to inhibit the target of its action.[27] In the setting of this current study which aims to investigate pharmacodynamic interaction rather than clinical endpoints, the latter definition was judged to be most suitable. The protocol included placebo cycles giving information on pre- and post ASA thrombocyte function values. Based on previous literature a cut-off value of ≥ +40% CT-shift was chosen to identify ASA non-response.[19]

Following pharmacodynamic and pharmacokinetic laws the extent and duration of an NSAID's action on thrombocyte COX-1, and consequently the occurrence of any significant ASA inhibitory effect, is determined by the NSAID's absorption kinetics, bioavailability, half-life and COX-1 affinity. The results of our study follow the theoretical positive correlation between NSAID COX-1 affinity and strength of ASA inhibition. Ibuprofen and naproxen, which are both non-selective NSAIDs, inhibit ASA's anti-thrombocyte effect below the nonresponse threshold, whereas the COX-2 selective NSAIDs meloxicam and etoricoxib cause no significant ASA inhibition. The NSAIDs evaluated in this study differ in pharmacokinetic characteristics. Systemic T_{max} ranges from approximately one hour (etoricoxib) to up to six hours (meloxicam), and steady state characteristics from approximately 12 hours (ibuprofen) to five days (meloxicam). Therefore the results of our study can be influenced by differences in portal NSAID concentrations at the time of ASA administration. The double blinded study design did not allow to differentiate the timing

of NSAID-ASA dosing schedules. The two hours interval between NSAID and ASA administration was chosen considering that peak portal plasma concentrations will precede peak systemic concentrations. The study's dosing schedules, administering ASA two hours after each NSAID, were not designed to further investigate the effect of differences in the NSAID's pharmacokinetics on their interference with ASA anti-thrombocyte effect.

Conclusion

This study shows that COX-1 affinity determines the pharmacodynamic interaction between NSAIDs and ASA on thrombocyte function. The non-selective NSAIDs ibuprofen and naproxen inhibited ASA's antithrombocyte effect, whereas the COX-2 selective NSAIDs meloxicam and etoricoxib did not. Before these results can be translated into guidelines for clinical practice they should be weighted in the context of data on NSAID associated cardiovascular risk. In such guidelines also gastrointestinal risks of the combined use of NSAIDs and ASA should be considered. More studies are needed to enable the clinical practitioner to appreciate the risk a patient will be facing when using ASA for cardioprotective purposes and NSAIDs to kill the pain.

Key messages

NSAIDs and ASA are often co-prescibed in rheumatic patients with cardiovascular comorbidity.

ASA's antiplatelet effect may be blocked by NSAIDs through pharmacodynamic interaction at the COX enzymes.

Relative COX-1 affinity determines the pharmacodynamic interaction between NSAIDs and ASA on platelet function.

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Chapter 8

Non-steroidal anti-inflammatory drugs:

overview of cardiovascular risks

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Abstract

While aspirin may offer protection, other non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) can cause serious cardiovascular side effects and complications. This has led to a general "black box" warning for cardiovascular adverse events for NSAIDs. This review explores the different mechanisms underlying the protective effects of aspirin, the NSAID associated renovascular effects causing hypertension, edema and heart failure, the cardiovascular effects causing myocardial infarction and stroke, and the possible deleterious interaction between NSAIDs and Aspirin.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs in modern medicine. NSAIDs are very effective in the alleviation of pain, fever and inflammation, millions of patients worldwide have found relief in their use since the discovery of the soothing properties of the willow bark more than 3500 years ago. Furthermore, aspirin, the archetype of the NSAID family, has become the cornerstone of secondary prevention of thrombotic cardiovascular events. NSAID use is however associated with several serious treatment side effects, with considerable associated morbidity and mortality. Many of these side effects may be prevented by careful consideration of the patient's risk factors and by subsequent implementation of preventive strategies.

Methods

We searched Medline for English-language articles published up to 2010, using the keywords acetylsalicylic acid, aspirin, NSAIDs, cyclooxygenase-2, adverse effects, and cardiovascular. The abstracts were screened for relevance and the publications relating to aspirin and NSAIDs were obtained. Additional references were identified from the bibliographies of the retrieved reports and from review articles. Further sources of information were retrieved from the internet.

Results and Discussion

Prostaglandins and COX

Prostaglandins are the members of a group of lipid compounds derived enzymatically from fatty acids. They are rapidly metabolized, act locally and are involved in many processes that cause inflammation after injury or illness, regulate the constriction of the uterus, affect constriction and relaxation of blood vessels, and are involved in the aggregation of blood platelets. The first prostaglandins to be discovered were isolated from seminal fluid in 1935, independently by both the Swedish physiologist Ulf von Euler and the British pharmacologist M.W. Goldblatt, and were thought to be a prostatic secretion as reflected by their naming.[1;2]

Prostaglandins are found in most tissues and organs and are produced by all nucleated cells, except lymphocytes, from essential fatty acids: gamma-linolenic acid, arachidonic acid, and eicosapentaenoic acid. In the early 1960s both Swedish and Dutch scientists worked to elucidate

the mechanisms underlying the production and actions of these compounds. It was found that in humans, arachidonic acid is mobilized from cell-membrane lycerophospholipids by phospholipase A2. The subsequent biotransformation of arachidonic acid is catalyzed by prostaglandin G2/H2 synthase, resulting in the sequential formation of prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2) via the cyclooxygenase (COX) activities of the protein. Tissue-specific prostaglandin synthases convert PGH2 into other prostaglandins and thromboxane, having different functions in different tissues. For example, PGD2 is involved in sleep regulation and allergic reactions; PGF2 controls the contraction of the uterus and bronchoconstriction, and thromboxane A2 (TXA2) stimulates the constriction of blood vessels and induces platelet aggregation. Prostacyclin (PGI2) dilates blood vessels, inhibits platelet aggregation, and may protect against damage to the stomach lining; prostaglandin E2 (PGE2) is involved in pain, inflammation, and fever and also acts to prevent damage to the stomach.[3;4]

In 1989 Phillip Needleman confirmed the suspicion of two distinct isoforms of COX, being regulated and acting in distinct manners.[5] COX-1 showed to be constitutionally present in low abundance in most human tissues, acting as a housekeeping enzyme by regulating normal physiological processes like the maintenance of gastric mucosal integrity, kidney function, and platelet aggregation, whereas COX-2 was undetectable in most tissues under normal physiological circumstances and was selectively upregulated after exposure to inflammatory mediators or trauma, causing subsequent inflammatory responses and mediation of pain.

Both COX isozymes are membrane-associated proteins with a 3-dimensional structure of a long narrow channel ending in a hairpin bend, and internalize adjacent arachidonic acid which is released when membrane damage occurs.[6;7] Arachidonic acid is bound high within the COX enzyme and is biotransformed via PGG2 into PGH2, which is a subsequent substrate for other cell and tissue-specific terminal enzymes, such as PGI2 synthase which produces prostacyclin, thromboxane synthase which produces thromboxane, and glutathione S-transferase for the conversion to PGE2.

Aspirin's Affinity to COX

Aspirin exerts its effects by non-competitive and irreversible acetylation of the COX enzyme, in which an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme, rendering the COX enzyme permanently inaccessible for the biotransformation of arachidonic acid into PGH2 and thus effectively inhibiting subsequent prostaglandin production.[8;9] Nucleated cells, such as the cells of the gastric mucosa and inflammatory cells, are able to newly synthesize COX-1 and COX-2 and thus recover COX function and prostaglandin production despite inhibition by aspirin. Blood platelets on the other hand have no cellular nucleus and therefore lack the ability

to newly synthesize COX. Furthermore, in blood platelets TXA2 production is entirely COX-1 dependent, which is why COX-1 binding of aspirin in blood platelets will permanently prevent the production of TXA2 and subsequently inhibit platelet aggregation for the duration of the platelets' lifecycle, making aspirin a potent cardiovascular protective agent.[10;11]

Aspirin: Benefits and Risks

Nowadays, the main indication of aspirin is in the prevention of occlusive cardiovascular disease. A collaborative meta-analysis of individual participant data from 16 randomised trials (17000 individuals at high average risk, 43000 person-years, 3306 serious vascular events) on the secondary prevention of cardiovascular events, comparing long term aspirin with placebo on the occurrence of a new myocardial infarction or stroke or vascular death, showed a statistically and clinically significant reduction in serious vascular events (6.7% with aspirin vs. 8.2% with placebo per year), with similar results in both men and women.[12] The risk reduction was found in all subgroups of ischemic events, at the cost of an excess in major gastro-intestinal and other major extra cranial bleeds (RR 2.69, CI 1.25-5.76, data available from 5 out of 16 trials). However, the absolute incidence of major bleeding events was much lower, approximately 0.15% per year, resulting in an overall balance in favour of aspirin. For the primary prevention of cardiovascular events, the authors came to different conclusions. When analysing the data of 6 primary prevention trials (95000 individuals at low average risk, 660000 person-years, 3554 serious vascular events) a statistically significant 12% proportional reduction in serious vascular events was found (0.51% with aspirin vs. 0.57% in controls per year), mainly due to a reduction in non-fatal myocardial infarctions (0.18% vs. 0.23% per year), at the cost of an increase in haemorrhagic stroke (0.04% vs. 0.03% per year) and major gastrointestinal and extra cranial bleeds (0.10% vs. 0.07% per year).[12] In their discussion the authors argue that in modern times the risk-reducing effects of aspirin might be reduced by half by the prescription of other risk reducing medications, such as statins, while the risks of bleeding would remain the same, which would render the net beneficial effect in the primary prevention of cardiovascular events in low risk patients negligible.

Another meta-analysis, searching for adverse events of low-dose aspirin in 22 randomized placebo-controlled trials, found a relative risk of 2.07 for major gastrointestinal bleeding with aspirin, with an absolute annual increase of 0.12%.[13] With this low absolute risk increase, the number needed to treat with aspirin to cause 1 major gastrointestinal bleeding is 833. Strategies for the prevention of aspirin associated gastrointestinal bleeding should therefore be targeted at high-risk patients, such as patients with previous gastro-intestinal bleeding, age over 60 years, concomitant use of corticosteroids, non-aspirin NSAIDs, anticoagulants, other platelet inhibitors and serotonin reuptake inhibitors, infection with *Helicobacter pylori*, and co morbid conditions such as diabetes mellitus, heart failure, and rheumatoid arthritis.[14;15]

By inhibiting gastric COX-1, aspirin may reduce mucosal blood flow, causing local ischemic injury. Aspirin may also impair specific prostaglandin-dependent defences, which protect the gastric mucosa, such as the thick bicarbonate-containing mucous layer lining the interior of the stomach, which buffers luminal gastric acid and thus protects the stomach wall. When these defences have been weakened by aspirin induced inhibition of gastrointestinal COX-1, a second wave of injury caused by luminal gastric acid may facilitate deeper ulceration, bleeding, and even perforation of the stomach wall.[16] Strategies aimed at preventing aspirin and non-aspirin NSAID gastropathy either help to maintain the integrity of the stomach wall and mucous lining, such as the concomitant administration of prostaglandin analogues, or alternatively inhibit the secretion of gastric acid, such as concomitant histamine H2-receptor antagonists or proton-pump inhibitors (PPI).

Studies on the prevention of recurrent gastrointestinal bleeding are all on PPI based strategies, either PPI vs. placebo or PPI vs. H. Pylori eradication, colonisation with H Pylori being associated with an increased risk of recurrent ulcer bleeding. In 1 study, 123 *H. pylori*-positive patients who had developed bleeding ulcers with low-dose aspirin were treated with *H. Pylori* eradication therapy and subsequently randomized to lansoprazole 30 mg daily or placebo in addition to aspirin 100 mg daily.[17] At 12 months follow-up, the rate of recurrent ulcer complications was 1.6% with lansoprazole and 14.8% with placebo. Another study compared the efficacy of either *H. pylori* eradication or concomitant PPI treatment for the secondary prevention of aspirin ulcer bleeding.[18] This study enrolled 400 *H. pylori*-positive patients, 250 with low-dose aspirin and 150 with NSAIDs, who had presented with ulcer bleeding. Only the data for the 250 aspirin users will be presented here. After endoscopically confirmed ulcer healing with omeprazole 20 mg daily for 8 weeks or longer, patients were given aspirin 80 mg daily and then randomized to omeprazole 20 mg daily for 6 months or 1 week of *H. pylori* eradication therapy followed by placebo for 6 months. The probability of recurrent ulcer bleeding during the 6-month follow- up period was 1.9% for patients receiving eradication therapy and 0.9% for those treated with omeprazole.[18] From these and other studies we may therefore conclude that in high risk patients with previous aspirin associated gastrointestinal bleeding, PPI treatment offers significant reduction in the risk of recurrent bleeding.

The Family of Nonsteroidal Anti-Inflammatory Drugs

In 1959 John Nicholson from the Boots Company had, in collaboration with Stuart Adams, synthesized a drug with analgesic, antipyretic, and anti-inflammatory properties similar to aspirin. The drug was named ibuprofen and was marketed in 1969 under the brand name Brufen, despite performing no better than placebo in an initial clinical trial among 18 rheumatoid arthritis

patients.[19;20] Ibuprofen would, however, become the first in a long series of very successful non-aspirin NSAIDs. Nowadays, approximately 50 different NSAID preparations are available and, as a class, they are among the most commonly prescribed drugs worldwide. The main indications are mild to moderate pain of somatic origin. Due to their anti-inflammatory effect, NSAIDs may be especially effective in inflammatory diseases such as rheumatoid arthritis. NSAIDs may be grouped as salicylates (with as a prominent member aspirin itself), arylalkanoic acids (diclofenac, indomethacin, nabumetone, sulindac), 2-arylproprionic acids or profens (ibuprofen, flurbiprofen, ketoprofen, naproxen), *N*-arylanthranilic acids or fenamic acids (mefenamic acid, meclofenamic acid), pyrazolidine derivates (phenylbutazone), oxicams (piroxicam, meloxicam), sulfonanilides (nimesulide), and others. The efficacy of NSAIDs may vary by patient and by indication. In case of inefficacy, substitution by a NSAID from a different chemical class is a sensible therapeutic option.[10]

As a group, NSAIDs are structurally diverse and differ in pharmacokinetic and pharmacodynamic properties, but ultimately they share the same mode of action. Like aspirin, non-aspirin NSAIDs inhibit the production of prostaglandins by blocking the COX enzyme, causing analgesic, antipyretic, and anti-inflammatory benefits, but at a risk for increased gastro intestinal bleeding.[21] However, aspirin and non-aspirin NSAIDs differ fundamentally in the way the COX enzyme is inhibited. As mentioned previously, aspirin permanently inhibits COX by non competitive and irreversible acetylation. Conversely, non-aspirin NSAIDs competitively and reversibly inhibit the COX enzyme during only part of their dosage interval. This distinction is exemplified by their differential effects on platelet aggregation. As mentioned previously, blood platelets, unlike for instance inflammatory cells, have no cellular nucleus and are therefore unable to newly synthesize COX. Aspirin as an irreversible inhibitor of COX function permanently prevents the production of TXA2 and therefore inhibits platelet aggregation for the duration of the platelets' lifecycle, making aspirin a potent cardiovascular protective agent. Conversely, as a result of their competitive reversible binding of the COX enzyme, non-aspirin NSAIDs usually do not provide significant long-term inhibition of blood platelet aggregation.[10]

The classic non-aspirin NSAIDs block both COX-1 and COX-2 isozymes to varying degrees, by binding an arginine molecule at position 120 halfway up their channel, thereby inhibiting access of arachidonic acid to the catalytic site and thus ultimately inhibiting the synthesis of prostaglandins, PGI2, and thromboxanes.[22;23]

The discovery of the two isoforms of COX by Philip Needleman in 1989 and the subsequent clarification of their 3-dimensional structures provided the rationale for the development of COX-2 selective NSAIDs.[5] An ideal NSAID would selectively inhibit the inducible COX-2 isoform, thereby reducing inflammation and pain, without acting on the constitutive COX-1 isoform, thereby

minimizing toxicity. A group of rather bulky NSAIDs was developed, having a rigid side extension that binds within COX-2's unique side-pocket, thereby being able to access and block COX-2, but not the narrower COX-1 enzyme. The COX-2-selective covalent binding within the COX-2 side-pocket proved to be semi irreversible, thus lastingly inhibiting access of arachidonic acid to the catalytic site.[24] In the 1990s a number of pharmaceutical companies tested and developed this hypothesis and by 1995 the first generation of COX-2-selective NSAIDs, celecoxib (Celebrex®) and rofecoxib (Vioxx®), entered clinical trials, with many other variants eventually being approved for use in the treatment of pain, with rheumatoid arthritis and osteoarthritis being their main indications.

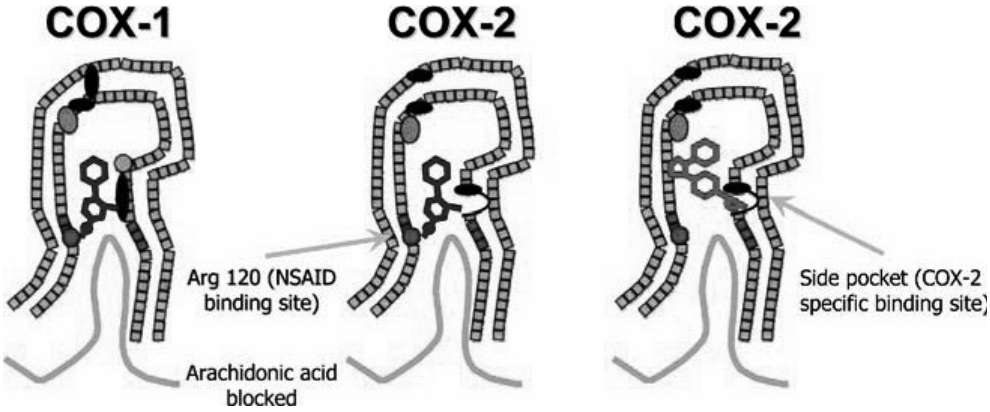

Figure 1 Left: schematic representation of the inhibition of COX-1 by a nonselective NSAID (central hexagonal figure). The entrance channel to COX-1 is blocked by the NSAID. Binding and transformation of arachidonic acid within COX-1 is prevented. Middle: inhibition of COX-2 by a nonselective NSAID (central hexagonal figure). Right: inhibition of COX-2 by COX-2 selective NSAID (central hexagonal figure). The COX-2 side pocket allows specific binding of the COX-2 selective NSAID's rigid side extension. The entrance channel to COX-2 is blocked. The bulkier COX-2-selective NSAID will not fit into the narrower COX-1 entrance channel, allowing uninhibited access of arachidonic acid into COX-1. Adapted from Hawkey CJ.[23]

The Dangers Associated with Pain Relief

It is widely agreed upon that NSAIDs are effective analgesic, antipyretic, and anti-inflammatory drugs, especially in arthritic diseases. However, their use is limited by serious adverse effects. The earliest recognised of these side effects was that NSAIDs share aspirin's trait of gastro-intestinal toxicity, mediated by the inhibition of COX-1 effects on the gastric mucosa. The spectrum of NSAID-related gastro duodenal toxicity can be categorized into 3 groups: (I) subjective symptoms like heartburn, dyspepsia, nausea, and abdominal pain are most common, occurring in 15 to 40% of NSAID users and motivating 10% to change or discontinue their NSAID use; (ii) superficial gastro duodenal mucosal lesions such as erosions and asymptomatic ulcers, occurring in 5 to

20% of NSAID users, which may heal spontaneously; (iii) serious gastro duodenal ulcers leading to life-threatening complications like perforation, symptomatic ulcers, and bleeding (perforation, ulcer, bleeding; PUB) occurring in 1 to 2% of chronic NSAID users, with an associated mortality rate of 10 to 15%.[10;25-27] Subjective symptoms are poorly correlated with the development of gastro duodenal ulcers. Most NSAID users with subjective symptoms show no endoscopic gastro duodenal damage, while up to 58% of patients who present with life threatening NSAID ulcer complications did not have prodromal symptoms.[28] Risk factors for the development of gastro duodenal ulcers are the same as for aspirin, the risk being higher with higher dosage of NSAIDs.[14;15] Much research has been done on preventive strategies for the development of NSAID related gastro duodenal toxicity. These are either directed at maintaining the integrity of the stomach wall and mucous lining, such as the use of COX-2-selective NSAIDs and the concomitant administration of prostaglandin analogues, or alternatively at inhibiting the secretion of gastric acid, such as concomitant use of histamine H2-receptor antagonists or proton-pump inhibitors (PPI) as described in the section on aspirin.[29-33] Eradication of H. Pylori in selected patients can further reduce the risk of gastro duodenal damage.[34;35] A detailed review of the effects of gastro protective measures in NSAID associated gastro-intestinal toxicity goes beyond the scope of this article.

In the early 2000s the endovascular functions of the COX enzymes were unravelled. COX enzymes proved to play important parts in thrombogenesis.[36] Activated blood platelets produce COX-1-dependent thromboxane TXA2, which acts as a prothrombotic platelet agonist and vasoconstrictor. Nearby endothelial and smooth muscle cells produce COX-2-dependent prostaglandin I2 (PGI2), especially after cell damage has occurred.[37] PGI2 is an antithrombotic platelet inhibitor and vasodilator and thus modulates the interaction between activated platelets and the endovascular wall. Cell damage, atherosclerotic plaques, and laminar shear forces selectively up-regulate the expression of COX-2 by endothelial cells in an attempt to maintain homeostasis.[38] Understanding these mechanisms, one could infer that, in clinical syndromes associated with platelet activation, COX inhibition by any NSAID, but especially by COX- 2-selective NSAIDs, may increase the risk for cardiovascular events.[37] As their effect is temporary and reversible, only continuous high dosage of nonselective NSAIDs will considerably inhibit COX-1 and COX-2. However, COX-2-selective NSAIDs may, by their irreversible covalent binding of COX-2, strongly impair the synthesis of endothelium derived antithrombotic and vasodilatory prostacyclin while lacking COX-1-inhibiting effects on platelet aggregation, thus tipping the scales of homeostasis in favour of thrombogenesis and vasoconstriction.[37] In 2004 Merck Sharp and Dohme was prompted to remove its COX-2-selective NSAID rofecoxib (Vioxx®) from the market because of the results of the Adenomatous Polyp PRevention On Vioxx study, showing an 18-month rate of thrombotic events of 1.5 per 100

patient-years with rofecoxib versus 0.78 per 100 patient years with placebo (relative risk, 1.92).[38] Since then many studies have investigated the effects of both COX-2-selective and nonselective NSAIDs on cardiovascular event rates with conflicting results. One meta-analysis assessed the effects of COX-2-selective and nonselective NSAIDs on the risk of vascular events in published and unpublished tabular data from 138 randomized trials that included a comparison of a COX-2-selective NSAID versus placebo or a COX-2-selective NSAID versus a nonselective NSAID with a treatment duration of at least 4 weeks.[39] Selective COX-2 inhibitors were associated with a moderate increase in the risk of serious vascular events compared with placebo (rate ratio, 1.42), which was chiefly attributable to an increased risk of myocardial infarction (rate ratio, 1.86). High-dose regimens of nonselective NSAIDs were associated with a similar increase in risk of vascular events compared with placebo (rate ratio, 1.51 for ibuprofen, 1.63 for diclofenac), with the exception of high-dose naproxen (rate ratio, 0.92).[39] Another systematic review and meta-analysis assessed the risks of serious cardiovascular events with individual COX-2- selective and nonselective NSAIDs in 17 case-control studies and 6 cohort studies.[40] Use of rofecoxib was associated with a significant dose-related relative risk of serious cardiovascular events during the first month of treatment (relative risk, 1.33 with 25 mg or less daily; relative risk, 2.19 with more than 25 mg daily). Celecoxib was not associated with an elevated risk (relative risk, 1.06). Among the nonselective NSAIDs, diclofenac had the highest risk (relative risk, 1.40). For the nonselective NSAIDs ibuprofen (relative risk, 1.07), piroxicam (relative risk, 1.06) and naproxen (relative risk, 0.97) no significant relationship with serious cardiovascular events was found.[40] These results were similar to a meta-analysis assessing the comparative risk of myocardial infarctions with COX-2-selective and nonselective NSAIDs in case-control studies, cohort studies, and randomized controlled trials in colonic adenomas and arthritis, which found an overall small risk of MI with NSAIDs and COX-2-specific drugs, rofecoxib showing the highest risk (relative risk, 1.25 in 6 cohort studies, 387,983 patient years), possibly due to the long half life of this drug compared to the other compounds. The pooled data of fourteen randomized controlled trials in arthritis with 45,425 patients showed more myocardial infarctions with COX-2-selective NSAIDs (odds ratio, 1.6), but fewer serious upper gastrointestinal events (odds ratio, 0.40).[41] A last meta-analysis on the cardiovascular risk of celecoxib on the patient-level pooled adjucated data from 7950 patients in 6 placebo controlled trials comparing celecoxib with placebo for conditions other than arthritis with a planned follow up of at least 3 years, showed an increase in risk with higher dose regimens, the risk being lowest and nonsignificant for the 400-mg-QD dose (hazard ratio, 1.1) and highest for the 400-mg-BID dose (hazard ratio 3.1).[42]

This relationship between dose and cardiovascular risk of NSAIDs that do not completely inhibit COX-1, might be caused by the degree of COX-2 inhibition of the individual compound, as

illustrated by the study of García Rodriguez.[43] In this study agents with a degree of COX-2 inhibition <90% at therapeutic concentrations (ibuprofen, meloxicam, celecoxib, and etoricoxib) where associated with an RR of 1.18 (95% CI 1.02-1.38) of MI, compared to an RR of 1.60 (95% CI 1.41-1.81) for agents with a degree of COX-2 inhibition ≥90% (rofecoxib, indomethacine, diclofenac, and piroxicam).

The results of two Danish studies warrant particular caution in prescribing both selective and non-selective NSAIDs in patients with previous myocardial infarction. In the first study on a cohort of 58432 patients discharged after a first-time MI between 1995 and 2002, 9773 experienced rehospitalisation for MI, and 16573 died. Usage of COX-2 inhibitors in all dosages, and nonselective NSAIDs in high dosages was associated with an increase in mortality, with low NNHs of 13 (95% CI 10-20) for rofecoxib, 14 (95% CI 10-24) for celecoxib, 45 (95% CI 29-102) for ibuprofen, 24 (95% CI 16-45) for diclofenac, and 143 (95% CI 10-20) for other NSAIDs respectively.[44] The second study, conducted between 1997 and 2005, used the same design on two apparently healthy samples of the Danish population. In the sample of 153465 individuals without any conceivable previous risk factor the NNHs for death of all causes were 14 (95% CI 10-25) for rofecoxib, 20 (95% CI 13-43) for celecoxib, 432 (95% CI 184-1251) for ibuprofen, and 77 (95% CI 51-158) for diclofenac.[45]

Based on a review of available data from long-term placebo- and active-controlled clinical NSAID trials, the FDA has concluded that an increased risk of serious adverse cardiovascular events may be a class effect for all NSAIDs, COX-2-selective and nonselective alike (excluding aspirin). Therefore the FDA has requested the package insert for all NSAIDs to be revised and to include a boxed warning highlighting both the presumed increased risk of cardiovascular events as well as the well-described risk of serious, and potentially life-threatening, gastrointestinal bleeding. The FDA has also requested that the package insert for all NSAIDs include a contraindication for use in patients immediately postoperative from coronary artery bypass graft surgery.[46] The EMEA, the European couterpart of the FDA, draws a different conclusion in its statements on COX-2 selective and non-selective NSAIDs from 2005 and 2006. This agency differentiates between the two groups, regarding COX-2 inhibitors contra-indicated in patients with ischemic heart disease or stroke, and cautioning the use of these compounds in patients with risk factors for cardiovascular disease, giving the non-selective NSAIDs the benefit of the doubt.[47]

An algorithm for the prescription of NSAIDs in patients based on individual gastro-intestinal and cardiovascular risk profiles, in accordance to the AHA and ACG guidelines, is presented in table 1.[48-50]

Table 1. Algorithm for NSAID prescription based on gastro-intestinal (GI) and cardiovascular (CV) risk factors

	Low GI risk	Moderate GI risk (one or two risk factors)	High GI risk (more than two risk factors)
Low CV risk	Non-selective NSAIDs	Non-selective NSAID + PPI or COX-2 + PPI	COX-2 + PPI
High CV risk	Naproxen + PPI	Naproxen + PPI	No NSAIDs

GI risk factors include history of ulcers, age over 60 years, high dosage of NSAID, concomitant corticosteroids, anticoagulants, aspirin, platelet inhibitors, and serotonin reuptake inhibitors, *Helicobacter pylori*, diabetes mellitus, heart failure, and rheumatoid arthritis. Proton pump inhibitor (PPI) may also be read as misoprostol 400 to 800 mg. Evaluation of CV risk is according to the judgment of the prescribing physician. Patients with a high CV risk should receive prophylactic low-dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID. Naproxen should be taken 2 hours after aspirin. COX-2: COX-2 selective NSAID. Adapted from ref.[48]

NSAID use has also been associated with the development of hypertension and edema and with exacerbation of pre-existing heart failure. These complications of NSAID use can be explained by NSAID induced inhibition of the physiologic production of vasodilatory prostaglandin in individuals with an increased activation of the renin-angiotensin and sympathetic nervous system, as is the case in hypertension or states of effective volume depletion, such as heart failure, cirrhosis, and true volume depletion. In these situations NSAID use may induce systemic vasoconstriction by blocking the compensatory release of vasodilatory prostaglandins, causing an increase in afterload and a reduction in cardiac contractility and cardiac output.[51] Depending on the patient's cardiac reserve, volume status, sodium balance and use of certain antihypertensive medications (with the exception of long acting calcium antagonists), use of NSAIDs can cause sodium and fluid retention, exacerbate heart failure or evoke an elevation in blood pressure averaging 3 to 6 mmHg.[52] Inhibition of renal vasodilatory prostaglandins, which in these situations preserves renal blood flow and glomerular filtration rates by relaxing preglomerular resistance and antagonizing the local vasoconstrictor effects of angiotensin II and norepinephrine, may disrupt a fragile balance and cause reversible renal ischemia, with a subsequent decline in glomerular hydraulic pressure and glomerular filtration rate, leading to acute renal failure.[53]

One meta-analysis in observational studies and randomised controlled clinical trials to determine the risks of cardiac failure with NSAIDs, showed an increase in the occurrence of cardiac failure by 30-100%, the risk being alike in COX-2-selective and nonselective NSAIDs. However, the absolute risk remains small: less than one patient developed NSAID attributable heart failure per hundred patient years of NSAID treatment. Pre-existing heart failure was associated with the highest risk. Other studies found NSAID use not to be associated with a first occurrence of heart failure, but only with exacerbations of pre-existing disease.[54-56]

The risk of developing hypertension in persons without a previous history of hypertension was investigated in the Nurses' Health Study II, a prospective study of over 80,000 women of 31 to 50 years of age. In this study the relative risk for the development of hypertension after 2 years of follow-up was 1.86 with NSAIDs compared with non-NSAIDs, with the exception of aspirin (115). In a recent meta-analysis of 51 randomized clinical trials involving COX-2-selective NSAIDs, with a total of 130,541 participants in whom blood pressure data were available, significantly increased rates of incident hypertension were found in users of COX-2-selective NSAIDs compared to placebo (risk ratio 1,49) and compared to nonselective NSAIDs (risk ratio 1,12).[57] The results were mainly driven by rofecoxib (risk ratio 1,87 vs. placebo and 1,53 vs. nonselective NSAID) and etoricoxib (risk ratio 1,52 vs. nonselective NSAID). Comparisons between COX-2-selective NSAIDs and naproxen versus COX-2-selective NSAIDs and non-naproxen nonselective NSAIDs showed a higher risk ratio for the development of hypertension (1,31 COX-2 vs. naproxen; 1,08 COX-2 vs. non-naproxen), but smaller weighted mean differences in systolic and diastolic blood pressure for naproxen vs. non-naproxen NSAIDs.[57]

In a study on the effect of COX-2 inhibition on renal function in healthy sodium depleted elderly patients that were randomized to rofecoxib 12.5 mg daily, rofecoxib 25 mg daily, indomethacin 50 mg 3 times daily, or placebo for 5 days, it was found that glomerular filtration rate was significantly lowered with rofecoxib 12.5 mg (8.4 mL/min lower), rofecoxib 25 mg (7.8 mL/min lower), and indomethacin 150 mg (6.0 mL/min lower).[58] Another study, with a nested case control design, showed that hospitalization for acute renal failure was correlated with initiation of NSAID use among 121,722 patients older than 65 years of age.[59] The risk of acute renal failure was highest within 30 days of starting treatment and receded thereafter. The relative risk for acute renal failure was comparable among rofecoxib (relative risk, 2.31; 95% CI, 1.73 to 3.08), naproxen (relative risk, 2.42; 95% CI, 1.52 to 3.85), and nonselective, non-naproxen NSAIDs (relative risk, 2.30; 95% CI, 1.60 to 3.32) but was slightly lower with celecoxib (relative risk, 1.54; 95% CI, 1.14 to 2.09).

Finally, by unknown pathophysiologic mechanisms NSAID use is also associated with renal failure due to acute interstitial nephritis, membranous nephropathy, and minimal change disease nephrotic syndrome. Affected patients typically present with hematuria, pyuria, white cell casts, proteinuria, and acute renal insufficiency. Spontaneous recovery usually occurs within weeks to months after therapy is discontinued.[60] Subsequent administration of NSAIDs should be avoided as relapse may occur with rechallenge.

While the NSAID associated development of hypertension, edema, heart failure and renal insufficiency may occur with COX-2-selective and nonselective NSAIDs alike, one promising new development may offer some perspective. A new class of anti-inflammatory drugs currently under

development are the COX-inhibiting nitric oxide (NO) donators (CINODs). CINODs have been designed to provide the anti-inflammatory and analgesic efficacy of NSAIDs but with improved gastrointestinal and cardiovascular safety by coupling a COX-2 selective or nonselective NSAID with a NO-releasing moiety.[61] *In vivo* CINODs demonstrate similar COX inhibition and anti-inflammatory and analgesic properties compared to their reference NSAIDs while their NO release has been shown to improve gastric mucosal blood flow, to promote gastric healing, to inhibit platelet aggregation, to reduce systemic blood pressure and to preserve vascular, cardiac and renal function. One CINOD currently completing phase III trials is naproxcinod, which couples naproxen to a NO-donating moiety. In a randomized, double-blind, 13-week, placebo- and naproxen-controlled trial of 916 patients with osteoarthritis, naproxcinod significantly reduced systolic blood pressure compared to naproxen, especially in hypertensive patients treated with renin-angiotensin blocking agents, with a 6.5 mm Hg difference in mean change from baseline in systolic blood pressure between naproxen and naproxcinod ($p<0.02$).[62] Further trials are awaited.

Combining Aspirin and NSAIDs: the Devil in Disguise?

Since both aspirin and nonselective NSAIDs bind blood platelets' COX-1 enzyme, concomitant administration of both drugs may interfere with the beneficial effect of aspirin on the risk of thrombotic cardiovascular events. One study examined the effects of ingestion of 400 mg ibuprofen 2 hours before or 2 hours after a regular prophylactic dose of 81mg aspirin. Serum thromboxane B2 levels and platelet aggregation were maximally inhibited with the administration of aspirin before ibuprofen. In contrast, aspirin's inhibition of serum thromboxane B2 formation and platelet aggregation was prevented with a single daily dose of ibuprofen before aspirin, as well as when multiple daily doses of ibuprofen were given. The concomitant administration of rofecoxib, acetaminophen, or diclofenac before or after aspirin did not affect platelet inhibition.[63] Similar effects have been described with naproxen in 1 study, where a single dose of naproxen 2 hours before aspirin interfered with the antiplatelet effect of aspirin.[64] Nonselective NSAIDs compete with aspirin for a common binding site on the platelet's COX-1. The presence of a nonselective NSAID at this site prevents aspirin from binding and irreversibly acetylating a serine residue on COX-1.[51;65] The half life of a specific nonselective NSAID determines the duration of its clinically relevant aspirin blocking effect. Aspirin causes an irreversible and nearly complete blockade of COX at low doses, while the blockade caused by ibuprofen at therapeutic doses is reversible and much less complete, declining rapidly between dosage intervals, reflecting the short half life of the drug.[66] Therefore, one can reason that ibuprofen does not have an inherent platelet aggregation inhibitory effect. Even though naproxen itself has a strong blood platelet aggregation inhibitory effect, the previously mentioned study showed that concomitant use of

naproxen also may also give a significant inhibition of the antiplatelet effect of aspirin, albeit smaller than that of ibuprofen. These findings may have strong clinical relevance in patients with cardiovascular disease. Concomitant use of aspirin and ibuprofen or naproxen should be avoided, or at least the NSAID should be administered approximately 2 hours after aspirin.[10]
This pharmacodynamic interaction is not expected in relatively COX-2-preferential (diclofenac) or COX-2 selective NSAIDs.

Conclusions

Nowadays, one can hardly imagine medicine without aspirin or the nonaspirin NSAIDs, being the cornerstones of modern concepts of cardiovascular event prevention and pain relief. From a pain killing and antipyretic drug, aspirin evolved to a gastric toxin and finally a protector against recurrent thromboembolic cardiovascular events. NSAIDs, being uniquely effective against mild to moderate pain of somatic origin, especially when associated with inflammatory causes, stood their ground despite the emergent reports of several damaging side effects. Development of COX-2-selective NSAIDs significantly reduced the risk of gastrointestinal ulceration, however increased rates of myocardial infarction, heart failure, hypertension and acute renal insufficiency remained. The new class of COX inhibiting nitric oxide donators (CINODs) offers some perspective. The efficacy of both COX-2 selective and nonselective NSAIDs may vary by patient and by indication. In case of inefficacy, substitution by a NSAID from a different chemical class is a reasonable therapeutic option. Nonselective NSAIDs such as ibuprofen or naproxen can interfere with the protective platelet inhibitory effect of aspirin by competitive binding of COX-1. Physicians must take into account both the gastrointestinal and the cardiovascular risks and possible interactions in individual patients when prescribing NSAIDs. One should inform the patient about expected benefits and risks in the consulting-room. The impact of pain and priority of pain relief for patients is shown by a study among Canadian osteoarthritis patients, which showed that most patients were willing to accept some additional risk of ulcer bleeding and to a lesser extent heart attacks or stroke to alleviate their pains.[67]
As a central dictum in NSAID treatment, physicians should always prescribe the lowest effective dose for the shortest possible time. When starting on NSAIDs gastrointestinal, cardio- and renovascular risks should be estimated. When indicated gastro protective measures should be co prescribed. Patients with a high cardiovascular risk should receive prophylactic low-dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID, in combination with an adequate dose of a PPI or misoprostol, irrespective of the presence of additional gastrointestinal risk factors.[48] Naproxen should be taken 2 hours after aspirin. COX-2-selective NSAIDs should be avoided in patients with high cardiovascular risk. Patients with both a high cardiovascular risk and a high gastrointestinal risk should avoid NSAID therapy altogether.

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Summary and general conclusions

Summary

The aim of this thesis was to study cardiovascular risk in arthritis: Firstly, how do different rheumatic diseases compare in the patients' traditional cardiovascular (CV) risk factor profiles, and does this justify the general focus on rheumatoid arthritis regarding cardiovascular complications in rheumatic practice? Secondly, can we identify rheumatic disease specific factors, such as biomarkers, disease characteristics or treatment factors, that are associated with increased or decreased cardiovascular risk? Thirdly, does cardiovascular damage, manifesting itself through the occurrence of cardiovascular events, also occur if rheumatic disease is tightly controlled and average rheumatic inflammatory activity is low? And finally, what is the contribution of non steroidal anti-inflammatory drug (NSAID) use to excess cardiovascular events in rheumatic patients? For this purpose we initiated the Arthritis Center Twente CardioVascular Disease (ACT-CVD) cohort and performed an ex vivo pharmacodynamic experiment, the results of which are presented in this thesis.

Chapter 2 presents the first analysis of the ACT-CVD cohort, in which we studied the prevalence of CV risk factors among patients with different rheumatic diagnoses, in comparison with the general population. We conducted a cross-sectional comparison between this rheumatic outpatient cohort of consecutive patients (n=1233) attending the Arthritis Center Twente (ACT) in 2009: rheumatoid arthritis (RA; n=546), gout (n=129), osteoarthritis (OA; n=168), connective tissue disease (CTD; n=85), polymyalgia rheumatica (PMR; n=91), and chronic localized or generalized pain syndromes (CPS; n=214), and a random sample of the Doetinchem Cohort Study, a long-lasting population based health study in the Netherlands (n=4523).[1] Main outcome measures were hypertension (systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication), an abnormal cholesterol profile (total cholesterol≥6.5 mmol/L, and/or HDL-cholesterol<0.9 mmol/L and/or use of lipid lowering medication), overweight (body mass index ≥25 kg/m^2), obesity (body mass index≥30 kg/m^2) and cigarette smoking (self-reported current smoking). We found that compared to the general population ($P_{general}$), patients with rheumatic diseases (P_{ACT}) had a significantly higher prevalence of hypertension (P_{ACT}=68%, $P_{general}$=57%), overweight (P_{ACT}=72%, $P_{general}$=62%), obesity (P_{ACT}=30%, $P_{general}$=17%) and cigarette smoking (P_{ACT}=26%, $P_{general}$=21%). The worst risk profile was found in gout patients, who showed higher prevalence of all cardiovascular risk factors studied. We concluded that lifestyle associated, potentially modifiable cardiovascular risk factors are overrepresented along the whole spectrum of chronic rheumatic diseases, and not specifically in rheumatoid arthritis as was suggested by preceding literature.

In **Chapter 3** we investigated the impact of serum uric acid, inflammation and traditional cardiovascular risk factors on cardiovascular event risk in patients with gouty arthritis versus patients with non-gouty rheumatic disease. The study included both a cross-sectional and a prospective multivariate analysis of respectively the relationship between tertiles of serum uric acid and individual traditional cardiovascular risk factors and the relationship between tertiles of serum uric acid and incident first cardiovascular events in patients with gouty arthritis (GA, n=172), rheumatoid arthritis (RA, n=480) and osteoarthritis (OA, n=206) without prior cardiovascular disease, included in the ACT-CVD cohort between February 2009 and November 2011. Main outcome measures were systolic blood pressure, total cholesterol/HDL-cholesterol ratio, glycated haemoglobin (GlyHb), body mass index (BMI) and first cardiovascular events. We found that individual cardiovascular risk factors were significantly higher in patients with gouty arthritis (systolic blood pressure, total cholesterol/HDL-cholesterol ratio, BMI, $p<0.05$). In rheumatoid arthritis and osteoarthritis, the individual cardiometabolic parameters correlated with serum uric acid values (RA: systolic blood pressure, total cholesterol/HDL-cholesterol ratio, BMI; OA: systolic blood pressure, total cholesterol/HDL-cholesterol ratio, GlyHb, BMI; $p<0.05$). These correlations were not present in patients with gouty arthritis, possibly because of confounding by treatment with uric acid lowering therapy. In patients with non-gouty rheumatic disease, the highest tertile of serum uric acid (>0.34 mmol/L) and NT proBNP level were independent predictors of first cardiovascular events, against age and GlyHb level in patients with gouty arthritis ($p<0.05$). Patients with gouty arthritis and patients without gouty arthritis but with a serum uric acid $\geq$ 0.34 mmol/L had an equally significantly increased approximately three-fold hazard of first cardiovascular events within three years follow up. We concluded that in rheumatic outpatients, the presence of gouty arthritis or a baseline serum uric acid in the upper range are possibly stronger predictors of first cardiovascular events than some of the traditional cardiovascular risk factors or parameters of inflammation.

The objective of **Chapter 4** was to study cardiovascular risk in intensively treated, tightly controlled rheumatoid arthritis. That rheumatoid arthritis is associated with increased cardiovascular morbidity compared to the general population and compared to individuals with degenerative joint disease such as osteoarthritis has already been established, but most studies were performed before the introduction of biologic DMARDs and tight control treatment strategies aiming at rheumatoid arthritis disease activity remission. Since the introduction of intensive combination DMARD therapies, tight control treatment strategies and biologic DMARD therapy, the average level of chronic inflammation in rheumatoid arthritis patients has fallen dramatically. Because of the known association between chronic inflammation and cardiovascular disease, these therapeutic improvements may also result in changed patterns of rheumatoid arthritis associated

cardiovascular risk. After 3-years follow up of the ACT-CVD cohort we performed a prospective study of the occurrence of first cardiovascular events in tightly controlled low disease activity rheumatoid arthritis patients (RA: 480) compared to individuals with osteoarthritis (OA: 206), all without prior cardiovascular disease. As secondary analyses we 1) mirrored our findings with the self-reported incidence of ischemic heart disease and stroke in the Dutch general population, and 2) evaluated the contribution of treatment factors on cardiovascular event risk in rheumatoid arthritis. Baseline 10-year risk of cardiovascular death estimates did not differ between rheumatoid arthritis and osteoarthritis patients. The rheumatoid arthritis patients were 72.3% female with median disease duration of 4.2 years, 72.1% had a DAS-28 (Disease Activity Score in 28 joints) below 2.6 at baseline, which was regarded as remission. After 3 years follow up rheumatoid arthritis and osteoarthritis patients showed comparable frequencies of first cardiovascular events (RA 21.0/1000 py, 95% CI 13.0-32.1 vs. OA 29.7/1000 py, 95% CI 19.4-41.7). There was no trend towards decreased cardiovascular survival in rheumatoid arthritis. The results of the secondary analysis suggest that the incidence of cardiovascular events in ACT-CVD RA cohort was also comparable with the self-reported incidence rates of cardiovascular disease in the general population (RA 21.0/1000 py, 95% CI 13.0-32.1; GP 21.7/1000 py, 95% CI 13.6-33.0). Use of methotrexate was the only treatment factor significantly associated with improved cardiovascular survival in rheumatoid arthritis (HR 3.89, 95%CI 1.77-8.55). Seventeen out of 29 (58,6%) first cardiovascular events in the rheumatoid arthritis group were associated with methotrexate non-prescription at baseline. Non-prescription of methotrexate was associated with the patient characteristics increasing age, negative IgM rheumatoid factor and absence of erosions, factors which are generally associated with a milder disease course.

The results of this study suggest that a modern tight control treatment strategy may normalize or at least reduce the increased cardiovascular risk of rheumatoid arthritis.

In **Chapter 5** we investigated cardiovascular event mortality in tightly controlled rheumatoid arthritis. Preceding studies in the early 2000s and before found increased 30-day mortality (OR 1.6, 95% CI 1.2-2.2) after a first cardiovascular event and more frequent sudden death (HR 2.13, 95% CI 1.13-4.03) in rheumatoid arthritis patients compared to non-rheumatoid arthritis subjects.[2;3] In chapter 4 we showed that cardiovascular event incidence may be normalized or at least reduced by modern, tight control RA treatment. In chapter 5 we performed a prospective study of first cardiovascular event fatality in the same selection of ACT-CVD RA patients (n=480) after 3 years follow up. These results were then compared to historical data from previous studies that documented fatality of cardiovascular events in rheumatoid arthritis. After 3 years follow up of the ACT-CVD cohort 29 patients (6%) had experienced a first cardiovascular event, 2 fatal and 27 non-fatal, corresponding to a 6.9 % case fatality rate. Comparison with previous studies in

successive cohorts showed a trend towards decreasing cardiovascular event fatality in rheumatoid arthritis from 52.9% in 1998 to 6.9% in our cohort with inclusion from 2009 onwards. The results of this study suggest that a modern tight control treatment strategy may also reduce the excess cardiovascular event fatality in rheumatoid arthritis.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs to patients with rheumatic diseases, and although very effective in the treatment of nociceptive pain, the chronic use of NSAIDs also carries important risks of cardiovascular and gastrointestinal side effects. Most studies on the association between the use of NSAIDs and the occurrence of cardiovascular events have been performed in clinical trial populations. In **Chapter 6** we studied the association between NSAID treatment and first cardiovascular events in unselected rheumatic patients in daily clinical practice, including elderly patients and patients with multiple comorbidities and comedication. We performed a prospective analysis after 3-years follow up of the ACT-CVD cohort, evaluating the association between continuous use of frequently prescribed NSAIDs (naproxen, diclofenac, ibuprofen, meloxicam or COXIBs (etoricoxib or celecoxib)) and the occurrence of first cardiovascular events in rheumatoid arthritis and osteoarthritis patients. The statistical analysis was adjusted for baseline estimated 10-year cardiovascular risk score and intermittent NSAID usage. Of 686 patients, 46 (37/552 non-NSAID and 9/134 NSAID users), had experienced a first cardiovascular event after a median follow up of 36 months. COX regression analysis showed a significant association between baseline continuous use of ibuprofen (HR 3.59, 95%CI 1.08-11.93) or COXIBs (HR 4.86, 95%CI 1.47-16.11) and the occurrence of major cardiovascular events. Thus, after only 3 years of follow up the use of either ibuprofen or COXIBs was associated with a significant increase in cardiovascular event risk in an unselected population of patients with rheumatic diseases. Repeated analyses after longer follow up are needed to conclude on the cardiovascular hazard of diclofenac, meloxicam and naproxen in daily rheumatic practice.

Chapter 7 presents an ex-vivo experiment to evaluate the pharmacodynamic interaction between acetylsalicylic acid and different cyclo-oxygenase (COX)-2-selective and non-selective NSAIDs on thrombocyte function. NSAIDs and acetylsalicylic acid are often prescribed concurrently in rheumatic disease patients with nociceptive pain and cardiovascular comorbidity. Both classes of drugs may interact because each drug inhibits the same COX-enzymes for it to establish its therapeutic effect. The cardioprotective anti-thrombocyte effect of acetylsalicylic acid is entirely COX-1 dependent, NSAIDs can be either non- COX-1 and COX-2 -selective or relatively COX-2 selective. We performed a single blind, prospective, placebo controlled, ex-vivo, serial crossover trial of three-day cycles separated by washout periods of at least 12 days in 30 healthy volunteers, evaluating the pharmacodynamic interaction on acetylsalicylic acid's antithrombocyte effect by

naproxen, ibuprofen, meloxicam, and etoricoxib. All NSAIDs studied were taken two hours before the use of acetylsalicylic acid. Ex vivo thrombocyte function, closure time (CT) in seconds, was measured using the Platelet Function Analyzer 100 (PFA-100). The CT-prolongation during a cycle reflects thrombocyte inhibitory effect. Acetylsalicylic acid nonresponse was defined as CT-prolongation <40% in the placebo cycle. Acetylsalicylic acid nonresponders were excluded. NSAID effect on acetylsalicylic acid induced CT prolongation was statistically tested by Wilcoxon signed rank test. The results of this study showed a COX-1 affinity dependent effect; ibuprofen and naproxen inhibit acetylsalicylic acid's antithrombocyte effect below the nonresponse threshold, while etoricoxib and meloxicam did not cause relevant change in acetylsalicylic acid mediated thrombocyte inhibition. Naproxen caused an inherent weak thrombocyte inhibition that remained below the acetylsalicylic acid response threshold. The results of this ex vivo experiment suggest that an NSAID's COX-1 affinity determines the interaction between this particular NSAID and acetylsalicylic acid on thrombocyte function.

Chapter 8 presents a narrative literature review that summarizes what is known about the different mechanisms underlying the cardioprotective effects of acetylsalicylic acid, and NSAID associated cardiovascular and renovascular complications. In susceptible patients, NSAIDs may cause hypertension, edema and heart failure. Also, in clinical trial situations most NSAIDs have been shown to be associated with an approximately 1.5 fold increased risk of serious cardiovascular events, with the exception of naproxen and possibly of low dose celecoxib (≤ 100 mg daily). In 2005 the accumulating evidence on increased cardiovascular events in patients using NSAIDs led to a general "black box" warning for cardiovascular adverse events during NSAID use by the Federal Drug Administration. That patients using acetylsalicylic acid for cardioprotection may be under a particular threat of NSAID related cardiovascular complications is explained in the paragraph on combining acetylsalicylic acid and NSAIDs, in which the combination is called 'a devil in disguise'. As we also demonstrated with the ex-vivo experiment in Chapter 7, non COX-1 and COX-2 selective NSAIDs compete with acetylsalicylic acid for a common binding site on the thrombocyte's COX-1. Concomitant use may inhibit acetylsalicylic acid from binding at its COX-1 binding site, and thus result in interference with acetylsalicylic acid's thrombocyte aggregation inhibitory effect. Contrary to our conclusion in this chapter, which was based on previous literature, the results of our own NSAID- acetylsalicylic acid experiment in chapter 7 show that in increased cardiovascular risk patients using acetylsalicylic acid as a cardiovascular prophylaxis, naproxen may not be the NSAID of choice. Even though a pharmacodynamic interaction that inhibits acetylsalicylic acid anti-thrombocyte effect may be avoided by administering the NSAID intermittently, and approximately 2 hours after acetylsalicylic acid, in patients using acetylsalicylic acid for cardiovascular prophylaxis it is safest to avoid NSAID therapy altogether.

General discussion

In 1953 Sidney Cobb was the first author who described increased premature mortality in rheumatoid arthritis. In a study in 583 rheumatoid arthritis patients once hospitalized at the Massachusetts General Hospital and subsequently followed up for 6.5 years, he showed that in patients below 50 years of age at baseline, the death rate of men was 20.6 per 1000 py (3.9/1000 py expected) and of women 10.7 per 1000 py (2.9/1000 py expected). With increasing age the death rates of rheumatoid arthritis patients approached the death rates expected for the patients' age and sex. Cardiovascular disease was the major cause of death of the rheumatoid arthritis patients included in this study.[4] After this publication many studies followed that showed comparable results, the estimated rheumatoid arthritis associated increase in cardiovascular event risk being approximately 40-50%.[5-7] Currently rheumatoid arthritis is widely accepted as being an important independent cardiovascular risk factor.[8;9] Although less in number, several studies in other rheumatic disease populations suggest that diseases such as gout, psoriatic arthritis and ankylosing spondylitis may also be associated with an independent, rheumatic disease associated increase in cardiovascular risk.[10-15]

Pathophysiology

The pathophysiology underlying rheumatic disease associated cardiovascular disease is thought to be threefold: Firstly, increased occurrence of traditional lifestyle associated cardiovascular risk factors such as inactivity, obesity and cigarette smoking in patients with rheumatic diseases.[16-18] Secondly, chronic rheumatic inflammation with production of circulating inflammatory mediators such as hsCRP, TNFα, IL-1 and IL-6, that may mediate vascular wall activation and cellular influx, causing formation of instable atheromatous plaques. The same inflammatory mediators may also interfere with metabolic pathways of insulin handling, causing a state of relative insulin resistance and dyslipidemia.[19-21] Thirdly, adverse effects of medication, especially NSAIDs and glucocorticosteroids, may contribute to rheumatic disease associated cardiovascular risk.[22-24] Both NSAIDs and glucocorticosteroids are associated with hypertension, and each may adversely influence cardiovascular risk by other, partly unelucidated pathways as well. NSAID use may induce systemic vasoconstriction by blocking the compensatory release of vasodilatory prostaglandins which is regulated by selective upregulation of COX-2 in states of absolute or relative volume depletion, causing an increase in afterload and a reduction in cardiac contractility and cardiac output. Also, relatively COX-2 selective NSAIDs may disrupt the balance between COX-1 mediated thrombocyte activation and COX-2 mediated endothelial throbocyte aggregation antagonising mechanisms, thus causing a prothrombotic state.[25] Treatment with glucocorticosteroids is

associated with the occurrence of the insulin resistance syndrome, characterised by glucose intolerance, dyslipidemia, increased body weight and increased abdominal fat distribution.[26] The insulin resistance syndrome is generally associated with an estimated factor 1.5 to 1.8 increased risk of cardiovascular complications.[27] These unfavourable side effects are dose dependent and more severe with longer duration of treatment.[24-26]

Cardiovascular risk management

Because studies mostly focus on a single rheumatic disease, the information on rheumatic disease associated cardiovascular risk that reaches the practising clinician is fragmented and difficult to translate into clinical practice. The results of Chapter 2 of this thesis, where we evaluated cardiovascular risk factor patterns among different rheumatic diseases, show that traditional parameters of cardiovascular risk are highly prevalent in most patient groups attending a rheumatic practice. The individual's traditional cardiovascular risk profile should therefore be considered in the therapeutic management of any rheumatic patient.[8] Such awareness is not yet present among health professionals, as demonstrated by a retrospective study of rheumatoid arthritis, diabetes mellitus and general population patient records between 2007 and 2011. In this study, cardiovascular risk factors in rheumatoid arthritis patients were most frequently identified and managed by general practitioners, but general practitioners managed cardiovascular risk factors significantly less frequent in rheumatoid arthritis patients compared to the general population and patients with diabetes mellitus.[28]

Tightly controlled rheumatoid arthritis

Arthritis treatment may be an important determinant of arthritis associated cardiovascular risk, in negative ways as stated previously, but also in positive ways. Treatment of arthritis reduces systemic rheumatic inflammation, reduces the accrual of articular damage and improves the patient's physical performance.[29-31] Use of DMARDs, especially methotrexate and possibly also TNF inhibiting DMARDs, has been shown to be associated with improved survival and a decrease in cardiovascular events in rheumatoid arthritis.[32-34] In recent years the treatment of chronic rheumatic diseases, particularly rheumatoid arthritis, has changed dramatically through the wide availability of potent synthetic and biologic DMARDs and the introduction of protocolled tight control treatment strategies, aiming to achieve stable disease remission within the shortest possible interval after diagnosis.[31;35;36] It has been shown that through the use of a tight control treatment protocol, 70% of early rheumatoid arthritis patients may achieve a state of sustained DAS-28 remission (DAS-28 $\leq$2.6) within three years of their rheumatoid arthritis diagnosis.[31] Between 2010 and 2012, tight control treatment protocols have become the standard of rheumatoid

arthritis care, and it is expected that these treatment protocols will be widely implemented within the coming years.[37;38]

Whereas cardiovascular morbidity and mortality have been comprehensively studied in moderate and high disease activity rheumatoid arthritis patients, the frequency of cardiovascular complications in tightly controlled low disease activity rheumatoid arthritis patients is not yet known. Cohort studies on solid endpoints such as cardiovascular events and mortality in tightly controlled rheumatoid arthritis populations are lacking. However, a study of endothelial function, as measured by reactive hyperaemic index, suggested improvement of endothelial function in low disease activity rheumatoid arthritis patients treated with methotrexate and/or biologic DMARDs when compared to patients with active rheumatic disease.[39] Another study evaluating vascular wall inflammation by ^{18}F-fluorodeoxyglucose positron emission tomography and aortic stiffness in rheumatoid arthritis patients demonstrated a significant reduction of aortic inflammation after treatment with TNF inhibiting biologic DMARDs. In this study, treatment with TNF inhibiting biologic DMARDs was associated with a significant reduction of rheumatoid arthritis disease activity, but not remission (baseline DAS-28 6.52 ±0.78, 8 week DAS-28 4.38 ±1.61, P<0.0001).[40] The rheumatoid arthritis patients included in the ACT-CVD cohort were treated according to a standard of care tight control treatment protocol, which explains the low mean disease activity (mean DAS-28 2.6 ± 1.2) and high frequency of rheumatoid arthritis remission (DAS-28 ≤2.6, 72%) at baseline.[41] This cohort thus provides an excellent data source for studies designed to evaluate cardiovascular event risk and its determinants in a modern tightly controlled and low disease activity rheumatoid arthritis population. Patients in daily practice are more heterogeneous and show more variation in treatment variables than the highly selected patients that are usually included in clinical trials.[42] The use of data from 'real world' daily clinical care in the studies presented in this thesis improves the generalizability of the results to those patients that current rheumatologists encounter in their daily practice.

ACT-CVD analyses

This thesis commences with a cross-sectional analysis of the baseline cardiovascular risk profiles in different rheumatic disease categories within the ACT-CVD cohort. The baseline cardiovascular risk profile of each ACT-CVD disease category was more, as in gout, or less, as in rheumatoid arthritis and osteoarthritis, unfavourable in comparison with the general population. These findings were in line with previous studies in single rheumatic diseases.[16;43-45] The novelty of this thesis lies in the subsequent prospective analyses after three years follow up of the ACT-CVD cohort, describing the relative incidence of fatal and non-fatal cardiovascular events in low disease activity rheumatoid arthritis patients and comparing cardiovascular event incidences in patients with low disease

activity rheumatoid arthritis and other rheumatic diagnoses. These studies show a low relative cardiovascular event risk in this current tightly controlled low disease activity rheumatoid arthritis cohort, but the results may be difficult to interpret because of the comparator populations used. Both gout and osteoarthritis patient groups are known by either moderately (osteoarthritis) or severely (gouty arthritis) unfavourable cardiovascular risk factor profiles compared to the general population, which we also documented in our baseline analysis.[44;45] However, the indirect comparison with Dutch Health Statistics data described in chapter 4, suggests that the incidence of cardiovascular events in the ACT-CVD RA cohort is comparable with general population self-reported incidence rates of cardiovascular disease in the same time period (RA 21.0/1000 py, 95% CI 13.0-32.1; GP 21.7/1000 py, 95% CI 13.6-33.0; p>0.999).[46] In summary, the prospective analyses of the occurrence of first cardiovascular events in the ACT-CVD cohort presented in this thesis suggest that a modern tight control treatment strategy may reduce and perhaps even normalize the increased cardiovascular risk of rheumatoid arthritis.

Limitations of ACT-CVD data

Some limitations of these prospective studies of cardiovascular event risk in the ACT-CVD cohort should be mentioned. The results presented in this thesis may have been influenced by detection bias due to the relatively short duration of follow up. In previous studies in rheumatoid arthritis, disease duration was associated with an increasing relative incidence of cardiovascular events, probably reflecting accrual of vascular wall damage by chronically active systemic rheumatic inflammation. However, previous non-inception cohorts with comparable follow up duration did show high frequencies of CV disease and high cardiovascular case fatality rates in rheumatoid arthritis patients.[2;47;48] Also, although the ACT-CVD cohort is large in comparison to other single centre studies, such as the Dutch CARRE cohort and the rheumatoid arthritis cohort of the Cochin Teaching Hospital in France, the sample size is still too small to statistically detect subtle differences between groups and weak associations with multiple cardiovascular risk factors.[47;49] Future repeated analyses of the ACT-CVD rheumatoid arthritis cohort, with longer duration of follow up, should therefore teach us whether the low cardiovascular event rates in the studies presented in this thesis will stand firm over time. Also, such analyses may provide more information on rheumatic disease specific cardiovascular prognostic factors in addition to the currently demonstrated highly significant cardiovascular risk reduction by methotrexate treatment in patients with rheumatoid arthritis (HR 3.89, 95%CI 1.77-8.55). Methotrexate is a potent anti-inflammatory synthetic DMARD, and cardiovascular risk reduction associated with the use of methotrexate has been described previously in different chronic inflammatory disorders.[50] Previous studies in rheumatoid arthritis suggested stronger cardiovascular risk reduction by

methotrexate than by other synthetic, and possibly also TNF inhibiting DMARDs.[51] Methotrexate is the anchor DMARD in the Arthritis Center Twente tight control rheumatoid arthritis treatment protocol, and the most frequently prescribed DMARD in the ACT-CVD rheumatoid arthritis cohort (DMARD-use at the baseline screening: MTX 62%, anti-TNF 22%, non-MTX synthetic DMARD 27%), which may be a source of detection bias.[41]

The absence of a sample of age- and sex matched general population controls from the same geographic region within the ACT-CVD database is another limitation of the prospective analyses of the ACT-CVD cohort in this thesis. We could not directly compare the incidence of cardiovascular events in tightly controlled rheumatoid arthritis patients to the incidence of cardiovascular events in the general population, which would have provided us the most informative and reliable estimate of cardiovascular event risk in current tightly controlled rheumatoid arthritis. Performing such a comparison with general population cardiovascular incidence data will be an objective of future research.

Non-steroidal anti-inflammatory drugs

The cardiovascular risk of NSAID use is not specifically related to rheumatic diseases, but certainly of great relevance to the rheumatologic patient population because of its high frequency of NSAID use. The pathophysiology of the NSAID associated CV risk has been described in a previous section of this chapter, and may be adversely modulated by rheumatic patient characteristics such as pre-existing vascular wall activation by systemic rheumatic inflammation or unfavourable lifestyle associated cardiovascular risk factors.[16;19;44;45] Approximately 20% of the ACT-CVD patients received a continuous NSAID prescription at the baseline cardiovascular risk screening. In the study presented in Chapter 6 of this thesis, the continuous use of either ibuprofen (HR 3.59, 95%CI 1.08-11.93) or a COXIB (HR 4.86, 95%CI 1.47-16.11) was significantly associated with the occurrence of first cardiovascular events in rheumatoid arthritis and osteoarthritis patients, after only three years follow up in daily rheumatic care. Because of the short period of follow up and small number of events we should not draw any conclusions on the safety of the other NSAIDs evaluated: diclofenac, meloxicam and naproxen. The combined results of randomised clinical trials have shown that any NSAID may be associated with excess cardiovascular risk, naproxen being the only favorable exception. The study in chapter 6 may have underestimated the NSAID associated cardiovascular risk in the whole rheumatologic population, because of the exclusion of 39 patients with prior cardiovascular events (5.4% of all rheumatoid arthritis and osteoarthritis patients in the ACT-CVD cohort). This introduced a selection bias towards non-use of acetylsalicylic acid (acetylsalicylic acid use with no prior CV event 5.5 %, vs. with prior CV event 61 %, P<0.0001). The use of nonselective NSAIDs may significantly inhibit the

cardioprotective effect of acetylsalicylic acid, and therefore the NSAID associated risk may be particularly high in patients with prior cardiovascular events that receive acetylsalicylic acid as a secondary cardiovascular prophylaxis. However, the sample size of only 39 patients was too small to allow for additional analyses to confirm this hypothesis.

Future directions

The ACT-CVD cohort provides many opportunities for further research. Follow up data for cardiovascular events and death are periodically obtained from the electronic hospital information system, attending general practitioners and the Dutch National Registry of Death Certificates. Repeated analyses after 5, 10 and 15 or more years should provide us with more definite estimates of cardiovascular risk in patients with different rheumatic diagnoses, and on the consequences of tight control treatment strategies for the frequency of long-term cardiovascular complications in patients with longstanding low disease activity rheumatic disease. In the optimal scenario we would continue working with a general population sample for control data, as we did previously in very pleasant cooperation with the National Institute for Public Health and the Environment. After longer follow up and with a larger number of cardiovascular events it will also be possible to search for more disease specific cardiovascular risk factors. One of our objectives is to develop rheumatic disease specific cardiovascular risk estimate models. In the end the research on cardiovascular risk in rheumatic diseases should not just dwell on publications describing historical or current observational data. Clinicians need evidence based risk interventions based on the information provided by the abovementioned fields of research. The (cost)effectiveness of such interventions should be evaluated in clinical trials, but more importantly also after implementation in clinical practice.

Conclusions

The prevalence of lifestyle associated cardiovascular risk factors is high in different rheumatic diseases, and specific rheumatic diseases may have different cardiovascular risk patterns compared to the general population. Cardiovascular event risk in tightly controlled low disease activity rheumatoid arthritis patients may be lower than in the previously reported cohorts with moderate and high disease activity rheumatoid arthritis. This should be confirmed by direct comparisons to the general population and after longer follow up. Continuous use of NSAIDs is an important treatment factor that contributes to cardiovascular event risk in patients with rheumatic diseases, and should be particularly avoided in patients using low dose acetylsalicylic acid for cardiovascular prophylaxis.

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Samenvatting en conclusies (Summary in Dutch)

Samenvatting

In 1953 verscheen de eerste publicatie waarin een verhoogde cardiovasculaire mortaliteit werd beschreven bij patiënten met de diagnose reumatoïde artritis, een algemeen voorkomende chronische reumatische ziekte welke zich voornamelijk manifesteert in ontsteking van gewrichten.[1] Sindsdien is deze observatie vele malen bevestigd, de geschatte afname in levensverwachting van reumatoïde artritis patiënten ten opzichte van de algemene bevolking is vijf tot vijftien jaar.[2] De jaarlijkse kans op het krijgen van een cardiovasculaire ziekte of event, dat wil zeggen een myocardinfarct, acuut coronair syndroom, acuut hartfalen of een coronaire interventie, of om aan een cardiovasculaire ziekte te overlijden is bij een reumatoïde artritis patiënt ca 50% verhoogd ten opzichte van een gezonde leeftijdsgenoot van hetzelfde geslacht. Ook de jaarlijkse kans op een cerebrovasculaire ziekte lijkt verhoogd te zijn, maar in mindere mate, ca 40%.[3-6] Na de ontdekking van het met reumatoïde artritis geassocieerde verhoogde risico op ontwikkeling van cardiovasculaire mortaliteit en morbiditeit, is ook bij enkele andere chronische reumatische ziekten de frequentie van voorkomen van cardiovasculaire events onderzocht. Hoewel het aantal studies minder groot is, zijn er duidelijke aanwijzingen dat ook bij ziekten als jicht, psoriasis en artritis psoriatica, de spondylartropathieën en osteoartrose de kans op het krijgen van een cardiovasculair event bij patiënten hoger is dan verwacht op basis van leeftijd en geslacht.[7-12]
Reumatische patiëntenpopulaties worden regelmatig gekenmerkt door de aanwezigheid van traditionele cardiovasculaire risicofactoren zoals middelbare of oudere leeftijd, roken van tabak, overgewicht, hypertensie, diabetes en dislipidemie. Deze kunnen de toename in cardiovasculaire morbiditeit echter niet geheel verklaren.[13-15] Opvallend is dat bij atherosclerose, het proces dat door vorming, ruptuur en trombose van atheromateuze plaques in de arteriële vaatwand leidt tot het optreden van cardiovasculaire events, deels dezelfde ontstekings- of inflammatoire mediatoren en cellen betrokken zijn als bij chronische reumatische ziekten. Deze observatie vormt de grondslag voor de inflammatoire hypothese, waarbij chronische systemische reumatische ontsteking leidt tot arteriële vaatwand activatie en vorming van instabiele atheromateuze plaques, zich uiteindelijk openbarend in een cardiovasculair event.[16-18]
Ook de medicamenteuze behandeling van reumatische ziekten kan het cardiovasculaire risico van patiënten beïnvloeden. Dit kan door specifieke kenmerken van een medicament, of door een niet geneesmiddel specifieke remming van systemische reumatische ontsteking. Drie belangrijke groepen geneesmiddelen binnen de reumatologie zijn de non-steroïdale anti-inflammatoire pijnstillers (NSAID's), glucocorticosteroïden en de synthetische en biologische 'disease modifying anti-rheumatic drugs' (DMARD's). NSAID's worden vanwege hun gerichte werkingsmechanisme en effectiviteit veel toegepast voor behandeling van nociceptieve pijn bij reumatische patiënten.

De laatste decennia zijn vele gerandomiseerde studies verschenen waarbij bij één of meerdere NSAID's een verhoogd risico op cardiovasculaire ziekte werd beschreven ten opzichte van placebo. Inmiddels is met meta-analyses aangetoond dat de grootte van het NSAID gerelateerde cardiovasculaire risico ligt tussen een factor 1.21 (naproxen, 95% CI 0.78-1.93) en 2.26 (ibuprofen, 95% CI 1.11-4.89). Waarschijnlijk is van geen enkel NSAID het cardiovasculair risico neutraal, met als mogelijke uitzonderingen naproxen en lage dosis celecoxib (kleiner dan 100 mg per dag).[19;20] Ook behandeling met glucocorticosteroïden lijkt geassocieerd te zijn met meer cardiovasculaire ziekte. De geobserveerde frequentie van cardiovasculaire complicaties neemt toe met de cumulatieve en actuele dagelijkse dosering van het medicament.[21] In tegenstelling tot het mogelijk schadelijke effect van NSAID's en corticosteroïden, lijkt langdurig gebruik van DMARD's geassocieerd te zijn met een relatieve afname van cardiovasculaire events en mortaliteit. De literatuur hierover betreft voornamelijk reumatoïde artritis patiënten en het bewijs lijkt het krachtigst voor behandeling met methotrexaat, en in mindere mate de tumor necrosis factor α (TNF) blokkerende middelen.[22-24] Of TNF blokkerende middelen toegevoegde waarde hebben boven methotrexaat is nog onduidelijk, mogelijk wordt dit bepaald door de grootte van de algemene respons op de behandeling met TNF blokkerende middelen na 6 maanden.[25]

De laatste decennia is de medicamenteuze behandeling van reumatoïde artritis patiënten ingrijpend veranderd door de algemene beschikbaarheid van krachtige synthetische en biologische DMARD's en de introductie van geprotocolliseerde 'tight control' behandelstrategieën gericht op het bereiken van remissie van artritis binnen een zo kort mogelijk interval na het stellen van de diagnose. Als chronische systemische reumatische ontsteking inderdaad een doorslaggevende oorzakelijke factor is in de pathogenese van met reumatische ziekte geassocieerde cardiovasculaire events, zou men op basis van deze ontwikkeling een geleidelijke daling van cardiovasculaire events bij patiënten met reumatoïde artritis verwachten. Inmiddels hebben enkele studies bij reumatoïde artritis patiënten met een lage ziekteactiviteit ten opzichte van patiënten met een actieve reumatoïde artritis een daling in biomarkers van cardiovasculaire ziekte (hsCRP, totaal cholesterol/HDL-cholesterol ratio, NT-proBNP) en verbetering van vaatfunctie parameters laten zien.[26;27] Deze ontwikkeling wordt echter nog niet eenduidig bevestigd door de resultaten van onderzoekingen naar trends in reumatoïde artritis geassocieerde cardiovasculaire events en mortaliteit over de laatste 50 jaar.[3;28;29]

Hiertoe aangezet door de wetenschappelijke literatuur over het verhoogde cardiovasculaire risico bij patiënten met reumatische ziekten, is het ReumaCentrum Twente in 2009 gestart met het in de dagelijkse praktijk protocollair screenen van al haar patiënten op traditionele cardiovasculaire risicofactoren. Zowel chronische als nieuwe patiënten krijgen bij het eerstvolgende polikliniekbezoek van hun behandelend reumatoloog persoonlijke en schriftelijke informatie over doel en inhoud

van deze screening. Alle patiënten die toestemmen in deelname worden vervolgens gezien door een hiertoe opgeleide doktersassistente voor een kort gestandaardiseerd lichamelijk onderzoek en een korte enquête over demografische factoren, medische voorgeschiedenis, medicatiegebruik, rookgedrag en cardiovasculaire familieanamnese. Tenslotte wordt een nuchter bloedonderzoek verricht voor bepaling van een selectie cardiovasculaire biomarkers en ontstekingsparameters. Alle individuele resultaten van de screening zijn in gestructureerde vorm beschikbaar voor gebruik in de dagelijkse patiëntenzorg.

Om de resultaten van de screening te evalueren en prospectief onderzoek naar cardiovasculaire morbiditeit en mortaliteit van de eigen populatie mogelijk te maken, werd de Arthritis Center Twente CardioVascular Dsease (ACT-CVD) database gecreëerd. Alle patiënten die deelnemen aan de protocollaire cardiovasculaire screening worden tevens verzocht om informed consent voor inclusie in de database en periodieke follow up voor registratie van incidente cardiovasculaire events of overlijden. Deze follow up data worden verkregen door periodiek raadplegen van het elektronische ziekenhuisinformatiesysteem, en gevalideerd door controle van de medische status. Registratie van cardiovasculaire events en overlijden buiten het ziekenhuis vindt plaats door periodieke enquêtes van huisartsen en het raadplegen van de Nationale Register voor Overlijdensregistratie.

De geanonimiseerde patiëntendata van het ACT-CVD cohort zijn beschikbaar voor onderzoeksdoeleinden, mits in overeenstemming met de primaire doelstelling van het ACT-CVD project, en alleen na revisie en goedkeuring van het onderzoeksprotocol door de Wetenschappelijke Commissie van het ReumaCentrum Twente.

Ondanks de uitgebreide literatuur betreffende cardiovasculaire ziekten bij artritis patiënten, zijn er nog vele vragen onopgehelderd. Enkele van deze vragen vormden samen het startpunt van dit proefschrift: Ten eerste, hoe verhouden verschillende reumatische aandoeningen zich tot elkaar betreffende traditionele cardiovasculaire risicoprofielen, en rechtvaardigt deze verhouding de huidige algemene focus op reumatoïde artritis als het gaat om cardiovasculaire complicaties bij reumatische ziekten? Ten tweede, kunnen wij reumatische ziekte specifieke cardiovasculaire risicofactoren onderscheiden, zoals biomarkers, ziektespecifieke kenmerken of behandelfactoren, zodat we reumatische patiënten met een verhoogd cardiovasculair risico beter en in een vroeger stadium kunnen identificeren? Ten derde, treedt reumatoïde artritis geassocieerde cardiovasculaire schade, zich uitend in cardiovasculaire events, ook op in een actuele reumatoïde artritis populatie, die behandeld wordt volgens een 'tight control' protocol gericht op het bereiken van stabiele remissie van artritis binnen een zo kort mogelijk interval na het stellen van de diagnose reumatoïde artritis? Ten vierde, draagt het gebruik van NSAID's bij aan de associatie tussen het hebben van een reumatische ziekte en een verhoogde kans op het krijgen van een cardiovasculair event?

Hoofdstuk 2 presenteert een cross-sectionele studie naar de prevalenties van traditionele cardiovasculaire risicofactoren bij patiënten met verschillende reumatische diagnosen welke in 2009 werden geïncludeerd in het ACT-CVD cohort: reumatoïde artritis (n=546), jicht (n=129), osteoartrose (168), auto-immuun bindweefselziekten (n=85), polymyalgia rheumatica (n=91) en chronische gegeneraliseerde of lokale pijnsyndromen (n=214). Deze prevalenties worden vergeleken met de prevalentie van dezelfde risicofactoren in een steekproef van de Doetinchem Cohort Studie, een langlopende populatiestudie naar ontwikkelingen in leefstijl en gezondheidsproblemen in de algemene populatie (n=4523).[30] Primaire uitkomstmaten waren aanwezigheid van hypertensie (systolische bloeddruk ≥140 mmHg en/of diastolische bloeddruk ≥90 mmHg en/of het gebruik van antihypertensieve medicatie), een afwijkend cholesterolprofiel (totaal cholesterol ≥6.5 mmol/L en/of HDL cholesterol <0.9 mmol/L en/of het gebruik van cholesterol verlagende medicatie), overgewicht (body mass index ≥25 kg/m^2), obesitas (body mass index ≥30 kg/m^2) en door de patiënt zelf gerapporteerd actueel roken van tabak.
De prevalenties van hypertensie (P_{ACT}=68%, $P_{algemeen}$=57%), overgewicht (P_{ACT}=72%, $P_{algemeen}$=62%), obesitas (P_{ACT}=30%, $P_{algemeen}$=17%) en roken van tabak (P_{ACT}=26%, $P_{algemeen}$=21%) waren significant hoger bij patiënten met een reumatische diagnose dan in de controlepopulatie. Vergeleken met de controlepopulatie was het cardiovasculaire risicoprofiel van jicht patiënten het meest ongunstig, met significant verhoogde prevalenties van alle onderzochte risicofactoren. Met deze studie toonden wij dat traditionele, deels leefstijl geassocieerde en potentieel te beïnvloeden cardiovasculaire risicofactoren significant meer voorkomen bij patiënten met een reumatische diagnose in het algemeen, en niet alleen bij patiënten met reumatoïde artritis zoals gesuggereerd door voorafgaande literatuur.
In **hoofdstuk 3** onderzochten wij de mogelijke associaties van serum urinezuur spiegels, inflammatie en traditionele cardiovasculaire risicoparameters met het risico op cardiovasculaire events bij patiënten met jichtartritis (n=172) en patiënten met reumatoïde artritis (RA) of osteoartrose (OA) (n=686, 480 RA, 206 OA) met blanco cardiovasculaire voorgeschiedenis en geïncludeerd in het ACT-CVD cohort tussen februari 2009 en november 2011. Primaire uitkomstmaten waren systolische bloeddruk, totaal cholesterol/HDL-cholesterol ratio, geglycosyleerd hemoglobine (GlyHb) en body mass index (BMI) bij inclusie, respectievelijk de incidentie van eerste cardiovasculaire events.
De individuele cardiovasculaire risicofactoren systolische bloeddruk, totaal cholesterol/HDL-cholesterol ratio en body mass index bleken significant ongunstiger bij patiënten met jicht dan bij patiënten met een andere reumatische diagnose ($p<0.05$). Bij zowel reumatoïde artritis als bij osteoartrose patiënten correleerden de individuele cardiometabole risicofactoren met de serum urinezuurspiegel (RA: systolische bloeddruk, totaal cholesterol/HDL cholesterol ratio, BMI;

OA systolische bloeddruk, totaal cholesterol/HDL cholesterol ratio, BMI, GlyHb; p<0.05). Deze correlaties waren afwezig in patiënten met jicht. Bij niet-jicht patiënten waren een urinezuurspiegel in het hoogste tertiel (>0.34 mmol/L) en NT-proBNP spiegel onafhankelijke voorspellers van het optreden van een eerste cardiovasculair event, tegen leeftijd en GlyHb spiegel bij patiënten met jichtartritis (p< 0.05). Ten opzichte van niet-jicht patiënten met een serum urinezuur <0.27 mmol/L hadden zowel patiënten met jichtartritis als patiënten met een andere reumatische diagnose, maar met een urinezuur spiegel >0.34 mmol/L, een vergelijkbare significante 3-voudig verhoogde hazard ratio voor het optreden van een eerste cardiovasculair event binnen 3 jaar follow up. De aanwezigheid van jichtartritis, danwel een hogere urinezuurspiegel is derhalve bij patiënten met een reumatische aandoening mogelijk een betere predictor voor het optreden van een eerste cardiovasculair event dan sommige traditionele cardiovasculaire risicofactoren of inflammatoire parameters.

De doelstelling van **hoofdstuk 4** was meer informatie te verkrijgen over het cardiovasculaire risico in patiënten met reumatoïde artritis die behandeld worden volgens een intensieve 'tight control' behandelstrategie gericht op het behalen van een situatie van stabiele remissie van artritis binnen een zo kort mogelijk interval na het stellen van de diagnose. Wij verrichtten een prospectieve studie in het ACT-CVD cohort naar het optreden van eerste cardiovasculaire events bij reumatoïde artritis patiënten (n=480) behandeld volgens een eerder beschreven 'tight control' behandelprotocol en een gemiddeld lage ziekteactiviteit (n=480, 72% remissie, gemiddelde DAS-28 2.5 ±1.2 (ziekteactiviteitsscore in 28 gewrichten, remissie is gedefinieerd als een score ≤2.6)), vergeleken met patiënten met osteoartrose (n=206).[31] In een secundaire analyse spiegelden wij de incidentie van eerste cardiovasculaire events bij patiënten met reumatoïde artritis aan de zelfgerapporteerde incidentie van cardiovasculaire ziekte in de Nederlandse algemene bevolking.[32] Een andere secundaire uitkomstmaat was de bijdrage van behandelfactoren op het risico op eerste cardiovasculaire events bij reumatoïde artritis patiënten. De statistische analyses werden gecorrigeerd voor 10-jaars cardiovasculair risico scores bij inclusie in het ACT-CVD cohort. Na gemiddeld 3 jaar follow up was de incidentie van eerste cardiovasculaire events bij patiënten met reumatoïde artritis (21.0/1000 py, 95% CI 13.0-32.1) gelijk aan de incidentie bij patiënten met osteoartrose (29.7/1000 py, 95% CI 19.4-41.7). Er was geen trend naar een slechtere overleving bij reumatoïde artritis patiënten. De incidentie van eerste cardiovasculaire events bij patiënten met reumatoïde artritis was ook vergelijkbaar met de zelfgerapporteerde incidentie van cardiovasculaire ziekte in de algemene Nederlandse bevolking (RA 21.0/1000 py, 95% CI 13.0-32.1; GP 21.7/1000 py, 95% CI 13.6-33.0; p>0.999). Het gebruik van methotrexaat was als enige behandelfactor significant geassocieerd met een betere cardiovasculaire overleving bij reumatoïde artritis patiënten (HR 3.89, 95%CI 1.77-8.55). De resultaten van deze studie suggereren een

vergelijkbare incidentie van eerste cardiovasculaire events bij patiënten met intensief behandele reumatoïde artritis en patiënten met osteoartrose, en mogelijk ook de algemene bevolking. Behandeling met methotrexaat is significant geassocieerd met een geringere kans op het krijgen van een eerste cardiovasculair event bij reumatoïde artritis patiënten.

Hoofdstuk 5 presenteert een prospectieve studie naar het aandeel fatale cardiovasculaire events in het totaal van cardiovasculaire events (oftewel de 'case fatality') binnen de eerste 3 jaar follow up van het ACT-CVD cohort. Voorgaande studies in reumatoïde artritis populaties vonden een toegenomen 'case fatality' na myocardinfarct en een hogere frequentie van plotselinge hartdood ten opzichte van de algemene bevolking.[33;34] Het doel van deze studie was de cardiovasculaire 'case fatality' te onderzoeken in een actuele, volgens een 'tight control' strategie behandelde populatie reumatoïde artritis patiënten. De resultaten van deze prospectieve analyse werden middels een literatuur overzicht vergeleken met cardiovasculaire 'case fatality' in historische cohorten. De studie werd verricht in 480 patiënten met reumatoïde artritis en blanco cardiovasculaire voorgeschiedenis die tussen februari 2009 en november 2011 werden geïncludeerd in het ACT-CVD cohort. Met een COX-regressie analyse gecorrigeerd voor 10-jaars cardiovasculair risico scores bij baseline werd het risico op cardiovasculaire events bepaald en werden eventuele predictoren geïdentificeerd. De patiënten met reumatoïde artritis waren overwegend vrouw (72.3%) met een mediane ziekteduur van 4.2 jaar en hadden een gemiddelde DAS-28 score van 2.5 (±1.2 SD). Na een 3 jaar follow up hadden zich 29 eerste cardiovasculaire events voorgedaan, waarvan 2 fataal en 27 niet-fataal, corresponderend met 6.9% cardiovasculaire 'case fatality'. In vergelijking met voorgaande studies in in de tijd opeenvolgende cohorten suggereert deze bevinding een afnemende trend in het aandeel fatale cardiovasculaire events bij patiënten met reumatoïde artritis van 52.9% in 1998 naar 6.9% in het ACT-CVD cohort.

NSAID's behoren tot de meest frequent voorgeschreven geneesmiddelen binnen de reumatologie. Hoewel zeer effectief in de behandeling van nociceptieve pijn, brengt het chronisch gebruik van NSAID's ook belangrijke risico's op cardiovasculaire en gastro-intestinale complicaties met zich mee. De meeste literatuur over de associatie tussen het gebruik van NSAID's en het optreden van cardiovasculaire events betreft populaties van klinische trials. In **hoofdstuk 6** bestudeerden wij de associatie van NSAID gebruik met het optreden van eerste cardiovasculaire events in de dagelijkse praktijk in een ongeselecteerde populatie patiënten met reumatische ziekten, inclusief patiënten van middelbare en oudere leeftijd en patiënten met comorbiditeit en comedicatie. Na 3 jaar follow up van het ACT-CVD cohort deden wij een prospectieve analyse naar de associatie tussen continu gebruik van de meest frequent voorgeschreven NSAID's (naproxen, diclofenac, ibuprofen, meloxicam en COXIBs (etoricoxib en celecoxib)) en het optreden van eerste cardiovasculaire events bij patiënten met reumatoïde artritis of osteoartrose. De statistische analyses werden

gecorrigeerd voor 10-jaars cardiovasculair risico scores bij baseline en het intermitterend gebruik van NSAID's. Van in totaal 686 geïncludeerde patiënten kregen 46, 37/552 niet-NSAID gebruikers en 9/134 NSAID gebruikers, een cardiovasculair event binnen een mediane follow up van 36 maanden. COX regressie analyse toonde een significante associatie tussen continu gebruik van ibuprofen (HR 3.59, 95%CI 1.08-11.93) of een COXIB (HR 4.86, 95%CI 1.47-16.11) bij baseline en het optreden van eerste cardiovasculaire events. Continu gebruik van ibuprofen of een COXIB was derhalve in een ongeselecteerde populatie patiënten met reumatoïde artritis of osteoartrose geassocieerd met een significante toename van het risico op eerste cardiovasculaire events na slechts 3 jaar follow up. Overwegende de relatief korte duur van follow up en de kleine patiëntenpopulatie kan op basis van deze gegevens niet geconcludeerd worden dat het langdurig gebruik van de andere onderzochte NSAID's, diclofenac, meloxicam en naproxen wel veilig is in de dagelijkse reumatologische praktijk. Hiervoor zijn herhaalde analyses na langduriger follow up noodzakelijk.

Hoofdstuk 7 presenteert een ex-vivo experiment naar de farmacodynamische interactie tussen acetylsalicylzuur en verschillende cyclo-oxygenase (COX)-2-selectieve en niet-COX-1 of -2 selectieve NSAID's (naproxen, ibuprofen, meloxicam en etoricoxib) op de functie van trombocyten. NSAID's en acetylsalicylzuur worden vaak tegelijkertijd voorgeschreven aan reumatische patiënten met nociceptieve pijn en cardiovasculaire comorbiditeit. Hierbij kan interactie optreden omdat beide geneesmiddelen aangrijpen op de COX-enzymen voor hun therapeutisch effect. Het cardioprotectieve trombocyten aggregatie remmende effect van acetylsalicylzuur is geheel COX-1 afhankelijk. NSAID's kunnen of COX-1 en -2 selectief of alleen COX-2 selectief zijn. De studie was opgezet als een enkel blind, prospectief, placebo gecontroleerd, ex-vivo, serieel cross-over onderzoek bestaande uit driedaagse cycli gescheiden door wash-out perioden van minimaal 12 dagen. De studie werd uitgevoerd bij 30 gezonde vrijwilligers. Alle onderzochte NSAID's werden 2 uur vóór acetylsalicylzuur ingenomen. De ex-vivo trombocytenfunctie, uitgedrukt in closure time in seconden, werd gemeten met behulp van de Platelet Function Analyzer 100. Een verlenging in closure time bij opeenvolgende metingen tijdens één cyclus impliceerde een trombocytenremmend effect. Non-responders op acetylsalicylzuur, gedefinieerd als een verlenging in closure time <40% in een placebocyclus, werden uitgesloten van deelname. De significantie van geobserveerde verschillen in closure time werd statistisch getoetst met de Wilcoxon signed rank test. De resultaten van deze studie lieten zien dat de COX-1 en COX-2 selectieve NSAID's ibuprofen en naproxen het door acetylsalicylzuur veroorzaakte trombocytenremmend effect terugbrengen tot onder de non-respons drempel. De overwegend COX-2 selectieve NSAID's etoricoxib en meloxicam veroorzaakten geen significante verandering in het acetylsalicylzuur gemedieerde trombocytenremmende effect.

Samenvattend suggereren de resultaten van dit ex-vivo experiment dat de COX-1 affiniteit van een NSAID de grootte en daarmee het klinisch belang van de farmacodynamische interactie tussen het NSAID en acetylsalicylzuur bepaalt.

Hoofdstuk 8 betreft een literatuuroverzicht waarin de kennis over de verschillende mechanismen achter de cardioprotectieve effecten van acetylsalicylzuur en de aan NSAID gebruik gerelateerde cardio- en renovasculaire complicaties wordt samengevat. In kwetsbare patiënten kan NSAID gebruik hypertensie, oedeem en hartfalen veroorzaken. Ook hebben analyses in klinische trial populaties laten zien dat gebruik van de meeste NSAID's gepaard gaat met een circa 1.5 voudig verhoogd risico op ernstige cardiovasculaire events, uitgezonderd naproxen en mogelijk celecoxib in lage dosering (≤100 mg per dag). De groeiende bewijslast aangaande het cardiovasculair risico van NSAID gebruik heeft in 2005 geleid tot een algemene 'black box' waarschuwing vanuit de Federal Drug Administration van de Verenigde Staten van Amerika. Het mogelijk additieve risico bij gelijktijdig gebruik van acetylsalicylzuur voor cardiovasculaire profylaxe wordt besproken in de paragraaf over gecombineerd gebruik van acetylsalicylzuur en NSAID's. Hier wordt de combinatie beschreven als 'een duivel in vermomming'. Zoals ook reeds getoond in het ex-vivo experiment dat werd beschreven in hoofdstuk 7, competeren NSAID's met zowel COX-1 als -2 affiniteit met acetylsalicylzuur om eenieders bindingsplaats op het COX-1 enzym te bereiken. Gelijktijdig gebruik kan de binding van acetylsalicylzuur op het COX-1 enzym blokkeren, en hierdoor interfereren met het trombocytenremmende effect van acetylsalicylzuur. Hoewel de beschreven farmacodynamische interactie kan worden voorkomen door inname van het NSAID twee uur na acetylsalicylzuur, wordt aangeraden NSAID's in het geheel niet voor te schrijven bij patiënten die ook acetylsalicylzuur als cardiovasculaire profylaxe gebruiken.

In **Hoofdstuk 9** werden de bevindingen van de voorafgaande hoofdstukken samengevat en bediscussieerd. Dit proefschrift heeft laten zien dat reumatische ziekten in het algemeen ten opzichte van de algemene bevolking geassocieerd zijn met een hoge prevalentie van meerdere traditionele cardiovasculaire risicofactoren, waarbij het patroon van individuele risicofactoren per reumatische ziekte kan verschillen. Waar in voorafgaande literatuur de focus voornamelijk lag op ongunstige cardiovasculaire risicofactoren bij reumatoïde artritis zagen wij dat dit risicoprofiel niet uniek is binnen een reguliere populatie van een polikliniek reumatologie, en mogelijk zelfs nog duidelijker aanwezig is bij andere patiëntengroepen zoals patiënten met jichtartritis. De belangrijkste bevindingen van dit proefschrift betreffen echter de resultaten van de eerste prospectieve analyses van het ACT-CVD cohort na 3 jaar follow up. Ten opzichte van voorgaande cohorten lijkt het additionele cardiovasculaire risico van reumatoïde artritis patiënten te normaliseren of in ieder geval te dalen: ten opzichte van patiënten met osteoartrose, en mogelijk zelfs ten opzichte van de algemene bevolking. Ook lijkt er sprake te zijn van een daling van het aandeel fatale events in

het geheel van acute cardiovasculaire problemen. Het gebruik van methotrexaat is geassocieerd met een lager risico op cardiovasculaire ziekte bij reumatoïde artritis patiënten. Continu NSAID gebruik, vooral ibuprofen en COXIBs, kan het risico op cardiovasculaire complicaties bij patiënten met een reumatische aandoening verhogen. Zowel het mogelijk beschermend effect van methotrexaat als een mogelijk cardiovasculaire gevaar van NSAID's, al dan niet voorgeschreven in combinatie met acetylsalicylzuur, werden eerder beschreven in de literatuur. De resultaten van de studies beschreven in dit proefschrift bevestigen het respectievelijk belang in de actuele dagelijkse reumatologie praktijk. Zeker bij hoog risico patiënten die al acetylsalicylzuur als cardiovasculaire profylaxe gebruiken, en waarbij COX-1 selectieve NSAID's door farmacodynamische interactie het cardioprotectieve effect van acetylsalicylzuur kunnen blokkeren, moet het gebruik van NSAID's omwille van het voorkomen van cardiovasculaire complicaties indien mogelijk worden vermeden. Het ACT-CVD cohort biedt vele mogelijkheden voor vervolgonderzoek. Follow up data over cardiovasculaire events en overlijden worden periodiek verzameld. Herhaling van onze analyses over 5, 10 en 15 of meer jaren zal ons een steeds definitiever beeld verschaffen van het cardiovasculaire risico van patiënten met verschillende reumatische ziekten en de consequenties van 'tight control' behandelingen voor de frequentie van cardiovasculaire complicaties op lange termijn. In de optimale situatie zouden wij hiervoor graag weer gebruik willen maken van een controlepopulatie uit de algemene bevolking van dezelfde geografische regio, zoals wij eerder konden dankzij de samenwerking met het Rijksinstituut voor Volksgezondheid en Milieu. Ook zal bij langere follow up en een steeds groter aantal cardiovasculaire events de mogelijke invloed van reumatische ziekte specifieke risicofactoren beter onderzocht kunnen worden. Eén van onze doelen is te komen tot ziektespecifieke risicomodellen voor de verschillende reumatische ziektebeelden. Uiteindelijk dient het onderzoek naar reumatische ziekte geassocieerde cardiovasculaire aandoeningen niet te blijven steken in beschrijving van de huidige situatie. Er is behoefte aan gerichte risico-interventies, gebaseerd op de resultaten van de bovenstaand beschreven onderzoeksgebieden. De (kosten) effectiviteit hiervan moet worden getoetst in klinische trials, maar belangrijker nog na implementatie in de klinische praktijk.

Conclusies

De prevalentie van leefstijl geassocieerde cardiovasculaire risicofactoren is hoog bij reumatische ziekten in het algemeen, specifieke reumatische aandoeningen kunnen verschillen in cardiovasculair risicopatroon vergeleken met de algemene bevolking. Het cardiovasculaire risico van patiënten met een stabiel lage artritis activiteit en 'tight controlled' reumatoïde artritis is mogelijk lager dan geschat in historische cohorten van patiënten met matige tot hoge artritis activiteit. Deze observatie moet nog worden bevestigd in directe vergelijkingen met de algemene bevolking en

na langduriger follow up. Continu gebruik van NSAID's is een belangrijke behandelfactor die bijdraagt aan het cardiovasculair risico bij patiënten met reumatische ziekten. NSAID's moeten vooral worden vermeden in die patiënten welke tevens behandeld worden met acetylsalicylzuur in het kader van cardiovasculaire profylaxe.

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Curriculum Vitae

Inger Louise Meek werd op 8 februari 1977 geboren te Hoogezand-Sappemeer. In 1995 behaalde zij het VWO diploma aan de CSG Vincent van Gogh te Assen. Zij studeerde geneeskunde aan de Rijksuniversiteit Groningen en behaalde in 2002 het doctoraal- en artsexamen. Na het behalen van het artsexamen werkte zij van 2002 tot 2005 als arts-assistent inwendige geneeskunde in het Deventer Ziekenhuis. Tijdens haar opleiding tot internist werd haar belangstelling voor systemische auto-immuunziekten gewekt, waarna zij besloot de overstap te maken naar de reumatologie. Zij verhuisde naar Enschede en voltooide in 2009 in het Medisch Spectrum Twente de opleiding tot reumatoloog (opleider Prof. dr. M.A.F.J. van de Laar). In de laatste maanden van deze opleiding startte zij met het onderzoek zoals beschreven in dit proefschift. Van 2009 tot 2013 werkte zij in deeltijd als reumatoloog in het Medisch Spectrum Twente en als onderzoeker aan de faculteit Gedragswetenschappen van de Universteit Twente. In 2013 verliet zij Enschede en ging naar Nijmegen, waar zij nu werkt als reumatoloog bij de afdeling Reumatische Ziekten van het RadboudUMC. Samen met Nancy Ter Avest Schotmeijer vormt zij het bestuur van Stichting ReumaRun, een project dat voortkwam uit haar onderzoek.

Inger Louise Meek was born in Hoogezand-Sappemeer on February 8, 1977. After graduating from secondary school at the CSG Vincent van Gogh in Assen in 1995, she studied Medicine at the University of Groningen. She graduated as a Medical Doctor in 2002, and afterwards started as a resident Internal Medicine in the Deventer Hospital. While working she acquiered a passion for systemic auto-immune disease, and decided to specialize in Rheumatology. For this purpose she moved to Enschede where she became a resident in Rheumatology in 2005, and a Rheumatologist in 2009. In 2009 she also started her PhD project, supervised by Prof. dr. Mart van de Laar and dr. Harald Vonkeman, on the determinants of cardiovascular risk in current rheumatic practice at the Twente University. In 2012 she left Enschede to continue her career as a Rheumatologist at the Department of Rheumatology and Immunology of the RadboudUMC in Nijmegen. Her research inspired her to co-establish the ReumaRun Foundation, with Nancy Ter Avest-Schotmeijer.

List of publications

Meek IL, van de Laar MAFJ, Vonkeman HE. Non-steroidal anti-inflammatory drugs: an overview of cardiovascular drugs. *Pharmaceuticals* 2010;3;2146-2162.

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Hartmann M, Meek IL, van Houwelingen GK, Lambregts HP, Toes GJ, van der Wal AC, von Birgelen C. Acute left ventricular failure in a patiënt with hydroxychloroquine-induced cardiomyopathy. *Neth Heart J* 2011;19(11):482-485.

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Meek IL, Vonkeman HE, Kasemier J, Movig KL, van de Laar MA. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: A placebo controlled, ex vivo, serial crossover study. Eur J Clin Pharmacol 2013;69(3):365-71.

Inger Meek is a rheumatologist. The research for het PhD thesis was done at the Arthritis Center Twente of the Medisch Spectrum Twente hospital and Twente University.

Atherosclerotic cardiovascular disease is an important complication of chronic rheumatic inflammation. This thesis describes the prevalence of cardiovascular risk factors and occurrence of cardiovascular events in a current, tightly controlled rheumatic patient population, and the contribution of the use of non-steroidal anti-inflammatory drugs to cardiovascular event risk in rheumatic patients.